

Commentary on “Rethinking the International Response System to Global Health Threats: Strengthening International Collaboration to Ensure Vaccine Equity and Combat Vaccination Hesitancy”

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Coronavirus disease 2019 (COVID-19) vaccination rates remain insufficient to achieve worldwide herd immunity with respect to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Two issues are primarily responsible for this. Many countries want to achieve herd immunity through mass vaccination against SARS-CoV-2 virus but do not have the resources to do so. These countries may have a great supply of willing arms but have an insufficient supply of vaccine doses and/or other resources necessary to distribute and administer the needed vaccine doses to achieve herd immunity. Ironically, and sadly, many resource-rich countries, particularly the United States, have abundant vaccination supplies but limited numbers of individuals willing to receive vaccinations.

Perhaps it is time to stop waiting for more people in resource-rich countries to accept COVID-19 vaccinations and focus more efforts on the large population that resides in resource-limited countries that do not have access to COVID-19 vaccines. Perhaps such an approach will achieve much greater marginal value for COVID-19 vaccine doses by increasing vaccination rates more quickly for much more of the world’s population than by waiting indefinitely for vaccine nonaccepters to change their behaviors. Achieving a vaccination rate of >80% of people living in a community or country has been proposed to be the necessary vaccination prevalence threshold to achieve herd immunity. Thus far,

vaccine rejecters have caused many communities and countries to fall far short of this threshold for many months, particularly in the United States^{1,2}

In this issue of the *Southern Medical Journal*, Dr Ramin Walter Parsa-Parsi, an expert in global public health, discusses the compelling need to sufficiently increase COVID vaccination rates to achieve herd immunity effectively and equitably in resource-poor areas of the world.³ This will require major support and international collaboration from resource-rich countries. Not doing so places resource-poor areas at great risk for disproportionately high and prolonged preventable morbidity and mortality caused by the COVID-19 pandemic.

International efforts to help resource-poor countries achieve herd immunity through vaccination may benefit the whole world as well as targeted locales. Local benefits in targeted communities may include substantial lessening of preventable unfavorable outcomes such as morbidity/mortality, economic costs, political/economic/social destabilization, and other outcomes if timely and effective infection control and vaccination interventions can be instituted on a large-enough scale. For example, the risk of future COVID-19 surges and/or emergence of even worse mutant strains of SARS-CoV-2 may be lessened by reducing the number of uncontrolled reservoirs capable of exporting SARS-CoV-2 virus. International goodwill may be generated and contribute to productive collaboration that further improves global pandemic responses and/or other international issues.

This sentiment also is echoed by the World Health Organization (WHO) and the World Medical Association (WMA).³ Both WHO and WMA are advocating for the intensification of international support, particularly to enable resource-limited countries to perform mass COVID-19 vaccination for their populations. Both also recommend the intensification and prioritization of international collaboration to support and ensure reasonable equity with respect to distribution of knowledge, products, and other interventions that can effectively further mitigate or prevent severe COVID-19 disease in resource-limited areas. This strategic approach may yield greater COVID-19 vaccine

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utility because some major vaccine-producing countries have been unable to achieve herd immunity through mass vaccination because of high rates of vaccine nonacceptance. The remainder of this Commentary discusses some important pandemic response barriers that are delaying or preventing mass vaccination efforts from achieving herd immunity in some places, especially among vaccine nonaccepters in the United States. Better mastery of some of these issues may be crucial for optimal benefits to be realized from pandemic responses throughout the world.

Parsa-Parsi mentions some of these same issues as potential barriers that may need to be anticipated and/or managed in resource-limited countries. The key barriers operating in resource-limited countries include economic and healthcare system limitations that preclude the acquisition and administration of COVID-19 vaccines. Parsa-Parsi advocates for increased international collaboration to rapidly and equitably overcome various barriers that prevent doses of COVID-19 vaccine from being administered to the many people living in resource-limited areas of the world.³ Such efforts may more equitably and quickly reduce unnecessary morbidity/mortality in resource-limited areas and align with disaster response paradigms that prioritize the survival of as many at-risk people as possible.

Parsa-Parsi notes correctly that many countries of the world have sufficient capabilities and capacities to make significant contributions to such efforts.³ These countries can begin the necessary work to specify and meet the needs of countries with limited resources urgently and collaboratively. Parsa-Parsi further identifies some international organizations that already exist. These resources may facilitate collaboration among parties interested in helping with efforts to reduce COVID-19 disease in resource-limited areas of the world.³

He specifically notes some critical issues that seriously interfere with the responses to the COVID-19 pandemic in many resource-limited and several resource-rich countries such as the United States.³ Some of these issues may interfere with the ability of donor countries to supply support to resource-limited countries and/or the ability of recipient countries to optimize the benefits of the support they receive.

Should Nonacceptance of/Nonadherence to Pandemic Response Efforts Be Surprising?

Adherence is the “active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result.”⁴ Never starting treatment is termed “nonacceptance.” Persistence may be another component of adherence that requires a willingness to complete a prescribed duration of therapy.⁴

The degree of agreement regarding therapeutic goals between patient and provider is defined as concordance. The scope of concordance may include the degree of physician and patient agreement regarding therapy during the consultative process. Other elements may include communications and supports for patients regarding therapeutic interventions.⁵

Many clinicians encounter instances of nonacceptance/nonadherence in their practices for conditions other than COVID-19. These experiences may sometimes demonstrate that encouraging patients to accept, adhere to, and persevere with clinical recommendations can be extremely difficult, even impossible. Should nonacceptance of/nonadherence to potentially life-saving or disability-preventing clinical recommendations be surprising in the context of the COVID-19 pandemic? Probably not, because many people already fail to accept and/or adhere to effective preventive or therapeutic recommendations for management of many other serious medical issues.

One familiar example is the high nonacceptance/nonadherence rates associated with recommendations to abstain from smoking and other forms of nicotine/tobacco use to eliminate the almost-guaranteed serious morbidity/mortality that develops with persistent usage. Other significant examples may include failure to accept or adhere to recommendations to always use seatbelts and obeying traffic laws to avoid injury from traffic accidents; failure to follow recommendations regarding the management of common chronic disease conditions (eg, hypertension, diabetes mellitus, obesity) that can delay end-stage or terminal disease; failure to properly follow directions for medications; and failure to follow guidelines to reduce risks for other types of serious injuries, illnesses, or conditions.

Various factors may interfere with achieving acceptance and adherence with medical recommendations despite compelling information to do so and strong encouragement and support from providers, family members, caregivers and/or other individuals. These factors may include issues associated with the patient directly. Examples of these types of issues may include factors that interfere with a patient’s ability to understand the nature of his or her condition, how to perform recommended interventions properly, and/or psychological/emotional responses that occur in association with the medical condition (eg, anxiety, fear, denial). Sometimes secondary issues may be important barriers (eg, economic issues; addiction/withdrawal issues; conflicts with social, religious, or other cultural/tribal norms).

Some of the aforementioned barriers to acceptance/adherence may change as a result of time or events. For example, at the onset or diagnosis of a condition or during disaster responses, people initially may tend to be hypersensitized to the unfamiliar condition and associated risks. People may tend to have increased levels of anxiety or fear. Anxiety or fear can greatly decrease the ability of people to understand or process information contained in medical or disaster response recommendations. People at this stage of reacting to a condition or disaster often tend to want more information and more interventions. Clamoring for more use of technology also may occur. These tendencies often are driven by psychological/neurological hypersensitivity contributing to anxiety and fear. As people endure the effects of a condition or disaster for longer periods, they tend to become progressively desensitized to the risks. This tends to result in increasing fatigue or frustration with continuing therapeutic or disaster responses. Desensitization-induced lapses of risk-reduction efforts can lead

to poor outcomes. This pattern of psychologic reactions to serious clinical risks or disaster events seems to have held true with the recurring COVID-19 surges so far as we enter the third year of the pandemic.

The psychology of chronic health risks and disasters also tends to make at-risk people more willing to change their behaviors as their risk of being seriously affected by a condition becomes more likely, more imminent, or both. Perhaps sensing a more imminent and likely risk of prolonged hospitalization and/or serious morbidity and mortality caused by the delta variant may be a significant reason some people suddenly decided to be vaccinated despite adamantly refusing COVID-19 vaccinations previously. A very poignant example of this occurs when hospitalized patients request vaccination while they are being informed that they will die soon of COVID-19.

How Can Nonacceptance of/Nonadherence to Public Health Interventions Be Decreased Sufficiently to Better Mitigate the COVID-19 Pandemic?

History and earlier experience in the COVID-19 pandemic has demonstrated that existential threats from infectious disease epidemics and pandemics can be mitigated or controlled more effectively by public health and medical interventions. Nonacceptance of/nonadherence to these types of interventions negates the benefits of these interventions.

Substantial clinical research exists regarding strategies to increase adherence to clinical interventions for many conditions. A Cochrane meta-analysis a few years ago concluded that many studies of interventions to reduce nonadherence may have limited utility because the inclusion of nonadherent patients was not included in the study design of 184/190 of the studies analyzed. The Cochrane review found that this study design criterion was important for understanding the attributes of adherent versus nonadherent study patients to accurately determine whether an intervention was truly beneficial for improving adherence to a specific condition or context.⁶ This study design issue may have led to incorrect conclusions in many of the reviewed studies. The Cochrane review therefore suggests more well-designed clinical study is needed to determine best practices regarding the management of nonacceptance/nonadherence. This review further suggests that clinical evidence regarding adherence may be more limited than many clinicians appreciate.

Shared decision making is a commonly used contemporary clinical practice that allows providers and patients/caregivers to reach concurrence regarding therapeutic plans of care. It may not always successfully address nonacceptance or nonadherence behaviors that may arise, however. Analysis of options using a medical ethics framework may be another alternative approach to try to achieve mutually acceptable plans of care in some instances. Reasonable attempts to empathetically discuss the risk-benefit or other pros and cons of nonacceptance/nonadherence behaviors can be made, but such approaches may not be successful.

If the patient or key caregivers are not willing to listen or consider a change in their approach, then attempts to discuss COVID-19 vaccination with nonaccepters in my experience often are unsuccessful. Clinicians may not be as skillful as presumed regarding their ability to achieve acceptance and adherence by patients.

Overcoming nonacceptance /nonadherence regarding personal protection measures and vaccinations to control the COVID-19 pandemic is an urgent issue at present for nonaccepting individuals because longer intervals of nonacceptance/nonadherence create increasing cumulative risk for serious harm, particularly death, from COVID-19 infection. Other people in the community also may have an increased risk of harm to their health from increased transmission rates of COVID-19 associated with the nonacceptance/nonadherence behaviors of other individuals in their community.

Overcoming nonacceptance/nonadherence behaviors sufficiently and soon enough to interrupt the delta and omicron variant surges may require interventions designed to compel acceptance/adherence when reasoning is impossible or unsuccessful. Physicians generally cannot directly force people to accept/adhere to personal protection and vaccination recommendations. Some physicians do not accept new patients and/or dismiss established patients from their practices if they refuse personal protective measures or refuse indicated vaccines. Whether this makes any difference in ultimate acceptance/adherence rates is unknown.

Some precedents already exist regarding the management of individuals who refuse to adhere to public health and medical interventions needed to control and/or eliminate serious morbidity/mortality related to a communicable disease in a community. Historical or recent examples may include the enforcement of measures to control isolated cases or outbreaks of tuberculosis, polio, smallpox, Ebola, measles, and several other infectious diseases. Instances of enforcement of measures to control noninfectious conditions also exist, including enforcement of prohibitions on tobacco smoking in public places to minimize harm caused by secondhand smoke, enforcement of traffic laws, and enforcement of rules controlling disposal of toxic materials.

Interventions used in the past to control the transmission of infectious diseases with some precedents for enforcement include measures to prevent person-to-person transmission. Precedents to reduce person-to-person transmission already have been used during the COVID-19 pandemic to force individuals or groups of people to comply with public health and/or medical interventions. Various public health mandates to wear masks are probably the most well known. Unfortunately, nonacceptance/nonadherence, disobedience, and contesting public health mandates have become a serious issue that has negated any benefits of mandates in some places. Authorities empowered to issue mandates in many communities have refused or failed to do so for various reasons. Some authorities have even engaged in nonproductive mandate/counter-mandate battles with one another. It is hoped that the high nonacceptance rates associated with COVID-19 vaccinations in the United States will not spread to other areas of the

world and will abate in the United States and elsewhere sooner rather than later.

Some individuals and nongovernmental organizations can influence nonacceptance/nonadherence behaviors. For example, to some extent, individuals can choose to not interact with people who do not comply with public health measures. Many businesses are refusing to interact in various ways with people who refuse to adhere to personal protection measures and/or to be vaccinated. Business managers are recognizing the onerous costs of the COVID-19 pandemic. Reducing these costs is important to businesses because they must remain profitable to survive.

Business management science has studied how to improve individual behavior/performance extensively because of the substantial economic return potential from such efforts. Businesses generally try to diagnose reasons for poor behavior/performance and then tailor interventions to fix the problem. Remediation efforts are used to rectify problems caused by knowledge or skill deficits. Rewards and discipline are used to reinforce or extinguish behaviors.⁷ Many businesses now require the use of personal protection measures and receipt of vaccinations for COVID-19 as a condition of employment or doing business with other parties. This approach may alter nonacceptance/nonadherence behaviors to some degree in some businesses and other organizations.

As noted by Parsa-Parsi, disinformation and communication issues are interfering with effective responses to the COVID-19 pandemic.³ Misinformation has been plentiful in the United States and other countries for many months. Some people and organizations seem to have accepted and acted on the misinformation being communicated by many different sources, particularly some leaders, officials, “authorities,” and others trying to advance self-serving agendas. Unfortunately, recognition, elimination, and correction of such misinformation has been difficult and has not always occurred. For the foreseeable future, misinformation may continue to spread and to influence some people to continue to exhibit nonacceptance/nonadherence behaviors regarding personal protective measures and vaccination against COVID-19. Mass communication of misinformation also seems to have contributed to some of the anger, frustration, stress, and divisiveness associated with the pandemic in the United States and in other places.

Misinformation seems to promote distrust. The development of distrust may be a critically important factor leading to reduced progress with antitransmission and vaccination efforts aimed at controlling COVID-19. The social fabric of human relationships relies on trust. Restoring trust may be a keystone for achieving control of the pandemic sooner rather than later.⁸

The motivation for producing and widely communicating misinformation is not always clear. In some instances, advancement of the agendas of individuals or groups (eg, economic, political) seems to be a driver. In some cases, transmitting misinformation seems to be a marker of committed membership in a tribe or support of an agenda. Anger, anxiety, disruption, distrust, fear, and possibly other factors associated with disasters may tend to create opportunities that some people or groups perceive may advance their influence, power, or other self-interests.

One serious direct impact of the misinformation/communications issue seems to be an extreme and irreconcilable divide that arises between those who support and those who do not support some types of pandemic mitigation efforts. Insurmountable frustration and anger seem to develop with some frequency among some parties with opposing points of view. Occasional violent events have resulted. It is unclear to what degree such frustration and anger may have contributed to nonacceptance/nonadherence with pandemic response measures that contributed to the delta and omicron variant surges (as of this writing) or earlier COVID-19 surges. Another serious potential impact is the unnecessary number of cases and fatalities earlier in the pandemic that may have resulted from such behaviors and interactions. The roles played and relative impact attributable to some individuals, groups, organizations, political activities, news outlets, commentators, and social media users/content suppliers are unclear and controversial. Effective solutions to mitigate the misinformation being circulated are still being debated in the United States.

Continuing misinformation and communications issues raise concerns about their potential to promote continuing nonacceptance of/nonadherence to pandemic response measures by large numbers of people. Such an impact could substantially delay the ability to achieve herd immunity. This could result in many more people unnecessarily dying from COVID-19 (and conditions unrelated to COVID-19 because the surge capacity of medical resources has been consumed totally by COVID-19 cases). This also may increase the risk of further surges of COVID-19 in the future.

Many people have difficulty understanding relative risk. It may be more meaningful and effective for some people to have COVID-19 risks for unvaccinated and vaccinated individuals expressed as relative risks to common everyday risks such as dying in a car wreck or dying of some other condition during the year.

Although political, economic, social, education, and other reference frames have been used by various individuals, groups, organizations, and politicians to identify rationales to justify different responses to the pandemic, including nonacceptance/nonadherence behaviors, none of these frames of reference have yielded substantial evidence of lower rates of COVID-19 cases or morbidity/mortality compared with the rates seen when the public health/healthcare frame of reference is used. This argues that the public health/healthcare frame of reference that emphasizes reducing morbidity/mortality still may be best for guiding and prioritizing responses to the pandemic.

So far, the only substantially effective method to overcome nonacceptance/nonadherence behaviors in the United States seems to be the use of public and/or private mandates to require acceptance of and adherence to public health recommendations regarding personal protection measures and COVID-19 vaccinations. Such approaches have not been totally effective because of conflicts and disobedience to various degrees in some communities and states. For example, some jurisdictions have experienced lengthy conflicts involving officials and/or courts regarding who can issue mandates and what they can mandate. In general, private individuals

and organizations have had some success with “mandating” what public health measures must be adhered to on their own property.

Perhaps a more sanguine emphasis on individual morbidity/mortality risks from COVID-19 infections in unvaccinated people can be made a more compelling reason than the rationalizations people are using to not accept vaccinations.¹

What Does the Stress Test of the SARS-CoV-2 Delta Variant Surge Tell Us?

The delta variant virus surge caused huge negative effects. Extraordinary numbers of COVID-19 cases and rates of hospitalizations and deaths affected many countries of the world, particularly the United States and several countries in Europe, Asia, and South America.^{9,10} In many communities, the rates of these outcomes surpassed those noted earlier in the pandemic.^{9,10} Worse yet, COVID-19 cases caused by the delta variant exceeded the baseline and surge capacity of medical and social care systems in many communities and states.¹¹ Economic and opportunity costs were extraordinary in many places.

The delta variant surge can be viewed as a stress test of pandemic responses by individuals, communities, countries and the global population.^{12,13} Stress tests can help identify weak strategies and processes involved in responding to disasters. Stress tests also may distinguish authentic (sincere and bona fide) from inauthentic (misleading or misaligned) behaviors and values of individuals, organizations, and societies.^{12,13}

The delta variant surge showed that the COVID-19 pandemic was not controlled well enough to acceptably mitigate the extraordinary adverse impacts of the pandemic. Interventions to intensify and/or revise pandemic response efforts are indicated by this finding.^{9,10} Continuing those responses likely did not yield dramatic and rapid improvements. Processes continue to yield similar results if they are not modified. Changing processes (eg, pandemic responses) is needed to achieve different results.

More consistent and widespread use of proven, immediately available interventions to decrease person-to-person transmission of SARS-CoV-2 strains capable of continuing the COVID-19 pandemic is needed desperately. These interventions proved effective and easy to perform for most individuals and many communities during earlier surges of the pandemic. Increased rates of COVID-19 vaccinations are urgently needed as well. COVID-19 vaccines (eg, Moderna, Pfizer) represent the sole highly effective preventive intervention available to the world to substantially prevent severe COVID-19 and its associated morbidity/mortality. The development and testing of effective COVID-19 vaccines has been a miraculous accomplishment. Greater leveraging of COVID-19 vaccinations is the key to controlling COVID-19. The ultimate vaccination rate goal should be high enough to reach the herd immunity threshold.^{1,14} Some evidence suggests that increasing vaccination rates will provide marginal benefit until the herd immunity threshold is reached. Once the herd immunity threshold is achieved, then the pandemic

should involute because of the inability of the virus to infect susceptible people fast enough to sustain the pandemic.¹

One of the main reasons that the delta variant surge was so overwhelming seems to be insufficient rates of vaccination in many areas of the world. Two different mechanisms seem to cause most of the insufficient rates of vaccination in the world. Some countries seem able to produce or procure adequate vaccine doses to meet their needs but are hamstrung by large rates of vaccine nonacceptance. As noted by Parsa-Parsi, many resource-limited countries are experiencing low vaccination rates as a result of their inability to gain access to sufficient vaccine doses.³ If vaccine-producing countries can produce enough extra doses and support the development of effective distribution and administration processes to adequately support resource-limited countries, some dampening of the COVID-19 pandemic likely will occur.¹ The necessary prevalence of vaccinated individuals in a community or state is projected to be roughly 80% to substantially control COVID-19.^{1,14}

Further progress with COVID-19 vaccines may be required in the future. What types and numbers of further booster or strain-specific vaccine doses may be needed in the future is unclear.¹⁵ A vaccine for young children has been developed and tested in the United States. Preliminary results indicate that this pediatric vaccine is effective. It will probably become available soon in the United States and other countries as regulatory approval processes are completed.¹⁶ Unfortunately, the second reason for low vaccination rates results from nonacceptance/nonadherence behaviors by large numbers of people. This has become commonplace and is causing low vaccination rates in large parts of the United States and other places. This is occurring despite the fact that COVID-19 vaccinations have been proven to prevent serious COVID-19 disease.^{2,17} In the months of June, July, and August 2021, approximately 287,000 unvaccinated people in the United States have required hospitalization at an estimated average cost of \$20,000/admission and an overall cost exceeding \$5.7 billion. Many of these individuals also died or developed chronic health issues.¹⁸ In September 2021, the total deaths in the United States from COVID-19 surpassed the US death toll for the 1918 influenza pandemic (an estimated 675,000 deaths), the previous most deadly pandemic event to affect the United States.¹⁹ Most of these COVID-19 deaths were preventable. A significant number of those who died chose to remain unvaccinated.

None of the nonacceptance/nonadherence behaviors seem to have mitigated the pandemic and its costs to society as robustly as already recommended personal protection and vaccination efforts. Until many more people accept and adhere to recommended personal protection and vaccination measures, mitigation and control of COVID-19 illnesses will likely remain suboptimal in the United States and other places with severe vaccine nonacceptance issues.

A secondary result of the huge number of COVID-19 cases has been loss of healthcare surge capacity in many communities and states.¹¹ This has caused inadequate access to medical care, and significant morbidity and mortality have followed. This

inability to access medical care, especially inpatient and intensive care unit care, may persist until nonacceptance/nonadherence behaviors can be decreased enough to allow vaccination rates to approach or exceed the herd immunity threshold needed to slow or halt the pandemic.

Only small changes in rates of vaccination seem to have resulted from the adverse outcomes of the delta variant surge.² This suggests the increased poor outcomes of the stress test have not influenced many people to choose to abandon nonacceptance/nonadherence behaviors. The true motivations for nonacceptance/nonadherence behaviors remain obscure in many cases. Communication of information is another important issue that has interfered significantly with measures to respond to the delta variant surge in the United States and elsewhere.³

Multiple problems related to the quality of information about the pandemic provided by various sources have been noted. Communications made by some officials and other sources may have intentionally or unintentionally misled, distracted, or influenced people to abandon recommended interventions to mitigate the delta strain. Psychological issues such as fear and/or anxiety caused by the pandemic (eg, economic uncertainties, limitations on socialization and/or grieving, psychological fatigue from chronic stress) may have contributed to misunderstanding some communications. Sadly, some individuals have been harmed by misleading information.

Many people who choose to not accept or not adhere to recommended COVID-19 countermeasures do so quietly. Some choose to not accept or not adhere less quietly. And some believe they should encourage or pressure others to behave as they do. The true drivers of such points of view and behaviors often remain unclear. Attempts to understand or change these behaviors often are unsuccessful. Perhaps some of these people behave as they do because they have chosen less effective psychological defense mechanisms such as denial.

Worsening amplification of the already severe stress induced by the pandemic seems to be occurring in some US communities and states and perhaps elsewhere. This may be related to frustration and the loss of trust among people who have divergent points of view regarding the best ways to respond to the pandemic. In some places (eg, Florida, Texas), such antagonism seems to have caused profound and nonproductive discord and conflicts between some officials, citizens, and organizations. In some instances, the discord has been sufficient to severely interfere with pandemic response efforts of many communities. In some locales, this has been manifested by various officials and/or citizens undertaking huge efforts to battle one another in the media, in court, or in other public venues about their disagreements rather than compromising and pulling together to make better and timely responses to mitigate the pandemic. Many of these disagreements seem to be rooted in emotion or fealty to a cause, a tribe, or an organization. Such arguments seem to generally remain irreconcilable despite attempts at evidence-based or logical discourse in many cases. Rebuilding trust between the parties involved may be a prerequisite for the resumption of more effective pandemic

responses, but it may be very hard or even impossible to achieve.⁸

Battling among parties with opposing viewpoints has interfered with and delayed efforts to improve pandemic responses in many areas of the United States. Many of these areas had some of the worst pandemic statistics in the United States during the delta variant surge.^{2,17} In contrast, several other locations in the United States where vaccination rates are approximately 70% or higher experienced much smaller COVID-19 surges caused by the delta variant.^{2,10,17} These states also seem to have maintained substantial surge capacity in their medical systems. These states did not experience many of the other struggles to as severe a degree as other states with much lower vaccination rates. These observations suggest that achieving vaccination rates high enough to reach the herd immunity threshold may be the most beneficial intervention to reduce COVID-19 cases going forward.¹ COVID-19 vaccination rates in many communities and countries are still inadequate to substantially prevent large numbers of COVID-19 cases or large numbers of seriously ill COVID-19 cases. It seems that herd immunity will remain impossible to achieve for a significant interval given the large numbers of people who seem extremely resolute about continuing to refuse to receive COVID-19 vaccines.

The morbidity/mortality of earlier COVID-19 surges caused by infections with earlier SARS-CoV-2 strains were profound. The delta strain surge caused similarly profound or worse effects. As clinical experience with therapies for COVID-19 has grown, some improvement in outcomes has occurred, but poor outcomes remain much too frequent and extremely costly in terms of lives lost and total economic costs. So far, normally healthy people who have received COVID-19 vaccinations have been largely protected against serious COVID-19 disease.²⁰

The stress test resulting from the delta variant surge further demonstrates that many patients are still dying despite inpatient or intensive care unit efforts to treat serious illness caused by SARS-CoV-2 infections, particularly the delta variant. More effective therapy is certainly needed. COVID-19 vaccination may be able to act as a bridge that prevents serious disease until better therapies are found.

The stress test of the delta variant surge suggests that vaccine nonacceptance will persist, particularly in the United States, except for modest numbers of people who choose to be vaccinated because of personal fear of COVID-19 disease because of close proximity to severe COVID-19 outcomes and/or compelling mandates from government authorities, employers, businesses, or others. This stress test also suggests that more people will be vaccinated because of mandates rather than fear of serious COVID outcomes.

Conclusions

Interventions to remove barriers interfering with pandemic response efforts in many countries of the world clearly are indicated to achieve better control of the COVID-19 pandemic. The

usual epidemic response practices are relevant and should continue to be applied. Increasing adherence to personal protection measures and acceptance of COVID-19 vaccinations likely are the best responses to further mitigate and then control the pandemic in areas where nonacceptance/nonadherence behaviors are commonplace. Achieving herd immunity with vaccinations is probably the most important strategy to pursue.

The easiest barriers to overcome may be the economic and healthcare system limitations that exist in resource-limited countries. Strong international collaboration and support can supply the needed economic capital, vaccine doses, and vaccine distribution/administration resources.

The hardest barriers to overcome may be the nonacceptance/nonadherence behaviors that prevent more progress in the United States and other places. Mandates seem to be the only interventions capable of overcoming vaccination nonacceptance in a timely and substantial enough manner to allow herd immunity to be reached in the near future.

Perhaps the world should reap the benefits of overcoming the easiest barrier first until a solution is found that expeditiously overcomes the resolute nonacceptance/nonadherence behaviors that are prevalent in many parts of the United States and elsewhere.

Postscript

In a press release on September 14, 2021, US President Joe Biden announced that the United States will work with other nations to increase the vaccination rate to 70% of the world's population before September 2022.²¹ The program will include 1 billion additional vaccine doses beyond the 2 billion doses already pledged by wealthy nations. A total of \$10 billion by participating nations will be pledged for vaccine readiness, administration, procuring ancillary supplies, and overcoming vaccine hesitancy. The program will include all 92 resource-limited countries, except India (India has decided to use its own Serum Institute to meet its needs for vaccine doses). The WHO COVID-19 Vaccines Global Access (COVAX) program will be used to facilitate the delivery of vaccine doses to the countries that need international help. Attempts to create intellectual property waivers may be included in the program to allow more rapid creation of larger supplies of vaccine doses more rapidly. If this news becomes reality, then the thoughts of Dr. Parsa-Parsi may be implemented fully without major modifications.³

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