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Federal Anti-Virus Strategy Must Encourage Broader Innovation to Expand Treatment Options

by Glenn G. Lammi

Infections from a new COVID-19 Omicron variant are on the rise, as are hospitalizations. The federal government has relaunched a program providing free COVID-19 tests. And the Food and Drug Administration has approved updated vaccines it says are effective against the new variant.

But public health officials can, and must, do more. Booster uptake is anticipated to be sluggish at best, and some people, including some seven million immunocompromised Americans, either cannot vaccinate or get less benefit from the shot. Patients need access to an expanded array of reliable prevention and treatment options. Several additional tools are within reach, but the government's narrow focus on a few therapies, along with federal regulatory rigidity and overcaution, threatens to halt investment and development.

One of those additional anti-virus tools is a monoclonal antibody (mAb), a treatment that figured prominently during the pandemic. While vaccines stimulate antibody production, mAbs are bioengineered to target and block the spike proteins on SARS-CoV-2 that allow the virus to attach to and infect human cells. Recognizing the promise of mAbs, FDA issued Emergency Use Authorizations (EUA) to five manufacturers for use in the fight against COVID-19.

Beginning in November 2020, healthcare providers used monoclonal antibodies to reduce the severity of infection. A 2023 study of nearly 168,000 patients showed that between November 2020 and November 2022, mAb treatment cut the odds of hospitalization by 50% and of emergency-room visits by 24%. A JAMA Network Open commentary noted that these results were "observed against a backdrop of remarkable safety, with only 0.2% of patients experiencing any kind of adverse event." Doctors can also use monoclonal antibodies preventatively alongside or in place of a vaccine.

Monoclonal antibodies are an especially appropriate anti-virus tool for patients who have undergone organ transplants, or those suffering from HIV, cancer, or autoimmune disorders. Unlike vaccines, mAbs do not require a healthy immune system to be effective. Also, because the body metabolizes biologics differently than non-biologics, immunocompromised patients, as well as older patients on multiple medications, face far less risk of drug interactions with mAbs than with other treatments.

As SARS-CoV-2 mutated, the spike proteins targeted by antibodies changed form, reducing the effectiveness of existing mAbs' against new variants. As such, in 2022, FDA allowed most EUAs

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to expire. The agency extended an EUA (which has since expired) for a double dose of one mAb aimed at Omicron BA.1. But as new variants emerged late in 2022, the most vulnerable patients and their doctors began to realize that soon, no mAbs would be available. One immunocompromised woman told *The Atlantic*, "It feels like we're back at square one. I get COVID, and it's 'go it alone.'" A network of patient-advocacy groups, concerned about their members getting left behind without treatments, urged FDA and the White House to broaden support for alternatives to vaccines and other anti-virals, such as monoclonal antibodies.

Despite these increasingly desperate calls, the federal COVID-19 policy has relegated mAbs to the back burner while HHS has pointed fingers at Congress for refusing to approve funding for more research. In May of this year, Representatives Dan Crenshaw (R-TX) and Lori Trahan (D-MA) wrote to FDA Commissioner Robert Califf, encouraging the agency to "focus[] on expanding treatment options that broaden protection for everyone" and asking questions about FDA's ability and motivation to accelerate review of alternative anti-viral tools.

Commissioner Califf's June 23 response was calculated and bureaucratic. While the letter acknowledged the existence of unmet medical needs and stated that FDA would "exercise flexibility when appropriate," the Commissioner's answers reflected little agency interest in departing from the drug-approval status quo. He did not explain why the agency used that flexibility to accelerate COVID-19 vaccine review even amid questions of efficacy but was unwilling to do the same for mAbs. Instead, the letter touted guidance documents and FDA's workshops with foreign counterparts.

The Commissioner's letter did not, however, cast doubt on mAbs' value in the treatment of COVID-19. If neither Congress nor the White House are willing to encourage variant-specific mAb development, then FDA should minimize biopharmaceutical companies' regulatory risk. The agency has the statutory authority, and the experience, to get it done.

The Crenshaw-Trahan letter suggested one promising expedited approach. FDA could assess and approve a specific platform for mAb producers to follow when bioengineering variant-specific antibodies. FDA has used this approach both in time-sensitive situations such as COVID-19 vaccines and variant-specific boosters, and for the now-routine modification of influenza vaccines for yearly immunizations. As Commissioner Califf stated in replying to the Representatives' questions, FDA has "over 20 years of experiences in regulating mAbs." A plethora of safety and efficacy data also exists from the past three years' development of antibodies for COVID-19.

Once a variant significantly compromises the effectiveness of an mAb, manufacturers could use the approved platform method to develop compatible antibodies and then pursue FDA authorization through a Supplemental Biologics License Application. Because SARS-CoV-2 variants emerge and spread so rapidly, a standard full-clinical-trial approach would not be feasible. FDA would thus need to work with mAb manufacturers on viable alternatives to establish efficacy. When contemplating this streamlined approach, federal officials should consider that mAb development will target a much narrower population than vaccines and are meant for patients with few or no treatment options.

That risk-benefit calculus must remain top of mind both now, when COVID-19 infections are on the rise, and when infections dip but the virus remains endemic. When questioned on the pace of its drug approvals, FDA and its acolytes argue strict adherence to its process saves lives. But the agency has long failed to appreciate that its inflexibility and overcaution can be just as deadly. Resistance to alternative approaches will reduce treatment options and severely complicate doctors' ability to adapt to the ever-shifting viral landscape. If the pandemic taught us anything, it is that American private-sector innovation can change lives for the better. The federal government should abide by that lesson and engage in its own innovation.

