

Twitter Thread by Sandy Douglas

Sandy Douglas

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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 ■

Short cut to JCVI rationale behind extending interval between doses of #covidvaccine (thanks @mgtmccartney)

Note efficacy is "calculated" rather than proven at this stage. <https://t.co/EbZWcJYkFt>

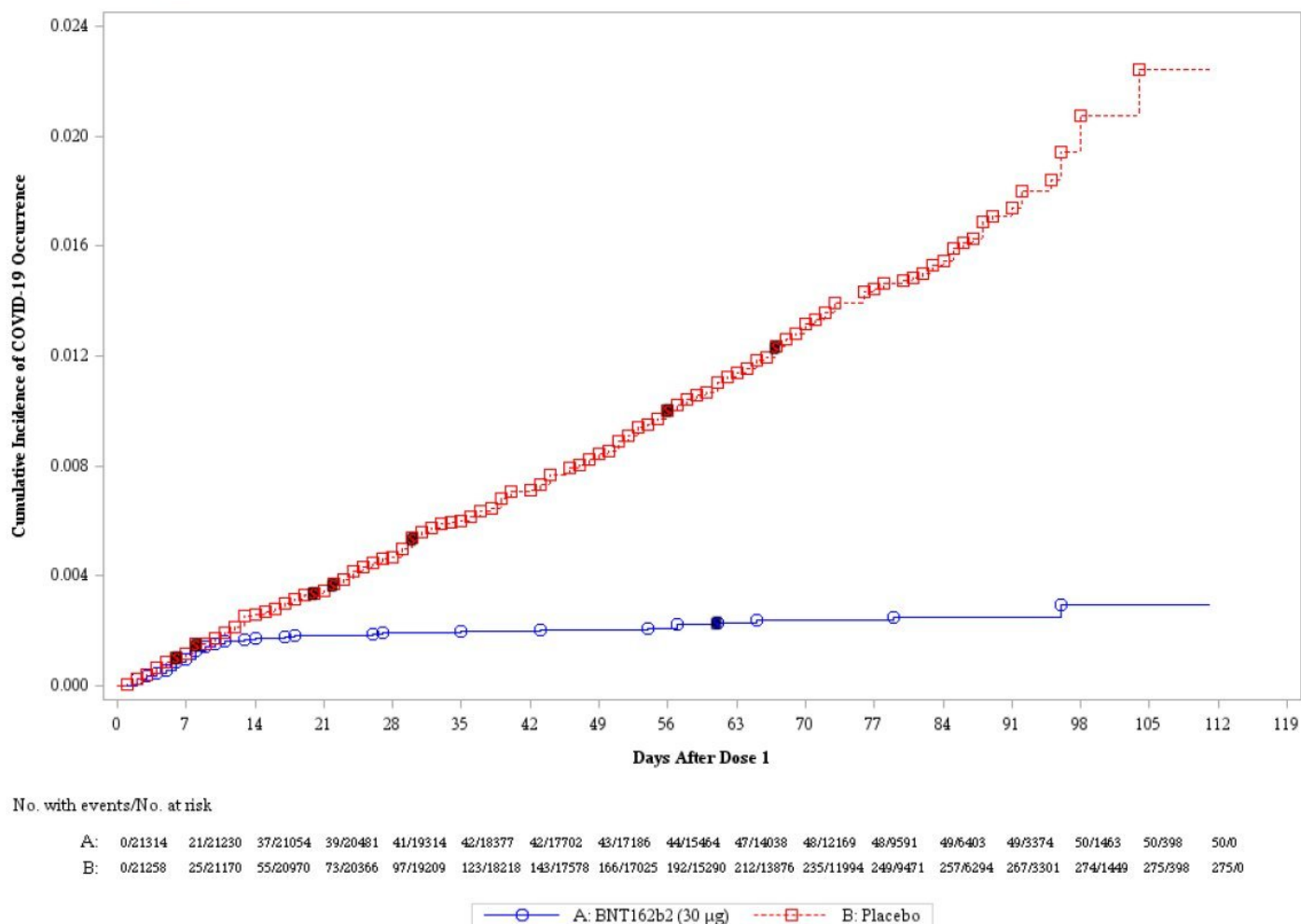
— Dr Mark Porter (@drmarkporter) January 1, 2021

For the Ox/AZ vaccine, it's fairly simple. The trial demonstrated efficacy at a range of dose intervals. Antibody responses after the boost were significantly stronger with longer intervals - see table 3.

<https://t.co/10KPvahJ64>

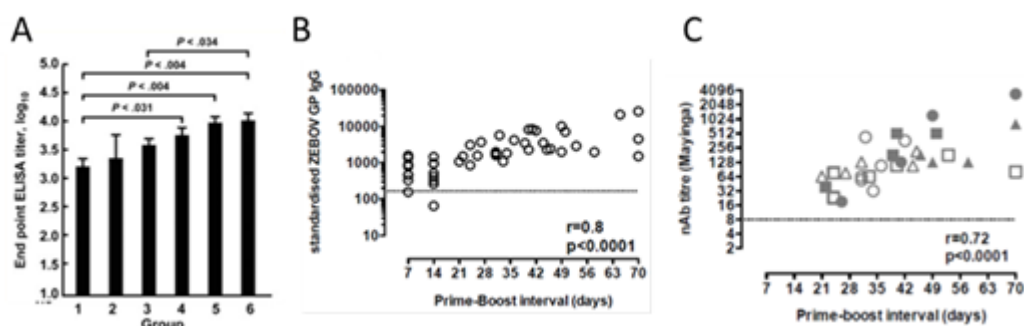
(so in response to @drmarkporter's point, higher immune responses with a longer interval is proven & now public. I haven't seen a similar analysis for efficacy against disease but the data exists and I suspect the regulators & JCVI committee have)

For Pfizer, there isn't direct evidence of efficacy with a >3wk interval. But as widely publicised, efficacy in the period from 14 days after first dose to 21 days is high.



Can we extrapolate from this to a longer interval? It's a judgment call. On one hand is evidence-based medicine's scepticism of anything not directly proven 'beyond reasonable doubt' in an RCT; on the other is a 'balance of probabilities' approach based upon the biology.

Based upon the biology, I'd eat my hat if the Pfizer vaccine is substantially less effective with a longer dose interval. Most vaccines induce stronger immune responses with longer intervals. A couple of examples below. There are more.



A is from Ledgerwood et al., *J Infect Dis*, 2013. 208(3): p. 418-22.

This was a Phase I trial of DNA prime – inactivated vaccine boost flu regimes. Graph shows ELISA data 14 days post-boost. Group 1 received licensed inactivated vaccine prime-boost. Groups 2-6 had DNA prime – inactivated vaccine boost intervals of 4, 8, 12, 16, 24 weeks.

B & C are from Ewer, K., et al., *N Engl J Med*, 2016. 374(17): p. 1635-46

This was an Ebola vaccine study, using varying doses and intervals of an adenovirus prime and another viral vector (MVA) as the boost.

Regimes like the Ox/AZ use the same adenoviral vector to prime & boost so face 'anti-vector immunity' (immunity from the first dose to the viral 'postman' which must deliver the spike protein 'message' for the boost). This favours longer intervals specifically for Ad/Ad but...

...the above shows that longer intervals are better for regimes with different viral vectors, DNA priming, inactivated virus boosting - this isn't just an adeno effect. It's v rare for a 3wk interval to give stronger responses than 8+ wks (I can't think of examples, can you?)

Mechanistically, at 3w, the immune response to prime isn't complete- it hasn't yet produced all the memory B cells which give the best response to the boost. Once they are made, the memory cells last years! They won't forget how to respond to a boost in a few months.

I appreciate mechanistic arguments often prove to be wrong, and RCT evidence with Pfizer at longer intervals should definitely be produced ASAP... but as [@zeynep](#) has written in an excellent article today:
<https://t.co/WrNVW5jRaW>

We've had a year to learn—about the importance of early action, of acting decisively even in the face of uncertainty, of not confusing absence of evidence with evidence of absence. A year to learn to aim not for perfection in knowledge but for maximal impact even while considering the trade-offs. And most important, a year to learn to not wait when faced with threats with exponential dynamics but to act as early and as decisively as we can—and to adjust and tamper later, if warranted.

There is a good debate:

[@Bob_Wachter](#) has written thoughtfully <https://t.co/wZgvN937DV>

[@trishgreenhalgh](#) [@EricTopol](#) [@nataliexdean](#) have all argued the other way from me - would welcome their thoughts on the above ■

U.S. is now considering idea of a single vaccination shot, delaying shot #2 until months later. Last wk, I thought that was a bad idea \u2013 the trials that found 95% efficacy were 2 shots; why add extra complexity & a new curveball. But facts on the ground demand a rethink. (1/7)

— Bob Wachter ([@Bob_Wachter](#)) [December 31, 2020](#)

I haven't yet seen a vaccine immunologist who has personally done experiments giving vaccines at different intervals and who is concerned about the longer interval... but I look forward to hearing that view too...