

# SARS-CoV-2 Subvariants & the Future of Monoclonal Antibodies; Monkeypox Update

November 12, 2022

## Q&A

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- 1. Given the recent VA study with data that Paxlovid decreased incidence of long COVID symptoms, do you think Paxlovid should be offered to more than just high risk groups?**

Dr. Carlos Del Rio: My take on this is that we need an RCT to really show that Paxlovid decreases risk of long-COVID. At this point we should limit use of Paxlovid to those > 60 or with risk factors where there is clear evidence of benefit. The problem is that we are simply not using enough Paxlovid!

- 2. What is the similarity between immunization against flu and COVID-19? How long do the antibodies last after the flu shot? How long does the immune cell mediated protection last? If people need annual booster, it means that the protection against hospitalization declines within 1 year. It looks similar to vaccination against COVID-19. Thanks**

Dr. William Werbel: hello, this is a complex question given the virus and the vaccine technologies differ. in both cases we consider ~14 days post vaccination to be the time that significant antibody has mounted. for these vaccines, antibodies gradually wane after a peak that usually is around 1 month post vaccination. for flu, there can be a 10% loss of effectiveness against infection per month post peak, hence why we time before winter surges to provide good coverage through the key 3-4 month peak. cellular immunity is harder to measure, particularly when considering durability, but T and B memory compartments are longer lasting by design.

- 3. How do we address institutional IRB requirements if you have 2nd or more patients that require VIGIV?**

Dr. Jennifer Cope: Please reach out to our Regulatory Affairs colleagues at Regulatory Affairs (CDC) [regaffairs@cdc.gov](mailto:regaffairs@cdc.gov) for assistance with this question.

- 4. Any link between severity of mkpx illness and time of initiating tpoxx?**

Dr. Jennifer Cope: This is certainly an area of interest but there are currently no data to say that earlier initiation of tpoxx leads to less severe monkeypox illness. It does seem reasonable for clinicians to consider treating immunocompromised patients with monkeypox early with tpoxx.

**5. Can you explain the current IDSA guidelines regarding high-titer Covid Convalescent Plasma, especially in light of the current/coming variants lack of susceptibility to bebtelovimab and Evusheld? What role do you see it playing in the near future?**

Dr. William Werbel: we will discuss plasma during this talk and some of the nuances thereof

**6. What is the evidence for resistance to tecovirimat emerging during therapy?**

Dr. Christina Hutson: Thus far the specimens that have been sent to CDC for resistance concerns have all been sensitive; we are currently investigating 2 potential cases for resistance. Final results of those lab results will be in the HAN. It is important to know that tecovirimat is virostatic, meaning it slows the virus but does not kill it. By slowing the viral spread, allowing the immune system time to catch up/clear it. But immune response must be sufficient. We have two preliminary lab results we are currently investigating for potential resistance. Information such as this will be included in the HAN.

**7. I've been involved in the care of 2 of the patients included in the series (monkeypox). Both had a huge delay in treatment initiation with tecovirimat. In our own clinic we stopped treating some people we would have before the early CDC report warning against resistance emergence. How can CDC convey the message of early treatment vs stewardship and risk of resistance? Should ALL proctitis patients be started on Tpoxx from the get go?**

Dr. Jennifer Cope: We do want clinicians to know they can use tecovirimat if it's clinically indicated. A couple of things to consider when administering oral tecovirimat is 1. It must be taken with a high-fat meal (equivalent to a cheeseburger and fries) to ensure absorption. If there are concerns that a patient has absorption issues, then IV tecovirimat should be considered to ensure they are getting adequate levels of tecovirimat. 2. Most monkeypox disease will resolve during the standard 14 day course of tecovirimat so it should not be used longer than needed. Attention to these two points can help prevent the development of tecovirimat resistance.

**8. Is there any evidence of specific nucleotide substitutions impacting susceptibility to Paxlovid?**

Dr. William Werbel: Dr. Gandhi and I will likely touch on this a bit, but in short, these changes in the variants are not to my knowledge predicted to lead to resistance to the direct antivirals. prolonged exposure to Paxlovid in a chronically infected individual could, perhaps, drive different trajectories of mutations and would be important to better understand

Dr. Robert Shafer: There are many mutations that have been identified during in vitro passage experiments, but most are associated with reduced virus replication. I'm aware of one report from Pfizer in which one mutation developed in 3 persons receiving Paxlovid (package insert).

**9. How is the protection against all these sub-variants in someone who has had bivalent booster? I know we are going to be talking about therapeutics but wanted to get an idea re: vaccine too.**

Dr. Natalie Thornburg: The predominate circulating variants have sequences that are very similar to the bivalent vaccine, with just a couple of changes in the spike. We expect they should work well. We don't have real-world vaccine efficacy data yet, but hope to soon.

**10. Dr. Cope: Can CDC please add a recommendation for HIV testing (and other STIs) to the monkeypox Clinical Recognition page (at <https://www.cdc.gov/poxvirus/monkeypox/clinicians/clinical-recognition.html> - last updated 8/23/2022)? This 9/29/2022 HAN (<https://emergency.cdc.gov/han/2022/han00475.asp> ) is very helpful with HIV testing recommendations, though there's no reference or link to it on the Clinical Recognition page - can this HAN please be posted prominently on the Clinical Recognition page? Locally, we still have 46% of our monkeypox cases with unknown HIV status, since clinicians are often not tested for HIV in suspect/known monkeypox cases during clinical visits in spite of risk factors. Much of CDC's recent guidance has focused on considerations in persons with (already known) HIV, where HIV testing has already occurred, though adding an explicit recommendation for HIV screening/testing in patients at risk would help address/customize treatment recommendations to optimize outcomes. Thank you.**

**I would add the critical need for syphilis testing as well in those groups--MPX cases coming in to care**

Dr. Jennifer Cope: Thank you for this suggestion.

**11. Why has BN.1 be substituted for BA.2.75.5.1 nomenclature--this obscures the lineage and adds even more confusion within an already confusing terminology. This obscures the relationship and origin of this variant.**

Dr. Natalie Thornburg: We use Pango lineages to track viral evolution. That is the naming convention they have come up with. I agree that is has gotten confusing and difficult to track. We have ongoing conversations about finding better ways to present this very complex genomic data.

**12. Given that the common sublineages are highly related to BA4/5, does the bivalent vaccine protect against those related sublineages?**

Dr. Natalie Thornburg: The predominate circulating variants have sequences that are very similar to the bivalent vaccine, with just a couple of changes in the spike. We expect they should work well. We don't have real-world vaccine efficacy data yet, but hope to soon.

**13. Any recent data which addresses different clinical presentation and new variants of sars cov 2?**

Dr. Natalie Thornburg: There is no data indicating these current Omicrons present differently than earlier Omicrons.

**14. Any information or opinion regarding COVID treatment for patients who received a full course of Paxlovid or molnupiravir as outpatient but don't improve and get admitted to a hospital? Would these patients possibly benefit from then getting remdesivir or at that point just dexamethasone and/or IL-6 inhibitor such as tocilizumab?**

Dr. William Werbel: in my practice, this depends on the nature of the host's immune system and where they appear to be falling on the "viral" to "immunoinflammatory" part of the COVID-19 spectrum. we do sometimes give remdesivir to ill hospitalized patients with immunodeficiency if admitted post an outpatient antiviral course.

**15. Is there a likelihood that there will be a commercially available SARS-COV2 viral load test? How much is that used in research?**

Dr. William Werbel: I would presume that the necessary lab requirements to do quantitative viral load testing is prohibitive for community use. it is used in research and in the clinical trials. loose proxies such as cycle threshold values are used more clinically (with expert input). and the antigen tests do have (again a loose) semi quantitative aspect (dark immediate line vs faint delayed line) but they are subject to sample collection and quality and may vary among tests.

**16. Can someone comment on if Evusheld is still a good idea in immunocompromised patients. And if yes, why?**

Dr. William Werbel: this will be discussed to some degree by Dr. Gandhi. this decision should be driven by local subvariant prevalence (I.e., % resistant to Evusheld). with evidence of convergent evolution across variants, we cannot rely on Evusheld as a sole protective measure, but that is also not how it was generally authorized (rather as a complement to full vaccination)

**17. Will Evusheld be updated to cover omicron subvariants better?**

Dr. William Werbel: I will briefly touch on this - several companies have drugs in various stages of development to update mAbs to broaden activity against omicron sublineages.

**18. Will the current rapid covid tests still pick up the new variants?**

Dr. Natalie Thornburg: The FDA continues to track the performance of diagnostic devices, including the rapid tests. They post any up-to-date information regarding the performance characteristics of antigen diagnostic tests here: <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-antigen-diagnostic-tests-sars-cov-2>

**19. I was disappointed to hear recently from Dr. del Rio that there was nothing in the pipeline to replace Evusheld due to anticipated lack of profitability. Is there any way the government can intervene to create incentives?**

Dr. Meghan Pennini: HHS continues to stay engaged in the development of additional options for COVID, including mAbs for both prophylaxis and treatment.

**20. Why not just remove bapteovimab completely?**

Dr. William Werbel: I think that reasonable use varies by local subvariant prevalence. can be debated what the minimum sensitive variant % should be to not use the drug (eg 15-20% sensitive? this can be debated)

**21. Are there additional monoclonals in the pipeline????**

Dr. Robert Shafer: There are "pan-sarbecoviruses" mAbs that have been identified but to my knowledge they are only in pre-clinical or the earliest clinical stages of development.

**22. Any data on combination therapy for COVID 19 (using drugs with different MOAs)?**

Dr. William Werbel: there is interesting pre-clinical / in vitro data on various combination of antivirals which can be synergistic due to different MOAs. we only have case reports and case series for real-world use of these combinations. but important to further study.

**23. Is there any patient group for whom you would consider a monoclonal antibody + antiviral agent at the same time? could there be added benefit or is there any reason why not to give them simultaneously?**

Dr. William Werbel: at the moment, for a high-risk patient who gets bebtelovimab I personally lean toward recommending an accompanying oral or IV antiviral given high and increasing circulation of beb-resistant variants. we routinely gave and give combination therapy to high risk B cell depleted patients and organ transplant recipients who are not predicted to mount robust vaccine immunoprotection.

**24. Related to Dr. Werbel's point about planning ahead for how best to treat high risk patients: Is anyone aware of a center/institution/hospital/etc that has established anything like a pharmacist-driven team to take on this advanced planning in a systematic way, with close attention to actual implementation of individualized plans?**

Dr. William Werbel: I know of several centers including my own that have a central panel (inclusive of at least one pharmacist) that works on an ongoing basis to fine tune advice and recommendations for use of drug. what I do not know is how many and which centers for example preemptively parse their patient mix to flag charts or given guidance for COVID-19 selection which I think would be challenging and system-specific

**25. I am surprised by the convalescent plasma recommendation for transplant (and other?) patients-- the large trial data obtained early during the pandemic showed no efficacy and the subgroup analysis were underwhelming to say the least--why is this being considered now?**

Dr. William Werbel: this EUA has evolved several times during the pandemic amid these very valid concerns. at present, if a blood bank can ensure (very) high titer plasma ideally from a donor with hybrid immunity after infection during the Omicron era is available for a high-risk individual early in disease, I feel comfortable using it akin to how we use mAbs. but that includes a number of caveats and I am fortunate to be at a center that prioritizes and checks units in this way.

**26. How efficacious is the bivalent vaccine against the new Omicron variants**

Dr. Natalie Thornburg: The vast majority of current circulating variants are very similar to the component in the bivalent vaccines with either no, one, two or three changes in spike RBD. We expect the bivalent vaccines to work well, though don't have real world VE data yet. We hope to have some VE data very soon.

**27. Any data about whether to treat, how and when to treat immunocompromised patients with suspicion of prolonged shedding and intermittent clinical symptoms?**

Dr. William Werbel: the ASTCT published recent COVID-19 guidelines that does have some relevant information, but there is not consistency of treatment approaches in this setting:

[https://www.astctjournal.org/article/S2666-6367\(22\)01600-1/fulltext](https://www.astctjournal.org/article/S2666-6367(22)01600-1/fulltext)

**28. @Dr Pennini, your chart notes that for exposed individuals "None authorized for us in any US state or territory." are any being used in other countries?**

Dr. Meghan Pennini: That was in reference to some of the previous mAbs that were authorized for PEP (bam/ete, Regen-COV) but are no longer authorized due to the current variant landscape.

**29. I saw the statin comment in Q&A. Most statins can still be prescribed with dose reduction. I recommend they take half their dose rather than stopping. The exception is simvastatin and lovastatin which should be switched or stopped. Other statins do not need to be dose reduced esp if on a low dose. The recommendations for which statins and dose adjustments are the same as we have been doing for decades with ritonavir and cobi.**

Dr. William Werbel: Thank you, Dr. Aberg - we rely heavily on the groundwork laid by HIV/AIDS experts and PharmDs in this space.

**30. Is there a resource to identify sites that offer outpatient remdesivir?**

Dr. Meghan Pennini: None that I'm aware of, though we do think this would be valuable.

**31. For Flu A and/ RSV and SARS-CoV 2 co-infections in high risk patients, should they get treatment for all detected viruses?**

Dr. William Werbel: in highest risk groups such as post bone marrow transplant, yes, we may treat all simultaneously given potential poor outcomes. but this is case by base

**32. Can someone comment on the new information about the potential for Paxlovid to prevent long covid? It has generated a lot of interest in my patients.**

I am not personally aware of robust research regarding the direct antiviral drugs and effect on post-acute COVID-19 sequelae - as Dr. del Rio noted in another question, clinical trials data would be necessary to understand this. using claims data alone to characterize PASC is very challenging - it is a difficult diagnosis to make at the bedside!

to clarify, Dr. del Rio answered a question re: reinfection, whereas I am speaking about PASC