COVID-19 Variants, Testing and Treatment: The Latest

Jan. 21, 2023

Q&A

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1. **Are you using wastewater numbers?**

   Dr. Patel: We use wastewater surveillance to complement our case, hospitalizations, death and especially for early detection of a rise in cases.

2. **Is there evidence that Paxlovid when taken early lowers the incidence and severity of Long Covid as well as shorten its length of symptoms? Is this true regardless of age of occurrence of COVID, or its severity or if symptom free? Does long COVID occur after Sx-free COVID infection?**

   Attendee: See: VA Finds Nirmatrelvir Associated with Lower Risk of Long COVID AMA. 2022;328(24):2386. doi:10.1001/jama.2022.20051
   https://jamanetwork.com/journals/jama/fullarticle/2799927

   Dr. Gandhi: The VA study is important to highlight but it's not definitive in my opinion because of possibility of unmeasured confounding. I think randomized treatment trials need to follow participants for long Covid as this is one of the most important questions in the field.

3. **Status of combination antiviral rx, or with mAb, as we do with HIV? Given frequent long, debilitating courses keeping people from work or activities of daily living.**

   Dr. Gandhi: An important ongoing trial is STRIVE, which is looking at a protease inhibitor, ensitrelvir, in hospitalized patients. in the standard care group, remdesivir is allowed. So that important study will give insight into combination antivirals. We need more studies like this one to give a good answer to your important question.

4. **Can the panel please discuss or touch upon the phenomenon of immune imprinting in the context of newer variants and repeated vaccine boosters? This question has been coming up a lot recently.**

   Dr. Thornburg: The general idea of immune imprinting is that exposure to one "strain" of a virus blocks immune responses against other / newer "strains" of virus. It is a little bit unclear, still, if that will occur with SARS-CoV-2. With the Bivalent boosters, vaccine recipients did have nice / robust boost to ancestral spike, but still saw robust responses to the Omicron spike and cross neutralization of other variant spikes.

5. **Do we know that a Bivalent booster is more effective than a 4th dose of the previous vaccine, or has greater antibody longevity?**

Dr. Patel: Yes - please see MMWR reports below:

https://www.cdc.gov/mmwr/volumes/71/wr/mm7148e1.htm

https://www.cdc.gov/mmwr/volumes/71/wr/mm715152e2.htm

6. **Can you comment on the most recent concern about increased risk of ischemic stroke and bivalent vaccine in ages 65+?**

   Dr. Patel: CDC has summarized what we know about the situation here."
   https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/bivalent-boosters.html

   We are not changing our vaccine recommendations at this time. CDC continues to recommend that everyone ages 6 months of age and older stay up to date with COVID-19 vaccination; this includes individuals who are currently eligible to receive an updated (bivalent) vaccine. Staying up to date with vaccines is the most effective tool we have for reducing death, hospitalization, and severe disease from COVID-19, as has now been demonstrated in multiple studies conducted in the United States and other countries:

   Data have shown an updated COVID-19 vaccine reduces the risk of hospitalization from COVID-19 by nearly 3-fold compared to those who were previously vaccinated but have not yet received the updated vaccine.

   Data have shown that the updated COVID-19 vaccine also reduces the risk of death from COVID-19 by nearly 19-fold compared to those who are unvaccinated.

7. **USE OF PAXLOVID: in an at-risk patient have studies shown what is the best time frame to start Paxlovid? Obviously before 5th day, but does it help a patient to develop their hybrid immunity to hold off the Paxlovid for a good few days from positive symptoms /testing, rather than start them on day 1? Allowing them to fuel their T cell B cell workings?**

   Dr. Gandhi: I would recommend starting Paxlovid as soon as possible rather than waiting for theoretic effect on immunity. I think for most viral infections, including SARS CoV-2, the sooner, the better.

8. **Are these %-s of the variants similar to other countries?**

   Dr. Patel: The US has the highest prevalence of XBB.1.5. BA.5 is most prevalent globally but there is a lot of variation across countries regarding sequencing. See:
   https://www.who.int/activities/tracking-SARS-CoV-2-variants

9. **In naming the viruses, do Xbb or CH have any specific meaning? What do the letters stand for? How do you advise we best remember them?**

   Attendee: These terms come from Pango lineages. Pango has become the standard nomenclature system to classify SARS-CoV-2 genetic diversity. Nextclade is typically used to assign pango lineages to SARS-CoV-2 sequences There is a Usher tree that contains almost all SARS-CoV-2 sequences available through GISAID.

Dr. Thornburg: When the Pango name gets really long with many numbers, they get assigned an "alias" in order that they are assigned and not necessarily linked to the lineage. X names indicate recombinants. The naming convention has become very complicated.

10. **Does immunization reduce the risk of severe illness with XBB as it does with earlier variants?**

    Dr. Patel: I haven't seen data for XBB specifically, but the MMWR I cited was conducted during the time period during which XBB was one of the variants circulating in the US.

11. **We have formidable science and impressive science in addressing Covid. It's breathtaking. However, we have had great difficulty reaching the "non-believers and deniers". I fear the situation is getting worse and offsets medical knowledge. Any great ideas since without population support, we're pissing upwind?**

    Dr. Patel: This is something CDC is trying to address and we think some innovation and creativity is needed. Our surgeon general has made combatting misinformation one of his priorities so USG is actively thinking through how to do this. I do think health care providers can educate patients as a trusted source of information.

12. **Are there any preliminary reports of new variants felt to be a result of the opening up of the Chinese society, esp. with the Lunar New Year travel?**

    Dr. Gandhi: Not as far as I know but this is a critically important question.

13. **Are mRNA COVID vaccines being modified to an underlying commonality to all these subvariants? Is this possible?**

    Dr. Patel: We can ask experts to return on another call to address these types of questions.

14. **Wonderful speakers and thank you for excellent female representation. Could we talk about Bivalent Safety for general population vs those with prior cardiovascular risk factors. The public is so worried about this and how well these data have been assessed.**

    Dr. Patel: We don't have enough bivalent booster data right now to look at subpopulations by risk factor because bivalent booster uptake is so low. We will look at this when we have more data - the analysis will likely be published in the MMWR to ensure rapid dissemination.

15. **Do we need to recommend bivalent booster when circulating variants are different?**

    Dr. Thornburg: Even though the virus has evolved some from BA.4 / BA.5 lineage, the currently circulating lineages are still all Omicron, like the bivalent booster. The current lineages have a few changes in spike in comparison to vaccine. The best way for patients to be protected is to receive the bivalent booster.

16. **Are there any notable new symptoms associated with XBB.1.5 or CH1.1?**

    Attendee: No significantly different symptoms or risks. These Omicron variants have about the same clinical picture as the original Wuhan ancestral strain and are not as bad as the worse variant we have seen so far (the worst clinical outcomes were seen with the Delta Variant). See: Robinson ML, Morris CP, Betz JF, Zhang Y, Bollinger R, Wang N, Thiemann DR, Fall A, Eldesouki RE, Norton JM, Gaston DC, Forman M, Luo CH, Zeger SL, Gupta A, Garibaldi BT, Mostafa HH. Impact of SARS-CoV-2

variants on inpatient clinical outcome. Clin Infect Dis. 2022 Dec 19:ciac957. doi: 10.1093/cid/ciac957. Epub ahead of print. PMID: 36528815.

Dr. Patel: Agree - there does not seem to be a difference in symptoms or risks. We are monitoring this as well as severity of disease.

17. **Many "expired" antigen tests are sitting on people's shelves. Can you comment on the validity of assuming that if a home antigen test has a positive control, the test is likely still useful?**

    Dr. Thornburg: The FDA does not recommend using rapid antigen tests beyond their expiration date. BUT the FDA does have a table of RATS and have extended the shelf life of some. You can find the table here: https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/home-otc-covid-19-diagnostic-tests

18. **Most clinical labs don't have antigen tests. Can't we use PCR CT values to help determine likelihood of new or continuing Covid infection**?

    Dr. Thornburg: In general, it is not great to use Cts in that way. They can vary widely from person-to-person, assay-to-assay, lab-to-lab.

19. **In the context of newer evolving variants -This recent NEJM article has suggested bivalent boosters mainly for high-risk groups (e.g. older, immunocompromised, multiple comorbidities etc.) rather than the entire population – and hence this question has come up frequently lately. Can the panel please discuss the pros/cons of potential approach?**

    https://www.nejm.org/doi/full/10.1056/NEJMp2215780

    Dr. Patel: Thank you for your question. I did see this article and ACIP is meeting to discuss vaccine recommendations moving forward and certainly high-risk groups will be considered. We could follow up with another call on this topic.

20. **With XBB.1.5 how good are the Rapid Antigen Tests compared to prior Omicron variants?**

    Dr. Thornburg: The FDA has not posted any alerts regarding RATS and XBB.1.5, therefore we expect them to work ok with the caveat of delayed positivity that can often be seen.

21. **What do you recommend for someone testing positive on antigen test at day 12 and symptoms improved? Masking until negative?**

    Dr. Thornburg: Yes

22. **Thank you so much for this excellent presentation, Dr. Thornburg. These guidelines, understandably, are complex. Given how confusing they can be to healthcare professionals, can the CDC create easier to understand visual infographics and algorithms to ensure the public understands the testing guidance?**

    Dr. Thornburg: We agree. Once our new guidance is complete, we will encourage our comms teams to generate infographics.

23. **With a symptomatic patient who is retesting several times prior to turning positive, wouldn't that be past the 5-d window for Paxlovid?**

    Dr. Thornburg: Yes, which is why pragmatically it makes more sense to seek a reflex NAAT if someone would qualify for Paxlovid rather than wait for multiple RATs.

24. **Re Interpreting negative test results: Do you think that the multiple wait periods for a symptomatic patient testing negative, hold true for a severely immunocompromised patient, especially if they cannot take Paxlovid?**

    Dr. Thornburg: I would think pragmatically better to seek a NAAT and alternative diagnoses if a RAT is negative.

25. **For organizations supporting individuals living in non-healthcare congregate settings with minimal resources, multiple repeat antigen tests might not be feasible. Do you have recommendations about testing cadence in these situations when there have been outbreaks and exposures, etc.?**

    Dr. Thornburg: In this context, NAAT tests may be a better choice if feasible.

26. **Thornburg-Pls define "recent" in recent infection?**

    Dr. Thornburg: Within 90 days

27. **Any comparison of hybrid immunity with Omicron infection and monovalent vaccination versus bivalent boosted immunity in terms of efficacy of XBB infection?**

    Dr. Thornburg: There are some posted studies with neutralization assays. Those with hybrid immunity have higher neutralization titers in general than those who have only received vaccine. Post-Monovalent booster sera had greater lose in neutralization against XBB viruses than post-bivalent booster sera.

28. **Evusheld is still recommended for IC. is there data that despite no effect on current circulating strain we still see some benefits in this patient population?**

    Dr. Gandhi: in the next section, I'll comment on Evusheld. In most places in the US, the prevalence of resistant variants is >90% so I think Evusheld is unlikely to be helpful in those regions. All the more reason for immunosuppressed to stay up to date on vaccines, take measures to avoid infection and, if symptomatic, test and seek treatment if positive. Thanks for question and will discuss further.

29. **Do mRNA vaccines lead to mucosal antibodies?**

    Dr. Thornburg: Yes, but it varies person-to-person. Additionally mucosal IgA has a very short half-life. This is true for infection as well.

30. **Is there any data of Bi-valent vaccine and the impact on long COVID symptoms?**

    Dr. Patel: With low booster uptake and the time needed to examine long COVID, we do not have the data currently to look at this.

31. **Please comment on risk of stroke following bivalent vaccines.**

    Dr. Patel: Please see CDC statement here:

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/bivalent-boosters.html

32. **Why bother vaccinate if you get sick anyway? Don't accept the premise- the first goal of the vaccine is to stop Death and Hospitalization. Preventing infection is bonus. It tell patients I wish I had a perfect magic shield to give them against COVID, but let's not make perfect the enemy of the Really good!**

    Dr. Patel: Hopefully the mucosal vaccine will be a game changer. Time will tell but the mRNA vaccines do perform very well against severe outcomes.

33. **Now that it is well known that vaccines are performing well to protect against severe disease, hospitalization and death, plus the number of cases is undercounted due to decreased testing, is it time for the CDC to start changing the focus of tracking the number of cases and hospitalizations and also include the number of long covid cases which are increasing?**

    Dr. Patel: We are considering a pivot but are waiting for the right time. The pandemic is not over and we have continued tracking these metrics due to the rise in XBB.1.5 recently.

34. **Does the continuation of testing positive on an RAT for several days (beyond the 8-10 day mark) though no longer infectious, hold true for the over 65 or for immunocompromised?**

    Dr. Thornburg: Immunocompromised persons can shed culturable virus for an extended period of time, beyond the 5-10 day window. Older adults, if otherwise healthy, can clear virus in a typical timeframe.

35. **Is age really a more important risk factor than severe immunocompromise?**

    Dr. Patel: We are currently reviewing these data. Age is a significant driver though and I imagine there is variability based on the type of immunocompromising condition one has - transplant recipients have the lowest response to vaccines for example.

36. **You said "Breakthrough infections" might be higher in HIV/immunocompromised. I am unclear what you mean by "breakthrough infection." Does your use of the term "breakthrough infection" mean an infection that "breaks through" the vaccine or "rebound" infection after initial infection/treatment? Or something else?**

    Dr. Gandhi: In the CIVET study (in JAMA Network Open), breakthrough was infection that occurred despite prior vaccination. In people with HIV who had CD4 <350 (and especially <200) compared with people with high CD4 counts, breakthrough infection was associated with higher rate of hospitalization.

37. **How about effect of treatment on long covid?**

    Dr. Patel: See print from the VA:
    https://www.medrxiv.org/content/10.1101/2022.11.03.22281783v1

38. Dr. Gandhi, why is the focus on acute sequalae? What about the VA study by Xie et Al. That shows benefit in prevention of long Covid including in vaccinated persons?

Dr. Gandhi: The VA study is important to highlight but it's not definitive in my opinion because of possibility of unmeasured confounding. I think randomized treatment trials need to follow participants for long Covid as this is one of the most important questions in the field.

39. How many days should the atorvastatin be stopped before starting Paxlovid? and how many days after last Paxlovid dose can you resume the atorvastatin or rosuvastatin?

Dr. Gandhi: I stop statin on the day patient starts Paxlovid. I resume statin about 8 days later (3 days after stopping Paxlovid)

40. Dr. Raj can you define "older" for treatment of Paxlovid regardless of vax status?

Dr. Gandhi: It's a great question. Certainly, I am concerned and treat those over age 65 years regardless of vax status and other comorbidities. People over the age of 50 appeared to benefit in the Mass General Brigham study I showed, so that age threshold is also reasonable. If a person has substantial comorbidities, like heart/lung disease, etc., then would treat even younger.

41. Should the occurrence of Long COVID be a required measure in future comparison studies?

Dr. Gandhi: As I mentioned in reply to previous comment, I fully agree that long term outcomes should be part of ongoing and future randomized treatment trials.

42. Dr. Gandhi: Regarding treatment of "older" patients regardless of vaccination status, is the threshold 50 years and older? Or different? Thank you.

Dr. Gandhi: It's a great question. Certainly, I am concerned and treat those over age 65 years regardless of vax status and other comorbidities. People over the age of 50 appeared to benefit in the Mass General Brigham study I showed, so that age threshold is also reasonable. If a person has substantial comorbidities, like heart/lung disease, etc., then would treat even younger.

43. Has there been an application filed at the FDA for authorization for VV116?

Dr. Gandhi: Not as far as I know. I think other RDV analogues are in trials and, if efficacious, those would move forward.

44. Two of your vaccinated populations receiving treatment (UK, China) wouldn't likely have gotten mRNA vaccine. Do you think that vaccination with mRNA products would reduce the benefit of antiviral treatment?

Dr. Gandhi: It's a good question. In the UK, the AZ vaccine was used but so were mRNA vaccines. I don't know whether in Panoramic, they specified the proportions.

45. **Is concern with avoiding Paxlovid in persons on amiodarone based on real world observations or is it a theoretic concern? I have seen cardiologists recommending Pax in those on only 100mg/day since this is a group at high risk for Covid severity.**

    Dr. Gandhi: NIH and Liverpool guidelines state not to use Paxlovid with amiodarone. Details from Liverpool site are below. Coadministration has not been studied and is contraindicated. Amiodarone is metabolized by CYP3A4 and concentrations may be increased due to inhibition of CYP3A4 by nirmatrelvir/ritonavir thereby increasing the risk of arrhythmias or other serious adverse reactions. Note, amiodarone has a long elimination half-life, and the risk of drug-drug interactions may not be overcome even by stopping amiodarone administration. Consider an alternative COVID-19 treatment.

46. **Any new mAbs coming?**

    Dr. Gandhi: I don't know of any that are coming imminently. I hope there will continued efforts to develop new drugs and antibodies.

47. **During Post-Paxlovid rebound, is there infectious virus or is this just residual viral RNA that is being detected?**

    Dr. Gandhi: as mentioned, in some cases, there have been culturable virus but not in all rebound cases.

48. **Please comment on the safety of remdesivir administration in the presences of renal insufficiency, including dialysis.**

    Dr. Bhimraj: There are subgroup analysis from trials, observational studies which did not demonstrate toxicity (renal and hepatotoxicity) even in patients with creatinine clearance of <30. The main concern was due to cyclodextrin, but the quantity of that used with IV remdesivir is low as well, so I think it is safe to use where it is indicated especially if there are no other alternatives, with the caveat that this is based mostly on observational data.