Evidence, Experience, Expertise, and the U.S. COVID-19 Public Health Response

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The U.S. response to the COVID-19 pandemic underscores the need for evidence-based approaches to public health and clinical interventions. Charged with providing public health guidance and responding wherever the need is urgent, the U.S. Centers for Disease Control and Prevention (CDC) and state, tribal and, local, and territorial health departments assess individual and population level health outcomes, available and promising interventions, and downstream consequences when crafting public health recommendations and interventions. Over the past year, this pandemic response has demonstrated that a transparent, collaborative, and science-based approach that adapts to complex and rapidly evolving conditions is and will continue to be critical to bringing an end to the pandemic.

Data-driven guidance begins with clear terminology characterizing the evidence. National reports have demonstrated the numbers of COVID-19 cases involving hospitalization and death have directly correlated with overall reported SARS-CoV-2 infections [1]. As we look forward, particularly with increased vaccine and treatment availability, SARS-CoV-2 infection may lead to varying clinical outcomes, and the correlation with severe COVID-19 disease may not be as straightforward. As U.S. COVID-19 hospitalizations and deaths decrease, reported mild or asymptomatic SARS-CoV-2 infections might not decrease at the same pace in all communities. Adapting the current case definition of COVID-19 [2], which assigns the same importance to mildly symptomatic infection as severe disease, to the appropriate context, with more rigorous delineation between asymptomatic or mildly symptomatic viral infection and a severe clinical syndrome, can facilitate informed clinician-patient conversations, targeted clinical and epidemiologic studies, evidence-based recommendations and policy, and effective resource allocation. We should aim to understand this distinction in every setting and subpopulation where we apply evidence and experience. This is analogous to the adoption of new nomenclature and disease classification that occurred as more was understood about HIV infection being a clinically distinct from AIDS or latent TB infection as distinct from TB disease. Precision in how we characterize the epidemiology of infections at the local level will be critical for sustaining control of transmission and accelerating recovery.

In this supplement, we provide a snapshot of some of the science, experience, and experts supporting the response. We touch on five major topics with these articles: clinical sequelae of SARS-CoV-2 infection, SARS-CoV-2 testing, COVID-19’s interaction with other infectious diseases, COVID-19 and disproportionately affected persons, and SARS-CoV-2 transmission.

**Clinical Sequelae of SARS-CoV-2 Infections**

The impact on patients and healthcare burden of minimally symptomatic SARS-CoV-2 infection is unequivocally different from the burden of severe COVID-19. Chevinsky et al. demonstrate that the timing and type of post-COVID sequelae differ between hospitalized inpatients and patients managed in outpatient settings compared to control patients without COVID-19 [3]. This cohort study of 27,589 inpatients and 46,857 outpatients diagnosed with COVID-19 and matched to control patients without COVID-19 through a 4-month follow-up period, using electronic health record data and propensity score matching, demonstrates notable differences in long-term outcomes in patients diagnosed with COVID-19 compared to control patients without COVID-19, stratified by whether or not the patient required hospitalization at diagnosis.

In addition to severity of SARS-CoV-2 infection at diagnosis, many underlying medical conditions accelerate progression to severe disease, and pregnancy is one of the most common medical conditions in our population. Two studies in this supplement look exclusively at pregnant women with COVID-19. Using CDC’s Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET), Galang et al.
found that among 5,963 pregnant women identified as COVID-19 cases, certain risk factors, such as gestational diabetes, age 30–39 years, and healthcare occupation were associated with moderate-to-severe COVID-19 [4]. Ko et al. expand upon these findings using data from a healthcare database of 703 hospitals and identified that after adjusting for maternal age, race/ethnicity, primary payor, and selected underlying medical conditions, a documented COVID-19 diagnosis at delivery hospitalization was associated with increased risk for sepsis, shock, acute renal failure, thromboembolic disease, adverse cardiac events/outcomes, intensive care unit admission, and death [5].

The goal of preventing hospitalization and death for those at higher risk of acquiring SARS-CoV-2 infection and progressing to severe COVID-19 directly informed vaccination program planning efforts in the United States, with Advisory Committee on Immunization Practices (ACIP) recommendations aimed to target early vaccination distribution to persons in long-term care facilities, persons aged ≥65 years, frontline essential workers, and persons aged 16-64 years with high-risk medical conditions [6]. Sami et al. demonstrate that in a sample of hospitalized patients from 14 academic centers in the United States, over 90% met ≥1 of these risk factors for severe COVID-19 [7]. These findings support continued emphasis on efforts that most effectively provide vaccination for persons with higher risk medical conditions, even as vaccines become widely available.

**SARS-CoV-2 Testing**

Alongside vaccine rollout, this year the public also witnessed the launch of more detailed CDC recommendations for SARS-CoV-2 testing [8], and more widespread SARS-CoV-2 testing across a variety of settings. Testing brings both opportunity and complexity. Fox et al. demonstrate how incorporating testing as part of a shortened quarantine protocol can facilitate implementation of quarantine protocols on college campuses, and reduce time lost from classroom and other campus commitments [9]. These data support CDC’s recommendations to reduce quarantine duration using diagnostic testing [10]. Recognizing the importance of maintaining essential public health services during the pandemic even prior to vaccine availability, Laws et al. describe the Ugandan Ministry of Health supplementing prevention measures with SARS-CoV-2 universal testing and isolation of persons with positive tests to continue an in-person HIV training activity [11].

Testing alone, however, cannot be the sole intervention to prevent SARS-CoV-2 outbreaks. Moreno et al. describe over 30 confirmed secondary cases that occurred within a university athletics program after the index patient attended a meeting while infectious, despite a negative antigen test on the day of the meeting [12]. Vaccination, in addition to masking, distancing, isolation of cases, quarantine of close contacts, and other mitigation measures remain essential to reduce transmission.

Interpreting a positive or negative SARS-CoV-2 test result requires consideration of multiple contextual factors. Test type, body site of specimen collection, and how and why the specimen is collected are all important to consider. Shah et al. evaluate the BinaxNOW antigen test in a community setting in Wisconsin, concluding that immediate repeat antigen testing is highly consistent with 99% concordance, supporting use of this platform in broader sectors [13]. Choice of specimen for testing also matters. In the study by Gable et al. evaluating less invasive specimen types, investigators compared matched oropharyngeal swabs, anterior nasal swabs (ANS), and saliva collected from each participant across the course of their infections [14]. Saliva yielded more reverse transcription-polymerase chain reaction (RT-PCR)-positives at later time points, suggesting that saliva-based diagnostics may lead to more unnecessary infection control actions by identifying (RT-PCR)–positive individuals who are no longer infectious. ANS yielded the most RT-PCR positives at earlier time points and culturable virus more
often than oropharyngeal specimens, suggesting test positivity with this specimen may be a better indicator of infectivity. Finally, with goals of increasing patient acceptance and conserving healthcare resources, Marx et al. evaluated self-collected saliva or ANS for SARS-CoV-2, compared with clinician-collected nasopharyngeal swabs in Denver, Colorado [15]. While self-collected saliva and ANS were less sensitive for SARS-CoV-2 than NPS, these data suggest that reliable detection of SARS-CoV-2 offers many practical advantages and may be most useful for symptomatic patients.

**COVID-19’s Interaction with Other Infectious Diseases**

Widespread testing and the overwhelming presence of COVID-19 in medical systems has the potential to lead clinical and public health practitioners astray, particularly when other infectious diseases are present. Narita et al. describe three clear examples from Seattle, WA where patients with risk factors for tuberculosis (TB) were repeatedly tested only for SARS-CoV-2 upon presentation to care, only many tests later to be diagnosed with late-stage, infectious TB, including one death from TB [16]. Conversely, Schrod t et al. characterize a long term care facility outbreak where, based on initial rapid testing, there appeared to be concurrent outbreaks of influenza and SARS-CoV-2; however, all patients initially suspected to have influenza were later found to have false positive tests [17]. These articles highlight that even during a pandemic, infectious disease and public health expertise from the pre-COVID-19 era and careful consideration of the overall clinical context remain critical to appropriate interpretation of SARS-CoV-2 test results.

**COVID-19 and Disproportionately Affected Persons**

Beyond the direct impact of SARS-CoV-2 infection itself, other consequences of the pandemic have resulted in a disproportionate burden on persons at risk of other diseases. Based on National Emergency Medical Services Information System (NEMSIS) data describing 911 Emergency Medical Services (EMS) activations in 2020, EMS activations as a percentage of total activations increased during the early pandemic period for cardiac arrest, on-scene death, and opioid-related events, remaining above baseline levels through the end of the year [18]. Further, many groups that have been marginalized depend on their employers to align with national or local guidance, and workplace-specific challenges may prevent prompt detection, intervention and prevention of COVID-19 outbreaks [19]; this may foreshadow similar challenges for preventive measures such as vaccination.

There has been focused attention on disproportionately affected persons beginning with the ACIP recommendations referenced above, but also in other aspects of the pandemic. Marks et al. characterize the potential for 14,000 Health Resources and Services Administration (HRSA) Health Center Program service delivery sites to deliver COVID-19 vaccines to up to 30 million patients. With the exception of non-Hispanic Black and American Indian/Alaska Native persons, there were more health center influenza vaccinations among racial/ethnic minorities, particularly among Hispanics, in comparison with county racial/ethnic demographics [20]. Further, Wilson et al. describe the implementation of the Infection Prevention and Control (IPC) Global Webinar Series to bring together subject-matter experts and IPC professionals to share guidance and implementation examples across healthcare communities who no longer, or previously did not, have access to traditional modes of knowledge dissemination [21].

**SARS-CoV-2 Transmission**
Lastly, in regards to both COVID-19 and other upper respiratory viral diseases, two studies provide continued support for current CDC recommendations on fundamental mitigation measures that are important for control of SARS-CoV-2 as well as other upper respiratory viral infections during periods of widespread community transmission. Carter et al. describe multi-state SARS-CoV-2 transmission among approximately 462,000 persons attending a variety of outdoor and indoor activities at a national motorcycle rally held in South Dakota in August 2020 [22]. COVID-19 was diagnosed in participants not only in South Dakota, but also in Minnesota, Montana, North Dakota, Nebraska, and Wyoming, confirming increased risk of widespread SARS-CoV-2 transmission from mass gatherings where attendees travelled from outside the local area. Basic nonpharmaceutical interventions have implications for respiratory viruses beyond SARS-CoV-2. Rodgers et al. describe findings from an analysis of emergency department (ED) visits reported to the National Syndromic Surveillance Program according to chief complaints and diagnosis codes, excluding visits with diagnosed SARS-CoV-2 infections [23]. For each week during March 1, 2020–December 31, 2020, percent positivity for influenza virus, respiratory syncytial virus, human parainfluenza virus, adenoviruses, and human metapneumovirus were lower in 2020 than 2019, suggesting that non-pharmaceutical interventions to mitigate spread of SARS-CoV-2 likely also reduced transmission of other pathogens.

In conclusion, the U.S. public health response has required a coalition of federal, state, and local public health officials and researchers, academic and pharmaceutical partners, and clinicians working tirelessly to apply evidence, experience, and expertise in the development, implementation, and evaluation of national COVID-19 recommendations. The studies in this supplement provide insights into some of the most important aspects of the pandemic – who is at highest risk for which severe outcomes, how we can accurately track SARS-COV-2 infections while maintaining awareness of other concurrent or mimicking illnesses, and opportunities for public health and clinical medicine to bring expertise and experience together to combat one of the largest threats to health of the past century. While in the United States deaths from the pandemic have reached more than half a million in the past year, through steady vaccination rollout and consistent implementation of evidence-based interventions by individuals, communities, public health practitioners and frontline clinicians, we will pass from darkness into the dawn.

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