

Research News Quarterly

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Letter from the Editor

Our feature this month is an interview with the director of the NIH's National Institute on Minority Health and Health Disparities (NIMHD), Eliseo Perez-Stable, MD. In the interview, Dr. Perez-Stable discusses NIMHD's mission to catalyze research to understand and address minority health and health disparities to promote health equity, including through its science visioning process. He outlines the institute's initiatives to address COVID-19 health disparities and other projects related to respiratory disease, including asthma and risk factors for exacerbations such as electronic nicotine delivery systems (ENDS). Dr. Perez-Stable also discusses the steps NIMHD is taking to engage more individuals from minority backgrounds to pursue careers in research.

The March Research News Quarterly includes NIH opportunity announcements for early career scientists, first on the availability of no-cost extensions for early career awardees, followed by summer research training experiences for under-represented faculty through the PRIDE programs.

1. Justin R. Ortiz, MD, MS, and Meagan Deming, MD, PhD, from the Center for Vaccine Development and Global Health at the University of Maryland School of Medicine, Baltimore, "**The Rapid Clinical Development of SARS-CoV-2 Vaccines**"
2. S. Elizabeth Williams, MD, MPH, Department of Pediatrics, Vanderbilt University School of Medicine, and Marie R. Griffin MD, MPH, Departments of Health Policy and Pediatrics, Vanderbilt University School of Medicine, TN, "**Hesitancy Surrounding COVID-19 Vaccines.**"

We round out the Quarterly with a report from our Washington Office on health research funding.

Sincerely,

James K. Brown, MD

Editor

Chair, Research Advocacy Committee

RESEARCH NEWS QUARTERLY FEATUREInterview with **Eliseo J. Perez-Stable, MD**, Director, National Institute on Minority Health and Health Disparities (NIMHD)**1. What is your vision for the institute over the next few years?**

I am excited about our future because we have accomplished so much over the last 10 years since we have been an institute. We are moving in the right direction to continue advancing minority health and health disparities research across the lifespan.

One way we are charting the course is through our Institute's [science visioning](#), which provides a roadmap to catalyze research to understand and address minority health and health disparities across multiple diseases and conditions to promote health equity. We are being guided by the 30 strategies developed from the process as we continue to advance the science of minority health and health disparities.

One important development resulting from the science visioning is establishing a [research framework](#) for minority health and health disparities. This framework is specifically designed to address the complex influences on minority health and health disparities. It considers how outcomes can be measured at many levels and how these levels interact with different domains of influence, such as biology, behavior, the sociocultural environment, and the health care system. The framework encourages NIMHD and NIH-wide

supported research to address the complex and multifaceted nature of minority health and health disparities, locate research gaps and create opportunities for new research.

We are also focusing on developing and promoting tools that will make examining minority health and health disparities more rigorous. We are facilitating this through the [PhenX Toolkit](#) for social determinants of health (SDOH). This toolkit encourages researchers to collect data in a standardized way so that data from separate studies can be analyzed together. Recently, we worked with an expert panel to use the PhenX process to establish a new site on the Social [Determinants of Health Assessments Collection](#) to promote the use of standard measures by researchers. This is an exciting development and a huge step toward promoting standard use of measures so that researchers can compare analyses and increase our understanding of minority health and health disparities. We also launched the [HDPulse](#) tool, an online collection of resources related to minority health and health disparities. The tool is designed for persons to easily access data related to health disparities and explore minority health in their state.

Over the next few years, we hope to expand our training and mentorship programs to build the research

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Quarterly Feature: Interview with NIMHD Director *(Continued from page 2)*

capacity at under-resourced institutions. One such program is the [Research Centers in Minority Institutions \(RCMI\)](#). This research program supports NIMHD's vision to advance the science of minority health and health disparities research by enabling all investigators within the program to engage in rigorous, mentored research experiences focused on diseases that disproportionately affect minority and other health disparity populations. Another important program is the NIMHD-supported [Tribal Epidemiology Centers](#), which we plan to expand.

2. How is NIMHD engaging with other NIH Institutes to expand health disparities research in disease focused areas?

We are always exploring opportunities to work with our colleagues across NIH. Engaging in partnership with other Institutes is a critical part of NIMHD's mission. We cannot make any significant headway in advancing the science of minority health and health disparities by operating in a silo. Engaging in research partnerships is vital to what we do.

One key collaboration is the [Adolescent Brain Cognitive Development \(ABCD\)](#) study, which involves several institutes and offices at NIH and is led by NIDA. The study enrolls and follows more than 10,000 children from age 9 or 10 into early adulthood to better understand how their experiences affect brain development and behavior. About half of the participants are from racial and ethnic minority populations. Part of the research that we support is investigating how a young person's substance use over a period relates to their ethnic identity and their experiences with discrimination.

Another important effort we support is the [Jackson Heart Study \(JHS\)](#), in partnership with the National Heart, Lung, and Blood Institute (NHLBI). This robust research effort was initiated in 1998 to address the disproportionate burden of cardiovascular disease among African Americans. It is the largest study of inherited, behavioral and environmental risk factors associated with this health disparity. We are proud to be associated with this study, which has advanced the scientific knowledge of cardiovascular disease and implemented these findings at the community level to help lower the rate of heart disease among African Americans.

We are also supporting a study directed by the NHLBI—the [Hispanic Community Health Study/Study of Latinos](#). The project started in 2006 to gain a better understanding of health and disease among U.S. Latinos. In particular, this study aims to determine how heart and lung diseases, along with other chronic conditions, affect various Latino heritage groups, including Mexicans, Puerto Ricans, Cubans, Dominicans, and Central Americans. These and [many other projects](#) are being supported by NIMHD in partnership with our NIH colleagues.

3. What key project(s) focused on minority respiratory health has NIMHD previously funded and what health disparities research related to respiratory diseases is the Institute interested in funding in the future?

Documented evidence shows that there are higher rates of asthma among minority children, especially among Puerto Rican and African American children. In addition, higher rates of asthma related morbidity and mortality are also observed in these groups. NIMHD has participated in several efforts to reduce asthma disparities. For example, we are part of the [President's Task Force on Environmental Health Risks and Safety Risks to Children](#), a coordinated federal action plan to reduce racial and ethnic asthma disparities. Our main priority is to help accelerate efforts to identify and test interventions that may prevent the onset of asthma. The plan identifies four strategies and action plans to address the preventable factors leading to asthma disparities, and NIMHD is a key organization involved in three of those strategies.

[Research funded by NIMHD](#) demonstrated that Puerto Rican and African American children with asthma were significantly less responsive to albuterol, a short-acting β_2 -agonist, when compared with European American children. Poor response to asthma therapies could play a role in asthma disparities.

We have also supported studies to better understand asthma, including the factors that might cause its onset. In one [study](#), investigators examined the relationship of secondhand electronic nicotine delivery systems (ENDS) aerosol exposure and asthma exacerbations among youth with asthma. They found that exposure to secondhand ENDS aerosols increased the risk of an asthma attack by 27

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Quarterly Feature: Interview NIMHD Director *(Continued from page 3)*

percent. We are also supporting a study of how epigenetics can help explain asthma differences between Puerto Ricans, who have very high asthma rates, and Mexican Americans, who have much lower asthma rates. In addition, we support research into the connection between dietary patterns and asthma. We recently funded a [study](#) that suggests dietary patterns may alter immune responses and increase asthma risk or affect lung function in Latino adults.

NIMHD supports promotion efforts for the National, Heart, Lung, and Blood Institute (NHLBI) in the [Breathe Better Network](#), a partnership of organizations around the United States working to raise awareness about lung health at the local level. The Network helps to increase understanding of medical management of lung health, while encouraging people to actively talk to their health care providers about their lungs, and signs and symptoms they may be experiencing.

4. With regards to the COVID-19 public health emergency, what initiatives does NIMHD plan for investigating the specific effects of SARS-CoV-2 infection in minorities, as well as health disparities that have become evident during the pandemic?

As we use the power of science to understand and contain the COVID-19 pandemic, it's equally crucial for us to consider factors such as race, ethnicity, socioeconomic status, the built environment, the social environment, and health systems. The pandemic has shone a spotlight on health disparities, and we have an opportunity here to investigate and address the causes of these inequities.

I am privileged to lead a research institution and collaborate with others at NIH and externally to support research that will guide the science of community-engaged interventions.

NIMHD plays a co-lead role in the [RADx Underserved Populations \(RADx-UP\) program](#) that supports 53 testing interventions, 16 research studies, and a large Coordination and Data Collection Center (CDCC) in 32 institutions that cover 33 states, Washington, D.C., and Puerto Rico. Our goal is to promote COVID-19 testing among underserved and vulnerable populations and to develop strategies to reduce disparities in testing. These studies were funded as

competitive administrative supplements to existing grants; several are managed by NIMHD including the CDCC.

Another important project we are leading with the National Heart, Lung, and Blood Institute (NHLBI) is an NIH-wide effort called the [Community Engagement Alliance \(CEAL\) Against COVID-19 Disparities](#). We launched CEAL in the summer of 2020 in response to the high rates of infection, hospitalization and deaths among African American, Latino, American Indian, and Pacific Islander communities in the U.S. It is a significant initiative to address mistrust in science and misinformation about COVID-19 and vaccines, and to promote inclusion in therapeutic and vaccine clinical trials for populations disproportionately affected.

5. How does implementation science fit within the mission, research framework, and programs led by NIMHD?

Implementation science may include clinical and community approaches. NIMHD is interested in funding and evaluating interventions that decrease known inequities in care, whether in diagnosis, therapy, or chronic management. We look forward to the opportunity to collaborate with experts in pulmonary diseases who are interested in proposing innovative and multilevel strategies to implement care effectively.

6. What are the opportunities for collaboration with ATS and other respiratory societies?

The prevalence of bronchial asthma is known to be elevated among African Americans and Puerto Ricans, with up to three to four times the incidence and mortality. Chronic obstructive pulmonary disease (COPD) may also be more prevalent among selected populations with high exposure to air pollution and smoking. Cystic fibrosis and Hermansky-Pudlak syndrome (which is associated with remarkably undiagnosed and fatal pulmonary fibrosis) have been recognized among Puerto Ricans and are frequently missed by standard genetic screening of newborns. Exacerbation or undertreatment of bronchial asthma and COPD is a public health issue among children and adults from underserved and low-income backgrounds.

The similarities in clinical presentation between advanced lung disease and heart failure pose a challenge in early recognition of the disease and its prompt treatment and preservation of quality of life, which is exacerbated by inadequate or delayed access to health care experienced by populations with health care disparities.

These are examples of opportunities to foster research in disease mechanisms, the clinical manifestation of the disease, effectiveness of guidelines of care, and the interaction of social determinants of health and interventions to improve prognosis and quality of life.

We have an [FOA \(PA-20-172\)](#) on the long-term effects of disasters on health care systems serving populations with health care disparities. Research on effective health care systems, personal preparedness and recovery, community-led strategies, and the interaction between health care and school facilities could reveal potential interventions and lessons learned that could prevent further exacerbation of health disparities.

7. What are the Institute initiatives to engage more individuals from minority backgrounds to pursue careers in research?

A more diverse workforce promotes innovation and leads to better science. At NIMHD we encourage and support the development of a diverse and well-trained research workforce, which is critical to achieving our national research goals. African Americans, Latinos, American Indians/Alaska Natives, and Native Hawaiians and other Pacific Islanders are underrepresented in the biomedical workforce. At the rate that this gap is being addressed now, it will be over 100 years before parity is achieved. This is why we have embarked on several initiatives to provide [training and career development opportunities](#) at NIMHD to promote more diversity in the biomedical workforce.

One way we are taking steps to engage more individuals from diverse backgrounds to pursue careers in research is through R01 grants. This is important to us because, in general, they are less likely to receive awards overall. For example, in 2019, 1.2 percent of researchers across NIH who received R01 grants were African Americans; however, at NIMHD, it was 12.9 percent.

NIMHD is committed to nurturing the next generation of skilled minority health and health disparities researchers. We established the [NIMHD Health Disparities Research Institute](#) in 2016 to support the research career development of promising early-career minority health and health disparities research scientists, and stimulate new research ideas. This year the event will be held virtually from August 9 to 13, 2021; researchers will receive consultation on how to develop their research interest into a grant application and participate in a mock review session.

We also participate in the [NIH Medical Research Scholars Program \(MRSP\)](#), which is an initiative that places medical and other health professional students within the intramural labs across NIH to provide them with hands-on experiences in biomedical, population and/or behavioral research. NIMHD encourages research to examine health disparities through this program, and hosts scholars within the Institute's intramural program and through the director's laboratory at the National Heart, Lung, and Blood Institute.

NIH's [Faculty Institutional Recruitment for Sustainable Transformation \(FIRST\)](#) program was announced as an NIH Common Fund program in 2020 to increase the participation of underrepresented groups in biomedical research at NIH-funded institutions. The aim of the program is to enhance inclusive excellence, with diversity and equity at its core. Two funding announcements were released in December as part of the program. These funds will enable biomedical research institutions to hire a diverse cohort of early-stage research faculty committed to inclusive excellence and diversity. This program will help underrepresented scientists secure a seat at the table to leverage their diverse perspectives and develop relevant research to advance discovery in their field and reduce health disparities.

And finally, I want to highlight the [NIMHD William G. Coleman, Jr., PhD, Minority Health and Health Disparities Research Innovation Award](#), named after the first scientific director of NIMHD's Intramural Research Program, who was a staunch proponent of mentoring. This award supports researchers across the NIH intramural program who pursue projects on health disparities or minority health. ■

NIH-SUPPORTED OPPORTUNITIES

NIH Offers No-Cost Extensions for K and F Awardees Whose Career Trajectories Have Been Impacted by COVID-19

The COVID-19 pandemic and the wide-ranging mitigation measures required have adversely affected biomedical research. Evidence from various sources, including a survey that NIH issued to its extramural research workforce, indicates concerns about career trajectory for early career scientists. To address these issues within existing constraints of available funding, NIH plans to support early career scientists whose career trajectories have been significantly affected by the pandemic. NIH is providing an opportunity for recipients of NIH Fellowship (“F”) and NIH Career Development (“K”) awards who have been impacted by COVID-19 to request certain types of extensions. Please see [NOT-OD-21-052](#) for more information.

PRIDE Summer Training Opportunities for Under-Represented Junior Faculty

The NHLBI-supported [PRIDE Summer Institute Programs to Increase Diversity Among Individuals Engaged in Health-Related Research](#) are now accepting applications. Space is limited for the 2021 mentored summer training programs so apply early!

The PRIDE programs provide intensive summer research training experiences over two summers, a mid-year meeting, an annual conference, and an opportunity to apply for small research project grant funding. Choose from among several unique Summer Institute programs (see below), each with year-round mentored training opportunities to enhance research skills and promote the scientific and career development of trainees. Trainees will learn effective strategies for preparing, submitting and obtaining external funding for research purposes, including extensive tips on best practices. Research emphasis varies by program.

Created in 2007, PRIDE programs have mentored and trained over 400 mentees. The PRIDE program coordinating center is located at Washington University in St. Louis.

Eligible applicants are junior-level faculty or scientists with a background that is under-represented in the biomedical or health sciences, and are United States citizens or Permanent Residents. Research interests should be compatible with those of the NHLBI in the prevention and treatment of heart, lung, blood, and sleep (HLBS) disorders. Programs typically are all expenses paid including travel, meals, and housing. Mentees can apply to more than one program, but may attend only one. Application Deadline: Rolling admissions until positions are filled.

Summer Institute Programs

(Dates subject to change. Verify on website):

[Impact of Ancestry and Gender on Omics of Lung Diseases \(AGOLD\)](#)

(Aug.16 – 27, 2021)

Location: University of Colorado, Denver, Aurora, Colorado

PI(s): A. Sonia C. Flores, PhD; Oliver Eickelberg, MD, FERS, ATSF; Kathleen Barnes, PhD

[Advanced Respiratory Research for Equity \(AIRE\)](#)

(Aug. 5 – 13, 2021)

Location: Arizona Health Sciences Center, University of Arizona, Tucson, Arizona

PI(s): Joe GN “Skip” Garcia, MD; Francisco Moreno, MD; Sairam Parthasarathy, MD

[Behavioral and Sleep Medicine \(BSM\)](#)

(July 11 – 23, 2021)

Location: NYU Langone Medical Center, New York, New York

PI(s): Girardin Jean-Louis, PhD; Gbenga Ogedegbe, MD, MPH

[Obesity Health Disparities \(OHD\)](#)

(TBA, 2021)

Location: University of Mississippi Medical Center, Jackson, Mississippi

PI(s): Bettina M Beech, DrPH, MPH; Keith C Norris, MD, PhD

[Research in Implementation Science for Equity \(RISE\)](#)

(July 19 – 30, 2021)

Location: UCSF Center for Vulnerable Populations, San Francisco Gen. Hospital

PI(s): K. Bibbins-Domingo, PhD, MD, MAS; A. Fernandez, MD; M. Handley, PhD, MPH

VETERANS ADMINISTRATION

Veterans Health Administration Rolls Out New Program for Lung Cancer Research and Care

By **James K. Brown MD**, Chair, ATS Research Advocacy Committee

The Veterans Health Administration has embarked on an ambitious endeavor to transform and enhance research and care related to lung cancer among the 6 million Veterans within the VA's 1255 health care facilities. The new program, called the Lung Precision Oncology Program (LPOP), is a joint effort between the VA's Office of Research and Development (ORD) and its National Oncology Program Office (NOPO) in partnership with the Office of Healthcare Transformation. The two aspects of lung cancer that the program will focus on are (i) precision oncology and (ii) lung cancer screening. After a competitive review of applications, in November 2020 the VA announced the award of funding to 18 VA Hub sites (centers of expertise) that will form a national network, working to implement genetic testing, clinical trials using precision oncology, and early detection using low-dose chest CT scans to screen for lung cancer among high-risk Veterans.

LPOP is led by an executive steering committee and co-chaired by ORD's Chief Research and Development Officer Rachel B. Ramoni, D. M. D., Sc.D., and by Michael Kelley, M.D., National Program Director for Oncology in the VA. The work of the program is being facilitated by the Cooperative Studies Program Coordinating Center at the West Haven VA, along with program staff from ORD and NOPO.

The 18 LPOP sites are the Bronx – James J. Peters VA Medical Center (Bronx, NY), the VA Connecticut Health Care System (West Haven, CT), the VA Greater Los Angeles Healthcare System (Los Angeles, CA), the Jesse Brown VA

Medical Center (Chicago, IL), the Long Beach Veterans Health Administration (Long Beach, CA), the Louisville VA Medical Center (Louisville, KY), the Pittsburgh Veterans Health Administration (Pittsburgh, PA), the Denver VA Eastern Colorado Health Care System (Aurora, CO), the Houston Michael E. DeBakey VA Medical Center (Houston, TX), the Minneapolis VA Medical Center (Minneapolis, MN), the Virginia Veterans Administration Hospital (Richmond, VA), the Veterans Health Administration (Ann Arbor, MI), the W. G. Hefner VA Medical Center (Salisbury, NC), the Durham VA Medical Center (Durham, NC), the St. Louis VA Medical Center (St. Louis, MO), the San Francisco VA Medical Center (San Francisco, CA), and the Puget Sound (Seattle) VA Healthcare System (Seattle, WA).

The sites are distributed to ensure that nearly all the VA's regional health networks, called VISN's (Veterans Integrated Service Networks), are represented in LPOP. Associated with each Hub site will be several "Spoke" sites that are smaller regional VA hospitals providing care to more rurally based Veterans. The goal will be to markedly increase access to cutting-edge clinical trials, as well as lung cancer screening, across the nation in the Veterans Health Administration regardless of where the Veterans live, including (through use of the Hub and Spoke model) in less urban and rural areas.

The VA is making a significant investment in LPOP's foundational elements of infrastructure, operation and organizational leadership to build a sustainable program over the next 5 years. Each site will be led by two principal investigators, an oncologist to oversee precision oncology trials and a pulmonary physician for direction of lung cancer screening programs. In addition to its clinical, research and administrative staff, VA will be looking to leverage the expertise of its academic affiliate partners to bring best-in-class cancer care to Veterans while engaging in a robust research agenda. It is anticipated that the LPOP network will engage in a diverse set of research activities that enable partnerships with the NIH, DOD, industry and others to support research funding, leverage resources, collaborate and synergize to accelerate discoveries and translation to the clinic.

The Veterans Health Administration has a strong background in precision oncology through its VA National Precision Oncology Program¹, which has long

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provided tumor sequencing and consultative services for the treatment of Veterans with cancer, and through its Precision Oncology Program for Cancer of the Prostate (POPCaP) Network², a joint effort of the VA and the Prostate Cancer Foundation. In 2011, screening for lung cancer using low-dose chest CT scans first was established to be effective and lifesaving for those at high risk for lung cancer³. The VA responded quickly by initiating its own 8-site Demonstration Project, which established the feasibility of implementing screening effectively in the VA⁴. The American Thoracic Society recognized early on the importance of this approach to lung cancer screening and has advocated strongly for its value within the VA.

The *Research News Quarterly* will provide periodic updates on developments in the establishment of this exciting and important new program. ■

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RESEARCH PERSPECTIVES

The Rapid Clinical Development of SARS-CoV-2 Vaccines

By **Justin R. Ortiz, MD, MS**, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD & **Meagan Deming, MD, PhD**, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD

Only 11 months elapsed from the submission of the SARS-CoV-2 sequence data to GenBank to the authorization of the first vaccine in the United States. The unprecedented speed to develop vaccines against the pandemic virus was due to many factors, including previous vaccine development efforts against other novel coronaviruses, the advanced stage of mRNA vaccine platforms, and massive investments in clinical research and manufacturing at risk. The purpose of this report is to describe how vaccines against SARS-CoV-2 were developed so quickly while adhering to best research practices and regulatory standards.

Four seasonal human coronaviruses circulate globally. They typically cause mild upper respiratory symptoms and are among the viral etiologies of the “common cold.” Coronaviruses are also enzootic in nature, with the potential for cross-species transmission.¹ In the last two decades, three novel coronaviruses have emerged from animal reservoirs and caused major outbreaks of human disease: Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012, and SARS-CoV-2 in 2019. The SARS-CoV outbreak was controlled by non-pharmaceutical interventions, and no human cases have been reported since 2003.² The MERS outbreak has been smaller, but it continues to cause sporadic infections and remains a pandemic threat.³

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The Rapid Clinical Development of SARS-CoV-2 Vaccines *(Continued from page 8)*

Given the ongoing risk of emergent coronaviruses, vaccine development against novel coronaviruses has been ongoing since they were first identified. A large body of research detailing the role of the spike glycoprotein in coronavirus immunity had advanced several vaccine candidates to human trials by the time of the SARS-CoV-2 emergence.^{4,5} Early SARS-CoV-2 vaccine candidates were informed by advanced research conducted by NIH, BionTech, and the University of Oxford in MERS vaccines. These products would eventually become the first SARS-CoV-2 vaccines receiving authorization in the United States and Europe and manufactured by Moderna, Pfizer/BioNTech, and AstraZeneca.

Research advancements in vaccine platforms that predated the pandemic were pivotal to the rapid development of SARS-CoV-2 vaccines. The first two vaccines authorized for use in the United States were based on mRNA technologies. Manufacturing nucleic acid vaccines can be achieved in weeks, compared to the year-long timetable required for producing the cell lines and clinical-grade subunit proteins required for more traditional vaccine platforms.⁶ The production speed of mRNA vaccines, compared to other vaccine platforms, partly explains why they were some of the initial products to become authorized for use. Nucleic acid vaccines also have the advantage of being immunogenic and eliciting both humoral and cellular immunity.⁷ Candidate mRNA-based SARS-CoV-2 vaccines also benefitted from pre-pandemic research in protein structural biology.^{8,9} An example was the development of pre-fusion stabilized spike proteins for MERS that were more immunogenic at lower doses than wild type spike proteins.⁹ The chimpanzee adenovirus-vectored vaccine, (ChAdOx1)-MERS, which expressed the full-length spike glycoprotein, was even further along in development, having completed phase 1 clinical trials before the emergence of SARS-CoV-2.⁴

The rapid clinical development of SARS-CoV-2 vaccines benefited from massive funding that supported the advancement of multiple diverse vaccine candidates, facilitated the compression and overlap of research stages, enabled well-powered efficacy studies, and

supported large scale manufacturing of vaccines before regulatory authorizations. Typically, clinical trials proceed in a step-wise fashion, with each trial phase taking two years or more. In the United States, an investigational new drug application is filed with the FDA. Then a phase I clinical trial is performed involving less than 100 subjects to determine the initial safety profile and to obtain preliminary vaccine immunogenicity data.⁷ If the trial findings are satisfactory, the candidate vaccine proceeds to phase II trials to further evaluate immunogenicity, to determine appropriate dosing, and to optimize vaccination strategies in up to 200 more subjects.⁷ Finally, the subsequent phase III trials are large and costly, and are typically designed to evaluate efficacy and safety. If phase III trials meet predefined endpoints, a biologics license application is filed with the FDA in a process that can take another 1-2 years.⁷

These clinical phases were compressed by SARS-CoV-2 vaccine development. Early phase trials were conducted in parallel, laboratory analyses were expedited, and planning for subsequent trials was done at-risk before results became available. SARS-CoV-2 vaccine clinical trials could therefore proceed rapidly and far faster than traditional clinical development. Similarly, the multiple vaccine candidates were manufactured according to regulatory standards so that once a product achieved authorization for use, stores would be available for rapid deployment.

After the SARS-CoV-2 outbreak was declared a public health emergency in February 2020, the Secretary of the US Health and Human Services declared that the severity of the pandemic justified authorization of emergency use of vaccines and therapies directed at COVID-19. These Emergency Use Authorizations (EUAs) are intended to allow for the rapid deployment of vaccines broadly to a healthy population; thus, strict standards for safety and efficacy are required. At least one well-designed and well-controlled phase three trial must demonstrate significant benefits that outweigh any known or potential risks of the vaccine.¹⁰ Specifically, efficacy outcomes are required to demonstrate that these vaccines prevent or mitigate severe outcomes (i.e., hospitalization or death)

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The Rapid Clinical Development of SARS-CoV-2 Vaccines *(Continued from page 9)*

of SARS-CoV-2 infection and with a minimum efficacy of 50 percent better than placebo.¹⁰ The sponsors must also demonstrate that they can support sufficient manufacturing quality and consistency for broad distribution.¹⁰ Biologics License Applications (BLA) for full approval are expected to follow these EUAs, with longer follow-up of participants for additional safety data.

In the United States, new vaccines also undergo a series of independent expert reviews. Vaccine efficacy trials have independent Data Monitoring Committees (DMCs) comprised of experts that regularly review data accumulating from the trial. A DMC advises sponsors of the trial regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The FDA is the vaccine regulatory authority in the United States. FDA coordinates the Vaccines and Related Biological Products Advisory Committee (VRBPAC), which gives the agency advice related to a product's suitability for use. VRBPAC reviews and evaluates data concerning the safety, effectiveness, and appropriate use of vaccines.¹¹ The Advisory Committee on Immunization Practices (ACIP) advises the US Centers for Disease Control and Prevention on vaccine policy recommendations. VRBPAC and ACIP members have relevant expertise for their committee functions. The committees publish member declarations of interests, and the advisory meetings are public with published agendas and public domain records of their deliberations.

The rapid clinical development, process development, and manufacturing scale-up would not be possible without substantial resources and complex planning. In 2020, the US Government launched Operation Warp Speed as a public-private partnership to facilitate and accelerate the development of COVID-19 vaccines, therapies, and diagnostics.¹² The program started with a goal of distributing 300 million doses of SARS-CoV-2 vaccines by mid-2021.¹² To accomplish the herculean task of running all the vaccine development streams in parallel, massive financial resources were expended at substantial financial risk. The relatively high rates of

community transmission of SARS-CoV-2 resulted in the phase 3 trials rapidly accumulating the necessary case counts for efficacy analyses.

The confluence of these factors allowed for the compressed timeframe of SARS-CoV-2 vaccine development. While much work is still needed to ensure that all those who would benefit from vaccination can receive it, the SARS-CoV-2 vaccines available in the United States followed rigorous procedures to evaluate safety and efficacy. ■

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Hesitancy Surrounding COVID-19 Vaccines

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Vaccine hesitancy, defined by the World Health Organization as “the reluctance or refusal to vaccinate despite the availability of vaccines”, remains a priority threat to public health globally.¹ Despite rigorous studies conducted to dispute myths associated with vaccination, hesitancy remains, and it is in fact gradually worsening.² The impact of these beliefs leads to lower vaccination rates, which result in higher burdens of vaccine preventable diseases in hesitancy-prone communities.³ While outbreaks of measles, pertussis, and mumps are reported in the U.S., the most frequently recommended vaccine that is declined by the U.S. population is influenza vaccine. Unfortunately, evidence suggests similarly high levels of vaccine hesitancy is seen with vaccines to protect against COVID-19.⁴

Hesitancy surrounding COVID-19 vaccines is likely multifactorial. In addition to commonly recognized reasons for vaccine refusal, such as misinformation about the safety or efficacy of a vaccine, distrust in government institutions, as well as the perceived rushed rate of development and emergency approval are also contributing to COVID-19 vaccine hesitant beliefs.⁵ In order to control the pandemic, infectious disease experts predict that approximately 75 percent of the population

needs to be vaccinated against COVID-19 with the goal being to induce herd immunity. Thus, as health care providers, we must be prepared to address these concerns with confidence.

Evidence suggests that healthcare providers are the most trusted source for vaccine decision making.⁶ Given the mistrust surrounding the development of these vaccines, an understanding of the safety, effectiveness, and accelerated timeline for development of the new vaccines will be valuable to answer patients' questions. In the U.S., all vaccines are being tested in trials of at least 30,000 people and are designed to include persons that reflect the racial/ethnic diversity of the U.S. The rapid timeline was possible for several reasons: previous work on vaccines for the prevention of SARS COV-2 and MERS, years of research on innovative new vaccine platforms; the financial backing by the government to rapidly enroll thousands of volunteers; and the pace of the epidemic which resulted in a large number of COVID-19 cases among placebo recipients such that the efficacy of the vaccines was evident quickly (please see accompanying article in this issue).

Common side effects of the vaccines include local (injection site) and systemic (fever, headache, malaise) reactions that resolve in a few days. No common major safety issues were identified during the trials. Monitoring of coronavirus vaccines continues after emergency use authorization (EUA) to identify less common adverse events. To date, anaphylaxis has emerged as a rare side effect, that is 11.1 and 2.5 episodes per million doses with Pfizer and Moderna vaccines, respectively.^{7, 8} Although serious, most occur within 15 minutes of vaccination and are easily treatable. FDA provides updated information sheets for caregivers and vaccine recipients for all vaccines the receive an EUA.⁹

Researchers have also identified specific communication styles that have greater success for vaccine ‘fencesitters’, labeled as such by hesitancy research pioneer Deborah Gust.¹⁰ Fencesitters include individuals who may be amenable to acceptance of recommended vaccines but only with encouragement and reassurance. For these individuals, evidence suggests that utilizing a presumptive approach towards the vaccine may be more successful

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than a participatory approach.¹¹ To demonstrate the difference between the two styles, a provider implementing the presumptive approach would introduce the COVID-19 vaccine in a manner similar to “today we are going to give you your COVID-19 vaccine” or “have you scheduled your COVID-19 vaccine yet?” In contrast, the participatory approach opens the opportunity for discussion prior to the recommendation (e.g. “How do you feel about receiving the COVID-19 vaccine today?”, or “Are you planning to get the COVID-19 vaccine?”).

Further, newer evidence suggests that utilizing motivational interviewing techniques can be beneficial for patients who remain hesitant about vaccines even after the value of the vaccine has been introduced.¹² This motivational interviewing approach would include using the ‘elicit, provide, elicit’ framework. First, one would elicit the patient’s concerns about the vaccine, then ask the patient if you can provide additional information you have to specifically address these concerns, and then finally elicit their thoughts on the vaccine upon learning more information. If they are still hesitant, you start the cycle again and continue until you reach a point where there is no further information you can provide to change their minds at that time.

Another critical component related to vaccine hesitancy is historical mistrust of research and medicine among minority groups. It is important to understand the historical medical malfeasance experienced by those in disadvantaged minority populations and ways in which this history understandably may lead to distrust. Health care providers can acknowledge these concerns and also confirm that the coronavirus vaccine trials intentionally sought and enrolled volunteers that represent the diverse U.S. population. Finally, it is clear that disadvantaged minority populations have experienced a disproportionate burden of COVID-19 disease. It will be important to provide vaccine in settings that are easily accessible to these highly affected populations.

Early evidence suggests that a substantial proportion of the U.S. population may be hesitant to receive vaccination against COVID-19. Understanding and addressing the concerns of this part of our population in a culturally

appropriate way, utilizing evidence-based communication styles, may help address this challenge. ■

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WASHINGTON UPDATE

Research Funding

Congress will begin working on fiscal year (FY) 2022 funding for health research and services programs, including the NIH and CDC, by late March 2021. President Biden has not yet released his proposed FY2022 budget so we do not know what funding levels the Administration is proposing for health programs. We expect the Administration may release some top-level agency budgets sometime in March, but program level details may not be released until later in the spring.

We expect that with continued bipartisan support for addressing the COVID pandemic and new Congress and White House controlled by Democrats, NIH and CDC should fare well, but ATS member advocacy will be needed to push for funding increases that permit real growth in agency budgets to address public health needs, including for people with respiratory diseases. ■

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