reassured by the strong human safety record of its MERS vaccine. But vaccine trials are being approved “without the usual amount of preclinical safety/tox data available for guidance,” says Gilligan.

Given the urgency, the US Food and Drug Administration and European Medicines Agency may have little choice but to give the go ahead to enter the clinic. Novavax launched a phase 1/2 trial of its vaccine, a stable prefusion SARS-CoV-2 spike protein trimer nanoparticle vaccine with a saponin-based adjuvant, in late May. The company is experienced with viral vaccines: its nanoparticle flu vaccine recently met its phase 3 endpoints. The SARS-CoV-2 virus “is not new territory,” Glenn says, adding that Novavax and other vaccine companies can assay for whether antibodies can block spike protein–receptor binding, or neutralize the virus, or both, which should prevent infection.

And ADE? “One has to address it,” Glenn says, but he points out that ADE is only a theoretical COVID-19 vaccine risk. “It’s hypothesized from animal studies,” he says. “I think the way forward is to take it seriously, do some animal studies, show you

don’t have enhancement, monitor during the trial. My view is, we can’t let this issue keep us from getting to a vaccine that will save millions of lives.”

But Anne De Groot, CEO of EpiVax, argues for a more nuanced approach. EpiVax develops T-cell-directed vaccines, using computational tools to select viral T cell epitopes. The company found SARS-CoV-2 sequences that would appear human to T cell receptors.

This could be a problem for any vaccine. “The T cells either don’t respond as strongly, because they think that the [coronavirus] spike is human, or that sequence can trigger a regulatory T cell response,” says De Groot. Such T cells can interfere with beneficial antibody production and “you don’t get neutralizing antibodies, you get the kind of antibodies that actually potentially enhance infection.” In other words, ADE.

Showing vaccine safety in primates does not guarantee safety in humans, De Groot points out, because primates express different major histocompatibility complex (MHC) molecules, which alters epitope presentation and the immune response.

Other vaccine makers are also building a strong T-cell response into their vaccines, although not an epitope-specific response. Such T cells address ADE to some extent because they will clear infected cells, even in the presence of disease-enhancing antibodies. But to prevent ADE, De Groot also argues for removing epitopes responsible for stimulating regulatory T cells, which most vaccine makers are not doing. EpiVax partners Entos Pharmaceuticals and Immunomic Therapeutics are developing such T cell epitope-specific COVID-19 vaccines.

For now, the risk of ADE remains theoretical. “At this stage, what the world needs is a vaccine that’s effective,” says Ahmed. “I think the priority will be, do you get a neutralizing antibody, do you get a reasonably good T-cell response in the vaccine. And I think one would have to move forward with that vaccine as soon as we can.”

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Around the world in a month

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