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Forum for Evidence-Based Medicine

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COVID–19
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A note from Dr. Cohen: Sunsetting of the COVID Forum

Fourteen months into our pandemic our case rates are in a sustained decline and the flow of new research is diminishing. As such, unless the trajectory of the pandemic changes, this will be the last issue of the COVID Forum. We will highlight any important new COVID-19 research as part of the Optum Forum for Evidence-Based Medicine and write ad hoc issues of the COVID Forum should the need arise. Drs. Hitt, Heyer and I hope that the information we shared helped you manage your patients through the pandemic and with any luck, the end may be nearing reality.

Should the COVID-19 vaccine be mandated?

Large-scale COVID-19 vaccination is needed to establish herd immunity. Yet recent surveys have demonstrated that nearly a quarter of adult respondents are hesitant to receive the vaccine.[1] In September 2020, 14% reported that they will probably not get vaccinated, and 20% reported that they definitely will not get vaccinated. Factors associated with vaccine hesitancy in this survey included being Republican (42%), age 30–49 (36%), residing in a rural area (35%), and being Black (35%).[1] Given the broad-ranging consequences of vaccine hesitancy, the authors of a recent *JAMA Viewpoint* examined if and how vaccine mandates could be imposed.[2]

State mandates: States have long upheld vaccine mandates for childhood vaccinations as a condition of school entry; although, all states grant medical exemptions and 45 states and Washington, DC grant religious exemptions. Adult vaccination mandates have been rare. At least 16 states require influenza or hepatitis B vaccinations for postsecondary education. Given the rarity of adult mandates, the authors suggest that states are unlikely to enact adult COVID-19 vaccination mandates.

Employee mandates: The Equal Employment Opportunity Commission (EEOC) has ruled that businesses can require workers to be vaccinated as a condition of employment. The EEOC, however, also requires that employers grant medical exemptions and offer reasonable accommodations based on religion or disability. Businesses may mandate vaccination, especially when the nature of the business poses high risks of COVID transmission, but accommodations for medical, religious, and disability reasons would also be necessary.

Student mandates: Student vaccine mandates could be enacted for primary and secondary education, especially given the public health justification for safely reopening schools. But broad mandates are not possible until FDA approval for vaccine use in younger individuals.

Customer mandates: It is conceivable that businesses could require proof of vaccination as a condition of service. This would be especially relevant where customers would be at increased risk of transmission, such as plane, train, or bus travel, restaurants, theaters and sporting events. Local and state governments could enforce such vaccination policies. Although states may be constitutionally barred from requiring vaccines to participate in religious worship, places of worship could impose vaccination mandates for their congregates.

The authors argue that implementing vaccine mandates among populations where vaccination is not widely supported could be counterproductive and ultimately undermine public support. They offer the opinion that limited mandates in special high-risk or high-value settings and the development of longer-term safety data may lead to improved long-term immunization coverage. The authors fail to address how policy can improve public awareness, even change public opinion. There once was a time when few people wore seatbelts and airplanes had smoking sections.

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Continue to mask or not continue to mask? That is the question.

It is now well appreciated that increase vaccination rates along with use of nonpharmaceutical interventions (NPI) will most likely control the COVID-19 pandemic. This is particularly important as the public is increasingly demonstrating a desire to relax NPI as vaccination rates increase. In the recently published Morbidity and Mortality Weekly Report (MMWR), the CDC used six different models across four scenarios each with varying levels of vaccination coverage and NPI use to estimate COVID-19 cases, hospitalizations and death.[3]

The models varied the vaccine efficacy, use of NPI and the number of vaccines administered. The model then projected across four different combinations of vaccine use and effectiveness, and projected COVID-19 cases, hospitalizations and deaths in the United States from March through September of 2021.

All models showed that even modest reductions in NPI adherence undermined vaccine-related gains in pandemic control over the following two to three months. Importantly, decreases in NPI adherence coupled with the emergence of variants with increased transmissibility were projected to lead to surges in hospitalizations and deaths. The authors emphasize the need to continue NPI where transmission risk may be elevated (crowded indoor spaces, etc.) as the vaccine rollout continues.

India variant of concern B.1.617

The new variant of concern (VOC), B.1.617, has become the driving force behind the severe surge of COVID-19 cases and associated deaths in India and parts of southeast Asia.[4] This VOC has been identified in least 49 other countries, with most of the cases arising in India, but others in the United Kingdom, U.S. and Singapore. It is now the most rapidly increasing variant in the UK (see chart below). There are several sub-lineages, including the B.1.617.1 and B.1.617.2 which were first identified in India in December 2020, and have been detected at increasing prevalence since that time. B.1.617 includes several mutations present in other VOCs including L452R, P681R, and E484Q.

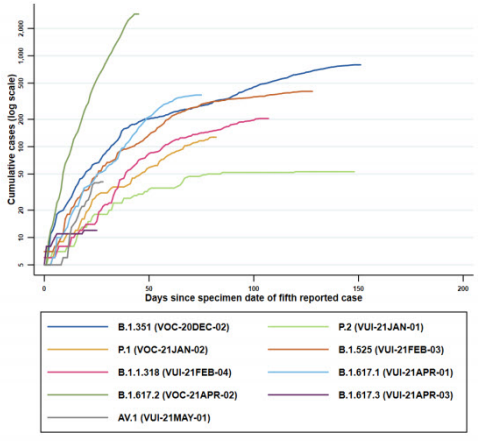
The L452R mutation, in particular, has been identified in another VOC, B.1.427/ B.1.429 (California), which has been associated with increased transmissibility, a reduction in neutralization by some (but not all) monoclonal antibody treatments, and a moderate reduction in neutralization in post-vaccination sera in the U.S. Laboratory studies suggest that convalescent samples from individuals who had natural infection may have reduced neutralization against variants with an E484Q mutation. This is an important point as B.1.617.2 is currently the most rapidly rising variant in the UK.[5]

In terms of vaccine susceptibility, preprint data in a small number of cases showed well-preserved efficacy for the Pfizer and AstraZeneca (AZ) vaccines.[6] With the Pfizer vaccine, two-dose effectiveness was reduced from 93.7% for the B.1.1.7 variant to 87.9% with B.1.6.172. With the AZ vaccine (not available in the U.S.), two-dose effectiveness was reduced from 66.1% for B.1.1.7 to 59.8% with B.1.617.2. It is also notable that in a small lab study (n=28), recipients of Novavax-Covaxin, were able to neutralize the B.1.617 variant.[7] It is likely that vaccine effectiveness against more severe disease outcomes will be even greater.

SARS-CoV-2 variants of concern and variants under investigation

Figure 2. Cumulative cases in England of variants indexed by days since the fifth reported, data as of 18 May 2021
(Find accessible data used in this graph in underlying data)

Figure 2 demonstrates the rapid identification of VOC-21APR-02 (B.1.617.2) cases over a short period of time.



At the time of this publication, India is still recording over 300,000 cases daily. Other drivers of the surge in India and elsewhere may include challenges around the implementation and adherence to public health and social measures and social gatherings (including mass gatherings during cultural and religious celebrations). Further investigation is needed to understand the relative contribution of these factors. It remains unclear how generalizable laboratory-based studies of limited sample sizes, as well as studies of other variants with similar key mutations, are to the wider circulating B.1.617 variants. Further robust studies into the impacts of these variants, including impacts on epidemiological characteristics (transmissibility, severity, reinfection risk, etc.) are urgently needed.

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Vaccine efficacy of BNT162b2 vaccine against B.1.1.7 and B.1.351 variants

There has been concern about the vaccine efficacy (VE) of existing COVID-19 vaccines against emerging variants of the SARS-CoV-2 virus. Of particular concern is the VE against the B.1.1.7 (the UK variant) and the B.1.351 (the South African variant), both known to have increased infectivity and increased mortality. Researchers in Israel and Qatar have now demonstrated the Pfizer mRNA vaccine, BNT162b2, has remarkably preserved VE against severe disease produced by both variants.

In Israel, more than 6.5 million persons have been vaccinated against COVID-19.[8] Researchers followed this population for seven weeks post-vaccination and calculated VE. Fully-vaccinated individuals were considered those more than seven days post the second vaccine dose. Cases of SARS-CoV-2 total infections, symptomatic, and asymptomatic infections were tracked. COVID-19 related hospitalizations and severe or critical hospitalizations and deaths were also tracked (Table 1). B.1.1.7 prevalence was estimated using a test which identifies specific variant mutations which are found in B.1.1.7. The prevalence of B.1.1.7 in Israel during the study was estimated to be 94.5%.

In Qatar, 265,410 persons had received two doses of BNT162b2 and were followed beginning 14 days after receipt of the second dose for any SARS-CoV-2 infection, hospitalization and death.[9] VE was determined for each outcome (Table 1). In Qatar, both B.1.1.7 and B.1.351 were present representing 44.5% and 50% of cases respectively in March of 2021.

In both studies the VE efficacy against severe disease with both B.1.1.7 and B.1.351 variants were largely preserved (bold results in Table 1). The VE against B.1.351 disease is reduced by 20% in the prevention of any infection with SARS-CoV-2. This highlights the importance of continuing to emphasize vaccination and the importance of tracking variants and VE as the pandemic continues to evolve.

Table 1. Vaccine efficacy of BNT162b2 against B.1.1.7 and B.1.351 variants

Condition	Number of patients	Vaccine efficacy							
		Any COVID	Symptoms	No symptoms	Hospitalization		Death	Severe infection with	
					any	severe		B.1.1.7	B.1.351
Israel	6538911	**95.3**	97	91.5	**97.2**	**97.5**	**96.7**	**95+**	NR
Qatar	265410	87/72*	NR	NR	NR	MR	**97.4**		

*B.1.1.7 and B.1.351 variants respectively; + Estimated given prevalence of B.1.1.7 of 95%

Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection

My colleagues at OptumLabs and I published this study in the *BMJ* on May 20, 2021. We looked at 266,000 patients with COVID-19, predominantly outpatients and all under age 65 years.[10] We examined the pattern of their ICD-10 codes to determine the incidence of Long COVID in this population. We only looked at sequalae that were first diagnosed at least three weeks after the onset date of their infection. Fourteen percent of patients had at least one sequela identified. We then looked at comparison groups, including a 2020 noninfected group and a 2019 prepandemic group with viral lower respiratory infection. The difference in risk for new sequelae in the COVID-19 group was ~5% higher than in the comparison groups, suggesting that this is the incidence of late sequelae for which medical attention was sought in this population.

There were a myriad of sequalae that were significantly elevated in this population including respiratory failure, myocarditis, cardiac arrythmias including orthostatic tachycardia, hypercoagulability with thromboses, cognitive difficulties and memory loss, peripheral neuropathy, type 2 diabetes, abnormal liver tests, anxiety and fatigue (see Figure 2 on the next page). Symptoms such as anosmia and myalgias were likely under-reported as these are not often captured in ICD-10 codes. As would be expected, the frequency of late sequelae was highest in those who were hospitalized, older, or had underlying comorbidities; but a significant number of these patients were younger with no comorbidities. In some individuals, symptoms of the sequelae were still present six months post-infection.

Given that there are now over 165 million cases worldwide, even this relatively low incidence of late sequelae would account for over 8 million cases of Long COVID. This underscores the need to accurately define the natural history of Long COVID, a process which is helped with these data. Based upon these and other data, we can begin to define the appropriate evaluation and management of this large population of patients.

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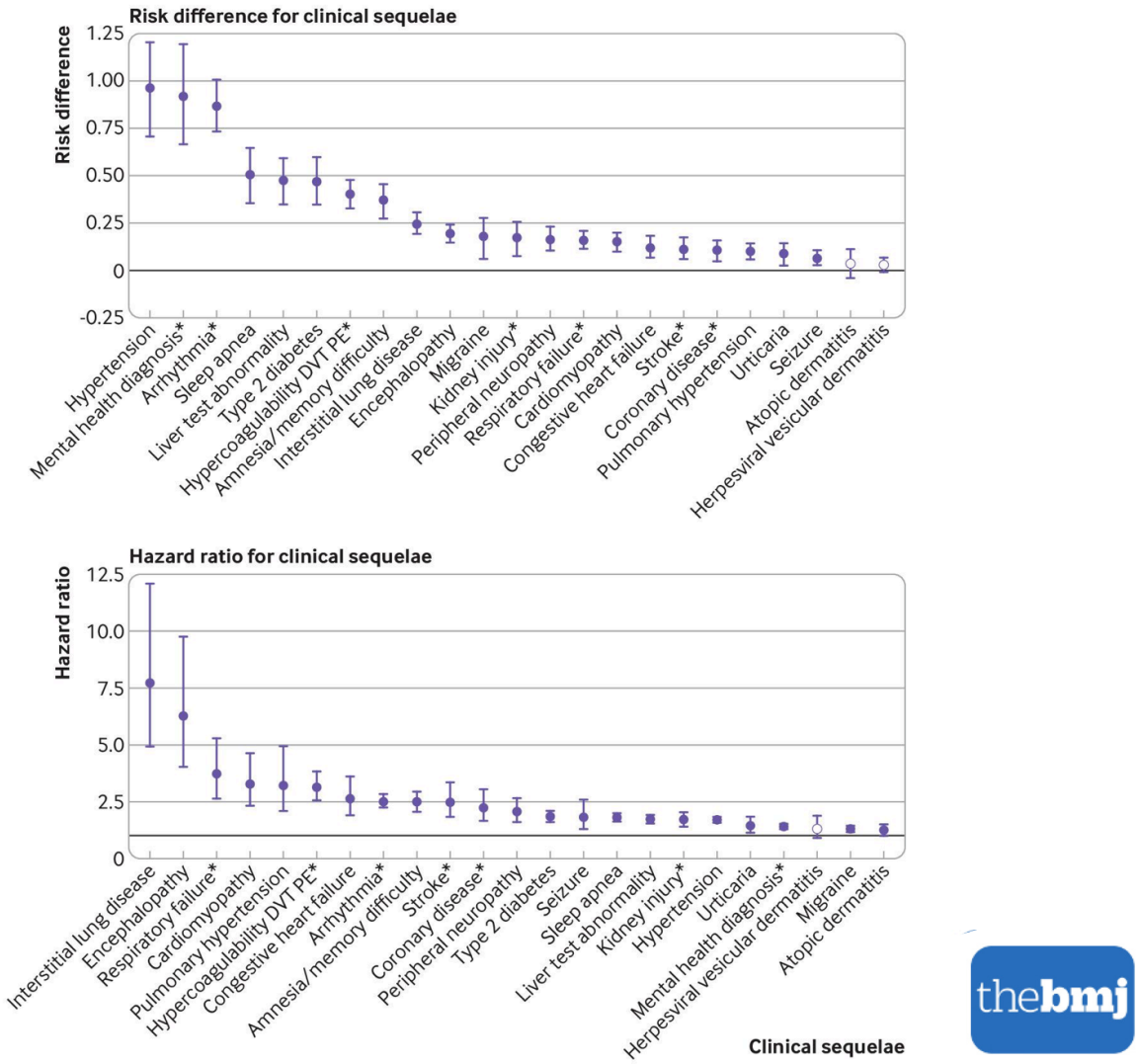

Risk difference (per 100 individuals) and hazard ratios for the most common clinical sequelae in the SARS-CoV-2 versus the 2020 comparator group, UnitedHealth Group Clinical Discovery Database up to 31 October 2020. DVT=deep vein thrombosis; PE=pulmonary embolism

 Sarah E Daugherty et al. BMJ 2021;373:bmj.n1098

All-cause mortality far exceeds predicted values in 2020

Using data from 2014 through 2019, the expected death rate was predicted for 2020. Investigators compared the actual numbers of deaths to the predicted values from March 1, 2020 through January 1, 2021.[11] This study complements a previous analysis from March through July of 2020.[12]

During the study period, there were 2,801,439 deaths in the U.S., 22.9% more than predicted, representing 522,368 excess deaths. The large majority of these deaths were attributed to COVID-19 but the number also included deaths not attributed directly to COVID-19, as discussed below. The death rate was higher among non-Hispanic Black individuals, likely reflecting racial disparities in COVID-19 mortality. Regional surges were also evident. The authors attribute these surges in death rate to regional changes in pandemic control measures and early lifting of restrictions.

Deaths not attributed to COVID-19 were also in excess. There are several possible explanations this including delayed mortality from COVID-19, undocumented COVID-19, and deaths related to the pandemic but not directly caused by infection. Possible examples of the latter include an increased rate of suicide during the pandemic and pandemic-related changes in the medical management of acute and chronic diseases.

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Kenneth Roy Cohen, MD, FACP

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He served as Chief Medical Officer from 1995 to 2020. He now serves as the Executive Director of Clinical Research for UHG R&D and Senior National Medical Director for OptumCare. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.