CDC/IDSA Clinician Call

The Latest on COVID -19 Vaccination;

Plus Update on Avian Influenza

May 4, 2023

Q&A

This is the Q&A transcript from the Zoom webinar held on May 4, 2023. The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.

1. **Question 1: Should non-immunosuppressed people over the age of 65, in receipt of one bivalent booster 4 months or more in the past, opt to receive an additional bivalent booster now, or wait through a time of relatively low prevalence and likely low transmission, i.e. the remainder of the Spring, and potentially Summer and receive the bivalent booster in the Fall when vaccine effectiveness may be more likely to last during potential increased number of cases and likely transmissibility?**

   Dr. Wolfe: I'll be interested in my colleagues' thoughts here also, but the way we are strategizing this, is to move forward dosing now for individuals who are not only >65 but especially those with comorbidities. We have certainly seen ongoing transmission through most summer months, and I don't see that changing this year. So, for my older patients with meaningful cardiorespiratory disease, I think this is still important. These individuals are still meaningfully represented in our hospitalized patient populations.

2. **If a non-immunosuppressed person over the age of 65 receives a bivalent booster now, will he / she be eligible for another bivalent booster in 4 months' time, prior to a potential increase in cases in the Fall and Winter?**

   Dr. Marks: Yes - that is the case. Those getting a bivalent booster now will be eligible again for the updated vaccine in the fall - they should leave about 2 months between, so if they want to get the updated vaccine in September, they will want do get boosted by sometime in June.

3. **Please comment on the advisability of a woman who is expecting to try and get pregnant in the near future obtaining a second bivalent booster. Thank you.**

   Dr. Wolfe: Great question Michael - I think it depends on their other medical issues frankly. For most women of child-bearing age, they really should have made strong immunologic memory from the prior doses. So, for someone who was otherwise well, I feel ok not rushing to re-vaccinate. But if that person was also on any form of immunomodulation, then I think that becomes a different, and frankly much more individualized issue, where i would consider.

4. **For an unvaccinated adult who is receiving a mixed Pfizer/Moderna series, which interval should be followed? For instance, if a person gets Moderna #1 then Pfizer #2, is the appropriate interval 4 weeks or 3 weeks between the doses?**

   Dr. Oliver: If an adult (or anyone 6 and over), only 1 bivalent dose is recommended now! So now interval between 2 doses

5. **Age 5 Years – Unvaccinated + ImmunoCOMPETENT – can either receive Moderna or Pfizer.**
   a. If Moderna, then administer 2 doses of Moderna Blue Cap/Gray Label (0.25ml/25 mcg).
   b. If the 1st dose is Moderna, are you able to give 2nd dose as Pfizer? If so, does this change to a three-dose series like the 6 month to 4 year old population receiving two different bivalent doses?

   Dr. Oliver: There's a separate table for those who are ages 5 years at the Interim Clinical Considerations. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html

6. **For Age 5 years – Previously Vaccinated + Immunocompromised – If they previously had 1 or 2 doses of Moderna Monovalent previously, they are also authorized to receive a heterologous Pfizer Bivalent dose (0.2 ml/10mcg). If additional doses are necessary, do the additional doses have to be homologous to the Pfizer Bivalent dose administered or can it be from either manufacturer?**

   Dr. Pergam: Either is appropriate.

7. **I would love to hear Dr Oliver's thoughts on the newly approved RSV vaccine (Arexvy) for seniors.**

   Dr. Pergam: Think this is a great topic for another webinar, as a lot more to come from ACIP regarding the new vaccines.

8. **At CDPH, we have received numerous complaints from COVID-19 vaccine providers related to administration errors for the two Moderna COVID-19 bivalent vaccine products authorized and recommended for children 6 months to 5 years. Significant confusion and concern remain despite many ongoing efforts to communicate changes to providers, including presentations, email messages, job aids, and system labeling changes.**
   Dr. Marks, would FDA consider simplifying the Moderna vial recommendations for children 6 months to 5 years by limiting authorizations to one product? Options include:
   o Removing the pink cap/yellow label product and authorizing a 10ug (0.10mL) dose of blue cap/gray label product when indicated.
   o Use pink cap/yellow label only for children 6m to 5y and authorizing 0.5mL for 25mcg doses when indicated.

   Dr. Marks: We completely understand the issues here and are working with the company to see what can be done to address this potential confusion - we agree that one composition/vial type would be most ideal.

9. **Will we have annual COVID vaccine + RSV vaccine + influenza vaccine during respiratory virus season fall-winter in the N Hemisphere? Question 2: combination vaccines? Question 3: Novavax? This may appeal to people who don't want mRNA vaccines.**

   Dr. Oliver: Novavax is still available and recommended for those who don't want mRNA vaccines- then we look forward to combo vaccines and RSV vaccines in the future. No recommendations yet but stay tuned to FDA/ACIP/CDC!

10. **Will primary vaccination now be a single dose for 6 years and older?**

    Dr. Marks: That's exactly correct - unless they are significantly immunocompromised.

11. **What about nasal vaccination**

    Dr. Wolfe: Hi Andrea, there's a good amount of work being done in this space, but I don't believe anything has moved beyond phase 1/2 dosing, so i think we're still a couple of years away for covid vaccines at least.

    Dr. Pergam: Ongoing studies in this area - so expect more to come.

12. **In the elderly/immunocompromised, are there studies on T cell immunity which indicate more solid immunity than titers? Also, what is the status of combined COVID/Influenza vaccines in the future?**

    Dr. Wolfe: Hi Roger, some of the combination work is moving forward - there's covid/flu mRNA offerings from Moderna that have moved forward into trials, and some also with RSV. But from all I've seen none will be available ahead of this coming winter. Would certainly be ideal, given we're on the cusp of recommending 3 annual vaccines (covid / flu / rsv). As for the t-cell immunity data, we have some of that in our transplant patients at least, showing additional benefit over and above humoral response, as you suggest, but quantifying that, and translating it into a protective measure is not at all straight forward. I haven't seen that sort of granularity in data yet, after the first bivalent dose. Perhaps others on the call might have

13. **Can you please comment on the ability of the newer variants' ability to re-infect omicron variants from end of 2022?**

    Dr. Wolfe: There's now some data coming out looking at antibody neutralization against XBB in particular being rather mediocre, if you were infected by BA1, 2 or 5. So I think the reality is likely that people who were infected with prior omicron variants can be reinfected. Protection against severe infection, if you had a prior vaccine or earlier infection is still likely, that's the reassuring part.

14. **Please do explain the celestial body names for these new Omicron subtypes...I have been searching for that information to no avail! Please Dr Marks!**

    Dr. Marks: XBB.1.9.1 was the first variant to receive a nickname using the new system: "Hyperion", after a moon of Saturn. XBB.1.9.1 (Hyperion)

1st descendant of the 9th descendant of the first descendant of XBB

It is not descended from XBB.1.5 (Kraken)

15. **Immunocompromised, 5 y.o – can receive either Moderna Bivalent Blue Cap/Gray Label or Pfizer Bivalent Orange Cap. Can this group receive a Dark Pink Cap/Yellow Label instead?**

    Dr. Oliver: There's a table specifically for 5 year olds in the Clinical Considerations that goes over doses and vials: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#immunocompromised

16. **Do we have adequate surveillance systems for COV-2 infection?**

    Dr. Wolfe: I think there's always a chance for "we can do more", but we're much better than we were a few years ago. Data flow is better to CDC, hospital reporting is cleaner, and surveillance for variants is better. But ultimately, we will miss cases given we now have the luxury of so many at-home tests that never get reported. But the trends are consistent and reliable.

    Dr. Pergam: Yes, we do, but the move in the community to more antigen testing (in the home), our overall data has changed. There are enough systems in place to manage and monitor for new variants and to assess major increases in the community.

17. **Are you now focusing only on preventing severe outcomes of Covid-19, given people can get reinfected every 3 months, vaccinating once a year does not seem to address this? With WHO stating this week that 1/10 infections lead to Long Covid, how is this once yearly vaccination regimen aligned with preventing this significant disability?**

    Dr. Wolfe: Really good question on long covid, and you're right, we still see this even after vaccination, although it is statistically less common, both because you do prevent some of the breakthroughs, and even in those who become infected, they seem to develop LC less frequently. The way I address this, frankly, is to make sure all my colleagues and patients are still aware this risk hasn't gone away, and no matter how frequently I prop up immunity through vaccine, the risk is still there. So as everyone else drops mitigation efforts, we should be cautious.

18. **Since private or Gov insurance will "call the shots" after May 11, are you going to be more precise and clearer on recommendations. If too wishy-washy-insurance will reject the approved added doses for higher risk individuals.**

    Dr. Pergam: I think this is an important point. My take is that insurance companies will cover immunosuppressed patients based on national guidelines (from major patient-specific subgroups, such as AST, ASTCT, etc.). The guidelines are pretty clear for others and will continue to evolve.

19. **Dr. Broder: Is CDC going to recommend going forward, not administering Covid vaccination simultaneously with an influenza vaccine?**

    Dr. Broder: CDC continues to recommend that everyone eligible for a bivalent mRNA COVID-19 vaccine or an influenza vaccine get vaccinated. Please see the interim clinical considerations for

COVID-19 vaccines. (section on co-co-administration for guidance): https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#timing-spacing-interchangeability

20. **If a pt >65 had an adverse event to bivalent vaccine (pericarditis/pericardial effusion), what options should be considered regarding revaccination, i.e., Novavax a possibility? Avoid re-vaccination entirely? Any flexibility available?**

    Dr. Broder: CDC's Interim Clinical Considerations for Use of COVID-19 Vaccines | CDC states that a history of myocarditis or pericarditis after any COVID-19 vaccine is a precaution to future COVID-19 vaccinations. At this time a subsequent dose of any COVID-19 vaccine, including mRNA vaccines and Novavax, should generally be avoided in a patient who had myocarditis or pericarditis after a COVID-19 vaccine dose. After their episode has fully resolved, considerations for subsequent COVID-19 vaccination might include myocarditis or pericarditis considered unrelated to vaccination (e.g., due to SARS-CoV-2 or other viruses), especially if the diagnosis of myocarditis or pericarditis occurred more than 3 weeks after the most recent dose of COVID-19 vaccine or personal risk of severe acute COVID-19. Risk assessment is best done by the patient's clinical team, including a cardiologist. CDC's Clinical Immunization Safety Assessment (CISA) Project can provide consultation to assist healthcare providers.

21. **How strong is the evidence that an immunocompetent person age 65 and older who has already received one bivalent mRNA booster vaccine receive another one at least 4 months later? Is this really needed?**

    Dr. Wolfe: it's getting stronger, but worth knowing it varies a lot by age. There's data from Israel, where they have a good closed system to collect data from, that protection starts falling between 3-6 months, but ESP for those in the >80 years. So, the older someone is, the stronger the data. For the healthy 65yr old, probably the number-needed-to-vaccinate to prevent a hospitalization with another dose is now high.

22. **What is the recommendation for medical personnel?**

    Dr. Wolfe: at this stage it's no longer different to patients. >65 or immunosuppressed should be reconsidered.

    Dr. Pergam: We are recommending the booster for those who are >=65 or immunosuppressed, but expect that all will be available to get a booster in the fall

23. **Will 3rd party payers abide by the "flexibility" in decision making regarding repeat immunization decided by patient and physician?**

    Dr. Wolfe: Great question - given many of the guidelines societies have also backed up the enhanced vaccine schedules (eg: AST, IDSA) we shouldn't have this problem, but I agree with your concern - we need to make sure there's coverage.

24. **Please clarify COVID vax requirement for international travelers coming into the USA, for e.g. from Africa.**

    Dr. Wolfe: I believe these rules are being taken down with the lowering of the pandemic proclamation later this month. Then we can just assess what people have had or not, and slot them into the routine guidelines, but the travel requirement gets dropped. (Frankly hasn't been enforced for a long time anyway)

25. **Any changes for HCWs?**

    Dr. Wolfe: I don't believe so Andy. We are applying the standard guidelines (>65 or immunosuppressed) to our staff and using that. Fortunately, most are young and healthy.

26. **I am confused by the last speaker's presentation. Is there an increased risk of ischemic stroke with the Pfizer bivalent vaccination even without also concomitant influenza vaccination being given?**

    Dr. Broder: The data are insufficient to conclude that a risk exists for ischemic stroke following Pfizer-BioNTech bivalent COVID-19 vaccination or following simultaneous bivalent COVID-19 and high-dose or adjuvanted flu vaccination. The ischemic stroke signal after bivalent Pfizer-BioNTech COVID-19 vaccine was detected in one system, the Vaccine Safety datalink. The finding in VSD has attenuated over time as more data has accumulated and has not met signaling criteria during the past 10 weekly analyses. This signal has not been detected in other surveillance systems. Statistical signals do not necessarily equate to increased risks or causal association for adverse events. CDC and FDA are engaged in epidemiologic analyses regarding simultaneous vaccination with bivalent mRNA COVID-19 vaccine and influenza vaccine.

27. **Can someone please explain that guidelines are totally independent from the history of whether the patient has had covid confirmed previously? Doesn't this influence your decision/immunity status?**

    Dr. Oliver: The vaccine recommendations are universal- vaccine recommendations are not dependent on prior infection. We know that for ~97+% of people ages 5 and older have had either COVID infection, vaccination, or both. We would also not want someone to require antibody testing prior to vaccination. The vaccines can provide a good 'boost' even after prior infection (although we do say that you can consider waiting ~3 months after infection for optimal vaccine response).

28. **For people who aren't sure about whether they have had a bivalent booster, could CDC add a "Booster Calculator" to the website, similar to the "Isolation and Exposure Calculator"?**

    Dr. Oliver: We've had that previously- on this webpage: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html Imagine it is in the process of being updated!

29. **If 1st dose is Moderna, are you able to give 2nd dose as Pfizer? If so, does this change to a three dose series like the 6 month to 4 year old population receiving two different bivalent doses?**

    Dr. Oliver: This is addressed in the Interim Clinical Considerations, so would refer there for details. In general, we recommend that if you finish the series with what you started with- but can interchange in exceptional circumstances. So, if someone receives Pfizer in that young age group, it would be a 3-dose series.

30. **Is there solid evidence that COVID-19 vaccination is associated with a lower risk of developing long COVID?**

    Dr. Wolfe: this was nicely associated as the vaccines rolled out, especially in UK. It's harder to prove it as we get more and more doses into patients, but I think the data is certainly there. Similarly, there are variant differences. Omicron appears to be a little less. Not perfect though, i still have patients coming in now with new onset PASC.

31. **In the last several months, I've noticed 90% of new cases are occurring in those > 90% y/o. With less prevalence in younger workers, the risk of exposure to elders appears to be from other elders. Has this been observed nationally?**

    Dr. Wolfe: I think there's probably 3 parts to this - first is some observer issues, given the patients are much more likely to present for care when they are extremes of age. (As opposed to younger adults who may no longer even recognize their mild covid). Secondly the elderly are also more likely immunoscencent and have waning immunity. Thirdly, I think with the relaxation of many of our mitigation efforts, especially in skilled nursing facilities, i do suspect we are seeing transmission chains again sadly that we need to be acutely aware of.

32. **What is the vaccine recommendation for patients with PACS or who has a history of severe covid related illness?**

    Dr. Wolfe: I believe they continue to be the same as your standard recommendations - it' more a lack of good data on the best strategy for these patients, sadly. My sense is there might be some niche here for more aggressive vaccination in certain patent groups you describe, but there's just not enough confirmatory data.

33. **Is there any role for molnupiravir in treatment at this point?**

    Dr. Wolfe: I certainly still liberally use it. We have a ton of patients with drug interactions that become prohibitive, and logistically it's difficult to give remdesivir. With heavy vaccination and milder omicron, i think molnu is still very useful there. The mutagenesis just has not been borne out in real world data as being as problematic as we first were concerned about. So, the place in the line, is certainly appropriately 3rd, but there's role.

34. **What do you recommend for bivalent vaccinated women (last year) who are breastfeeding their newborns?**

    Dr. Wolfe: i usually do not recommend further vaccination, unless they have concomitant immunosuppression, mainly because they are likely to still have decent antibody titres and protection, some of which will transfer passively to the child, who will also be protected by mum not getting sick.

35. **There is still a lack of awareness of the public in USA about Paxlovid, based on my American relatives missing out on it.**

    Dr. Wolfe: sigh… totally agree. true for so many elements of our public health response still. Why these calls remain really critical, even as the pandemic notification gets dropped.

36. **Do you still need a positive test to prescribe Paxlovid? I thought that it had changed to provider clinical diagnosis too.**

    Guest Response: It was changed — you do not need a positive test for Paxlovid, remdesivir or molnupiravir as per FDA change.

    Dr. Wolfe: Agree - you don't need anything other the patient's description of their test. With home testing it rapidly became impossible to confirm these, so we go on patient's word of their infection.

    Attendee: Pharmacists can still rx

37. **Are you still using Remdesivir?**

    Dr. Wolfe: we still have an outpatient clinic at Duke that we use primarily for the highest risk patients. We have a number of transplant or comorbidly unwell folk who just can't take Paxlovid because of DDI's, where this is the right choice. Logistically it's super hard, so 'm hopeful Gilead's work on the oral prodrug will come to fruition, but there's certainly a good space for it.

38. **Slightly off topic: Is there any reliable data on Paxlovid associated early relapse (10-21 days)? A good pulmonologist is telling his patients its 30%. I thought both Paxlovid treated and non-treated patients had a 5-10% chance of a "biphasic" infection. Which is correct? Does vaccination play a role in decreasing relapse?**

    Dr. Wolfe: you're absolutely right - the Activ2 data showed a good amount of "rebound" even in the placebo arms. I've not seen data supporting 30%, that seems notably higher and I suspect prone heavily too reporting and detection bias. Certainly occurs, but not that often, and does sometimes occur with molnu, and placebo.

39. **T- cell responses often not measured but are produced in those who may not mount antibody responses. Protects against severe disease. Important to vaccinate.**

    Dr. Wolfe: completely agree - this is EXACTLY the reason we push forward, even with our patients who've had drugs like Rituximab or Oblinutuzumab, where they don't make antibodies… they do still respond in other attenuated ways.

40. **The need for active moabs to prophylax COVID-19 in immunocompromised patients is critical. Will the FDA start approving promising moabs on the basis of a surrogate of achieving neutralizing antibody titers (as vaccines may be), at least for an EUA?**

    Dr. Wolfe: that's the way the current trial for AZD3152 is structured. Hopefully successful, I agree it's a big need.

41. **How do we define 'response' to the vaccine clinically, what Antibody threshold are we using? (if T cell response is not something we can readily determine)**

    Dr. Wolfe: there are thresholds in research used - depends on the assay. Most also tie in neutralization, not just antibody titres. 250 I/u is usually the cut off a lot of trials have used. We just need to recognize it's not a clean-cut answer on an individual patient level, but more reliable in large trials.

42. **From my experience, there is a lot of Paxlovid misuse -- patients are not receiving the drug because of purported drug-drug interactions that would preclude Paxlovid's use. Anecdotally, many of these drug-drug interactions can be worked around. Patients are receiving molnupiravir when Paxlovid is clearly the preferred drug per NIH. Dr. Oliver or Dr. Marks -- please feel free to comment if you wish.**

    Dr. Wolfe: I agree - many people can move around the DDI's with careful adjustments. I use the U. of Liverpool drug interactions site routinely to help me navigate these. Very few are real contra-indications, although there are some. I still influence our teams at Duke to shy away from prescribing for DOACs, triazoles, warfarin, transplant calcineurin inhibitors etc. But many of the other interactions can be overcome, and i agree, the data is stronger for Nirmatrellvir than molnu.

43. **It sounds like you are supporting checking antibody responses, yet the FDA still has not authorized the use of antibody tests to inform vaccine response and NIH guidelines recommend against checking Spike IgG. How does one know if someone has responded to vaccine? Neutralizing ab tests are not available**?

    Dr. Wolfe: I don't check antibodies, as they just don't impact the end decision, which is that there are multiple arms of immune defense, that do benefit even in the absence of direct humoral response. We've never known what to do with the antibody titre, other than to use it to continue to counsel patients on mitigation. I think the recommendations to - as a general rule - continue to not rely on Ab titres to guide your decisions are still accurate.

44. **Dr. Marks, that is a fallacy argument you make. The question is not about not getting vaccinated but rather avoiding unnecessary imprinting because FDA is using the WT in a bivalent vaccine, WT was from 2020 when in 2023, it is now irrelevant.**

    Dr. Marks: Don't disagree - we do want to avoid unnecessary imprinting, that's why we are updating the vaccine composition as we learn more.

45. **For an unvaccinated immunocompromised adult who is receiving a mixed Pfizer/Moderna series, which interval should be followed? For instance, if a person gets Moderna #1 then Pfizer #2, is the appropriate interval 4 weeks or 3 weeks between the doses?**

    Dr. Marks: There is no perfect answer to this but would likely recommend weeks.

46. **What's the ideal interval between T-cell active immunosuppressants such as abatacept and immunization? How long after a maintenance dose should one wait as a minimum?**

    Dr. Wolfe: boy, great question, and super variable depending on the drug. I usually try to wait at least 3 months for most immunosuppressive drugs, (or dose 2+ weeks before hand if i can) but it's counterbalanced by getting them some protection ahead of any surge. Equally, I've gone back in past years, and called in people who were recently immunosuppressed, when we saw a highly active variant appear. I still think that's an appropriate strategy for high-risk people.

47. **Is there any chance that if a >65 year old patient opts to receive a second bivalent booster now could interfere with that person being eligible to receive an updated booster in the fall?**

    Dr. Oliver: We anticipate that people who get the second booster now will still be able to receive a fall booster. Previously there was a 2 month interval between doses, so that may occur this fall as well. But a dose in the next several months should not interfere with a dose this fall.

48. **For HCW that will not get vaccinated for COVID-19 for whatever reason, what is recommended to mitigate spread- masking universally except when eating, until community transmission is low? How are hospitals enforcing or implementing this? Badge indicators or their supervisor monitors daily/ employee self-polices?**

    Dr. Wolfe: This is a great question - not sure for others, but the way we've handled this has been to (a) have a primary series, and booster requirement., but also (b) maintain masking in the highest risk areas of our hospital for everyone. We can still all get breakthroughs, even though less common in the vaccinated, so we have been deliberately cautious about removing masking from inpatient areas of the hospital and high-risk clinics. That, plus the encouragement of "if you're sick, stay home", is a good happy medium to us, given most people are now well protected and transmission rates are less.

49. **Any movement in the HCW mandatory vax?**

    Dr. Wolfe: https://www.whitehouse.gov/briefing-room/statements-releases/2023/05/01/the-biden-administration-will-end-covid-19-vaccination-requirements-for-federal-employees-contractors-international-travelers-head-start-educators-and-cms-certified-facilities/

    I think the rules get dropped, but states may take their own position is my understanding.

50. What about children <12 who have no T cells - what are the antiviral options given vaccine is not effective?

Dr. Pergam: Very difficult group, as there are limited antivirals that are approved for those <12, where neither oral agent (Paxlovid or Molnupiravir is approved). The only current option would be Remdesivir which is licensed for those in that age range. There is good data that outpatient remdesivir use can limit risk for inpatient admission and subsequent complications - so it is an option, though more complicated than currently EUA approved oral agents for adults. As per an FDA announcement:

"The FDA has approved a supplemental New Drug Application for remdesivir (Veklury; Gilead) for the treatment of pediatric patients who are older than 28 days, weighing at least 3 kg, and are either hospitalized with COVID-19 or have mild-to-moderate COVID-19 and are considered high risk for progression to severe COVID-19, including hospitalization or death."

51. Then how do the speakers know if someone has responded.? I find the discussion on vaccine non-responders to be very unhelpful. I do not find the comments helpful on timing of boosts based on physician discretion. What does any of this mean? How does one advise pts and their providers without specific guidance?

Dr. Pergam: This is a challenging question - as our only tool in the toolbox at the moment is spike Ab. I do not routinely recommend testing for spike Ab even among the IC hosts who are immunocompromised (IC). There are likely other aspects of the immune system that provide protection beyond antibodies (e.g. T-cells), that are not captured in such antibody assays. The true correlates of protection outside of antibody responses are still being investigated. I am cautious getting antibodies in immunosuppressed patients because a) they can lead to a false sense of security in those with positive responses and b) negative results may not tell the whole story.

In terms of the first comment, many assays do not give a Ab level, but may only give a positive or negative result (qualitative response vs. a quantitative response). Protection is on a spectrum, as higher levels of antibody are more protective (>= 1000) compared to low level responses. So a patient who get a positive Ab on a qualitative assay, may not know if they are truly protected only that they had some response to the vaccine. In addition, patients who get positive results may shift how the interact with others in the community, believing that they are fully protected. They way we often approach vaccines is to give the standard doses as recommended for immunosuppressed patients (we currently recommend 3 initial doses and one to two boosters) and to not test for antibodies. With the new CDC recommendations, some may be tempted to check antibodies after a standard "IC Host series" but this may lead to a vicious cycle of repeat vaccinations and repeat titers.

Some patients with their underlying conditions may not respond regardless. I think having negative antibodies may in some increase fear and lead to more social isolation. For those who do get a "full series", and who end up getting tests and have no antibodies - I have a discussion about continuing to follow protective measures in the community (e.g masking, avoiding crowds) and assure that they call their primary team with any new respiratory virus symptoms (or have antigent tests at home for quick assessment) so they can test and get started on therapy if they are positive. I remind them

that current treatment regimens are important to preventing major complications, but that they need to get them early in their disease course to provide the most protection.

Dr. Wolfe: I don't routinely test, because i don't think antibody tests adequately reflects the breadth of response to a vaccine or native infection, nor modifies my mitigation recommendation to someone who is concerned enough to do the test in the first place (i.e.: immunosuppressed). If they're doing the test to support their concern about side effect profile of the vaccines, that's a different discussion, and certainly I've had people request testing, so they don't go and get more vaccination. But most just want some level of reassurance, which I don't think the test accurately gives them. As Steve noted, at least if they're going to get one anyway, despite my recommendations, make it quantitative. Perhaps the only time when I've intentionally gone and run a serology test, is when I wanted to know if someone had had Covid. In that situation, you can ask for a 'nuclear capsid' antibody, in addition to the anti-spike, and it differentiates natural immune from vaccine immune. But these days, I can't remember the last time when that was actually helpful. I did it a little bit in 2020 / 2021. But again, never to stratify if i should re-vaccinate.

The person asking the question wanted to know what I do use then to guide my re-vaccination decision, and frankly now it's an array of things. How old, how comorbidly unwell, are there any key life events coming up that i really want to avoid knowing you'll be maximally protected 2-4 weeks after vaccination (e.g.: wedding, travel, chemo, transplant etc.), and how far since last infection or vaccination, and how severe was the last time they had covid? These are all softer reasons, none precise, and all based on my reading of the generalized community-wide data for vaccine benefit and waning, rather than any individual blood test i can do for that patient.

52. Regarding the stroke signal with COVID-19 vaccine, what do you think the cause is? Or, do you think this is a false positive safety signal?

Dr. Broder: At this time, the data are insufficient to conclude that a risk exists for ischemic stroke following Pfizer-BioNTech bivalent COVID-19 vaccination or following simultaneous bivalent COVID-19 and high-dose or adjuvanted flu vaccination. The ischemic stroke signal after bivalent Pfizer-BioNTech COVID-19 vaccine was detected in one system, the Vaccine Safety Datalink (VSD). The finding in VSD has attenuated over time as more data have accumulated and has not met signaling criteria during the past 10 weekly analyses. VSD Investigators suspect there may reasons for the finding other than vaccination, including confounding. This signal has not been detected in other surveillance systems. Statistical signals do not necessarily equate to increased risks or causal association for adverse events. CDC and FDA are engaged in epidemiologic analyses regarding simultaneous vaccination with bivalent mRNA COVID-19 vaccine and influenza vaccine.

53. What about allergies associated with bivalent vaccination, related to polyetiological, is there is reported incidence of this?

Dr. Broder: In CDC surveillance, there are no data to suggest that that the risk of anaphylaxis or non-anaphylaxis allergic reactions following bivalent mRNA COVID-19 vaccines is higher than for monovalent mRNA COVID-19 vaccines. CDC's interim clinical considerations Clinical Guidance for COVID-19 Vaccination | CDC includes precautions and contraindications for receipt of COVID-19 vaccines (Appendix E). It is likely the population who have received the bivalent mRNA COVID-19 vaccines do not include people who had a contraindication for this dose of: 1) severe allergic reaction (e.g., anaphylaxis) after a previous dose or 2) to a component of a COVID-19 vaccine or a known (diagnosed) allergy to a component of a COVID-19 vaccine (which includes Polyethylene glycol (PEG)). The specific mechanism for anaphylaxis after mRNA COVID-19 vaccines is unknown.

54. **What data were used to support these updates?**

Dr. Oliver: Data to support updated recommendations have been presented and discussed at the February and April ACIP meetings. FDA also posts Decision memos to support the recommendations. Overall, both agencies are reviewing the same data to inform updated authorizations and recommendations.

April ACIP meeting slides:

https://www.cdc.gov/vaccines/acip/meetings/slides-2023-04-19.html

Presentation on updated recommendations:
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-04-19/06-COVID-Oliver-508.pdf

February ACIP meeting slides (COVID at the end of the page):

https://www.cdc.gov/vaccines/acip/meetings/slides-2023-02-22-24.html

Specific presentations to inform updates to recommendation:

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-24/COVID-08-Oliver-508.pdf

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-24/COVID-10-Oliver-508.pdf

FDA Review Memos:

Moderna:

https://www.fda.gov/media/167306/download

Pfizer:

https://www.fda.gov/media/167258/download

https://www.fda.gov/media/167669/download

55. **What can I do if there are difficulties finding vaccine for young children?**

Dr. Oliver: CDC recommends children ages 6 months–5 years who are unvaccinated and recommended to receive more than 1 bivalent mRNA vaccine dose for initial vaccination receive all doses from the same manufacturer. In exceptional situations, **including when the same vaccine is not available**, a different age-appropriate COVID-19 vaccine may be administered when FDA authorization requires that a vaccine from the same manufacturer be used. A VAERS report is not required for these exceptional situations.
See CDC's guidance on interchangeability for more information.

56. **Questions about vaccine codes:**

Dr. Oliver: Vaccine codes are available at the following sites:

NDC codes: https://www2a.cdc.gov/vaccines/iis/iisstandards/vaccines.asp?rpt=ndc

CPT codes: https://www.ama-assn.org/find-covid-19-vaccine-codes

Feel free to reach out to your local/state health department or CDC contacts to assist with ordering.

57. **Can individuals who aren't immunosuppressed or over 65 years of age receive another bivalent dose?**

Dr. Oliver: If you're 6 through 64 years of age and not immunocompromised, CDC recommends 1 updated (bivalent) mRNA dose. An additional bivalent dose after your first updated (bivalent) dose is not currently authorized or recommended.

AVIAN INFLUENZA Q&A

58. **Dr Uyeki, have any of the spillovers to mammals of H5N1 lead to any significant spread within the infected species? You mentioned mink-to-mink...but with dense situations, that is not very significant**.

Dr Uyeki: There may have been H5N1 virus spread among farmed mink (densely housed) in Spain during September to October 2022, but that event was contained. Dieoffs of seals along the Atlantic coast in New England during 2022 were attributed to environmental contamination with H5N1 virus (from infected shorebirds) and not seal-to-seal transmission. There have also been large dieoffs of seals reported off the coasts of Peru and Chile, but it is not known whether there has been seal-to-seal H5N1 virus transmission versus environment-to-seal spread. To date, there is no evidence of sustained H5N1 virus transmission among mammals.

59. Has there been transmission to domestic animals?

Dr Uyeki: There have been a few reported sporadic cases of H5N1 virus infection of dogs and cats that were attributed to these pets consuming dead infected birds.

60. With lack of sustained transmission of H5N1, management is mainly about avoiding wild waterbirds or infected poultry. Is there any genetic data suggesting changes to H5N1 that could facilitate sustained transmission after spillover to humans or other mammals?

Dr Uyeki: Some studies have identified mutations that might allow H5N1 viruses to adapt to spread better in mammals. However, in order to spread more efficiently to and among people, H5N1 viruses would need to acquire the ability to bind efficiently to receptors that express alpha 2,6 sialic acids linked to galactose that are predominantly found in the upper respiratory tract of humans. Currently, H5N1 viruses have the ability to bind to receptors that express alpha 2,3 sialic acids linked to galactose that are primarily found in the lower respiratory tract of people, as well as in the respiratory tract and gastrointestinal tract of birds. See also: https://www.cdc.gov/flu/avianflu/spotlights/2022-2023/h5n1-technical-report.htm

61. With bird to human transmission resulting in severe pneumonia, what explains limited human to human transmission from these infected individuals?

Dr Uyeki: To date, H5N1 viruses have the ability to bind to receptors that express alpha 2,3 sialic acids linked to galactose that are primarily found in the lower respiratory tract of people. In order for more efficient transmission among people, H5N1 viruses would need to acquire the ability to bind efficiently to receptors that express alpha 2,6 sialic acids linked to galactose that are predominantly found in the upper respiratory tract of humans. Limited, non-sustained human-to-human H5N1 virus transmission was reported in a small number of clusters during 2004-2007 in which very prolonged unprotected close exposure occurred (taking care of a symptomatic H5N1 case-patient at home or in the hospital). See also: https://www.cdc.gov/flu/avianflu/h5n1-human-infections.htm

62. Is H5N1 picked up by our commercially available PCR for flu?

Dr Uyeki: Because H5N1 virus is an influenza A virus, it can be detected by commercially available influenza antigen and molecular assays, including RT-PCR assays. However, there are no commercially available H5N1 assays available in clinical settings. A positive result for influenza A in a patient with suspected H5N1 cannot be distinguished from seasonal influenza A viruses, or other novel influenza A viruses of animal origin. Therefore, if H5N1 virus infection is suspected, and the patient tests positive for influenza A by a commercially available antigen or molecular influenza assay, respiratory specimens should be subtyped at a public health laboratory for H1 and H3, and if positive for influenza A but negative for both H1 and H3, then specific testing should be done using H5-specific primers and probes.

See: https://www.cdc.gov/flu/avianflu/severe-potential.htm

63. Have we recognized that influenza spreads by aerosols? Will there be recommendations of using respirators in clinical care when there is a suspected case?

Dr Uyeki: Influenza viruses spread by large droplets and small particle droplet nuclei (aerosols). For care of patients with suspected or confirmed H5N1 virus infection, standard, contact (including goggles), and airborne (N95 respirator or higher level of protection) precautions are recommended.

See: https://www.cdc.gov/flu/avianflu/novel-flu-infection-control.htm

64. **What's the best cost-effective to do these multiple tests? Can we inoculate ONE viral transport tube with multiple Qtips from multiple sources for ONE charge, or should there be one viral transport specimen for each Qtip or source?**

    Dr Uyeki: For patients with mild illness, place one NP swab into one tube of viral transport media and also collect a nasal swab and a throat swab and place both swabs in one tube of viral transport media. You can test an aliquot from each tube of viral transport media separately by commercially available influenza assay, ideally by influenza molecular assay. If positive for influenza A, send an aliquot of both viral transport media specimens to a public health laboratory for influenza A virus subtyping and specifically request H5 testing. For patients with lower respiratory tract disease, send the same upper respiratory tract specimens, and also collect and send an endotracheal aspirate specimen for influenza testing and subtyping at a public health laboratory. See: https://www.cdc.gov/flu/avianflu/severe-potential.htm

65. **Do you have information on obtaining primers and probes for H5N1 PCR diagnostics?**

    Dr Uyeki: Response: See: https://www.internationalreagentresource.org/

66. **Does the current flu vaccine from last season offer any type of protection against H5N1?**

    Dr Uyeki: No, seasonal influenza vaccination does not provide any protection against H5N1 virus infection.

67. **In ill or exposed commercial poultry, should eggs be NOT harvested but disposed of? Have eggs ever transmitted virus to humans? If incubated, do eggs create infected chicks, or do chicks die prior to birth?**

    Dr Uyeki: Please contact USDA: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/avian/avian-influenza/ai

    https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/animal-disease-information/avian/avian-influenza/2022-hpai

    See also: https://www.usda.gov/sites/default/files/documents/avian-influenza-food-safety-qa.pdf

    See also: https://www.fda.gov/food/eggs-guidance-documents-regulatory-information/questions-and-answers-regarding-safety-eggs-during-highly-pathogenic-avian-influenza-outbreaks

68. **How were the asymptomatic cases detected? Surveillance? Post -exposure to a positive clinical case?**

    Dr Uyeki: A very small number of asymptomatic H5N1 virus infections were reported following investigation of contacts of a confirmed case or by testing an individual exposed to infected poultry. Some asymptomatic persons exposed to infected poultry have had upper respiratory specimens collected that tested positive for H5N1 virus. However, that does not necessarily mean that such individuals had H5N1 virus infection, and most such cases likely had transient detection of non-infectious virus. Recently, Spanish investigators reported that H5N1 virus detected in upper respiratory tract specimens collected from two asymptomatic poultry workers most likely resulted from environmental contamination.

See: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2023.28.8.2300107

69. Are H5N1 vaccines stocked in USA, should this become an epidemic? What about stocks of oseltamivir?

Dr Uyeki: No H5N1 vaccines are available, but for pandemic preparedness, H5N1 candidate vaccine virus development is ongoing. Oseltamivir and other antiviral drugs are stockpiled for use in an influenza pandemic.

See: https://www.cdc.gov/flu/avianflu/candidate-vaccine-virus.htm

See also: https://www.cdc.gov/flu/pandemic-resources/planning-preparedness/vaccine-medical-countermeasures.html

70. Have pet birds in first world countries become infected and /or transmitted H5N1 illness to humans?

Dr Uyeki: There have not been any cases of H5N1 virus transmission from pet birds to people.