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"It Ain't Over 'til It's Over"

Richard Simoneaux Steven L. Shafer, MD
Editor-in-Chief

Yogi Berra probably didn't have COVID-19 on his mind during the 1973 baseball season. The Mets were in last place, but his optimism helped drive them to the division title. Applied to COVID-19, this "Yogi-ism" is decidedly less optimistic. Yes, things are getting much better in the United States. As of today (May 26), over half of U.S. adults are fully vaccinated. Cases and deaths have been dropping for several months. In June, nearly all restrictions on activity will be lifted. Even the "worst-case" projections from the Institute for Healthcare Metrics and Evaluation and the University of Washington predict decreasing deaths for the rest of the year (Figure 1).

However, Yogi was right: "It ain't over 'til it's over." Consider:

- More infectious variants are rising everywhere.
- Variants of concern are pushing health systems to the point of collapse in India, Nepal, and South America. Nepal, India, and Iran are literally running out of medical oxygen (asamonitor.pub/3wyUTKV).

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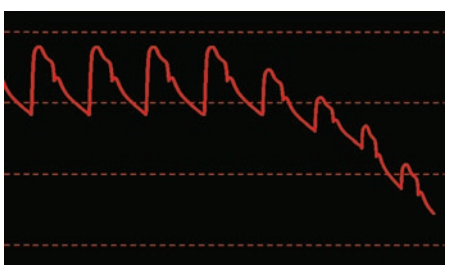
Peripheral I.V. Norepinephrine for Perioperative Hypotension

Dibash Kumar Das, PhD

Intraoperative hypotension arises during general anesthesia with an incidence ranging from 5% to 99% (*Anesthesiology* 2007;107:213-20). Continuous infusions of norepinephrine to treat perioperative hypotension are generally administered through a central venous catheter (CVC) and not through a peripheral I.V. line (PIV). Although commonly used in perioperative anesthesia care in Northern Europe, peripherally administered norepinephrine is uncommon in U.S. anesthetic practice because



of the perceived risk of extravasation and resulting tissue injury (*Eur J Anaesthesiol* 2015;32:571-80; *Am Surg* 2016;82:162-3).

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SPECIAL SECTION
The Burden of COVID-19
Guest Editor: Linda Hertzberg, MD, FASA 26–35

What's the Big IDEA? The Delicate Topic of Inclusion, Diversity, Equity, & Access

Zachary Deutch, MD, FASA Keya A. Locke, MD, MBA

Welcome to the summer 2021 edition of Ask the Expert! Please forgive the somewhat hokey title – for some reason I could not bring myself to put anything else at the top of this article. Fortunately, the content this month is extremely thought-provoking and very timely, and I feel confident that it will make up for the small transgression on my part.

This month, we will hear from Dr. Keya Locke, a close associate of mine here at UF Health-Jacksonville and someone who is now seen frequently on the national stage, speaking and writing about diversity issues and fairness in medicine (and in American society). Dr. Locke is a passionate, heartfelt, and thoughtful expounder on these polarizing, crucially important topics, and I am pleased to have her join us.

Remember, readers are encouraged to email me at zdeutch@yahoo.com with feedback of any type.

Keya, welcome and would you please begin by telling us about your current job and responsibilities?

I am currently in my fourth year as an attending at the University of Florida-Jacksonville College of Medicine. I serve as the Assistant Medical Director of Perioperative Services at UF Health North, an academic community hospital. I was recently elected to the UF Faculty Senate, and I am also a member of the UF College of Medicine admissions committee.

What does IDEA mean to you, and what prompted you to become vocal about it?

This type of question often makes me smile – for some, inclusion and equity are

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PERIODICALS

In the Know: "It Ain't Over 'til It's Over"

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- Asian countries that had previously contained the virus are seeing the variants overcome their strict mitigation measures (Figure 2).
- "Herd immunity" isn't going to protect anyone from COVID-19 if SARS-CoV-2 is freely circulating in the unvaccinated populations and if variants continue to emerge that escape acquired immunity (*EClinicalMedicine* 2021;32:100757).

Mitigation vs. elimination

For most of the past year, we have had neither vaccines nor effective therapies to treat SARS-CoV-2. Our only defense has been nonpharmaceutical interventions (e.g., public health interventions). Two opposing strategies emerged. China adopted a strategy of elimination, implementing exceptionally strict measures, including shutting down transportation, closing cities, isolating people in their homes, and quarantining individuals (seemingly without consent) to stop the spread of infection. The strategy worked exceptionally well, but few countries would tolerate Chinese-style government-imposed measures. Four Asian countries – Japan, South Korea, Vietnam, and Thailand – imposed measures nearly as strict as China but seemingly with more voluntary compliance. For most of the past year, the *per capita* rate of cases and deaths was 1/100th in these four Asian countries compared to the U.S. and Western Europe.

In contrast, most countries adopted a strategy of mitigation, not elimination. Mitigation public health measures sought to "flatten the curve." SARS-CoV-2 would continue to spread, but at rates that prevented COVID-19 from overwhelming local health care resources. Even these far less strict measures were met with public resistance, sentiments stoked in many countries for partisan gain (*Science Advances* 2021;7:eabd7204).

With the benefit of hindsight, epidemiologists recently evaluated elimination versus mitigation strategies (*Lancet* April 2021). The title of the paper states the conclusion: "SARS-CoV-2 elimination, not mitigation, creates best outcomes for health, the economy, and civil liberties." The authors compared the outcomes in countries that pursued elimination (Australia, Iceland, Japan, New Zealand, and South Korea) with those that pursued mitigation (Canada, Mexico, Israel, and a majority of European countries). Mitigation strategies yielded 25 times as many COVID-19 deaths per million population, as well as similar increases in the burden of long-term morbidities from COVID-19. At almost all time-points, the five nations that pursued an elimination strategy outperformed the 32 countries with the mitigation strategy. The authors noted "GDP growth returned to pre-pandemic levels in early 2021 in the five countries that opted for elimination, whereas growth is still negative for the other 32 Organisation for Economic Co-operation and Development (OECD) countries." Finally, the authors address the elephant in the room: civil liberties. The authors note that elimination strategies, such as those used by China, are considered anathema to civil liberties. The authors challenge this assertion using an index developed by University of Oxford researchers assessing the strictness of lockdown policies (*Nat Hum Behav* 2021;5:529-38). This index comprises eight containment/closure policy indicators, eight system policy indicators, and a public information campaign indicator. Using this index, liberties were negatively impacted the most in those countries choosing a mitigation strategy compared to those opting for elimination. The reason is that elimination strategies start quickly, are effective, and ultimately become "less strict and of shorter duration." In addition, countries that used elimination (other than China) appealed to common cause (e.g., civic duty) as part of the elimination strategy, a strategy that was generally not used in countries with mitigation strategies.

The authors conclude that "the consequences of varying government

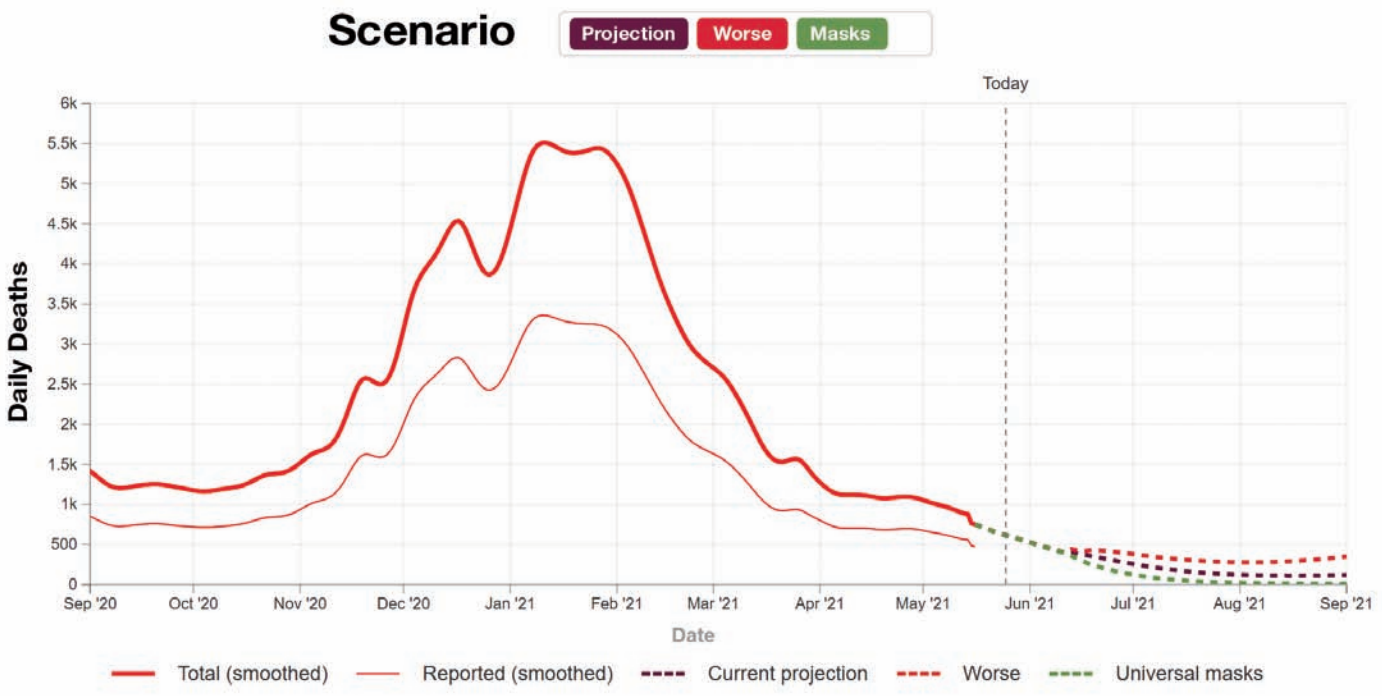


Figure 1: The projection from the Institute for Healthcare Metrics and Evaluation at the University of Washington shows deaths decreasing even in the worst-case scenario. It is important to note that the "best case scenario" where non-pharmaceutical interventions (masks) are maintained can potentially bring deaths to 0 by the end of summer. In other words, *it ain't over till it's over*.

See https://covid19.healthdata.org/united-states-of-america, published by the Institute for Health Metrics and Evaluation at the University of Washington, reproduced with permission based on Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

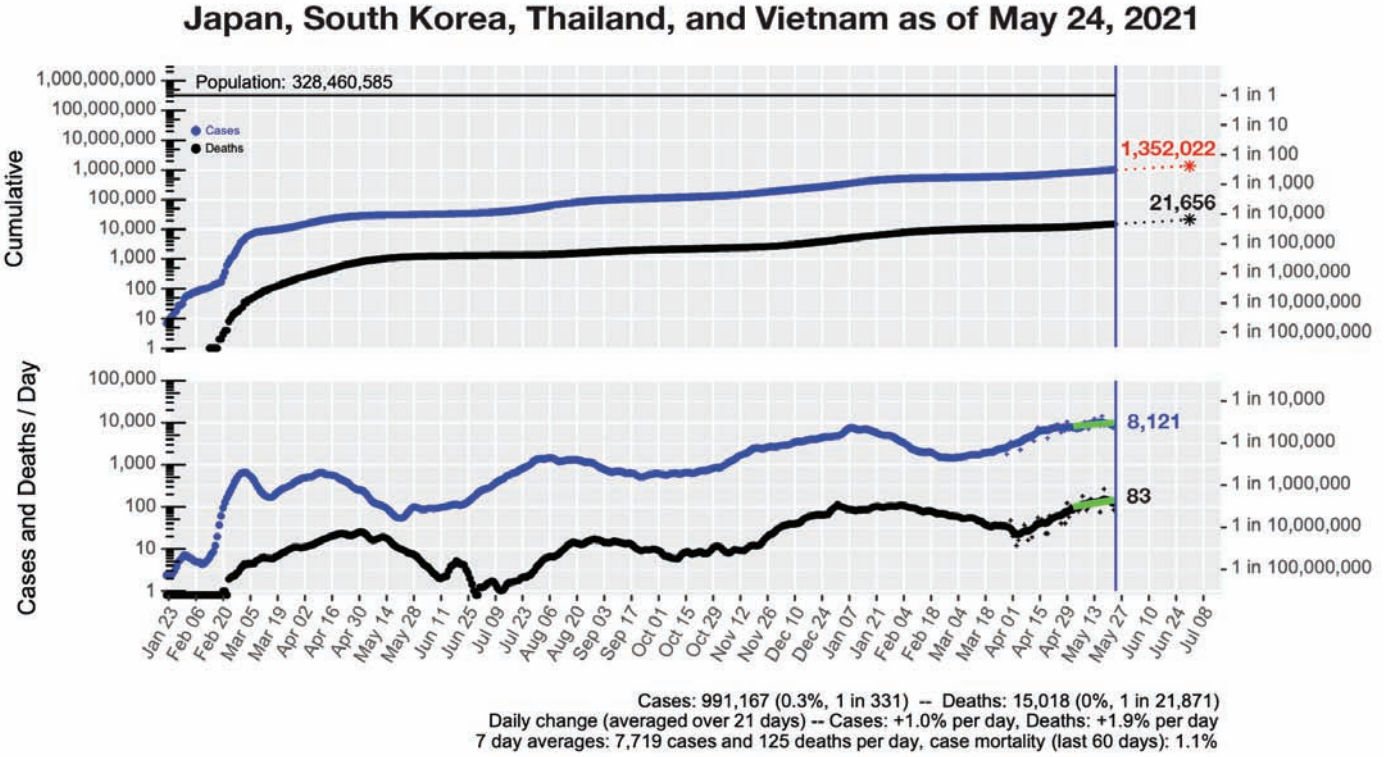


Figure 2: Asian countries with strong elimination policies have fared much better, but the cases are now surging as the previously effective policies are proving inadequate to eliminate the more infectious variants.

Reproduced from the author (SLS) daily COVID-19 modeling (available at asamonitor.pub/3hU8BDS).

COVID-19 responses will be long-lasting and extend beyond the end of the pandemic…. Early economic and political gains made by countries aiming to eliminate SARS-CoV-2 will probably pay off in the long run."

Given these findings, what are we to make of the surging cases in Japan, South Korea, Thailand, and Vietnam (Figure 2)? Since the paper was published, it is clear that seemingly successful "elimination" strategies must adapt to more infectious variants, and these countries aren't adapting fast enough. In other words, *it ain't over 'til it's over*.

Update on variants

The *New England Journal of Medicine* reported the cases of two women who developed COVID-19 after receiving the Pfizer or Moderna SARS-CoV-2 vaccine (*N Engl J Med* 2021;384:1952-4). Both women were infected with a SARS-CoV-2 variant after receiving both doses of vaccine. The viruses shared three alterations (D614G, T95I, and del144). One patient displayed the E484K escape mutation. This patient had neutralizing antibodies that recognized both E484K-mutant and B.1.526 variant SARS-CoV-2, but she nevertheless became infected. Neither viral sequence "precisely fit any known clade," demonstrating ongoing evolution of variants.

An article in MMWR detailed the epidemiologic characteristics of the B.1.526 variant SARS-CoV-2 (*MMWR Weekly* 2021;70:712-6). This variant has been shown to have two distinct subclades, one of which has the E484K escape mutation. As of April 5, 2021, approximately 40% of the samples from COVID-19 cases in New York City were of this variant. Of these, more than half (56%) displayed the E484K mutation. Eleven individuals in these analyses were fully vaccinated and had been infected with the B.1.526 variant 14 days or after the second injection. Eight of these bore E484K-mutant lineages, while three did not.

The *New England Journal of Medicine* also published a report from Qatar on effectiveness of the Pfizer BNT162b2 vaccine against the B.1.1.7 and B.1.351 variants (*N Engl J Med* May 2021). The Pfizer vaccine was 89.5% effective against PCR-confirmed infection from the B.1.1.7 variant and 75% effective against the B.1.351 variant at 14 days after the second dose. Most importantly, there were no cases of severe, critical, or fatal disease arising from infection with either the B.1.1.7 or B.1.351 variants 14 days or more after the second injection. Clearly, this is good news for those who received the mRNA vaccines.

Two recent articles provided efficacy assessments from South Africa of the Oxford-AstraZeneca and Novavax vaccines (*N Engl J Med* 2021;384:1885-98; *N Engl J Med* 2021;384:1899-909). The Oxford-AstraZeneca vaccine demonstrated an efficacy of just 21.9% against the development of mild-to-moderate COVID-19, nearly all of which were the B.1.351 lineage. The investigators concluded that the "two-dose regimen of the ChAdOx1 nCoV-19 vaccine did not show protection against mild-to-moderate Covid-19 due to the B.1.351 variant." The Novavax vaccine (NVX-CoV2373), which consists of 5 µg of recombinant spike protein and 50 µg of an adjuvant (Matrix-M1), demonstrated 49.4% efficacy among all patients, and 60.1% efficacy among HIV-negative patients. The investigators concluded that the vaccine was "efficacious in preventing Covid-19, with higher vaccine efficacy observed among HIV-negative participants." The overwhelming majority of SARS-CoV-2 infections were of the B.1.351 variant.

"Continued viral evolution in unvaccinated populations may give rise to variants for which existing vaccines would be ineffective."

Only global vaccination will end the pandemic

Returning to the paper in *The Lancet*, the authors note that that "history shows that vaccination alone can neither single-handedly nor rapidly control a virus and that a combination of public health measures are needed for containment" (*Science Advances* 2021;7:eabd7204). Both vaccine-based and non-pharmaceutical measures will need to defeat this tenacious virus. Since SARS-CoV-2 is global in nature, the pandemic won't be over without concerted international cooperation. Nations able to afford vaccination must assist nations that cannot afford mass vaccination to bring the pandemic to an end.

The authors point out that in addition to the obvious moral argument that vaccines should be globally available, there is also a strong self-interest argument. Continued viral evolution in unvaccinated populations may give rise to variants for which existing vaccines would be ineffective. We know that the P.1 variant in South America blew past "herd immunity" in Manaus, Brazil, and Iquitos, Peru (*Lancet* 2021;397:452-5; *Science* 2021;372:815-21; *Lancet Glob Health* May 2021). The rise of variants in unvaccinated individuals gives additional urgency to vaccinate the world, as "herd immunity is unlikely to be reached through natural exposure alone (*Lancet Glob Health* May 2021).

It ain't over 'til it's over. ■

Richard Simoneaux is a freelance writer with an MS in organic chemistry from Indiana University. He has more than 15 years of experience covering the pharmaceutical industry and an additional seven years as a laboratory-based medicinal chemist.

Calling All Aspiring Student Officers!

Natalie J. Koons

The ASA Medical Student Component (MSC) Governing Council is an elected eight-member committee that directs the programs and activities of medical students at the national level. Governing Council officer positions are a fulfilling way for students to gain leadership experience and interact with peers and mentors.

Medical students interested in serving in this leadership role are encouraged to apply by **September 1, 2021**. Positions available include:

- **President-Elect** *(first- and second-year students)*
- **Secretary**
- **Member at Large**
- **Senior Advisor** *(fourth-year students)*
- **Alternate Delegate to the AMA Medical Student Section**
- **Alternate**.

The election will occur in October, and terms begin immediately following. Candidates will be afforded an opportunity to address the voting delegates. Officer terms are one year, except for the President-Elect and Alternate Delegate, who assume the President and Delegate roles, respectively, the following year. The duties and requirements of each officer position can be found in the bylaws on the website. *Fourth-year students are asked to be mindful of applying as the term of service extends beyond traditional graduation dates*.

Eligibility:

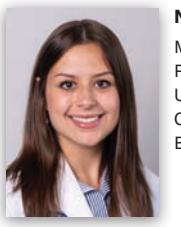
- Student is an ASA medical student member
- Student attends U.S. accredited allopathic or osteopathic medical school.

Requirements:

- One-page personal statement of interest (not to exceed 500 words)
- Curriculum vitae
- Strong letter of support from school faculty.

How to Apply:

Applicants may apply on the website: **asahq.org/education-and-career/asa-medical-student-component/msc-get-involved.** ■



Natalie J. Koons
Medical Student Component President-Elect, and MS 2, University of New England College of Osteopathic Medicine, Biddeford, Maine.

"Creating initiatives that directly impact medical students has been an incredible opportunity to learn true leadership skills. My experience working as a team, engaging in conversations that implement change, and networking with professionals in the field of anesthesiology has been an amazing way to continue my commitment for this specialty. If you are passionate about anesthesia, improving the future careers of medical students, and upholding the ASA mission of advancing the field of anesthesia, I encourage you to apply. I have learned the true value of comradery, leadership, and dedication."