Answered Questions

1. **Marc Lipsitch 06:34 AM**

Given that levels of antibody and cells are dynamic variables that can change a lot over time especially after the acute primary or secondary response, how does the time of measurement play into COP and correspondingly the time interval when protection is measured?

   a. **Peter Gilbert 06:40 AM**

   One can do 2 sets of correlates analyses.
   First, based on markers measured at the time point shortly after vaccination, correlate the markers with outcome by a fixed time point (say 3 months post vaccination, or 6 months post vaccination), and also study whether the association changes when counting cases through longer term follow-up.
   Second, based on measuring the markers at several time points over 1-2 years, model the trajectories of antibody markers over time, and use joint longitudinal survival models to correlate the current value of a marker with instantaneous risk, or use a causal model to study longitudinal mediation or a controlled effect. For this second kind, measuring the marker at COVID diagnosis samples of cases may help.

2. **David Vaughn 06:53 AM**

For Florian. If I heard correctly, you stated that memory B cells may afford protection due to relatively long incubation time for CoV2 (5 days?) without need for high levels of circulating Neut Ab to protect. What do you see as the minimum incubation time needed to see such protection (Hep A and B are much longer).

   a. **Florian Krammer 06:57 AM**

   Hi David, you can get pretty good plasmablast responses from memory B-cells within 5-7 days (and sometime earlier). So, I think if the incubation time is in that range or longer, this mechanism could be very helpful. But probably not as effective as for Hep A or B.

3. **Philip 06:46 AM**

Do you accept that there are re infections with SARS 2? I am thinking about the Hong Kong investigation in particular but I think there are others

This question has been answered live

   a. **Florian Krammer 06:48 AM**

   Yes. No protection is absolute. I think this is a question of probability and specifics about the individual immune response.

4. **CB Stauft 06:46 AM**

Dr. Krammer, what route of vaccination most closely mimics natural infection? Intranasal or inhalation?

   a. **Florian Krammer 06:52 AM**

I think both in a way do mimic natural infection. We see infections limited to the URT, but of course there are also many infections that go to the LRT. So, hard to say what would give better protection.

5. **Julianna.Pieknik 06:50 AM**

whoa, why is 15mg/kg antibody better in the first few days than 50?

   a. **Andrew Charles Adams 07:09 AM**

   We believe that this difference is likely related to variability in the assay, rather than any real difference between the doses.

6. **Amanda Gross 07:02 AM**

To Dr. Adams--are your models able to predict the effect of antibody mutations that may affect its half life, FcR binding, potential ADEI risk, etc?

   a. **Andrew Charles Adams 07:24 AM**

   We did conduct additional studies assessing effector function and ADE risk. We are in the interesting position of being able to work with both Bamlanivimab (has WT effector function) and the Junshi antibody component of our cocktail (LALA mutation, abrogating effector function). Both appear to be effective in neutralization assays preclinically, and in our clinical studies appear to be very efficacious in reducing viral load - thus I think antibody effector function is a topic requiring further study.

7. **Annie De Groot MD 07:51 AM**

Just to add to that, I personally would not be surprised if the correlates of protection to the RNA platform vaccines developed by BioNTech and Moderna include… T cell responses.

   a. **Julianna.Pieknik 08:01 AM**

   haha, you're not wrong and hey, Dan Barouch I think showed that CD8s (the CD8 depletion) were at least partly responsible for protection. Maybe the NHP model people will look for Tissue-resident t cells upon animal dissection for us since I don't imagine we'll be able to get that info from people.

   b. **rseder 08:47 AM**

   we are characterizing Trm now in NHP

8. **lynda stuart 07:20 AM**

Can we discuss correlates of transmission interruption? the monkey data implies the addition of CD8 will be required to block human to human infection and may be important to differentiate the public health impact.

This question has been answered live

   a. **rseder 08:42 AM**

Lynda

The NHP data was done following infection. We showed that we prevent upper airway sg RNA with the RNA vaccine and this is likely due to a very high titer of antibodies. Important to distinguish how the infection affects immunity which would likely be lower antibodies but higher T cells and mucosal T cells than vaccines which are very high antibodies - It might be important to generate CD8 t cell in the upper airway but this would require a different route of delivery:)

9. **Dapeng Zhou 06:22 AM**

For those who are looking for a robust and convenient assay to test neutralization activities of SARS-CoV2, we have developed a 3-plasmid system that is easy to use. The supernatant of transfected 293T cells may be directly used as virus source. No need to concentrate. You only need three plasmids and an ELISA reader for luciferase activity. The plasmids are available next week in Addgene: 12260, 161030 and 161029. https://www.addgene.org/161029/

10. **ihsan Gursel 06:35 AM**

To Florian, Is IgG2a more correlated to virus neutralization in mice? Any idea?

   a. **Florian Krammer 06:50 AM**

   We have some limited data with both IgG2a and IgG1 suggesting both work as long as they have strong neutralization activity.

   b. **ihsan Gursel 06:53 AM**

   Thanks, Is Adjuvant type impacts IgG1 vs IgG2a preference?

11. **César Muñoz-Fontela 06:35 AM**

With respect to memory B cells as a correlate of protection: Is there a danger of original antigenic sin in the case of SARS-CoV-2 as the virus evolves in the human population?

This question has been answered live

12. **Anonymous Attendee 06:50 AM**

Do we think that mAbs are a practical solution for COVID

   a. **Julianna.Pieknik 06:57 AM**

   they're expensive and cost-prohibitive. but work. so kinda?

   b. **Andrew Charles Adams 07:13 AM**

   Overall, we would argue that for those at high risk of development of severe disease, until vaccination is broadly available, antibodies represent one way to potentially reduce hospitalizations.

13. **Manish Gautam 06:58 AM**

Role of saliva in the study was not clear. This is the question from Krammer presentation.

a. **Florian Krammer 06:58 AM**

   We use saliva for both measuring mucosal antibodies as well as for performing NAAT for SARS-CoV-2.

14. **Anonymous Attendee 06:59 AM**

For the Lilly human studies, given that you saw a better effect within 7 days, what was the definition of day 0?

a. **Andrew Charles Adams 07:20 AM**

   We believe the earlier in the infection you intervene the better with neutralizing antibodies. Typically on average people entered our ambulatory study ~4.5 from onset of symptoms, with the day of infusion being day 1.

15. **Anonymous Attendee 07:00 AM**

Is there any evidence in humans that there is boosting of immunity following a secondary exposure. 2) Vaccination is able to induce significantly higher binding titer and neut responses than primary infection - you mentioned the ratio of binding titer to neuts is higher for vaccination - are you aware of any data that binding antibodies may also have a protective effect

a. **Florian Krammer 07:03 AM**

   We don't have good data on that (but will collect it). I have one anecdotal case where somebody with antibody was exposed to an infected individual (same household), never tested positive but got a boost in antibody titers. Regarding the binding antibodies: I only have mouse data and there I see no effect (for flu we often see an effect). But I have heard from other groups that they saw some protection from non-neut antibodies in hamsters.

16. **mary marovich 07:01 AM**

some unusual features of LY555 as far as ability to bind up or down spike?

a. **Andrew Charles Adams 07:15 AM**

   Great question, Mary. LY-CoV555 is able to bind the spike protein in both the up and down confirmation, which in our experience is a relatively rare property of the antibody and may contribute to its potency.

17. **Harish Rao 07:03 AM**

The correlation between titer to neuts put up as 1:7 vs 1:20 to 40 was in the context of which class of vaccine? RNA, Adeno vector based or protein subunit vaccine? Also the titer referred to was anti Spike?

a. **Florian Krammer 07:05 AM**

   RNA vaccine (BNT162b2), S1 versus neutralization

18. **Devan Mehrotra**

When will we know if the mrNA vaccines prevent SARS-CoV-2 infection? This is a secondary endpoint for the Moderna trial but not for the Pfizer trial based on their published protocols. Will CoP analyses also be done for infection endpoint analyses?

a. **David Benkeser 08:04 AM**

   These analyses are planned for OWS trials. If I remember right Moderna will collect serology at 6 month visit, which would mean data would be available early spring 2021.

19. **nmoreau 08:34 AM**

Hello, from whom can we get more information about flow cytometry studies on T cells?

a. **Karen Makar 09:09 AM**

   Julie McElrath at Fred Hutchinson Cancer Research Center is running the ICS analyses for Operation Warp Speed.

20. **Mike Busch 09:09 AM**

What is the source/characterization and when will the WHO International Standard for SARS-CoV-2 Abs be available from NIBSC. And like other International Standards will Ab test manufactures user labs receive only a small # of low volume aliquots of the SARS-CoV-2 IS with the expectation that they will have to develop or calibrate against secondary standards for use as calibrators and run controls and in EQA programs.

This question has been answered live

a. **Mark Page - NIBSC 09:16 AM**

   The collaborative study to evaluate that the IS is fit for purpose is complete and a report has been submitted to WHO. The WHO ECBS will meet in December to consider the report data. If aproved the IS will be available shortly thereafter. Labs will be expected to produce their own secondary standards, and a number of low volume samples will be supllied to perform the calibration. This limitation is necessary to bea ble to provide the International Unit for a 5-10 years timeframe.

21. **Rubhana Raqib 06:31 AM**

Many Companies claim that antibodies to the N are neutralizing detected by their kits. Is this a wrong claim?

a. **Florian Krammer 06:47 AM**

   There might be a loose correlation between anti-N antibodies and neutralization, but anti-NP antibodies do not neutralize.

22. **Ruben Donis 06:44 AM**

Does the evidence of protection from natural infection indicate a lower level of protection as compared to that elicited by mRNA vaccines?

a. **Florian Krammer 06:49 AM**
Hi Ruben, I don't think there is enough data to draw conclusions.

23. **najwa 06:50 AM**

which antibody test available commercially is best correlated with immunity

a. **Florian Krammer 06:51 AM**

None so far is correlated with protective immunity. However, some correlate very nicely with neutralization.

24. **Anonymous Attendee 07:22 AM**

are we able to access sampels through PHE for assay development

This question has been answered live

a. **Mark Page - NIBSC 07:24 AM**

Please go to NIBSC website for reagents you might find useful
www.nibsc.org/science_and_research/idd/cfar/covid-19_reagents.aspx

25. **Alethea Cope 07:31 AM**

Thanks Mark does tha include PBMC and sera

a. **Mark Page - NIBSC 07:33 AM**

Dear Alathea, it is sera/plasma mostly, no PBMC.

26. **Anonymous Attendee 07:29 AM**

To Florian, is it correct to compare immune response in clinical trials to reconvalescent titres of rather mild disease?

a. **Florian Krammer 07:31 AM**

I think we can make the comparison, but we need to take it with a grain of salt.

27. **Anonymous Attendee 07:40 AM**

Hi Mark yes thought so and thanks repsume no mucosal samples? Trying to leverage from a variety of sources....

This question has been answered live

a. **Mark Page - NIBSC 07:44 AM**

The plasma sample (20/130) and the upcoming International Standard do have IgA and IgM if that helps.

28. **Julianna.Pieknik 07:47 AM**

Based on the old adage that mice lie and monkeys exaggerate, comparing animal models' correlates of protection (mouse, hamster, NHP models) versus human correlates, does anyone have any suggestions or concerns we should be should consider?

a. **rseder 07:51 AM**

   There is a large NHP study with 4 clinical vaccines (Ad26, mRNA, Novavax-protein and sanofi-protein) with varying doses of each vaccine to define a correlate of protection in which all animals recieve the same challenge dose. This comparative and controlled study for viral challenge stock and dose should provide important information

29. **Ruben Donis 08:49 AM**

To Valentina: sorry, did not capture the throughput of the wt virus neut assay - can you confirm the estimated capacity and timeline?

a. **Valentina Bernasconi 08:51 AM**

   Average throughput is 450 samples per week at the moment; PHE is currently working to scale this up

b. **Dapeng Zhou 09:04 AM**

   that appears to be 90 samples per day, about 20 ELISA plates