0:00:00.05 –> 0:00:03.23 - [Fan] David Benkeser who is an assistant professor

0:00:03.23 –> 0:00:06.53 at the department of biostatistics and bioinformatics

0:00:06.53 –> 0:00:08.7 at Emory University.

0:00:08.7 –> 0:00:11.21 Dr. Benkeser got his PhD in biostatistics

0:00:11.21 –> 0:00:12.7 from University of Washington

0:00:12.7 –> 0:00:14.72 and had his post-doctoral fellowship

0:00:14.72 –> 0:00:17.423 from University of California at Berkeley.

0:00:18.27 –> 0:00:21.66 Dr. Benkeser is an expert in methods for machine learning

0:00:21.66 –> 0:00:24.07 and non-parametric statistical inference.

0:00:24.07 –> 0:00:25.76 He has made important contributions

0:00:25.76 –> 0:00:27.9 to integrate machine learning methods

0:00:27.9 –> 0:00:31.14 to draw causal inferences with observational data.

0:00:31.14 –> 0:00:33.66 He also has interesting work on preventative vaccines

0:00:33.66 –> 0:00:37.44 and HIV prevention, which he's going to share with us today.

0:00:37.44 –> 0:00:39.223 Welcome David, the floor is yours.

0:00:43.88 –> 0:00:45.81 - [David] Thanks, yeah, it's a great pleasure

0:00:45.81 –> 0:00:47.52 to be here today.

0:00:47.52 –> 0:00:51.28 Well, here today, but with you guys today giving this talk.

0:00:51.28 –> 0:00:54.59 So I did see that I think Tony Fauci

0:00:54.59 –> 0:00:57.62 spoke at Yale yesterday, so it was very nice of you Fan

0:00:57.62 –> 0:01:00.34 to book Tony Fauci as my opening act

0:01:00.34 –> 0:01:04.27 and I'll try not to disappoint him with my followup.

0:01:04.27 –> 0:01:07.12 So the talk I'm giving today is a very high-level talk.

0:01:07.12 –> 0:01:10.07 So the title is statistics and COVID-19 vaccine development,

0:01:10.07 –> 0:01:12.28 but it's really a talk mostly

0:01:12.28 –> 0:01:14.7 about COVID-19 vaccine development.

0:01:14.7 –> 0:01:18.71 There's not math until maybe slide like 29 out of 30.

0:01:18.71 –> 0:01:19.96 So really these are sort of

0:01:19.96 –> 0:01:23.01 just the high-level issues that have come up

0:01:23.01 –> 0:01:28.01 as I've worked with companies and government organizations

0:01:28.02 –> 0:01:30.04 on COVID-19 vaccine development.

0:01:30.04 –> 0:01:31.79 So I think there's a lot of really interesting stuff

0:01:31.79 –> 0:01:35.37 here and really, really glad to share it with you today.

0:01:35.37 –> 0:01:38.679 So if you want to kind of slide along with

0:01:38.679 –> 0:01:41.14 the slides they're available on GitHub

0:01:41.14 –> 0:01:43.19 so there's a link at the bottom there,

0:01:43.19 –> 0:01:44.267 and you can click on that

0:01:44.267 –> 0:01:45.87 and that'll pull up the HTML slide back,

0:01:45.87 –> 0:01:48.29 and I have sort of references hyperlinked in there.

0:01:48.29 –> 0:01:49.58 So that's an easy way to access

0:01:49.58 –> 0:01:51.89 the references there as well.

0:01:51.89 –> 0:01:54.52 Okay so I'm going to start just kind of talking

0:01:54.52 –> 0:01:57.75 about the biology a little bit of SARS-CoV-2,

0:01:57.75 –> 0:02:01.11 and segue into sort of how we can think about

0:02:01.11 –> 0:02:02.79 developing vaccines that will prevent

0:02:02.79 –> 0:02:05.55 an infection and COVID-19 disease.

0:02:05.55 –> 0:02:09.33 And so this is a nice little graphic that I ripped off

0:02:09.33 –> 0:02:11.74 from The Washington Post, who's very much better

0:02:11.74 –> 0:02:13.29 at making these cutesy little graphics

0:02:13.29 –> 0:02:16.14 than I am using PowerPoint or something.

0:02:16.14 –> 0:02:17.45 So let's kind of walk through this.

0:02:17.45 –> 0:02:19.52 And the goal here is to try to understand,

0:02:19.52 –> 0:02:21.62 you know, how SARS-CoV-2 is infecting your cells,

0:02:21.62 –> 0:02:22.92 how it's replicating,

0:02:22.92 –> 0:02:25.04 and then to understand what the mechanisms

0:02:25.04 –> 0:02:27.57 that immunological mechanisms of the vaccine are

0:02:27.57 –> 0:02:29.93 that can potentially block that infection

0:02:29.93 –> 0:02:31.12 and prevent clinical disease.

0:02:31.12 –> 0:02:32.95 So we'll just go quickly through this

0:02:32.95 –> 0:02:36.32 and this is sort of the story for most viruses, right?

0:02:36.32 –> 0:02:39.04 Is that viruses are really just genetic material

0:02:39.04 –> 0:02:42.162 in this case RNA that's wrapped up in the glycoprotein.

0:02:42.162 –> 0:02:45.19 So it's genetic material wrapped up in a protein.

0:02:45.19 –> 0:02:48.56 And so for SARS-CoV-2 you may have heard of a couple

0:02:48.56 –> 0:02:50.9 of these proteins in particular, the spike protein will play

0:02:50.9 –> 0:02:53.68 a large role when we talk about a vaccine development

0:02:53.68 –> 0:02:56.1 and why is this spike protein so important?

0:02:56.1 –> 0:02:58.17 Well, that's the guy that sort of latches

0:02:58.17 –> 0:03:01.375 onto your cell and it does that through this ACE2 pathway

0:03:01.375 –> 0:03:05.24 and it grabs onto your cell and insert itself inside

0:03:05.24 –> 0:03:07.11 you cell and once it's inside

0:03:07.11 –> 0:03:08.86 it releases its genetic material, right?

0:03:08.86 –> 0:03:11.41 It releases its RNA and kind of tricks

0:03:11.41 –> 0:03:13.43 your cell into replicating the virus, right?

0:03:13.43 –> 0:03:17.06 So that your cell is producing new copies of this virus,

0:03:17.06 –> 0:03:18.97 they're pieced together out of proteins that are released

0:03:18.97 –> 0:03:21.57 into your bloodstream to go infect more cells

0:03:21.57 –> 0:03:22.98 and more people.

0:03:22.98 –> 0:03:24.81 Okay so that's sort of the infection process

0:03:24.81 –> 0:03:26.74 and where along the lines do you know

0:03:26.74 –> 0:03:28.8 vaccines sort of halt this?

0:03:28.8 –> 0:03:30.67 So I'll walk through a few different

0:03:30.67 –> 0:03:33.13 of the major vaccine constructs that are being used

0:03:33.13 –> 0:03:34.86 for SARS-CoV-2 vaccines,

0:03:34.86 –> 0:03:37.08 and the details aren't super important here,

0:03:37.08 –> 0:03:38.32 but I do think it's sort of helpful

0:03:38.32 –> 0:03:39.953 to have a high level overview in comparison, right?

0:03:39.953 –> 0:03:42.97 Because there's so many vaccine products being developed,

0:03:42.97 –> 0:03:45.18 at least having some point of biological comparison
0:03:45.18 –> 0:03:47.27 of how they're working is useful.
0:03:47.27 –> 0:03:48.43 So to walk through these slides,
0:03:48.43 –> 0:03:50.44 all of these slides are basically going to be the same
0:03:50.44 –> 0:03:52.37 on the right hand side of the slide
0:03:52.37 –> 0:03:53.96 and how they're gonna differ is what goes
0:03:53.96 –> 0:03:55.58 into the vaccine on the left-hand side.
0:03:55.58 –> 0:03:57.837 So let's actually start on the right-hand side, right?
0:03:57.837 –> 0:04:00.25 And talk a little bit about immunology, right?
0:04:00.25 –> 0:04:02.997 And how your body tries to fight off infection.
0:04:02.997 –> 0:04:04.74 And we have a couple of different mechanisms
0:04:04.74 –> 0:04:06.02 of your immune system to do that.
0:04:06.02 –> 0:04:09.5 So there's a kind of T-cell responses, cytotoxic T-cells.
0:04:09.5 –> 0:04:12.21 So those are T-cells that recognize cells in your body
0:04:12.21 –> 0:04:13.85 that have been infected with a pathogen
0:04:13.85 –> 0:04:15.21 and destroy those cells, right?
0:04:15.21 –> 0:04:17.11 Because the cells are producing copies of the virus,
0:04:17.11 –> 0:04:18.84 releasing in the bloodstream.
0:04:18.84 –> 0:04:21.4 So if we're able to destroy infected cells,
0:04:21.4 –> 0:04:24.29 we can potentially stop infection, prevent disease,
0:04:24.29 –> 0:04:25.58 and then another key response
0:04:25.58 –> 0:04:27.51 that your immune system has is through antibodies.
0:04:27.51 –> 0:04:29.56 And that's sort of what's on the bottom here
0:04:29.56 –> 0:04:33.86 and is that B cells are able to produce antibodies.
0:04:33.86 –> 0:04:36.1 And what those antibodies do is they basically grab
0:04:36.1 –> 0:04:38.28 onto these surface proteins, right?
0:04:38.28 –> 0:04:40.28 So remember we talked about the spike protein,
0:04:40.28 –> 0:04:42.73 and what antibodies do is basically just bind onto that
0:04:42.73 –> 0:04:45.52 and sit there and so neutralizing antibodies.
0:04:45.52 –> 0:04:47.48 So there's two classes of antibodies that are kind
0:04:47.48 –> 0:04:48.47 of relevant for vaccines.

0:04:48.47 –> 0:04:50.113 So neutralizing antibodies really, you're just doing that.

0:04:50.113 –> 0:04:52.787 They're gonna sit on all of those spike proteins

0:04:52.787 –> 0:04:55.13 and because they're sitting there now the virus can't grab

0:04:55.13 –> 0:04:57.01 onto your cells to infect them.

0:04:57.01 –> 0:05:00.68 There's also binding antibodies, which are somewhat

0:05:00.68 –> 0:05:02.51 considered to be less important in this context,

0:05:02.51 –> 0:05:04.83 but what those guys do is bind onto those surface proteins,

0:05:04.83 –> 0:05:06.84 they don't neutralize the virus itself,

0:05:06.84 –> 0:05:09.16 but they send out chemical signals to other cells

0:05:09.16 –> 0:05:11.025 in your body that say, hey, here's a virus.

0:05:11.025 –> 0:05:13.03 Please come eat it for me.

0:05:13.03 –> 0:05:15.28 So those are the sort of antibody classes response

0:05:15.28 –> 0:05:16.113 that you can have.

0:05:16.113 –> 0:05:18.24 So there's these two sort of immune mechanisms

0:05:18.24 –> 0:05:22.46 that we have to neutralize infections by viruses.

0:05:22.46 –> 0:05:24.72 How do they learn to neutralize them?

0:05:24.72 –> 0:05:25.98 Well, there's this sort of middleman.

0:05:25.98 –> 0:05:27.79 So we're moving just to this middle panel here

0:05:27.79 –> 0:05:29.63 with these APC cells,

0:05:29.63 –> 0:05:31.83 so these antigen presenting cells, right?

0:05:31.83 –> 0:05:33.24 Those are the guys that what they're doing

0:05:33.24 –> 0:05:35.89 is basically digesting little bits

0:05:35.89 –> 0:05:40.347 of the virus in this case of the surface protein, right?

0:05:40.347 –> 0:05:42.54 And they're teaching or training your immune system

0:05:42.54 –> 0:05:44.25 to recognize that pathogen, right?

0:05:44.25 –> 0:05:46.79 So they're the ones that go and talk to the T cells,

0:05:46.79 –> 0:05:48.12 talk to the B cells and say,

0:05:48.12 –> 0:05:50.58 here's that how this virus looks,

0:05:50.58 –> 0:05:53.22 please go produce some antibodies or please recognize cells

0:05:53.22 –> 0:05:54.68 that have been infected with this

0:05:54.68 –> 0:05:56.33 and neutralize them for me.

0:05:56.33 –> 0:05:58.99 So really again, the whole right side of this plot

0:05:58.99 –> 0:06:00.22 is about your immune system.

0:06:00.22 –> 0:06:02.96 This is the way your immune system fights off infection.

0:06:02.96 –> 0:06:04.78 And what's different between this slide

0:06:04.78 –> 0:06:07.82 and the next few slides is basically how we present

0:06:07.82 –> 0:06:09.28 pieces of the pathogen pieces

0:06:09.28 –> 0:06:11.72 of the virus to these APCs, right?

0:06:11.72 –> 0:06:14.44 So how do we get these APCs, the material that they need

0:06:14.44 –> 0:06:18.86 for you to mount an immune response against SARS-CoV-2?

0:06:18.86 –> 0:06:20.7 And so the first class of vaccines

0:06:20.7 –> 0:06:22.83 I'll describe are nucleic acid vaccines.

0:06:22.83 –> 0:06:25.04 And so I'm talking about first

0:06:25.04 –> 0:06:27.05 because they're sort of the first wave of vaccines

0:06:27.05 –> 0:06:29.13 that are in phase three trials in the US.

0:06:29.13 –> 0:06:32.847 So Moderna and Pfizer, who are probably the most advanced

0:06:32.847 –> 0:06:36.897 candidates for US licensure are both mRNA vaccines.

0:06:36.897 –> 0:06:38.63 And so how are those vaccines made?

0:06:38.63 –> 0:06:41.83 Well, we take a little bit of messenger RNA,

0:06:41.83 –> 0:06:43.82 a little bit of viral genetic material,

0:06:43.82 –> 0:06:45.27 and wrap that in a lipid shell, right?

0:06:45.27 –> 0:06:46.71 That's the construct of the vaccine.

0:06:46.71 –> 0:06:49.19 And when you're injected that lipid shell

0:06:49.19 –> 0:06:51.24 latches onto your cell, right?

0:06:51.24 –> 0:06:53.71 Delivers that mRNA into your cell,

0:06:53.71 –> 0:06:55.49 just like a natural infection, right?

0:06:55.49 –> 0:06:57.47 Remember the SARS-CoV-2 grabbed onto your cell

0:06:57.47 –> 0:07:00.44 and inserted itself and then made copies of itself.

0:07:00.44 –> 0:07:02.99 So what is the mRNA doing once it's in your cell,

0:07:02.99 –> 0:07:04.58 it's actually just making copies

0:07:04.58 –> 0:07:06.81 of the spike protein itself, right?

0:07:06.81 –> 0:07:11.04 So you're manufacturing this protein within your own cells

0:07:11.04 –> 0:07:14.37 that are then released for these APCs to detect.

0:07:14.37 –> 0:07:16.89 So this is how we're getting these APCs,

0:07:16.89 –> 0:07:18.94 spike protein with an mRNA vaccine.

0:07:18.94 –> 0:07:21.79 We're basically using your cells as a warehouse

0:07:21.79 –> 0:07:23.637 to produce the antigen of the vaccine

0:07:23.637 –> 0:07:27.67 and so this is a really cool idea and a new idea, right?

0:07:27.67 –> 0:07:31.01 So, am mRNA or DNA vaccine has never been licensed before

0:07:31.01 –> 0:07:34.17 and that's not to say that we tried many times and failed.

0:07:34.17 –> 0:07:36.24 It's just to say that this is a very new technology,

0:07:36.24 –> 0:07:39.52 and it's sort of interesting that it's kind of come

0:07:39.52 –> 0:07:41.48 to the forefront in this context.

0:07:41.48 –> 0:07:43.94 So why do we like mRNA vaccines?

0:07:43.94 –> 0:07:45.61 Well, they're very fast to manufacturer.

0:07:45.61 –> 0:07:47.71 We'll talk about some of the other vaccine constructs

0:07:47.71 –> 0:07:50.21 where we're making this spike protein in a lab,

0:07:50.21 –> 0:07:52.25 and that is a long and arduous.

0:07:52.25 –> 0:07:53.95 It needs to be very careful process

0:07:53.95 –> 0:07:55.29 and when we're thinking about scaling up

0:07:55.29 –> 0:07:59.13 vaccine manufacturing, mRNA vaccines are very appealing

0:07:59.13 –> 0:08:01.77 in that sense, you can manufacture them

0:08:01.77 –> 0:08:03.3 very quickly at scale.

0:08:03.3 –> 0:08:04.87 They don't require a cold chain

0:08:04.87 –> 0:08:09.52 and so that's another great advantage these vaccines enjoy

0:08:09.52 –> 0:08:11.71 in terms of thinking about vaccine deployment,

0:08:11.71 –> 0:08:15.32 particularly in developing world settings.

0:08:15.32 –> 0:08:17 But again, this is a brand new technology.

0:08:17 –> 0:08:18.26 We don't have any safety data

0:08:18.26 –> 0:08:20.41 from past vaccines with this construct.

0:08:20.41 –> 0:08:22.4 We don't have any efficacy data.

0:08:22.4 –> 0:08:24.7 So, it's sort of an open question in the field

0:08:24.7 –> 0:08:26.85 as to how well these things are gonna work.

0:08:27.71 –> 0:08:30.117 So moving to sort of more classical, constructive vaccines

0:08:30.117 –> 0:08:32.68 and viral vector vaccines.

0:08:32.68 –> 0:08:34.15 So again, the right side of this picture

0:08:34.15 –> 0:08:35.07 is exactly the same.

0:08:35.07 –> 0:08:38.11 The story is how do we get an APC the right antigen?

0:08:38.11 –> 0:08:41.39 How do we show an APC a little bit of the spike protein?

0:08:41.39 –> 0:08:45.482 So a viral vector vaccine, right?

0:08:45.482 –> 0:08:48.96 Is going to take a different virus and splice

0:08:48.96 –> 0:08:52.13 a little bit of SARS-CoV-2 into that virus, okay.

0:08:52.13 –> 0:08:55.7 So for example, AstraZeneca, that's the Oxford that you may

0:08:55.7 –> 0:08:58.47 have heard of, they take a chimpanzee adenovirus,

0:08:58.47 –> 0:09:02.21 that's like, it's a virus that causes the common cold

0:09:02.21 –> 0:09:04.25 in chimpanzees and they splice in a little bit

0:09:04.25 –> 0:09:09.23 of SARS-CoV-2 into that and so that sort of host virus,

0:09:09.23 –> 0:09:12.12 that adenovirus holds genetic material

0:09:12.12 –> 0:09:15.69 infects your cells and your cells then produce the antigen.

0:09:15.69 –> 0:09:19.79 They produce the spike protein of SARS-CoV-2.

0:09:19.79 –> 0:09:22.42 So AstraZeneca and Janssen are using this construct again,

0:09:22.42 –> 0:09:26.35 both with adenoviruses, a very common virus vector.

0:09:26.35 –> 0:09:29.1 And again, we like these types of vaccines
0:09:29.1 –> 0:09:31.72 because they're quick to manufacturer,
0:09:31.72 –> 0:09:34.13 but a challenge of them is that your body
0:09:34.13 –> 0:09:36.74 can sort of develop separate immune responses
0:09:36.74 –> 0:09:39.45 against the vector itself, right?
0:09:39.45 –> 0:09:41.93 So you can develop a separate immune response
0:09:41.93 –> 0:09:44.51 against say an adenovirus right?
0:09:44.51 –> 0:09:47.36 Such that your body neutralizes those adenoviruses
0:09:47.36 –> 0:09:49.91 before they're able to infect your cells
0:09:49.91 –> 0:09:51.72 and produce the SARS-CoV-2 antigen.
0:09:51.72 –> 0:09:55.074 So we do see tendency a kind of faster waning
0:09:55.074 –> 0:09:58.47 vaccine effects with this class of vaccines.
0:09:58.47 –> 0:10:00.47 So moving on to subunit vaccine.
0:10:00.47 –> 0:10:02.94 So this is NovaVax and Sanofi's vaccine
0:10:02.94 –> 0:10:04.8 will be subunit vaccines
0:10:04.8 –> 0:10:06.25 and this is where I kind of mentioned before
0:10:06.25 –> 0:10:09.79 actually what happens here is these spike proteins
0:10:09.79 –> 0:10:11.7 or whatever the antigen is,
0:10:11.7 –> 0:10:14.38 is created and purified in a lab.
0:10:14.38 –> 0:10:17.01 So they actually use insect cells
0:10:17.01 –> 0:10:19.9 that they infect with SARS-CoV-2,
0:10:19.9 –> 0:10:23.31 those insect cells then produce the antigen that's purified
0:10:23.31 –> 0:10:25.92 and that's what goes into the vaccine
0:10:25.92 –> 0:10:27.47 are those protein subunits, right?
0:10:27.47 –> 0:10:29.8 So there we're just directly giving you the spike protein
0:10:29.8 –> 0:10:33.29 that we've grown outside of the host
0:10:33.29 –> 0:10:36.95 and that's how we're getting these APCs, those antigens.
0:10:36.95 –> 0:10:40.08 And so this is a commonly used vaccine construct.
0:10:40.08 –> 0:10:42.16 So the hep B vaccine is highly effective.
0:10:42.16 –> 0:10:43.89 HPV vaccine is highly effective.

0:10:43.89 –> 0:10:45.987 That's the construct of these, but the downside of course

0:10:45.987 –> 0:10:50.58 to it, so it's a well-trodden way of developing vaccines.

0:10:50.58 –> 0:10:52.75 But the downside is that they're slower to manufacturer.

0:10:52.75 –> 0:10:55.18 There's this whole process where we have to cultivate

0:10:55.18 –> 0:11:00.18 and grow these viruses in a lab, we have to purify them,

0:11:00.239 –> 0:11:03.93 and moreover they often also require an adjuvant.

0:11:03.93 –> 0:11:06.64 So that's really just sort of adding something a little bit

0:11:06.64 –> 0:11:10.66 extra that stimulates a better immune response in your body.

0:11:10.66 –> 0:11:12.76 So basically at the site of injection,

0:11:12.76 –> 0:11:13.93 it's something that increases

0:11:13.93 –> 0:11:15.77 your inflammatory response actually

0:11:15.77 –> 0:11:17.9 to kind of stimulate your immune system

0:11:17.9 –> 0:11:19.72 into recognizing those antigens

0:11:19.72 –> 0:11:22.36 and developing an immune response against them.

0:11:22.36 –> 0:11:24.36 So there's subunit vaccines.

0:11:24.36 –> 0:11:27.447 So the fourth class here is a weakened/inactivated vaccine.

0:11:27.447 –> 0:11:30.24 And so this is, I think, what most people like what

0:11:30.24 –> 0:11:32.98 my grandparents probably think all vaccines are,

0:11:32.98 –> 0:11:35.27 is basically we take a pathogen

0:11:35.27 –> 0:11:38.53 and we weaken it in some way, or we kill it, right?

0:11:38.53 –> 0:11:40.18 And then that's the construct of the vaccine

0:11:40.18 –> 0:11:42.13 and that's what's injected into you.

0:11:42.13 –> 0:11:45.44 And we go through this similar process there

0:11:45.44 –> 0:11:47.28 that literally mimics natural infection, right?

0:11:47.28 –> 0:11:51.23 Where your cells are infected by this weakened form

0:11:51.23 –> 0:11:53.07 of the virus, the virus replicates,

0:11:53.07 –> 0:11:55.81 and that's how we get antigens to the APCs.

0:11:55.81 –> 0:11:57.54 So this is the construct used in of course

0:11:57.54 –> 0:12:01.4 some classic vaccines like MMR, polio vaccine,

0:12:01.4 –> 0:12:02.97 but again, it's slower manufacturing, right?

0:12:02.97 –> 0:12:04.49 Because we have to cultivate the virus

0:12:04.49 –> 0:12:07.28 in the lab and then it also requires adjuvants.

0:12:07.28 –> 0:12:10.11 So I don't think there's currently any plans

0:12:10.11 –> 0:12:12.15 to have US phase three trials

0:12:12.15 –> 0:12:15.48 of weaken inactivated vaccines, but there are in China.

0:12:15.48 –> 0:12:17.383 So Sinopharm and Sinovac vaccines

0:12:17.383 –> 0:12:19.033 were using this construct.

0:12:20.554 –> 0:12:23.63 So that's just a bit of a background in immunology

0:12:23.63 –> 0:12:26.46 and how all this works and how we think about preventing

0:12:26.46 –> 0:12:29.46 infection with SARS-CoV-2 and hopefully preventing

0:12:29.46 –> 0:12:32.09 clinical disease COVID-19 disease.

0:12:32.09 –> 0:12:33.74 So now we're gonna segue to talk a little bit

0:12:33.74 –> 0:12:35.59 about the vaccine development process, right?

0:12:35.59 –> 0:12:37.51 'Cause this has all happened extremely fast.

0:12:37.51 –> 0:12:40.34 So let's talk about sort of the process whereby

0:12:40.34 –> 0:12:43.31 vaccine products are typically brought to market, right.

0:12:43.31 –> 0:12:44.81 And what looks a little bit different

0:12:44.81 –> 0:12:49.08 about the COVID-19 vaccine development process?

0:12:49.08 –> 0:12:52.35 So this is a figure from a nice New England journal paper

0:12:52.35 –> 0:12:53.65 that's referenced at the bottom

0:12:53.65 –> 0:12:55.56 that's just talking about sort of what's different

0:12:55.56 –> 0:12:57.73 this go around in terms of how are we accelerating

0:12:57.73 –> 0:12:59.73 the vaccine development process.

0:12:59.73 –> 0:13:01.12 And so I think as biostatisticians,

0:13:01.12 –> 0:13:04.101 anyone who works on clinical trials is fairly familiar

0:13:04.101 –> 0:13:05.89 with the traditional paradigm

0:13:05.89 –> 0:13:08.35 for bringing products to market, right.

0:13:08.35 –> 0:13:11.02 It involves sort of a lot of R&D

0:13:11.02 –> 0:13:12.9 in the lab, preclinical work

0:13:12.9 –> 0:13:15.82 and then you start doing human trials in phase one,

0:13:15.82 –> 0:13:19.38 these are small dose finding safety trials,

0:13:19.38 –> 0:13:20.78 checking whether these vaccines

0:13:20.78 –> 0:13:22.94 generate any immune response.

0:13:22.94 –> 0:13:25.34 And then what we'll often do is in vaccine trials

0:13:25.34 –> 0:13:27.1 is run a small randomized trial.

0:13:27.1 –> 0:13:28.58 That's a phase two trial, right?

0:13:28.58 –> 0:13:31.06 We're we'll have a placebo control,

0:13:31.06 –> 0:13:33.855 maybe pick out a particularly high risk population

0:13:33.855 –> 0:13:35.28 and start to see if we're getting

0:13:35.28 –> 0:13:37.1 any efficacy signal, right?

0:13:37.1 –> 0:13:38.97 And this is a very deliberate process, right?

0:13:38.97 –> 0:13:41 Phase one typically advances very slowly.

0:13:41 –> 0:13:42.38 We have lots of safety concerns.

0:13:42.38 –> 0:13:45.42 Phase two, we think very hard about whether the efficacy

0:13:45.42 –> 0:13:47.75 signal was really worth it to advance a candidate to

0:13:47.75 –> 0:13:50.8 phase three and it's a very deliberate process, right?

0:13:50.8 –> 0:13:53.01 To get to this phase three licensure trial, right?

0:13:53.01 –> 0:13:55.56 So the phase three trial is the big one involving

0:13:55.56 –> 0:13:56.53 the most participants.

0:13:56.53 –> 0:13:59.9 It's a randomized controlled trial, right?

0:13:59.9 –> 0:14:02.06 Enrolling many, many subjects that's well powered

0:14:02.06 –> 0:14:04.46 to detect ethicacy signals and based on the results

0:14:04.46 –> 0:14:06.9 of that phase three trial and safety data

0:14:06.9 –> 0:14:08.26 that's been accumulated throughout

0:14:08.26 –> 0:14:09.83 this whole process, right.

0:14:09.83 –> 0:14:13.69 We're able to provide licensure ideally for a product.

0:14:13.69 –> 0:14:16.51 And so that's sort of the clinical development process,

0:14:16.51 –> 0:14:18.76 but also in the context of COVID vaccines

0:14:18.76 –> 0:14:19.64 it's important to think about

0:14:19.64 –> 0:14:21.377 the manufacturing process, right.

0:14:21.377 –> 0:14:23.05 And how that looks a little bit different.

0:14:23.05 –> 0:14:27.01 So typically right, companies are very sort of hesitant

0:14:27.01 –> 0:14:30.64 to scale up manufacturing before they know that they have

0:14:30.64 –> 0:14:31.98 a product that will be licensed, right.

0:14:31.98 –> 0:14:34.04 Which makes sense, you know, they're sort of risk averse.

0:14:34.04 –> 0:14:35.71 We don't want to start manufacturing a product

0:14:35.71 –> 0:14:38.78 that may ultimately be shot down by the FDA.

0:14:38.78 –> 0:14:40.32 So really large scale manufacturing

0:14:40.32 –> 0:14:43.67 is not happening until after product licensure.

0:14:43.67 –> 0:14:45.01 So what's happening with COVID vaccine

0:14:45.01 –> 0:14:48.62 is basically this whole long deliberate timeline

0:14:48.62 –> 0:14:51.65 is being compressed into a shorter time period.

0:14:51.65 –> 0:14:53.37 And so how do we do that?

0:14:53.37 –> 0:14:55.68 Well, basically what happens is we've collapsed

0:14:55.68 –> 0:14:57.65 the phase one and phase two trials, right?

0:14:57.65 –> 0:14:59.79 So we're doing small safety studies.

0:14:59.79 –> 0:15:01.32 We're checking whether these vaccines

0:15:01.32 –> 0:15:02.84 are generating immune responses,

0:15:02.84 –> 0:15:05.956 but we're really not doing that smaller efficacy study

0:15:05.956 –> 0:15:10.15 that is typical of vaccine development.

0:15:10.15 –> 0:15:12.71 And so we're collapsing the phase one and two process,

0:15:12.71 –> 0:15:14.77 the phase three process is where we're at, right.

0:15:14.77 –> 0:15:16.42 We're doing these large scale trials, right?

0:15:16.42 –> 0:15:18.607 Because we need robust efficacy data

0:15:18.607 –> 0:15:21.52 and we need robust safety data to gain licensure,

0:15:21.52 –> 0:15:23.87 but a big thing that has changed, so the clinical process

0:15:23.87 –> 0:15:26.77 yeah a little bit compressed, but mostly the same,

0:15:26.77 –> 0:15:27.74 the big thing that's changed

0:15:27.74 –> 0:15:29.82 is the manufacturing process, right.

0:15:29.82 –> 0:15:33.25 Is we wanna make sure that once a vaccine is licensed

0:15:33.25 –> 0:15:36.5 and is proven to be safe and effective that we're able

0:15:36.5 –> 0:15:38.53 to start distributing that vaccine immediately.

0:15:38.53 –> 0:15:40.83 So that means that manufacturing needs to start ramping

0:15:40.83 –> 0:15:44.841 up right before we ever have a signal of efficacy

0:15:44.841 –> 0:15:47.49 and that's a huge risk for companies to take.

0:15:47.49 –> 0:15:51.19 So, I'll talk in a couple of slides about sort of how

0:15:51.19 –> 0:15:53.63 the government has come in to try to remove

0:15:53.63 –> 0:15:56.18 some of that risk from these companies

0:15:56.18 –> 0:15:58.67 and then the next slide I think is just showing sort of

0:15:58.67 –> 0:16:00.61 that it's really impressive that we're even talking

0:16:00.61 –> 0:16:04.77 about potentially having a COVID vaccine available this year

0:16:04.77 –> 0:16:07.63 or early next year, just given the timelines

0:16:07.63 –> 0:16:10.537 that are required to bring effective vaccines to market.

0:16:10.537 –> 0:16:12.6 And so here's just a few, you know,

0:16:12.6 –> 0:16:14.16 polio, measles, chickenpox, mumps,

0:16:14.16 –> 0:16:18.04 all multiple years of development for these vaccines,

0:16:18.04 –> 0:16:19.46 you could add malaria on this list.

0:16:19.46 –> 0:16:20.49 It took about 30 years

0:16:20.49 –> 0:16:24.21 to get a partially effective malaria vaccine to market.

0:16:24.21 –> 0:16:26.373 So this is typically a very long process, right?

0:16:26.373 –> 0:16:29.18 And for COVID, we're looking at hopefully doing this

0:16:29.18 –> 0:16:31.376 in just under a year or two.

0:16:31.376 –> 0:16:34.52 So how is the US government playing a role in this?

0:16:34.52 –> 0:16:37.05 Well, it's through this program that you may have heard of

0:16:37.05 –> 0:16:39.02 called Operation Warp Speed,

0:16:39.02 –> 0:16:43.84 which is this huge convoluted mess of an amalgamation

0:16:43.84 –> 0:16:45.35 of programs across the government

0:16:45.35 –> 0:16:49.81 from DOD to many branches of NIH, BARDA, NIAID,

0:16:49.81 –> 0:16:51.47 so it's sort of all over the place.

0:16:51.47 –> 0:16:54.49 And this is really just the same figure

0:16:54.49 –> 0:16:56.946 that I showed you from the New England journal paper.

0:16:56.946 –> 0:17:00.94 Just maybe a slightly more confusing

0:17:00.94 –> 0:17:02.77 if you ask me, I don't think Edward Tufte,

0:17:02.77 –> 0:17:04.63 he would be a big fan of graphic

0:17:04.63 –> 0:17:07 but the point here I want to mention

0:17:07 –> 0:17:09.5 is how is the government responding

0:17:09.5 –> 0:17:10.99 to COVID vaccine development?

0:17:10.99 –> 0:17:12.65 How are they contributing to that process?

0:17:12.65 –> 0:17:14.64 Well, there's really two ways that they've offered

0:17:14.64 –> 0:17:16.59 to accelerate the process.

0:17:16.59 –> 0:17:18.91 The first is through funding

0:17:18.91 –> 0:17:21.14 of phase three clinical trials, right?

0:17:21.14 –> 0:17:23.75 So a number of companies, six of the major companies,

0:17:23.75 –> 0:17:25.96 basically every company that's running a phase three trial

0:17:25.96 –> 0:17:29.63 in the US besides Pfizer that you've heard about

0:17:29.63 –> 0:17:31.64 is contracting with BARDA.

0:17:31.64 –> 0:17:33.57 That's an arm of the NIH,

0:17:33.57 –> 0:17:36.06 they're contracting with the government

0:17:36.06 –> 0:17:38.58 to have the government fund their phase three trials.

0:17:38.58 –> 0:17:40.45 So it's a joint agreement between the government

0:17:40.45 –> 0:17:42.14 and these companies where the government,

0:17:42.14 –> 0:17:44.93 you the taxpayer, right, are paying for these

0:17:44.93 –> 0:17:48.55 phase three trials that will eventually lead to licensure.

0:17:48.55 –> 0:17:50.3 So that's the first way that the government

0:17:50.3 –> 0:17:52.464 is sort of throwing money at this problem.

0:17:52.464 –> 0:17:55.85 It's through design and paying for these phase three trials.

0:17:55.85 –> 0:17:57.64 The second way is that they're paying

0:17:57.64 –> 0:17:58.73 for manufacturing, right?

0:17:58.73 –> 0:18:01.12 They're removing that risk for these companies

0:18:01.12 –> 0:18:03.81 by basically committing to buy a certain number of doses

0:18:03.81 –> 0:18:05.81 before we ever have any efficacy data.

0:18:05.81 –> 0:18:08.025 So we're in the hole basically to all of these companies

0:18:08.025 –> 0:18:10.54 for a fixed number of doses right.

0:18:10.54 –> 0:18:12.9 But that motivates the companies then to scale up

0:18:12.9 –> 0:18:14.813 their manufacturing ahead of the time

0:18:14.813 –> 0:18:16.693 that efficacy data are available.

0:18:17.527 –> 0:18:19.51 And that type of agreement has been entered

0:18:19.51 –> 0:18:20.9 into with Pfizer as well.

0:18:20.9 –> 0:18:24.46 So all of these companies that OWS Operation Warp Speed

0:18:24.46 –> 0:18:26.55 is running the phase three trials for

0:18:26.55 –> 0:18:28.98 also have this manufacturing agreement.

0:18:28.98 –> 0:18:31.38 Pfizer has that manufacturing agreement as well.

0:18:33.13 –> 0:18:37.73 So what role have I played in any of this big messy thing?

0:18:37.73 –> 0:18:40.58 So I work with a great group of scientists

0:18:40.58 –> 0:18:42.52 in the COVID-19 Prevention Network.

0:18:42.52 –> 0:18:45.45 So this was a clinical trials network established

0:18:45.45 –> 0:18:48.056 by National Institute of Allergies and Infectious Disease

0:18:48.056 –> 0:18:50.78 and NIAID so that's an arm of NIH,

0:18:50.78 –> 0:18:54.06 and it's basically anyone who works in clinical trials

0:18:54.06 –> 0:18:55.01 is fairly familiar

0:18:55.01 –> 0:18:56.84 with these clinical trials networks, right?

0:18:56.84 –> 0:19:00.7 It's an amalgamation of researchers and study sites,

0:19:00.7 –> 0:19:04.39 laboratories, people who focus on recruitment and retention

0:19:04.39 –> 0:19:06.72 of trial participants, statisticians.

0:19:06.72 –> 0:19:08.75 So it's researchers who are really experts

0:19:08.75 –> 0:19:10.27 in running clinical trials,

0:19:10.27 –> 0:19:12.29 designing clinical trials

0:19:12.29 –> 0:19:15.07 and ensuring their robust conduct.

0:19:15.07 –> 0:19:18.93 So the CoVPN was formed by basically leveraging

0:19:18.93 –> 0:19:20.59 four existing clinical trials networks.

0:19:20.59 –> 0:19:21.77 One of which I was a part of,

0:19:21.77 –> 0:19:23.82 which is the HIV vaccine trials network.

0:19:23.82 –> 0:19:27.04 And so from our group, we've really brought a great group

0:19:27.04 –> 0:19:29.7 of statisticians, many of whom are at the Fred Hutch

0:19:29.7 –> 0:19:34.48 in Seattle as well as great groups of laboratories at U Dub.

0:19:34.48 –> 0:19:35.81 And so what are the roles

0:19:35.81 –> 0:19:37.53 that we're playing in these trials?

0:19:37.53 –> 0:19:40.117 So in our statistical group,

0:19:40.117 –> 0:19:44.33 there's a couple of statisticians who are designated

0:19:44.33 –> 0:19:46.32 as like CoVPN representatives

0:19:46.32 –> 0:19:47.88 for each of these phase three trials.

0:19:47.88 –> 0:19:52.68 So I sit on calls with these trials and advise

0:19:52.68 –> 0:19:54.95 on their design and analysis approaches

0:19:54.95 –> 0:19:57.61 for their efficacy monitoring, for their safety monitoring.

0:19:57.61 –> 0:20:01.114 We help them address DSMB and FDA comments

0:20:01.114 –> 0:20:03.66 and sort of that's all happening in conjunction

0:20:03.66 –> 0:20:06.25 with both government statisticians, right.

0:20:06.25 –> 0:20:09.17 Representatives of BARDA and NIAID

0:20:10.01 –> 0:20:11.93 as well as company statisticians.

0:20:11.93 –> 0:20:14.47 And so we get on these calls and, you know,

0:20:14.47 –> 0:20:16.45 nerd out over clinical trials,

0:20:16.45 –> 0:20:20.63 statistical decision-making, and it's a good old time.

0:20:20.63 –> 0:20:23.66 Another aspect that we really contribute a lot on,

0:20:23.66 –> 0:20:26.17 or that CoVPN has sort of been tasked with taking

0:20:26.17 –> 0:20:28.87 the lead on is the development of immune correlates.

0:20:28.87 –> 0:20:30.59 And so that's the part of my talk

0:20:30.59 –> 0:20:32.1 where I'll get a little bit into statistics

0:20:32.1 –> 0:20:34.06 and talking about what immune correlates are,

0:20:34.06 –> 0:20:35.72 some of the types of analytic approaches

0:20:35.72 –> 0:20:38.253 we use to study those and the idea of immune correlates

0:20:38.253 –> 0:20:39.88 just to give you a teaser

0:20:39.88 –> 0:20:41.71 so you don't, you know, sign off Zoom early.

0:20:41.71 –> 0:20:45.43 So immune correlates are really the idea there is

0:20:45.43 –> 0:20:48.36 we're looking for immune responses that are predictive

0:20:48.36 –> 0:20:51.55 of the vaccines working, right.

0:20:51.55 –> 0:20:54.27 So what we'd really like to be able to do is understand,

0:20:54.27 –> 0:20:56.04 okay, if we're able to generate this level

0:20:56.04 –> 0:20:57.81 of neutralizing antibody,

0:20:57.81 –> 0:21:00.174 then that will lead to this level of protective effect

0:21:00.174 –> 0:21:01.81 of the vaccine, right?

0:21:01.81 –> 0:21:03.96 So that's the whole goal there is identifying

0:21:03.96 –> 0:21:05.441 what are these immune responses that are

0:21:05.441 –> 0:21:08.443 responsible for providing protection?

0:21:08.443 –> 0:21:11.41 Okay so I'm gonna walk through just a few of the design

0:21:11.41 –> 0:21:12.243 and analysis questions.

0:21:12.243 –> 0:21:14.16 And so these are things that have come up

0:21:14.16 –> 0:21:15.99 as we've worked with these company statisticians,

0:21:15.99 –> 0:21:19.63 as we thought about sort of the whole OWS vaccine program,

0:21:19.63 –> 0:21:21.86 what are some of the issues that statisticians

0:21:21.86 –> 0:21:24.12 are kicking around and people who have worked

0:21:24.12 –> 0:21:24.99 on clinical trials, right,

0:21:24.99 –> 0:21:27.14 a lot of these issues aren't gonna be new

0:21:27.14 –> 0:21:30.33 and one thing that I think is sort of interesting about this

0:21:30.33 –> 0:21:33.67 whole pandemic and operating as a public health professional

0:21:33.67 –> 0:21:36.974 in this and a clinical trial statistician in particular,

0:21:36.974 –> 0:21:39.13 is that a lot of things that we take for granted

0:21:39.13 –> 0:21:42.21 as scientists are either very confusing

0:21:42.21 –> 0:21:44.947 or sort of counterintuitive for a lot of the lay public.

0:21:44.947 –> 0:21:48.014 And so it's been sort of interesting to have that laid bare.

0:21:48.014 –> 0:21:49.81 In some of these issues, some of these things

0:21:49.81 –> 0:21:52.62 that we think are no-brainers like doing interim analysis

0:21:52.62 –> 0:21:55.76 for example are kind of highly controversial

0:21:55.76 –> 0:21:57.06 and have ended up being, you know,

0:21:57.06 –> 0:21:59.35 sort of areas of huge disputes.

0:21:59.35 –> 0:22:01.38 And so I just want to run through some of these issues

0:22:01.38 –> 0:22:03.73 that I think are quite fascinating, a lot of which,

0:22:03.73 –> 0:22:05.88 you know, really don't have a correct answer

0:22:05.88 –> 0:22:07.33 and they're really just sort of food for thought

0:22:07.33 –> 0:22:09.153 the types of things that we're thinking about

0:22:09.153 –> 0:22:11.46 when we're designing these trials.

0:22:11.46 –> 0:22:15.62 So I'll start by just giving a sort of more specific idea

0:22:15.62 –> 0:22:17.87 of what these trials look like and how they're conducted

0:22:17.87 –> 0:22:19.9 and I've picked AstraZeneca because that's the one

0:22:19.9 –> 0:22:22.6 I've worked on for the longest and most closely,

0:22:22.6 –> 0:22:25.886 but all of the trials sort of follow this similar design.

0:22:25.886 –> 0:22:27.08 And so the first thing I'll note

0:22:27.08 –> 0:22:28.66 is that you can read these trial protocols.

0:22:28.66 –> 0:22:31.23 So one of the interesting things that's happened

0:22:31.23 –> 0:22:33.37 in this COVID-19 development processes

0:22:33.37 –> 0:22:36.4 is there was a huge public push led by like Eric Topol

0:22:36.4 –> 0:22:39.42 and others to have the protocols of these trials

0:22:39.42 –> 0:22:42.92 made public, which when it happened was I guess

0:22:42.92 –> 0:22:45.22 when that push started happening, you know,

0:22:45.22 –> 0:22:46.66 I emailed all my colleagues and said,

0:22:46.66 –> 0:22:49.86 really do we not usually make protocols public?

0:22:49.86 –> 0:22:51.49 And that was just sort of interesting disconnect

0:22:51.49 –> 0:22:53.86 for me as an academic who's used to sort of everything

0:22:53.86 –> 0:22:56.92 being open science and that's a no brainer right.

0:22:56.92 –> 0:22:58.05 Working in this setting, right,

0:22:58.05 –> 0:23:00.489 where these protocols are really seen as trade secrets

0:23:00.489 –> 0:23:01.94 for pharmaceutical companies.

0:23:01.94 –> 0:23:04.79 So it's really unusual that actually these protocols

0:23:04.79 –> 0:23:06.3 for clinical trials have been made public.

0:23:06.3 –> 0:23:09.15 So it's sort of neat, but one of the things that happened

0:23:09.15 –> 0:23:12.01 is all of these protocols went public and reporters

0:23:12.01 –> 0:23:13.38 got their hands on them and said, wow,

0:23:13.38 –> 0:23:15.44 these are really dense documents, right?

0:23:15.44 –> 0:23:17.628 If you've ever looked at the clinical trial protocol,

0:23:17.628 –> 0:23:21.46 it's like a hundred pages of very specific definitions

0:23:21.46 –> 0:23:23.72 and safety monitoring and what symptoms lists

0:23:23.72 –> 0:23:25.84 you're gonna use and what surveys

0:23:25.84 –> 0:23:26.673 you're gonna give to people.

0:23:26.673 –> 0:23:28.35 So they're very sort of detailed documents

0:23:28.35 –> 0:23:31.81 that are kind of hard for the public to parse.

0:23:31.81 –> 0:23:34.43 So it's been sort of a be careful what you wish for thing

0:23:34.43 –> 0:23:37.53 in terms of releasing these protocols, but that's an aside.

0:23:37.53 –> 0:23:40.03 So let's talk about actually what these trials look like.

0:23:40.03 –> 0:23:41.56 So here's a schematic, and again,

0:23:41.56 –> 0:23:43.75 this is AstraZeneca in particular,

0:23:43.75 –> 0:23:47.23 but this is basically the design of most of these trials

0:23:47.23 –> 0:23:48.39 will look something like this.

0:23:48.39 –> 0:23:50.02 So who is the population?

0:23:50.02 –> 0:23:52.84 Most of these trials are gonna be primarily in adults.

0:23:52.84 –> 0:23:54.52 I think Pfizer has now started

0:23:54.52 –> 0:23:56.93 to talk about including children.

0:23:56.93 –> 0:23:58.684 I'm not exactly sure where that's happening,

0:23:58.684 –> 0:24:00.952 but adults for the most part,

0:24:00.952 –> 0:24:04.81 these are mostly healthy individuals

0:24:04.81 –> 0:24:07.31 that don't have, you know, chronic diseases

0:24:07.31 –> 0:24:09.97 that are at risk or high risk of death.

0:24:09.97 –> 0:24:11.89 And we're really looking at targeting individuals

0:24:11.89 –> 0:24:15.3 who are at an increased risk for SARS-CoV-2 acquisition

0:24:15.3 –> 0:24:17.15 and severe COVID disease

0:24:17.15 –> 0:24:19.1 and so the idea there is number one

0:24:19.1 –> 0:24:20.42 these are the people that are bearing

0:24:20.42 –> 0:24:22.52 the brunt of the pandemic, right?

0:24:22.52 –> 0:24:25.5 So we want to be able to get a product to those people

0:24:25.5 –> 0:24:26.52 as fast as possible.

0:24:26.52 –> 0:24:28.603 But number two also, right, that means that we'll accrure

0:24:28.603 –> 0:24:32.07 from a sort of cold hearted and statistician point of view

0:24:32.07 –> 0:24:34.39 that means we'll accrue end points faster.

0:24:34.39 –> 0:24:37.03 We'll observe more cases of COVID-19 disease

0:24:37.03 –> 0:24:39.55 and potentially get an efficacy signal a little bit faster.

0:24:39.55 –> 0:24:42.5 So there's a lot of interest in sort of recruiting

0:24:42.5 –> 0:24:45.05 and retaining individuals at high risk for COVID-19.

0:24:45.05 –> 0:24:47.51 So you can go onto the COVID-19 prevention trials network

0:24:47.51 –> 0:24:49.05 and fill out a survey, right.

0:24:49.05 –> 0:24:50.5 Then we'll basically under the hood

0:24:50.5 –> 0:24:52.53 assess your risk for COVID-19

0:24:52.53 –> 0:24:53.74 and if you're found to be at high risk,

0:24:53.74 –> 0:24:55.4 we'll aggressively email you and try to get you

0:24:55.4 –> 0:24:56.58 enrolled in one of these trials.

0:24:56.58 –> 0:24:57.413 If you're at low risk,

0:24:57.413 –> 0:24:59.04 we'll say, thanks for taking the survey,

0:24:59.04 –> 0:25:00.61 we'll be in touch and likely

0:25:00.61 –> 0:25:03.474 you won't hear from us anytime soon.

0:25:03.474 –> 0:25:05.39 Okay so that's the trial population.

0:25:05.39 –> 0:25:07.16 So how does the actual trial conduct look?

0:25:07.16 –> 0:25:09.83 So there's kind of a mixture here.

0:25:09.83 –> 0:25:12.63 AstraZeneca is using a two to one randomization scheme.

0:25:12.63 –> 0:25:15.928 So you have two chances of getting the active vaccine

0:25:15.928 –> 0:25:18.19 versus one chance of getting a placebo.

0:25:18.19 –> 0:25:21.5 And in this case, it's a true placebo, just a saline dose

0:25:21.5 –> 0:25:25.57 and then most of the vaccines, most all with Janssen

0:25:25.57 –> 0:25:27.99 being the accepted are two dose vaccines.

0:25:27.99 –> 0:25:29.77 So you receive the first dose at day one

0:25:29.77 –> 0:25:32.27 and the second dose about a month later.

0:25:32.27 –> 0:25:34.11 And in the interim, we take a couple of measurements.

0:25:34.11 –> 0:25:36.71 We have a phone call to assess reactogenicity right.

0:25:37.964 –> 0:25:41.08 Does your arm hurt, or have you experienced any adverse side

0:25:41.08 –> 0:25:44.01 effects of the first dose of vaccine?

0:25:44.01 –> 0:25:46.24 And then there's also an immune response measurement

0:25:46.24 –> 0:25:47.55 that happens after a couple of days.

0:25:47.55 –> 0:25:49.02 So we get an early signal

0:25:49.02 –> 0:25:51.247 of how immunogenetic these vaccines are.

0:25:51.247 –> 0:25:53.31 And so then individuals come in for their second dose

0:25:53.31 –> 0:25:55.1 of vaccine and it's a similar story, right?

0:25:55.1 –> 0:25:56.69 Did you have any reactions?

0:25:56.69 –> 0:25:59.44 We measure your immune response and after that,

0:25:59.44 –> 0:26:02 that's sort of when the clock starts for active follow-ups.

0:26:02 –> 0:26:06.193 So this day 57, that's two weeks roughly after,

0:26:07.45 –> 0:26:08.44 am I doing that math right?

0:26:08.44 –> 0:26:11.81 Well, it looks like roughly two weeks after the second dose

0:26:11.81 –> 0:26:13.81 of the vaccine is typically when this clock

0:26:13.81 –> 0:26:16.69 is gonna start and we're gonna start counting COVID events.

0:26:16.69 –> 0:26:21.05 And then it's sort of just the standard sort of game we play

0:26:21.05 –> 0:26:21.883 in clinical trials.

0:26:21.883 –> 0:26:23.31 We wait for events to accrue.

0:26:23.31 –> 0:26:24.93 We have certain monitoring plan

0:26:24.93 –> 0:26:26.84 for when we're gonna check for efficacy

0:26:26.84 –> 0:26:28.02 and we'll talk about some of that.

0:26:28.02 –> 0:26:30.35 So, I just want to note that there's sort of two ways

0:26:30.35 –> 0:26:31.59 that we're ascertaining events

0:26:31.59 –> 0:26:33.09 that are happening here, right?

0:26:33.09 –> 0:26:34.84 The first is passive monitoring.

0:26:34.84 –> 0:26:37.03 What that means is we basically wait for individuals

0:26:37.03 –> 0:26:39.23 to present with symptoms of COVID 19, right?

0:26:39.23 –> 0:26:41.4 So you get a cough, you lose taste, right?

0:26:41.4 –> 0:26:44.81 You call the study site, right?

0:26:44.81 –> 0:26:45.81 So I am having these symptoms.

0:26:45.81 –> 0:26:46.91 They say, come on in.

0:26:46.91 –> 0:26:49.642 You get a PCR test to see whether you're infected.

0:26:49.642 –> 0:26:51.31 And in that case, you would count

0:26:51.31 –> 0:26:52.9 as a COVID-19 endpoint, right?

0:26:52.9 –> 0:26:55.7 If you check off some check boxes for symptoms

0:26:55.7 –> 0:26:58.57 with COVID-19 disease, you have a PCR positive test.

0:26:58.57 –> 0:27:01.1 You'd go down as a COVID 19 endpoint.

0:27:01.1 –> 0:27:04 There's also these sort of active follow-up visits.

0:27:04 –> 0:27:07.559 So these like day 90, day, 180 and day 360,

0:27:07.559 –> 0:27:10.58 and at those visits we'll do a serology check.

0:27:10.58 –> 0:27:12.56 And what that means is we basically take a blood draw

0:27:12.56 –> 0:27:15.67 and we measure whether you have antibodies

0:27:15.67 –> 0:27:18.64 against SARS-CoV-2, right, antibodies that are distinct

0:27:18.64 –> 0:27:19.97 from the antibodies that are generated

0:27:19.97 –> 0:27:21.11 in response to the vaccine.

0:27:21.11 –> 0:27:24.13 So we're basically able to tell whether you were infected

0:27:24.13 –> 0:27:26.27 in this sort of interim period,

0:27:26.27 –> 0:27:28.74 when you show up for these visits.

0:27:28.74 –> 0:27:30.29 So that's active follow up

0:27:30.29 –> 0:27:31.27 and so there you're gonna be able

0:27:31.27 –> 0:27:33.39 to pick up sort of asymptomatic cases, right?

0:27:33.39 –> 0:27:35.94 'Cause if you never have symptoms, you'll never come in

0:27:35.94 –> 0:27:38.04 and be captured by passive followup.

0:27:38.04 –> 0:27:40.07 So we have to wait for these set clinic visits

0:27:40.07 –> 0:27:41.72 to do the serology testing,

0:27:41.72 –> 0:27:43.82 to ascertain it asymptomatic cases.

0:27:43.82 –> 0:27:46.01 And so this is gonna actually play a role

0:27:46.01 –> 0:27:47.6 in a little bit, when I started talking about, you know,

0:27:47.6 –> 0:27:50.11 what are the end points that we're thinking about measuring?

0:27:50.11 –> 0:27:51.53 Like, what do we want to know how well

0:27:51.53 –> 0:27:53.27 the vaccine works at preventing?

0:27:53.27 –> 0:27:54.83 Is it asymptomatic infection?

0:27:54.83 –> 0:27:55.99 Is it disease?

0:27:55.99 –> 0:27:57.47 Is it severe disease and so forth?

0:27:57.47 –> 0:27:58.87 So we'll talk through some of those issues,

0:27:58.87 –> 0:28:01.72 but just want to note already that the design has started

0:28:01.72 –> 0:28:04.35 to inform some of the challenges that we might see

0:28:04.35 –> 0:28:06.51 when we want to talk about how well the vaccine works

0:28:06.51 –> 0:28:09.113 against certain forms of infection and disease.

0:28:10.22 –> 0:28:12.97 And so I think if you read the newspaper and you'll see

0:28:12.97 –> 0:28:15.29 the term vaccine efficacy tossed around a lot.

0:28:15.29 –> 0:28:16.83 So the first thing I want to talk about is right,

0:28:16.83 –> 0:28:19.08 what is the primary hypothesis

0:28:19.08 –> 0:28:20.53 that these trials are trying to test?

0:28:20.53 –> 0:28:22.51 And what is the parameter?

0:28:22.51 –> 0:28:24.82 What is the estimate, right, that they're going after

0:28:24.82 –> 0:28:26.55 in these trials and for whatever reason

0:28:26.55 –> 0:28:28.8 nobody consulted me when they decided that VE

0:28:28.8 –> 0:28:30.933 would be measured in this way.

0:28:31.782 –> 0:28:35.22 But for whatever reason, we studied this that we quantify

0:28:35.22 –> 0:28:37.18 the efficacy of a vaccine in a sort of weird way.

0:28:37.18 –> 0:28:40.3 So a vaccine efficacy, we describe as the percent reduction

0:28:40.3 –> 0:28:43.04 in relative risk comparing vaccine to placebo.

0:28:43.04 –> 0:28:46.06 So it's this one minus a risk ratio.

0:28:46.06 –> 0:28:49.14 There's a one minus a risk ratio where you take the risk

0:28:49.14 –> 0:28:51.3 in the vaccine and the numerator and the risk

0:28:51.3 –> 0:28:53.41 in the placebo and the denominator.

0:28:53.41 –> 0:28:54.243 So, I mean,

0:28:54.243 –> 0:28:55.94 we can just play a quick little intuitive game, right?

0:28:55.94 –> 0:28:57.28 How do we get a VE close

0:28:57.28 –> 0:28:59.65 to one that would be a perfect vaccine?

0:28:59.65 –> 0:29:00.72 Well, we would make the risk

0:29:00.72 –> 0:29:02.84 in the vaccine close to zero, right?

0:29:02.84 –> 0:29:03.78 So that sorta makes sense.

0:29:03.78 –> 0:29:05.64 If you have a perfectly effective vaccine,

0:29:05.64 –> 0:29:08.35 there'll be no risk of infection and or disease

0:29:08.35 –> 0:29:09.31 amongst the vaccinated.

0:29:09.31 –> 0:29:11.21 So you would get VE close to one.

0:29:11.21 –> 0:29:13.498 But on the other hand, how do we make VE zero?

0:29:13.498 –> 0:29:15.66 Well, we would take the risk in the vaccine

0:29:15.66 –> 0:29:18.05 and set it equal to the risk in the placebo, right.

0:29:18.05 –> 0:29:20.68 In which case basically saying the vaccine's not doing

0:29:20.68 –> 0:29:22.62 anything and then on the other hand,

0:29:22.62 –> 0:29:23.86 a VE is negative, right?

0:29:23.86 –> 0:29:26.04 That's indicating that there's actually higher risk

0:29:26.04 –> 0:29:27.89 in the vaccine.

0:29:27.89 –> 0:29:30.84 So just to give you sort of a few reference points, right?

0:29:30.84 –> 0:29:34.2 So that VE of one is perfect, VE of zero is nothing

0:29:34.2 –> 0:29:37.59 and what we're really hoping for with these COVID trials

0:29:37.59 –> 0:29:39.73 is a VE of at least 50%.

0:29:39.73 –> 0:29:42.46 And that's sort of the cutoff that FDA guidance

0:29:42.46 –> 0:29:45.59 has stipulated is that you need to show a point estimate

0:29:45.59 –> 0:29:48.05 of VE for your primary end point.

0:29:48.05 –> 0:29:50.04 And again, we'll talk about what these primary end points

0:29:50.04 –> 0:29:52.62 are but we need a VE against a primary end point

0:29:52.62 –> 0:29:54.147 of at least 50%

0:29:54.147 –> 0:29:59.147 and we need to definitively rule out the possibility

0:29:59.48 –> 0:30:02.25 that the vaccine efficacy is less than 30%.

0:30:02.25 –> 0:30:04.5 So basically we have to reject the null hypothesis

0:30:04.5 –> 0:30:07.71 that VE is less than 30% along with having a point

0:30:07.71 –> 0:30:10.76 estimate of VE being greater than 50%, right.

0:30:10.76 –> 0:30:13.273 And we need to do that while controlling type one error

0:30:13.273 –> 0:30:14.863 at two and a half percent.

0:30:15.82 –> 0:30:18.62 Okay and so here, just one final note,

0:30:18.62 –> 0:30:19.99 since this is a statistics talk,

0:30:19.99 –> 0:30:21.21 I'll talk a little bit more

0:30:21.21 –> 0:30:23.11 about what I mean by risk, right?

0:30:23.11 –> 0:30:25.73 So risk here can be quantified in a number of ways

0:30:25.73 –> 0:30:26.563 and it often is.

0:30:26.563 –> 0:30:28.92 So we can quantify this using hazards, for example,

0:30:28.92 –> 0:30:31.21 like you can imagine fitting a Cox model, right.

0:30:31.21 –> 0:30:32.58 A proportional hazards model, right.

0:30:32.58 –> 0:30:34.72 That only adjusts for vaccine, right.

0:30:34.72 –> 0:30:36.88 And presenting like one minus a hazard ratio

0:30:36.88 –> 0:30:39.25 from a Cox model, that's something that's commonly done.

0:30:39.25 –> 0:30:41.43 You can also think about cumulative incidents, right?

0:30:41.43 –> 0:30:42.72 So like mapping,

0:30:42.72 –> 0:30:45.98 maybe one minus a survival probability as a way

0:30:45.98 –> 0:30:49.14 of quantifying risk, incidents rate ratios.

0:30:49.14 –> 0:30:51.99 So they're all sort of used for different vaccines.

0:30:51.99 –> 0:30:54.53 And usually we like to sort of argue

0:30:54.53 –> 0:30:55.89 about which one of these is better

0:30:55.89 –> 0:30:58.39 and I've thought a lot about that in my career.

0:30:58.39 –> 0:31:00.14 And in this setting, it turns out because COVID

0:31:00.14 –> 0:31:02.93 is such a rare event that all of these ways of quantifying

0:31:02.93 –> 0:31:05.22 rates are basically the same and you end up

0:31:05.22 –> 0:31:07.96 with almost identical operating characteristics of a trial.

0:31:07.96 –> 0:31:09.84 So it's really not worth sort of losing sleep over

0:31:09.84 –> 0:31:12.107 whether we're talking about VE in terms of hazard

0:31:12.107 –> 0:31:14.563 or incidents or incidents rate and so forth.

0:31:16.47 –> 0:31:18.83 So how are folks going about estimating this VE?

0:31:18.83 –> 0:31:21.95 Here's just a quick table of the four most advanced

0:31:21.95 –> 0:31:22.783 phase three trials,

0:31:22.783 –> 0:31:25.33 the ones that have released their protocols at least.

0:31:25.33 –> 0:31:28.2 So we see for Moderna, AstraZeneca, and Janssen,

0:31:28.2 –> 0:31:30.8 they're using pretty kind of the standard approaches.

0:31:30.8 –> 0:31:33.14 Moderna a Cox model as I describe,

0:31:33.14 –> 0:31:35.17 AstraZeneca a Poisson regression model,

0:31:35.17 –> 0:31:37.81 it's like, okay, that's basically a Cox model,

0:31:37.81 –> 0:31:40.66 and then Janssen is using a sort of exact binomial test

0:31:40.66 –> 0:31:43.681 with this sequential probability ratio rest.

0:31:43.681 –> 0:31:46.32 Pfizer is a little bit of the oddball.

0:31:46.32 –> 0:31:49.03 So they have stipulated a bayesian approach

0:31:49.03 –> 0:31:52.77 wherein they're basically specifying a prior

0:31:52.77 –> 0:31:55.29 for vaccine efficacy and are using sort of

0:31:55.29 –> 0:31:57.88 a beta-binomial bayesian approach to evaluate

0:31:57.88 –> 0:31:59.84 the posterior probability of the vaccine efficacy

0:31:59.84 –> 0:32:03.97 is greater than 30% and so at the end of the day,

0:32:03.97 –> 0:32:05.53 there's four different statistical methods here.

0:32:05.53 –> 0:32:08.85 Again, if you do a simulation study with parameters

0:32:08.85 –> 0:32:10.76 that are approximately similar to what we expect to see

0:32:10.76 –> 0:32:12.01 in these COVID trials,

0:32:12.01 –> 0:32:13.93 you're really not gonna see much difference in terms

0:32:13.93 –> 0:32:15.74 of operating characteristics across these.

0:32:15.74 –> 0:32:17.85 So it's interesting to notice that assertions

0:32:17.85 –> 0:32:19.41 that there's these different approaches,

0:32:19.41 –> 0:32:20.243 but at the end of the day,

0:32:20.243 –> 0:32:22.44 we're basically talking about how many vaccinated people

0:32:22.44 –> 0:32:25.08 get infected, how many placebo people got infected,

0:32:25.08 –> 0:32:27.41 and almost all of these methods are gonna yield

0:32:27.41 –> 0:32:29.01 very similar inference.

0:32:29.01 –> 0:32:30.5 When it comes down to brass tacks,

0:32:30.5 –> 0:32:33.19 how many numbers fall into those categories?

0:32:33.19 –> 0:32:35.71 So that's a little bit about sort of

0:32:35.71 –> 0:32:38.08 how we quantify VE in these settings

0:32:38.08 –> 0:32:39.92 but one of the big things I haven't described yet

0:32:39.92 –> 0:32:41.88 is VE against what, right?

0:32:41.88 –> 0:32:43.497 What is the end point that we're measuring here?

0:32:43.497 –> 0:32:47.28 And so here's a figure from a paper we just had come out

0:32:47.28 –> 0:32:50.04 in Annals of Internal Medicine, the link's here.

0:32:50.04 –> 0:32:52.08 So this is where we were spending a lot of time,

0:32:52.08 –> 0:32:54.23 you know, earlier this summer, thinking about,

0:32:54.23 –> 0:32:55.92 you know, what's the right end point,

0:32:55.92 –> 0:32:57.9 what's the right end point for a primary analysis

0:32:57.9 –> 0:32:59.257 of the clinical trial.

0:32:59.257 –> 0:33:02.53 And it's complicated for something like SARS-CoV-2, right?

0:33:02.53 –> 0:33:03.733 Because we know we can start up here

0:33:03.733 –> 0:33:07.03 with the SARS-CoV-2 infection, right?

0:33:07.03 –> 0:33:08.59 That's sort of the base, you can become infected

0:33:08.59 –> 0:33:10.93 and then a number of things can happen, right?

0:33:10.93 –> 0:33:14.27 You can go on to be infected but develop no symptoms.

0:33:14.27 –> 0:33:16.75 So we would call that an asymptomatic infection,

0:33:16.75 –> 0:33:18.41 or you can develop symptoms, right.

0:33:18.41 –> 0:33:19.7 In which case we don't call you

0:33:19.7 –> 0:33:21.3 a SAR-CoV-2 infection anymore,

0:33:21.3 –> 0:33:24.88 we call you a COVID-19 disease endpoint.

0:33:24.88 –> 0:33:28.48 You have a clinical manifestation of your infection.

0:33:28.48 –> 0:33:29.64 But even beyond that, right,

0:33:29.64 –> 0:33:31.22 amongst people who exhibit symptoms

0:33:31.22 –> 0:33:34.38 some of them, maybe many of them are quite mild, right.

0:33:34.38 –> 0:33:37.58 So we have this kind of category of non-severe COVID,

0:33:37.58 –> 0:33:40.73 whereas others we know that are extremely adversely

0:33:40.73 –> 0:33:45.33 impacted by infection and end up with severe COVID disease.

0:33:45.33 –> 0:33:48.74 So you have all of these choices of sort of

0:33:48.74 –> 0:33:50.82 which end points you might want to talk about

0:33:50.82 –> 0:33:53.05 and so I'll kind of walk through some what I see

0:33:53.05 –> 0:33:56.36 as the positives and negatives of this and then I'll also

0:33:56.36 –> 0:33:57.82 talk about this burden of disease

0:33:57.82 –> 0:34:00.907 very briefly end point that we've put together

0:34:00.907 –> 0:34:02.78 and so that's kind of a composite end point

0:34:02.78 –> 0:34:05 that we've suggested that could kind of bring all

0:34:05 –> 0:34:07.17 of these different end points together.

0:34:07.17 –> 0:34:09.36 Okay so starting with SARS-CoV-2 infection, right?

0:34:09.36 –> 0:34:12.39 Why might we like any sort of any infection, right.

0:34:12.39 –> 0:34:14.02 Asymptomatic, symptomatic don't care,

0:34:14.02 –> 0:34:16.73 let's count any infection as an event

0:34:16.73 –> 0:34:19.66 and measure VE against preventing infection.

0:34:19.66 –> 0:34:21.62 Okay and so that's definitely relevant, right.

0:34:21.62 –> 0:34:23.94 It's relevant the context of a pandemic.

0:34:23.94 –> 0:34:24.93 We're preventing infections,

0:34:24.93 –> 0:34:26.52 we're preventing spread of the disease,

0:34:26.52 –> 0:34:29.967 we're bringing our knot down, we're impacting the pandemic.

0:34:29.967 –> 0:34:33.08 And moreover, we're going to see many more infections

0:34:33.08 –> 0:34:35.58 than we will cases of symptomatic disease.

0:34:35.58 –> 0:34:37.22 We know that many people who were infected

0:34:37.22 –> 0:34:39.11 never go on to develop symptoms

0:34:39.11 –> 0:34:42.31 so thinking about having an answer faster, right.

0:34:42.31 –> 0:34:44.469 SARS-CoV-2 infection is a nice endpoint,

0:34:44.469 –> 0:34:45.78 but then the question is,

0:34:45.78 –> 0:34:47.43 is it a clinically relevant endpoint?

0:34:47.43 –> 0:34:52.085 So it's really not describing an impact on patients at all.

0:34:52.085 –> 0:34:55.51 So we could kind of question its relevance

0:34:55.51 –> 0:34:56.94 from that perspective.

0:34:56.94 –> 0:34:58.71 The other thing, right, is that we remember going back

0:34:58.71 –> 0:35:01.08 to the study design, we're only able to ascertain

0:35:01.08 –> 0:35:05.27 asymptomatic infections sort of very coarsely in time

0:35:05.27 –> 0:35:08.93 and moreover you have this phenomenon that happens

0:35:08.93 –> 0:35:12.16 is that when you're testing many, many individuals, right.

0:35:12.16 –> 0:35:13.587 It's sort of the classic biostat

0:35:13.587 –> 0:35:15.53 one-on-one problem that we give people, right.

0:35:15.53 –> 0:35:18.87 You're testing many individuals, but the prevalence is low.

0:35:18.87 –> 0:35:22.47 So even if you have high sensitivity and high specificity,

0:35:22.47 –> 0:35:24.62 you could end up with low positive predictive value.

0:35:24.62 –> 0:35:28.48 And the effect of that when you come to the time to analyze

0:35:28.48 –> 0:35:31.32 the data is that you'll be biasing VE towards the knoll.

0:35:31.32 –> 0:35:35.065 So it's actually, while it seems like maybe a nice end point

0:35:35.065 –> 0:35:36.92 from the perspective of observing many infections,

0:35:36.92 –> 0:35:40.343 it's a very challenging endpoint to analyze quantitatively.

0:35:41.19 –> 0:35:43.26 So moving down we could talk about COVID.

0:35:43.26 –> 0:35:45.69 So again, COVID is just infection,

0:35:45.69 –> 0:35:48.88 PCR confirmed infection with clinical symptoms.

0:35:48.88 –> 0:35:50.77 So that's of course more clinically relevant, right.

0:35:50.77 –> 0:35:52.56 Because we're starting to talk about

0:35:52.56 –> 0:35:56.83 an impact, excuse me, the endpoint that impacts patients.

0:35:56.83 –> 0:36:00.09 All right so that's more clinically relevant and moreover

0:36:00.09 –> 0:36:03.13 we'll expect to have a reasonable number of cases, right.

0:36:03.13 –> 0:36:06.41 By including more mild cases, for example,

0:36:06.41 –> 0:36:08.59 in this endpoint definition.

0:36:08.59 –> 0:36:10.36 But then on the other side of that coin

0:36:10.36 –> 0:36:12.28 is it really that clinically relevant

0:36:12.28 –> 0:36:14.54 if we're just talking about mild symptoms?

0:36:14.54 –> 0:36:16.01 We're talking about a disease where you get it

0:36:16.01 –> 0:36:17.93 and you end up with a little cough for a couple of weeks

0:36:17.93 –> 0:36:19.35 and that's it.

0:36:19.35 –> 0:36:22.02 So then maybe you suggest using severe COVID right.

0:36:22.02 –> 0:36:23.94 That's the most clinically relevant one.

0:36:23.94 –> 0:36:26.42 We want to be protecting the most vulnerable individuals

0:36:26.42 –> 0:36:28.48 so we should be quantifying how well our vaccines

0:36:28.48 –> 0:36:33.13 work towards preventing those most severe end points.

0:36:33.13 –> 0:36:34.99 And so most clinically relevant,

0:36:34.99 –> 0:36:36.93 and also there's sort of a long history

0:36:36.93 –> 0:36:40 of vaccine development where really we see the best VE

0:36:40 –> 0:36:42.89 against severe cases of disease.

0:36:42.89 –> 0:36:44.74 So that's really where we expect the vaccines

0:36:44.74 –> 0:36:47.15 to have the most impact is maybe we are not preventing

0:36:47.15 –> 0:36:50.58 you from being infected but we're lessening the symptoms

0:36:50.58 –> 0:36:52.41 once you become infected.

0:36:52.41 –> 0:36:54.88 So we're not totally blocking transmission

0:36:54.88 –> 0:36:56.73 but we're making a clinical impact on disease

0:36:56.73 –> 0:36:57.75 and that's sort of been seen

0:36:57.75 –> 0:37:00.28 for a number of vaccines in the past.

0:37:00.28 –> 0:37:01.67 The downside of this end point of course

0:37:01.67 –> 0:37:04.15 is that there's very few cases expected to be observed.

0:37:04.15 –> 0:37:05.35 So amongst all infections,

0:37:05.35 –> 0:37:07.42 only a fraction have any symptoms.

0:37:07.42 –> 0:37:08.64 Amongst those with any symptoms,

0:37:08.64 –> 0:37:10.33 only a fraction develops severe symptoms.

0:37:10.33 –> 0:37:13.04 So we're really whittling away the number of end points.

0:37:13.04 –> 0:37:14.5 So we need to do larger trials

0:37:14.5 –> 0:37:17.703 or have longer follow-up to evaluate this endpoint.

0:37:18.89 –> 0:37:21.39 And so in that paper, I'm sort of pressed for time

0:37:21.39 –> 0:37:23.7 so I won't spend too much time talking about this,

0:37:23.7 –> 0:37:26.28 we also proposed this burden of disease measure

0:37:26.28 –> 0:37:29.35 where you're sort of scoring these these outcomes, right?

0:37:29.35 –> 0:37:31.03 So maybe you would get a score of zero

0:37:31.03 –> 0:37:32.71 if you're an asymptomatic infection

0:37:32.71 –> 0:37:35.78 'cause it's really no burden on you as a patient, right?

0:37:35.78 –> 0:37:37.37 You don't have any symptoms.

0:37:37.37 –> 0:37:39.49 And then we're sort of assigning arbitrarily

0:37:39.49 –> 0:37:42.02 a score of one for non severe COVID so that's like

0:37:42.02 –> 0:37:44.61 mild cases of COVID and a score of two

0:37:44.61 –> 0:37:47.99 for severe cases of COVID and this end point actually

0:37:47.99 –> 0:37:50.68 has some nice operating characteristics we think,

0:37:50.68 –> 0:37:53.16 but of course it's subject to controversy, anytime you start

0:37:53.16 –> 0:37:57.37 talking about an ordinal scoring system, right,

0:37:57.37 –> 0:37:59.45 you start to raise questions about how you're assigning

0:37:59.45 –> 0:38:01.2 the burden of disease score, right?

0:38:01.2 –> 0:38:03.43 Why should severe cases be a two

0:38:03.43 –> 0:38:05.62 versus a three versus a five and so forth?

0:38:05.62 –> 0:38:07.46 So you can kind of get bogged down

0:38:07.46 –> 0:38:09.193 in some of the specifics of that.

0:38:10.22 –> 0:38:11.82 So what has FDA said about this?

0:38:11.82 –> 0:38:14.6 So FDA guidance documents states that either

0:38:14.6 –> 0:38:17.83 the COVID end point or SARS-CoV-2 infection

0:38:17.83 –> 0:38:19.31 is an acceptable primary endpoint

0:38:19.31 –> 0:38:22.18 and then somewhat ironically OWS has been telling companies

0:38:22.18 –> 0:38:23.95 that infection alone is not acceptable

0:38:23.95 –> 0:38:24.87 as a primary end point.

0:38:24.87 –> 0:38:27.59 So we had one company that was interested in including

0:38:27.59 –> 0:38:31.15 that as co-primary and for whatever reason we told them

0:38:31.15 –> 0:38:36.061 please don't do that, and then beyond that so COVID

0:38:36.061 –> 0:38:38.57 has sort of won out as the end point of choice.

0:38:38.57 –> 0:38:41.62 But beyond that FDA guidance states that companies should

0:38:41.62 –> 0:38:44.06 consider powering efficacy trials

0:38:44.06 –> 0:38:48.23 for the severe COVID endpoint as a co-primary or at least

0:38:48.23 –> 0:38:50.51 as a key secondary endpoint in the trial.

0:38:50.51 –> 0:38:53.69 And so so far only Janssen has taken them up on that offer

0:38:53.69 –> 0:38:55.8 of making severe COVID primary.

0:38:55.8 –> 0:38:58.01 And that's why, if you look at the number of individuals

0:38:58.01 –> 0:38:59.29 that are planning to enroll in their trial,

0:38:59.29 –> 0:39:02.53 it's twice as many as any of the other OWS trials.

0:39:02.53 –> 0:39:04.443 So like AstraZeneca is planning for 30,000,

0:39:04.443 –> 0:39:07.73 Janssen is planning for 60,000 in their trial.

0:39:07.73 –> 0:39:10.48 And that's the power, to see more cases of severe disease

0:39:10.48 –> 0:39:14.193 to be sufficiently powered to detect VE against that.

0:39:15.1 –> 0:39:17.337 So this is a controversial slide.

0:39:17.337 –> 0:39:20.33 Or this is virtual topic I found,

0:39:20.33 –> 0:39:22.48 again, something that clinical trials statisticians

0:39:22.48 –> 0:39:25.57 sort of take for granted is doing interim analyses, right?

0:39:25.57 –> 0:39:27.99 If the treatment is working and we have enough evidence

0:39:27.99 –> 0:39:29.43 to claim that a treatment is working,

0:39:29.43 –> 0:39:31.42 we'd like to stop that trial early

0:39:31.42 –> 0:39:32.99 to get that treatment to patients, right.

0:39:32.99 –> 0:39:34.83 One would think that that's true here

0:39:34.83 –> 0:39:36.34 and so many of these trials

0:39:36.34 –> 0:39:40.18 were designed with aggressive sort of interim looks, right?

0:39:40.18 –> 0:39:41.46 Because we're in the middle of the pandemic

0:39:41.46 –> 0:39:44.07 and we'd like to get a vaccine to individuals

0:39:44.07 –> 0:39:44.903 as quickly as possible.

0:39:44.903 –> 0:39:47.108 So I have a table, we won't go through it all here,

0:39:47.108 –> 0:39:50.37 just sort of the planned interim analysis

0:39:50.37 –> 0:39:52.01 for these different trials.

0:39:52.01 –> 0:39:55.71 I would say Pfizer seems to be the most aggressive so far.

0:39:55.71 –> 0:39:59.68 They have five interim looks or four interim looks

0:39:59.68 –> 0:40:01.77 and a final look at their data, right?

0:40:01.77 –> 0:40:03.34 So that's fairly aggressive.

0:40:03.34 –> 0:40:06.54 OWS again, the trials that we're running,

0:40:06.54 –> 0:40:08.85 we're really encouraging companies to be a bit

0:40:08.85 –> 0:40:10.83 more conservative in the approach to this

0:40:10.83 –> 0:40:12.74 and only maybe two or three

0:40:12.74 –> 0:40:14.29 and so you see what's been adopted

0:40:14.29 –> 0:40:17.11 by Moderna and AstraZeneca

0:40:17.11 –> 0:40:19.47 and so this was really a big point of contention

0:40:19.47 –> 0:40:22.27 I think when these protocols were made public is this idea

0:40:22.27 –> 0:40:25.39 that like, can you really know that a vaccine works

0:40:25.39 –> 0:40:27.41 based on 32 data points, right?

0:40:27.41 –> 0:40:30.37 We're talking about a vaccine that's going to be given

0:40:30.37 –> 0:40:31.89 to billions of people around

0:40:31.89 –> 0:40:33.28 the world based on these results

0:40:33.28 –> 0:40:34.72 and you're gonna do that based

0:40:34.72 –> 0:40:37.28 on the results in 32 individuals?

0:40:37.28 –> 0:40:39.72 And like, so I can stare at the math and say that like, yes,

0:40:39.72 –> 0:40:42.42 that appropriately controls type one error and so forth,

0:40:42.42 –> 0:40:44.78 but it still makes me just feel a little bit uncomfortable.

0:40:44.78 –> 0:40:47.5 There's a bit of dissonance between sort of my life

0:40:47.5 –> 0:40:50.21 as a statistician and just me being a human

0:40:50.21 –> 0:40:52.13 and saying 32 data points is probably not enough

0:40:52.13 –> 0:40:54.2 to decide to vaccinate billions of people.

0:40:54.2 –> 0:40:56.509 And so a lot of people I think sort of shared

0:40:56.509 –> 0:41:00.88 that viewpoint and in response FDA has now been sort of

0:41:00.88 –> 0:41:05.63 backpedaling in a way and asking companies to provide more

0:41:05.63 –> 0:41:10.02 data in order to grant an emergency authorization

0:41:10.02 –> 0:41:10.853 for their vaccine.

0:41:10.853 –> 0:41:14.49 So this EUA mechanism that FDA has of approving vaccines.

0:41:14.49 –> 0:41:16.73 And so in addition to an efficacy signal,

0:41:16.73 –> 0:41:19.84 now companies also are gonna be required, I think,

0:41:19.84 –> 0:41:22.65 and this is sort of still a moving target so this is maybe

0:41:22.65 –> 0:41:25.93 like data news at this point but I think prior to offering

0:41:25.93 –> 0:41:29.26 an EUA, FDA has now said that companies need to have 50%

0:41:29.26 –> 0:41:32.511 of participants complete at least two months of follow-up

0:41:32.511 –> 0:41:36.151 for safety signals and that you need to have at least

0:41:36.151 –> 0:41:38.56 six COVID cases in the oldest age group.

0:41:38.56 –> 0:41:40.82 Of course, that's an age group of particular interest

0:41:40.82 –> 0:41:43.72 in terms of severe cases and at least five cases

0:41:43.72 –> 0:41:45.4 of severe COVID in the placebo group.

0:41:45.4 –> 0:41:47.83 So they want to be able to see some data,

0:41:47.83 –> 0:41:50.09 even if you're not specifying severe COVID

0:41:50.09 –> 0:41:51.1 as a primary end point,

0:41:51.1 –> 0:41:52.8 they want to be able to see some data,

0:41:52.8 –> 0:41:54.5 some signal of efficacy against that

0:41:54.5 –> 0:41:55.913 in order to grant licensure.

0:41:56.77 –> 0:42:00.539 So I'll sort of, I won't go through this slide.

0:42:00.539 –> 0:42:01.96 It's just to say that like,

0:42:01.96 –> 0:42:03.98 sort of when Pfizer released their protocol,

0:42:03.98 –> 0:42:06.41 everyone was like, ooh a bayesian analysis

0:42:06.41 –> 0:42:08.76 and got very sort of skeptical, right?

0:42:08.76 –> 0:42:10.53 Because the Pfizer CEO has been out there

0:42:10.53 –> 0:42:12.51 sort of chest thumping and saying they're gonna have

0:42:12.51 –> 0:42:15.04 a vaccine before the election and so forth

0:42:15.04 –> 0:42:16.62 and then they came out with this bayesian design

0:42:16.62 –> 0:42:18.99 that was a little atypical and so everybody was asking

0:42:18.99 –> 0:42:21.21 the question, well, are they trying to hide something?

0:42:21.21 –> 0:42:22.67 So I sort of did a quick analysis

0:42:22.67 –> 0:42:25.12 and found that really it doesn't look that different

0:42:25.12 –> 0:42:28.08 than a classic kind of post hoc monitored design.

0:42:28.08 –> 0:42:29.55 And if you want to read more about that,

0:42:29.55 –> 0:42:32.919 I have some slides up on my GitHub about it.

0:42:32.919 –> 0:42:35.87 So let's see, I'm running low on time

0:42:35.87 –> 0:42:38.76 so I'm gonna skip over sort of the question

0:42:38.76 –> 0:42:40.83 of what happens if efficacy is declared early.

0:42:40.83 –> 0:42:43.33 So I have some reasons that we should be excited, right?

0:42:43.33 –> 0:42:45.537 If one of these trials stops earlier, I can get a vaccine.

0:42:45.537 –> 0:42:48.46 There's good data that the vaccine works

0:42:48.46 –> 0:42:49.79 and that's nice.

0:42:49.79 –> 0:42:52.31 I'd like to go back to something resembling normal

0:42:52.31 –> 0:42:53.75 as I'm sure you all would,

0:42:53.75 –> 0:42:55.62 but of course there's reasons to be concerned, right?

0:42:55.62 –> 0:42:58.34 If efficacy is declared early in particular,

0:42:58.34 –> 0:43:00.63 if that means that blinded follow-up

0:43:00.63 –> 0:43:01.84 in a study stops, right?

0:43:01.84 –> 0:43:02.91 Because that means we have no way

0:43:02.91 –> 0:43:05.18 to assess how durable the vaccine is.

0:43:05.18 –> 0:43:06.7 We won't be able to assess VE

0:43:06.7 –> 0:43:09.49 and key subgroups that we care about.

0:43:09.49 –> 0:43:11.13 We might not be able to assess VE

0:43:11.13 –> 0:43:13.39 formally against severe end points.

0:43:13.39 –> 0:43:15.26 So there's real sort of concerns

0:43:15.26 –> 0:43:16.94 about stopping these trials too early,

0:43:16.94 –> 0:43:18.21 and what the implications of that

0:43:18.21 –> 0:43:21.138 are both for evaluating the vaccine in question,

0:43:21.138 –> 0:43:23.04 but as well as how it impacts

0:43:23.04 –> 0:43:25.19 the other clinical trials that are ongoing.

0:43:26.12 –> 0:43:28.7 And of course in the current political climate,

0:43:28.7 –> 0:43:30.71 everybody's very concerned about the role

0:43:30.71 –> 0:43:33.04 political pressure might play in all of this.

0:43:33.04 –> 0:43:37.466 So yeah, so it's kind of a double-edged sword in some sense

0:43:37.466 –> 0:43:41.76 in terms of what happens if efficacy is declared early,

0:43:41.76 –> 0:43:43.19 but I want to save just a few minutes

0:43:43.19 –> 0:43:44.98 to talk about vaccine correlates 'cause I promised

0:43:44.98 –> 0:43:47.17 that I would show you some math and prove to you

0:43:47.17 –> 0:43:48.32 that I'm a real statistician.

0:43:48.32 –> 0:43:50.8 So let's do a little bit of that.

0:43:50.8 –> 0:43:52.52 So again, we're kind of shifting gears here.

0:43:52.52 –> 0:43:54.65 So that's the end of sort of talking about the primary

0:43:54.65 –> 0:43:56.29 analysis of these trials,

0:43:56.29 –> 0:43:58.38 what's gonna lead to their licensure.

0:43:58.38 –> 0:44:00.19 And the correlates of protection

0:44:00.19 –> 0:44:02.3 is sort of a key secondary analysis

0:44:02.3 –> 0:44:04.22 and so why is it so important

0:44:04.22 –> 0:44:07.33 that we're able to establish correlates of protection?

0:44:07.33 –> 0:44:08.51 Well, because it's gonna speed up

0:44:08.51 –> 0:44:11.64 the whole vaccine development process.

0:44:11.64 –> 0:44:14.21 So again, a correlative protection is really just,

0:44:14.21 –> 0:44:17.53 it's an immune response and really an assay

0:44:17.53 –> 0:44:20.15 to measure that immune response that's been validated

0:44:20.15 –> 0:44:22.71 to reliably predict vaccine efficacy.

0:44:22.71 –> 0:44:25.13 So why is that so important?

0:44:25.13 –> 0:44:27.75 Well, basically what we're hoping to achieve

0:44:27.75 –> 0:44:29.24 is the establishment of a surrogate

0:44:29.24 –> 0:44:32.02 endpoint for COVID disease right?

0:44:32.02 –> 0:44:34.35 So I've sort of mentioned the numbers that we're talking

0:44:34.35 –> 0:44:36.12 about in these phase three trials,

0:44:36.12 –> 0:44:39.64 enrolling 30,000 participants, 60,000 participants

0:44:39.64 –> 0:44:41.743 and ending up with one or two years of followup, right.

0:44:41.743 –> 0:44:44.13 Just to be able to answer the primary question, right.

0:44:44.13 –> 0:44:47.73 Does the vaccine prevent infection and/or disease?

0:44:47.73 –> 0:44:50.07 So that's a huge, expensive clinical trial.

0:44:50.07 –> 0:44:52.32 It takes a long time to get an answer

0:44:52.32 –> 0:44:56.08 and so it would be very nice if all we had to do right

0:44:56.08 –> 0:44:58.96 was give people the doses of vaccine that they need,

0:44:58.96 –> 0:45:02.18 wait two weeks and measure their immune response

0:45:02.18 –> 0:45:04.54 and understand does that vaccine work or not.

0:45:04.54 –> 0:45:07.385 That would be a much faster vaccine development process

0:45:07.385 –> 0:45:08.9 than where we're currently at

0:45:08.9 –> 0:45:11.13 in having to run these enormous phase three trials.

0:45:11.13 –> 0:45:14.46 So it's valuable for establishing a surrogate endpoint.

0:45:14.46 –> 0:45:17.48 It's also valuable for accelerating approval

0:45:17.48 –> 0:45:21.81 of vaccines that have been licensed in certain populations,

0:45:21.81 –> 0:45:22.643 but not others.

0:45:22.643 –> 0:45:25.1 For example, I mentioned that these phase three trials

0:45:25.1 –> 0:45:26.72 are mostly being conducted in adults.

0:45:26.72 –> 0:45:30 Well, what if we want to also obtain licensure for use

0:45:30 –> 0:45:31.87 of this vaccine in children?

0:45:31.87 –> 0:45:34.26 Well, if we had an established immune correlate

0:45:34.26 –> 0:45:35.093 we wouldn't have to do

0:45:35.093 –> 0:45:37.05 a large randomized trial in children.

0:45:37.05 –> 0:45:39.29 We could do it just a small immunogenicity study

0:45:39.29 –> 0:45:42.137 and use the correlates results to bridge the VE

0:45:42.137 –> 0:45:44.587 that we observed from the phase three trial.

0:45:44.587 –> 0:45:47.28 That's the immune response that we've observed

0:45:47.28 –> 0:45:49.26 in these children or pregnant women for example are

0:45:49.26 –> 0:45:51.21 another key population they're being

0:45:51.21 –> 0:45:53.42 excluded from these phase three trials

0:45:53.42 –> 0:45:55.44 but we'd like to understand if these vaccines

0:45:55.44 –> 0:45:58.65 are safe and effective in those women as well.

0:45:58.65 –> 0:46:01.13 So really this is one of the key goals

0:46:01.13 –> 0:46:04.9 of this whole OWS program and the key role

0:46:04.9 –> 0:46:07.47 that we're playing in the CoVPN is developing

0:46:08.322 –> 0:46:11.94 the sampling plan and the statistical analysis plan

0:46:11.94 –> 0:46:14.09 for the immune correlate studies

0:46:14.09 –> 0:46:16.62 and so it's just a little bit of the statistical issues

0:46:16.62 –> 0:46:20.14 that we're dealing with in these trials, right,

0:46:20.14 –> 0:46:22.14 is that sort of running assays

0:46:22.14 –> 0:46:26.21 so running these immuno assays on 30,000, 60,000 individuals

0:46:26.21 –> 0:46:29.9 takes a long time, it's expensive, and as it turns out,

0:46:29.9 –> 0:46:33.82 it's really overkill in terms of statistical power.

0:46:33.82 –> 0:46:35.31 So we can actually be a little bit more

0:46:35.31 –> 0:46:39.99 clever about how we design these correlate studies in order

0:46:39.99 –> 0:46:41.85 to get answers faster and more cheaply.

0:46:41.85 –> 0:46:45.07 So the way we do this is we use a case cohort design.

0:46:45.07 –> 0:46:46.69 So we're not gonna measure immune responses

0:46:46.69 –> 0:46:47.86 in all trial participants,

0:46:47.86 –> 0:46:49.8 we're gonna measure them in a sub cohort

0:46:49.8 –> 0:46:51.28 and that sub cohort will consist

0:46:51.28 –> 0:46:53.72 of a stratified random sub cohort.

0:46:53.72 –> 0:46:56.1 So we're gonna be sampling individuals randomly

0:46:56.1 –> 0:46:58.37 based on their baseline infection status.

0:46:58.37 –> 0:47:01.14 Were you infected with SARS-CoV-2 in the past?

0:47:01.14 –> 0:47:05.387 Based on your race, ethnicity, and based on age.

0:47:06.78 –> 0:47:08.76 And so based on that, we'll take a random draw

0:47:08.76 –> 0:47:12.133 of the trial population, about 1600 individuals,

0:47:13.16 –> 0:47:18.16 excuse me and everyone so I should mention right

0:47:18.93 –> 0:47:22 in the trial design everybody is having their blood drawn.

0:47:22 –> 0:47:23.69 And right now we're talking about whose blood

0:47:23.69 –> 0:47:26.5 are we gonna use to measure these immune responses?

0:47:26.5 –> 0:47:28.93 So we're gonna measure it in a random sample

0:47:28.93 –> 0:47:31.41 and then we're gonna wait until the trial is over

0:47:31.41 –> 0:47:34.87 or until one of these interim analysis concludes efficacy

0:47:34.87 –> 0:47:37.91 and we're gonna measure immune responses

0:47:37.91 –> 0:47:39.24 in all of the end points, right?

0:47:39.24 –> 0:47:41.89 Remember that like power in these analyses is drive

0:47:41.89 –> 0:47:45.62 by the individuals in which we observe endpoints.

0:47:45.62 –> 0:47:47.18 So we're gonna make sure we get immune responses

0:47:47.18 –> 0:47:49.31 in all the end point data, as in addition

0:47:49.31 –> 0:47:52.69 to this random sub cohort and it turns out that that's about

0:47:52.69 –> 0:47:56.92 as statistically efficient as running the immune assays

0:47:56.92 –> 0:47:58.89 on all 30,000 individuals in the trial.

0:47:58.89 –> 0:48:01.12 So this is this kind of classic case cohort design

0:48:01.12 –> 0:48:04 that Ross Prentice has been writing about for years

0:48:04 –> 0:48:06.16 that Norman Breslow did some sort of pioneering work

0:48:06.16 –> 0:48:10.51 on in the 2000s and I'll just talk a little bit about sort

0:48:10.51 –> 0:48:13.28 of how this complicates our life as statisticians

0:48:13.28 –> 0:48:16.04 and then maybe we'll leave a few minutes for questions.

0:48:16.04 –> 0:48:17.61 So here's the math, we made it.

0:48:17.61 –> 0:48:19.53 Well, the moment you've all been waiting for it

0:48:19.53 –> 0:48:20.88 to see some math.

0:48:20.88 –> 0:48:23.07 So just introducing, you know,

0:48:23.07 –> 0:48:26 why is this sampling design challenging

0:48:26 –> 0:48:28.74 from a perspective of generating estimators, right?

0:48:28.74 –> 0:48:31.16 Well, we can sort of immediately see that this isn't

0:48:31.16 –> 0:48:34.79 a totally random sample of the trial population, right?

0:48:34.79 –> 0:48:38.29 In particular we've over-sampled the individuals who end up

0:48:38.29 –> 0:48:42.15 getting diseased and it's fairly obvious

0:48:42.15 –> 0:48:44.9 that those individuals have potential to be very different

0:48:44.9 –> 0:48:47.2 than a randomly selected individual in the population.

0:48:47.2 –> 0:48:48.62 So we have a bias sub sample.

0:48:48.62 –> 0:48:51.95 So we need some statistical methodology to try to back out,

0:48:51.95 –> 0:48:53.52 you know, whatever this parameter is.

0:48:53.52 –> 0:48:56.15 We want to be estimating it in the whole trial population,

0:48:56.15 –> 0:48:58.56 not just in this biased sub samples.

0:48:58.56 –> 0:49:00.2 So how do we do that?

0:49:00.2 –> 0:49:02.1 So just a quick notation here,

0:49:02.1 –> 0:49:04.14 let's call W baseline covariates,

0:49:04.14 –> 0:49:06.83 A is a binary vaccine assignment,

0:49:06.83 –> 0:49:11.34 Y is your binary COVID endpoint for example

0:49:11.34 –> 0:49:13.36 and then we'll introduce this sort of indicators.

0:49:13.36 –> 0:49:17.57 Delta is one, if you're selected into this immune response

0:49:17.57 –> 0:49:20.05 sub cohort, either because you were a case,

0:49:20.05 –> 0:49:23.19 you were an end point or because you were randomly selected

0:49:23.19 –> 0:49:24.6 into the cohort.

0:49:24.6 –> 0:49:27.053 And then we'll call S your immune response.

0:49:27.89 –> 0:49:30.87 And then we'll just say, we'll represent this as Delta S,

0:49:30.87 –> 0:49:32.8 which just means we'll arbitrarily set everybody

0:49:32.8 –> 0:49:35.93 who's not in our sub cohorts immune response to be zero,

0:49:35.93 –> 0:49:38.17 that's arbitrary doesn't really matter.

0:49:38.17 –> 0:49:40.53 So let's talk about how estimation would happen.

0:49:40.53 –> 0:49:42.98 So let's pick a very simple parameter, right?

0:49:42.98 –> 0:49:45.11 Let's just say that we want to know what's the overall

0:49:45.11 –> 0:49:47.23 immune response in the whole population,

0:49:47.23 –> 0:49:49.63 not a particularly interesting parameter

0:49:49.63 –> 0:49:51.2 for actually measuring correlates,

0:49:51.2 –> 0:49:53.66 but just to motivate the types of statistical approaches

0:49:53.66 –> 0:49:56.09 that we use in these settings.

0:49:56.09 –> 0:49:58.92 So how can we control for the bias of the sampling design?

0:49:58.92 –> 0:50:00.73 Well, one of the most straightforward ways

0:50:00.73 –> 0:50:02.05 is to use the tried and true

0:50:02.05 –> 0:50:04.81 Horvitz-Thompson or IPTW estimator, right.

0:50:04.81 –> 0:50:07.83 Where we're just taking basically a sample mean

0:50:07.83 –> 0:50:11.2 but all our observations are sort of inverse weighted

0:50:11.2 –> 0:50:15.92 by their probability of being sampled into this sub cohort.

0:50:15.92 –> 0:50:17.997 And so that's, IPTW estimator if you're in causal inference,

0:50:17.997 –> 0:50:19.46 you're very familiar with this.

0:50:19.46 –> 0:50:20.71 If you're in survey sampling,

0:50:20.71 –> 0:50:22.03 very familiar with this.

0:50:22.03 –> 0:50:26.85 Very classical way of adjusting for this selection bias.

0:50:26.85 –> 0:50:28 It turns out that there's ways

0:50:28 –> 0:50:29.83 that we can be more efficient in doing this.

0:50:29.83 –> 0:50:33.086 We can use augmented estimators, AIPTW estimators.

0:50:33.086 –> 0:50:36.683 And the key idea there is that we take the IPTW estimator

0:50:36.683 –> 0:50:39.18 and we add a little bit of something to it

0:50:39.18 –> 0:50:40.85 and the key thing is that that little bit

0:50:40.85 –> 0:50:45.85 of something involves a regression of S the immune response

0:50:45.92 –> 0:50:49.97 onto the covariates that were used to sample individuals

0:50:49.97 –> 0:50:52.14 into the sub cohort.

0:50:52.14 –> 0:50:53.67 And so what's the intuition as

0:50:53.67 –> 0:50:55.7 to why this is more efficient?

0:50:55.7 –> 0:50:59.05 Well, you can imagine what if we had a perfect predictor

0:50:59.05 –> 0:51:01.16 of S measured at baseline, right?

0:51:01.16 –> 0:51:04.94 Then this regression here is essentially imputing

0:51:04.94 –> 0:51:06.36 the correct value of S

0:51:06.36 –> 0:51:08.86 for every single person in the population.

0:51:08.86 –> 0:51:11.48 So it's kind of like we're getting more data

0:51:11.48 –> 0:51:14.71 in some sense, and the nice thing about

0:51:14.71 –> 0:51:16.58 these approaches, these AIPTW approaches

0:51:16.58 –> 0:51:18.44 is that they're double robust and so again,

0:51:18.44 –> 0:51:21.1 if you work in causal inference a very familiar idea,

0:51:21.1 –> 0:51:22.63 and it turns out because we know

0:51:22.63 –> 0:51:25 the sampling probability by design,

0:51:25 –> 0:51:28.23 this regression doesn't have to be consistently estimated

0:51:28.23 –> 0:51:29.84 in order to obtain a consistent estimate

0:51:29.84 –> 0:51:30.73 of the parameter measures.

0:51:30.73 –> 0:51:32.96 So it's this really nice sort of double robustness property

0:51:32.96 –> 0:51:34.93 that says, yeah, you might be turned off

0:51:34.93 –> 0:51:36.11 from this augmented estimator

0:51:36.11 –> 0:51:37.74 because you have to do a little bit of extra work,

0:51:37.74 –> 0:51:40.3 you have to fit a regression model say,

0:51:40.3 –> 0:51:41.9 and maybe you're worried about missspecifying

0:51:41.9 –> 0:51:44.22 that regression well it turns out that because the sampling

0:51:44.22 –> 0:51:45.8 probabilities are known by design,

0:51:45.8 –> 0:51:47.43 you don't have to concern yourself with that.

0:51:47.43 –> 0:51:50.45 So it turns out you can use any old regression estimator

0:51:50.45 –> 0:51:52.54 here and still end up with a consistent estimate

0:51:52.54 –> 0:51:54.24 of the parameter of interest.

0:51:54.24 –> 0:51:55.29 And so we're applying this

0:51:55.29 –> 0:51:57.1 to much more interesting parameters.

0:51:57.1 –> 0:51:58.52 So we had a paper come out recently

0:51:58.52 –> 0:52:00.92 in biometrics that's linked here

0:52:00.92 –> 0:52:03.21 where we're starting to study a sort of causal inference

0:52:03.21 –> 0:52:05.65 flavored parameters in this context,

0:52:05.65 –> 0:52:07.77 things that we can really use to pin down,

0:52:07.77 –> 0:52:10.082 you know, mechanisms of these vaccines working.

0:52:10.082 –> 0:52:12.626 So, in this case, we're studying sort of the effect

0:52:12.626 –> 0:52:16.01 of a stochastic intervention, we call it.

0:52:16.01 –> 0:52:17.98 So it's sort of saying what would happen

0:52:17.98 –> 0:52:19.83 if we took everybody's immune response,

0:52:19.83 –> 0:52:22.42 this particular immune response that we observed,

0:52:22.42 –> 0:52:24.52 and we shifted it up just a little bit

0:52:24.52 –> 0:52:26.47 or we shifted it down just a little bit.

0:52:26.47 –> 0:52:29.58 How would that impact the risk of disease amongst

0:52:29.58 –> 0:52:30.413 the vaccinated individuals?

0:52:30.413 –> 0:52:33.77 So that's what this big, gnarly parameter is right here.

0:52:33.77 –> 0:52:35.24 And so you ended up looking at a plot

0:52:35.24 –> 0:52:36.11 that's kind of like this.

0:52:36.11 –> 0:52:38.54 So this is from an HIV vaccine trial.

0:52:38.54 –> 0:52:41.77 So at zero we're saying that's just the observed risk

0:52:41.77 –> 0:52:44.16 of the trial and as we move left we're saying,

0:52:44.16 –> 0:52:47.307 what would the risk be if we decreased your immune response?

0:52:47.307 –> 0:52:48.81 And so we can see in this example,

0:52:48.81 –> 0:52:51.77 we found that the risk would be increasing, right.

0:52:51.77 –> 0:52:53.36 And then if we're moving to the right

0:52:53.36 –> 0:52:56.587 is what would happen if we increase your immune response.

0:52:56.587 –> 0:52:58.53 And so we're kind of getting at something

0:52:58.53 –> 0:53:02.67 that's like a controlled effects mediation type parameter

0:53:02.67 –> 0:53:06.21 with this approach and so we're working out some

0:53:06.21 –> 0:53:10.37 of the details of the correlates plan currently

0:53:10.37 –> 0:53:11.46 and so when that's done

0:53:11.46 –> 0:53:13.07 we'll have it available for public comment.

0:53:13.07 –> 0:53:14.49 And again, we're academics, right?

0:53:14.49 –> 0:53:16.35 So we'll do it all open science.

0:53:16.35 –> 0:53:18.27 And then I'll just say like two words of conclusion

0:53:18.27 –> 0:53:20.69 and I'll shut up and leave some time for questions.

0:53:20.69 –> 0:53:22.97 So there's been a big concern

0:53:22.97 –> 0:53:26 in the current political climate that we're gonna sneak

0:53:26 –> 0:53:28.113 something through, that something's gonna be approved

0:53:28.113 –> 0:53:32.018 without sort of the standard amount of evidence

0:53:32.018 –> 0:53:33.113 that would be required, right.

0:53:33.113 –> 0:53:36.01 That there's political interference at the FDA

0:53:36.01 –> 0:53:38.56 and from where I sit, you know,

0:53:38.56 –> 0:53:40.52 I can say that the science behind the vaccine

0:53:40.52 –> 0:53:43.059 development program for COVID is extremely rigorous.

0:53:43.059 –> 0:53:45.9 These are exactly the type of people who you would want

0:53:45.9 –> 0:53:47.969 in charge of this decision making process

0:53:47.969 –> 0:53:51.27 and the type of people that will raise red flags

0:53:51.27 –> 0:53:54.19 as soon as sort of the process goes off the rails.

0:53:54.19 –> 0:53:56.87 So right now I feel good about where things stand.

0:53:56.87 –> 0:54:00.376 Of course, I watch presidential debates and hear, you know,

0:54:00.376 –> 0:54:03.62 garbage science coming out and I get a little bit concerned,

0:54:03.62 –> 0:54:05.01 but from where I sit right now,

0:54:05.01 –> 0:54:07.04 everything's looking pretty good.

0:54:07.04 –> 0:54:09.075 So overall, I'd say that the increased transparency

0:54:09.075 –> 0:54:10.96 by releasing these protocols

0:54:10.96 –> 0:54:13.49 has been good for scientists and consumers.

0:54:13.49 –> 0:54:15.11 We want to bring vaccines to market,

0:54:15.11 –> 0:54:16.91 but we also want people to trust those vaccine

0:54:16.91 –> 0:54:20.48 so increasing transparency in whatever way we can is great.

0:54:20.48 –> 0:54:23.05 And then finally, the final point is that a lot of these

0:54:23.05 –> 0:54:24.04 issues that I've talked about,

0:54:24.04 –> 0:54:25.58 how do we do interim monitoring, right?

0:54:25.58 –> 0:54:28.03 What's the right end point to be studying?

0:54:28.03 –> 0:54:29.59 What's the right S demand, right?

0:54:29.59 –> 0:54:31.58 These are really hard decisions

0:54:31.58 –> 0:54:34.23 and there are no right answers.

0:54:34.23 –> 0:54:36.65 And so one of the things that's been a little bit

0:54:36.65 –> 0:54:39.61 disconcerting or disheartening to me

0:54:39.61 –> 0:54:42.53 is the extent to which in the pandemic era,

0:54:42.53 –> 0:54:45.86 academic debates have been made very much public

0:54:45.86 –> 0:54:49.02 and I'm not against academic debates.

0:54:49.02 –> 0:54:52.08 It's just that most individuals aren't used to seeing them.

0:54:52.08 –> 0:54:55.33 And so what I'm worried is happening is that people

0:54:55.33 –> 0:54:59.76 see high profile academics debating these challenging

0:54:59.76 –> 0:55:01.87 problems where there's no real right answer.

0:55:01.87 –> 0:55:03.39 And they're saying, well, these guys don't know

0:55:03.39 –> 0:55:04.85 what they're talking about.

0:55:04.85 –> 0:55:07.81 So I think as academics and public health professionals

0:55:07.81 –> 0:55:09.92 in this pandemic, one thing that we can do

0:55:09.92 –> 0:55:12.344 is just to be very careful in how we're presenting,

0:55:12.344 –> 0:55:15.06 you know, the science that we're doing

0:55:15.06 –> 0:55:16.89 and acknowledge when there's not a right answer,

0:55:16.89 –> 0:55:18.59 that you're presenting your opinion.

0:55:18.59 –> 0:55:20.85 And that there is some validity, right?

0:55:20.85 –> 0:55:23.42 That this is very gray, unfortunately,

0:55:23.42 –> 0:55:25.26 that there's nothing black and white here.

0:55:25.26 –> 0:55:27.64 So maybe that's a controversial statement to end on,

0:55:27.64 –> 0:55:29.94 but I'll end there and then thanks again to Fan

0:55:29.94 –> 0:55:31.527 for giving me the opportunity to talk

0:55:31.527 –> 0:55:34.84 and I'm happy to take questions as there's time.

0:55:34.84 –> 0:55:36.43 I don't have anything scheduled after this,

0:55:36.43 –> 0:55:39.2 so I can stay a few minutes over as would be helpful.

0:55:39.2 –> 0:55:40.183 So thanks again.

0:55:41.386 –> 0:55:43.73 - [Fan] Thank you David for this very nice talk.

0:55:43.73 –> 0:55:46.46 I think we do have three to four minutes for questions

0:55:47.383 –> 0:55:50.423 from the audience, if there's any.

0:55:53.89 –> 0:55:55.39 - [Woman] Hi David, I have a question

0:55:55.39 –> 0:56:00.1 'cause right now for COVID situation and because of the time

0:56:00.1 –> 0:56:03.72 and the faster progress of the disease

0:56:03.72 –> 0:56:07.87 and it's a hard to keep the standard method,

0:56:07.87 –> 0:56:12.87 but do you have other proofed vaccine for other disease

0:56:13.89 –> 0:56:18.89 and have a quick trial have a similar way as COVID

0:56:19.45 –> 0:56:23.59 and apply the method you're using right now

0:56:23.59 –> 0:56:26.91 and we have standard results already

0:56:26.91 –> 0:56:31.84 and then compare to see how good the current method is.

0:56:31.84 –> 0:56:33.533 So that's my question.

0:56:35.11 –> 0:56:37.217 - [David] Yeah it's an interesting question.

0:56:37.217 –> 0:56:39.32 So let me try to restate, so you're saying,

0:56:39.32 –> 0:56:42.09 are there any lessons from vaccine development

0:56:42.09 –> 0:56:44.136 that we can try to draw from here

0:56:44.136 –> 0:56:47.59 to evaluate our methodology, whether it work?

0:56:47.59 –> 0:56:50.933 - [Woman] Yes, from other vaccines.

0:56:51.84 –> 0:56:54.92 - [David] So I guess what I would say is that at this stage,

0:56:54.92 –> 0:56:58.28 in phase three vaccines, these phase three trials

0:56:58.28 –> 0:56:59.82 look completely normal.

0:56:59.82 –> 0:57:02.68 So I would say the process of getting to the phase three

0:57:02.68 –> 0:57:04.92 looked very different and much more accelerated

0:57:04.92 –> 0:57:07.17 in terms of kind of squashing together

0:57:07.17 –> 0:57:11.3 phase one and phase two in terms of the manufacturing,

0:57:11.3 –> 0:57:13.41 but in terms of what's happening in a phase three trial,

0:57:13.41 –> 0:57:14.76 this is probably the phase three trial

0:57:14.76 –> 0:57:18.22 that would be done outside of the setting of a pandemic.

0:57:18.22 –> 0:57:20.22 Maybe the interim analysis would be a little bit

0:57:20.22 –> 0:57:23.39 less aggressive for some of these companies, but really,

0:57:23.39 –> 0:57:26.614 I think the approaches that the companies are taking

0:57:26.614 –> 0:57:30.903 would be fairly standard even in any other vaccine context.

0:57:34.831 –> 0:57:36.842 - -Woman] Yeah. I mean, even though

0:57:36.842 –> 0:57:39.913 for the established vaccine,

0:57:40.82 –> 0:57:43.26 there could be some field trial

0:57:43.26 –> 0:57:47.15 and that they also went through a phase three,

0:57:47.15 –> 0:57:50.54 but you can do the similar thing to enhance,

0:57:50.54 –> 0:57:55 to see whether it is possible to pass the current protocol

0:57:56.512 –> 0:57:59.473 and become some sort of false positive.

0:58:02.35 –> 0:58:05.543 - [David] Yeah and, you know, I think speaking,

0:58:07.93 –> 0:58:09.32 I mean, speaking of failed vaccines,

0:58:09.32 –> 0:58:11.497 as someone who works in HIV vaccines,

0:58:11.497 –> 0:58:14.7 we're very familiar with failure and learning from that.

0:58:14.7 –> 0:58:17.497 So again, I think the people who are running these trials

0:58:17.497 –> 0:58:20.13 are sort of the right people in terms of looking out

0:58:20.13 –> 0:58:22.43 for these false positive signals and so forth.

0:58:24.132 –> 0:58:25.132 - [Woman] Thank you.

0:58:26.513 –> 0:58:29.58 - [Fan] So I think we are just about the time

0:58:29.58 –> 0:58:32.04 and I'm sure that David is happy

0:58:32.04 –> 0:58:35.03 to take your questions afterwards by email.

0:58:35.03 –> 0:58:37.15 So I'll thank David more time.

0:58:37.15 –> 0:58:39.01 Again, thank you for sharing with us

0:58:39.01 –> 0:58:41.223 and we'll see everyone again next week.

0:58:43.07 –> 0:58:44.063 - [David] Thanks everybody.