COVID Information Commons (CIC) Research Lightning Talk

Transcript of a Presentation by Jeffrey Townsend (Yale University) April 24, 2023

Title: The durability of SARS-CoV-2 vaccine-mediated immunity and the optijmal timing of booster vaccination

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Transcript

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There we go, thank you for the introduction and thanks to both of the folks who preceded me for presenting a lot of interesting information about COVID-19 that that I fortunately don't have to talk about.

So I'm going to talk about the durability of SARS-CoV-2, vaccine mediated immunity, and the optimal timing of booster vaccination, which of course, is relevant to all of us now as we think about this disease. I just want to point out some of the people I collaborated with, particularly Haley Hassler, who's listed second here, who was a research assistant for this project but a very hands-on, very highly involved research assistant. She deserves enormous credit for this and also was the original author of the slide deck I'm going to present. So a lot of credit to her. And then Alex Dornburg, who's listed last here, who was a collaborator with me on the whole project from the very beginning and with whom I've enjoyed working on many projects.

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There've been innumerable questions regarding the COVID-19 pandemic. There have been questions: Can computer models be the key to better COVID vaccines? Could a universal COVID-19 vaccine defeat every variant? How often can I be infected with the coronavirus? Can you get a coronavirus from drinking Corona beer? (No.)

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But of the many many questions have arisen, one of the major ones that was very pressing early on was the question of how long does immunity to COVID-19 last? Research to try to give a result to this was sort of waiting for data to appear because the problem with immunity is it's something you see over time and without time you don't have data.

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One question: if I've already had COVID-19, will I get it again? You know, we all are familiar with the sort of itinerary of COVID-19 and how it has spread through communities and then spread through a second time, even a third time in some cases. Another question: if I'm fully vaccinated, am I immune to COVID-19? We've had a lot of people vaccinated around the globe - around 62% right now - and some people many times boosted. Some people a few times boosted. So there's a lot of variation there. Would we need to keep getting COVID-19 boosters forever? How will we answer that?

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We have previously provided estimates, as was mentioned, to answer the first question, which is: If you've already had COVID-19, will you get it again? The answer is largely, yes, unless there's some other preventive method being used. And that result came out in the paper "The durability of immunity against reinfection by SARS-CoV-2" which was a comparative evolutionary study, very interestingly, because as I said, until data accumulates over a very long period of time, you can't really accurately quantify how much immunity people get to a disease. But we do have an enormous amount of data over time accumulated for a variety of coronaviruses. The seasonal coronaviruses that Ellen Foxman and mentioned earlier, and that data allows us to understand things about SARS-CoV-2 because they're closely related and evolution is not something that dramatically changes such things over relatively short periods of time. These are not hugely diverged viruses.

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All right, so, what did we do to actually analyze these kinds of questions? We wanted to make estimates of how frequently people got reinfected. A very important data set was collected by Edridge et al, which is portrayed - these are just three samples from that dataset - looking longitudinally at the antibody levels for seasonal and endemic coronaviruses. We could take those seasonal endemic data for the known coronaviruses that has been around a long time HCoV-229E and NL63 and OC43. We could also take antibody information that we know about the decline of antibodies after infection from MERS-COV and SARS-CoV-1 and put all of that data with the little bit of data over a short period of time that's already been collected for SARS-CoV-2 and then place it on an evolutionary tree. That is, look at how each of these different pieces of information about how declines happen after infections for the seasonal coronaviruses. All three of them here, MERS-CoV, the SARS-CoV-1 and SARS-CoV-2, and actually look at how this decline in antibody levels happens for different diseases based on the viral divergence between them.

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That enables us to fill in not just the original short period of time that we have data on, but the entire trajectory anticipated for antibody decline for SARS-CoV-2. More than just the antibody decline, it also allows us to figure out whether individuals are likely to get infected or not and at what level of antibody that they have. We can infer that, again, based on the seasonal viruses for these other infective coronaviruses, especially SARS-CoV-2 which is now approaching endemicity here. One of the things I just want to emphasize is that our estimates from that analysis were actually validated by empirical studies. So as time went on, it became easier and easier to track how many people got reinfected after getting first infections. In one study by Malhotra et al, you know, 34% were of unvaccinated individuals were reinfected at 420 to 480 days. Our estimate from the evolutionary approach was that probably 34% reinfection would occur at 450 days. Another estimate was that 82% of people got infected at 275 to 300 days. Our estimate was at 82% - sorry - no reinfection at 270 days. So these were very very consistent estimates from empirical data for the projections that we made, you know, a year and a half before, based on comparative evolutionary analysis. It's the kind of analysis that works. It tells you the correct answers.

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Our research addresses final - two additional questions here. If you're fully vaccinated, are you immune to COVID-19? Not so much. Will you need to keep getting COVID-19 boosters forever? To answer that question, we looked at four different vaccines, the four that are most likely prescribed that have the greatest global reach, which is Pfizer, Moderna, Oxford AstraZeneca, and the J&J vaccine.

I just want to emphasize that the question is: Over six years, would you need to get that Pfizer vaccination or would you not and how frequently?

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So comparing the peak and antibody response of natural infection to that of the Pfizer BionTech allows us to project to the actual vaccinations what we expect the level of antibody - how much prevention of infection we expect antibodies to confer. We can look at the antibody levels over time for the different - for the different vaccines - and we see they have different curves. The point is that we get shorter immunity when this curve is lower here. When the peak normalized antibody levels are lower. And we get a longer immunity when it's longer. We can also look in at - by using that information about what antibody level people get infected for these different diseases, we can get a probability of no breakthrough infection over time. This is how many days after the original infection someone had and what the likelihood of infection will be. There's one thing that's not on my slides I just want to emphasize here: this accounts for the evolution of the organism over time because the seasonal coronavirus data included that evolutionary phenomenon as well. Seasonal coronaviruses, just like SARS-CoV-2, evolve. Getting infected by them once doesn't make you immune for the rest of your life. Same same phenomenon, all right?

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As I said, that longer and shorter is conveyed by that information. So we compared peak antibody response to natural infection to that of Pfizer BionTech. We needed a way to normalize all of them. What we did was we normalized all of them to the Pfizer BionTech data which had the strongest dataset comparing unvaccinated reinfection and vaccinated reinfection, etc. We find that the peak level - this is just a relative level of antibodies after - for the Pfizer BionTech vaccination is 1.5 compared to natural infection at one. Again, you can draw this out over time as to what that infection - what the antibody levels are over time.

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This is just a big plot to show you - we used a lot of data. We compared the Pfizer data to that of the other three vaccines. This is where, again, Haley Hassler did all of the extraction and work to do this. Essentially, looking at that normalized Pfizer data to natural infection. We then related the other three vaccines to BNT where we had comparative results within study using exactly the same markers, exactly the same technology, etc. within the lab to assess by antibody level. If you use different technologies, you get different numbers. The point is, all of these studies showed Pfizer plus Moderna, all of these studies showed Pfizer plus Oxford AstraZeneca, and these studies showed Pfizer and J&J.

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All of that data coming together enabled us to figure out information. We made sure for all that data that it was sampled near the peak antibody response, that they were COVID-19 naive subjects, that there was a proper vaccination timing being used, and that there was that, as I said, comparison to Pfizer BionTech.

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All right, given that we found that antibody levels for mRNA vaccines were higher than natural infection while viral vector vaccines were approximately similar to natural infection. Here are the plots for that. The red line is for Moderna and Pfizer - quite similar to each other in response, in terms of antibody response and decline. The blue and teal lines - the teal line is Oxford AstraZeneca. The blue line is J&J. What that tells you is that breakthrough infections for those vaccinated by either mRNA vaccine were predicted to typically occur over a longer period than natural infections or breakthrough infections following either viral vector vaccination. So here are the plots for that just conveying the number of days you're expected to get a breakthrough vaccination after vaccination with mRNAs, natural infection, and those two viral vector vaccines.

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Just to summarize it very simply: the mean time by which there's a 5% cumulative risk of breakthrough infection for mRNA vaccines is more than twice than that of natural infection or viral vector vaccines. Greater efficacy in protecting you over a longer duration from the MRNA vaccines.

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I'm just going to skip that to point out we compared the peak antibody response of primary vaccination to that of the boosting in order to assess what boosting did. What you see is that you get a higher dose after boosting. We were very careful about the timing involved here as well, but the point is we have a peak of about 1.54 when you get brought up by the boost in terms of your antibodies.

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That allows us to do the same question - I'm not going to go into the details about this - but just asking over time how frequently, what frequency of vaccination is going to give you what level of resistance to future infection by COVID-19? I just have this slide and one more. The point is that the cumulative probability of getting a breakthrough infection of course increases over time. This is over a six month period and the point is if you have no boosters, you have about an 87% chance of getting infected over a six year period. This is with endemic, not pandemic disease, so this is where we're headed not where we are. If you get one booster every three years it does not very much to reduce your chance of getting infected, from 87 to 77% over two years, it drops down to 64% every 1.5 years, drops it down to 51%. Then we really start getting somewhere with an every year vaccination, that's down to about 31%. One out of three people. If you get a vaccination every six months, these are in healthy people by the way, that's every 11%. That's only 11% over six years, so very low chance - a relatively low chance over an extended period of time. It has a tremendous benefit in terms of prevention of infection. I just want to emphasize that this is the result for the Pfizer BionTech.

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The result if I can get my slide to switch for mRNA is very very similar. The Moderna vaccine is very similar. We weren't able to do it for the other two because the data doesn't exist in the same format, but that's the general result for the those mRNA vaccines.

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With that I'll just finish with my conclusions. The MRNA vaccines provide immunity over a longer duration compared to natural infection or viral vector vaccines. Delayed administration of boosters is of high consequence to the cumulative probability of SARS-CoV-2 breakthrough infections, so if we want to suppress it, the administration of boosters on as much as a six-month scale would suppress the disease spread considerably, especially when you think about that as - those results I showed you are the results for an individual when it is spread at an endemic level, so they aren't accounting for the herd immunity provided by the vaccination itself. That's just supposing it stays at endemic level and you get vaccination, how likely are you to get infected? Last point: population-wide booster vaccination can forestall and potentially strongly suppress COVID-19. One aspect that maybe I just want to emphasize is that I think we all got a little bit jaded on the boosters in some sense because the booster kept being given that was to this ancestral strain. It makes a big difference to have these updated boosters and I think that has not

been widely understood by the public and actually even by many in the epidemiological community.

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Thanks to all my collaborators who helped me do this.