Twitter Thread by ■ Dr Grippo ■

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@Grippo77

@PaoloWalnuts I looked into this as I was very surprised and thought it could be quite dangerous to go against the trial design.

I learnt a lot while i was doing it! There are a lot of misunderstandings and quite a few counterintuitive bits as well.

Thread...

@pcmac41 @PaoloWalnuts There's some obvious stuff like the fact that the JCVI is a longstanding body with a lot of very bright folks on it. Also, again stating the obvious, immunology and immune responses are really complex.

I've worked on a mAb and i will happily admit i didn't get the details! 1/

@pcmac41 @PaoloWalnuts To digress a little, i think AZ have serendipitously learnt lots about adenovirus vaccines through the seeming unplanned hiccups in their study. This is all brand new tech and it wasn't entirely obvious beforehand that small initial dose and long interval would be good. 2/

@pcmac41 @PaoloWalnuts It makes sense afterwards (for an adenovirus vx) and it also confirms why longer time between doses can be good. You let the vx get all the way through "teaching the body how to respond a little bit, and once it's developed its response it's way more efficient with the booster 3/

@pcmac41 @PaoloWalnuts Which begs a critical question that really bothered me: why did pfizer go with a 21dy regime? We have to trust what they say don't we? 4/

@pcmac41 @PaoloWalnuts Well... it's complicated.

I know how limited pfizer are in what they can claim. If they don't have data to prove something they can't claim it, even if it *really* is obvious. They have data on 21 days so they either stay quiet or they say the data support 21dy interval. 5/

@pcmac41 @PaoloWalnuts That's basically the law on how you can market any drug, and companies have rightly got into big trouble in the past for promoting use of medicines in ways they don't have data to support. 6/

@pcmac41 @PaoloWalnuts Key thing here is that an absence of proof that something works is just that. It's NOT proof that something won't work.

So, why choose 21 days? 7/

@pcmac41 @PaoloWalnuts A lot of the time spent developing drugs is in phase 2a where you try to find an effective dose and an effective dosing regime. Where you have a single dose that's easy: run three groups of pts - placebo, dose 1, dose 2. Which is best and do you have dose dependent effects? 8/

@pcmac41 @PaoloWalnuts But this is a pandemic and we need this vx yesterday. We don't have 2-3 years to get this perfect as there'll be lots of dead people this vx can save. (Also being first to market is a good thing for the company).

21 days should long enough to work but quick enough to get data 9/

@pcmac41 @PaoloWalnuts So in many ways it kind of is that simple, and the theory behind a longer duration is sound.

I'll try to hunt out the threads i came across. 10/

@pcmac41 @PaoloWalnuts One thing did strike me though. A lot of the people criticising this plan were bright folks: Drs, biologists, medics, even the odd chemist. Generally folks who do believe in science ahs in the regulators. What gives? 11/

@pcmac41 @PaoloWalnuts Well, partly, it's folks bright enough to be dangerous but who are not experts in the complexities of immunology (hello! ■).

I also think it's been poorly communicated though. I understand why - in many ways JVCI, SAGE, MHRA et al have a lot to worry about right now! 12/

@pcmac41 @PaoloWalnuts But it's also something that sounds initially odd, that cobras some bright folks and is really quite scary for those who are directly affected. It's horrible and frightening to be told your appt is being delayed. Better communication would be good. 13/

@pcmac41 @PaoloWalnuts Also, the rationale is excellent. If i have 20 doses and 20 people i can give all of them 85%* protection or half of them 95% protection.

Clearly, in this case, giving everybody 1 dose will provide much more protecting and save very many lives.

*I'm coming on to this... 14/

@pcmac41 @PaoloWalnuts The pfizer data clearly show that the vx is giving excellent protection after 20 days. But wait? It's only 50% effective after 20 days? Right?

15/

@pcmac41 @PaoloWalnuts Wrong.

The numbers are skewed by all the pts who were infected before they were given the vx, or in the 7-14 days after it was administered. The fact that those folks get covid doesn't tell us how effective the vx is (just how long it takes to start working). So? 16/

@pcmac41 @PaoloWalnuts So we ignore them when working out how effective it is. And when we do that we can see that the first dose prevents about 85% of the infections that are seen in the placebo group.

We don't need to worry about the vaccine being effective after 1 dose. It is, stunningly so. 17/

@pcmac41 @PaoloWalnuts What we don't know is how quickly the response to the first dose will fade. But the intervals only increased to 12 weeks, not 12 months and as i said earlier there's reason to imagine that this may well be more effective for similar reasons to why it works for the AZ/ox vx 18/

@pcmac41 @PaoloWalnuts Enough now. I'll try to find the threads and the tweeters who deserve to be followed in this and link them below. Fin.

@pcmac41 @PaoloWalnuts It was a conversation with @ChrisMcQuilla13 and @chemistrykaren got me thinking twice about my initial instinct that this was the wrong thing to do. Chris also made a summary point that i think is bang on the money:

https://t.co/5nw32LPiEk

> What it suggests to me is that the projections for January and February must be properly frightening.
>
> — Chris McQuillan (@ChrisMcQuilla13) January 1, 2021

@pcmac41 @PaoloWalnuts @ChrisMcQuilla13 @chemistrykaren That introduced me to @sandyddouglas with this fascinating thread

https://t.co/WkD6pFZVbz

@Sandyddouglas

> This issue is, appropriately, contentious. As a vaccinologist - & citizen & relative of people in at-risk groups - I fully support the UK decision to increase dose intervals of both our Ox/AZ product and the Pfizer product. I'd happily receive either with a >8w gap. Here's why \U0001f9f5 https://t.co/PZaxgGJUj4
>
> — Sandy Douglas (@sandyddouglas) January 1, 2021

@pcmac41 @PaoloWalnuts @ChrisMcQuilla13 @chemistrykaren @sandyddouglas Later I also came across this thread where @petermbenglish (via @trishgreenhalgh) gave me a lightbulb moment about why pfizer chose 21 days

https://t.co/U3OEnGOrpw

Like me, \u2066@petermbenglish\u2069 changed his mind about the one v two vaccine dose controversy. He blogs why here. https://t.co/W8I5cm7LAk

— Trisha Greenhalgh \U0001f637 #RejoinEU (@trishgreenhalgh) January 2, 2021