Twitter Thread by Sandy Douglas

Sandy Douglas
@sandyddouglas

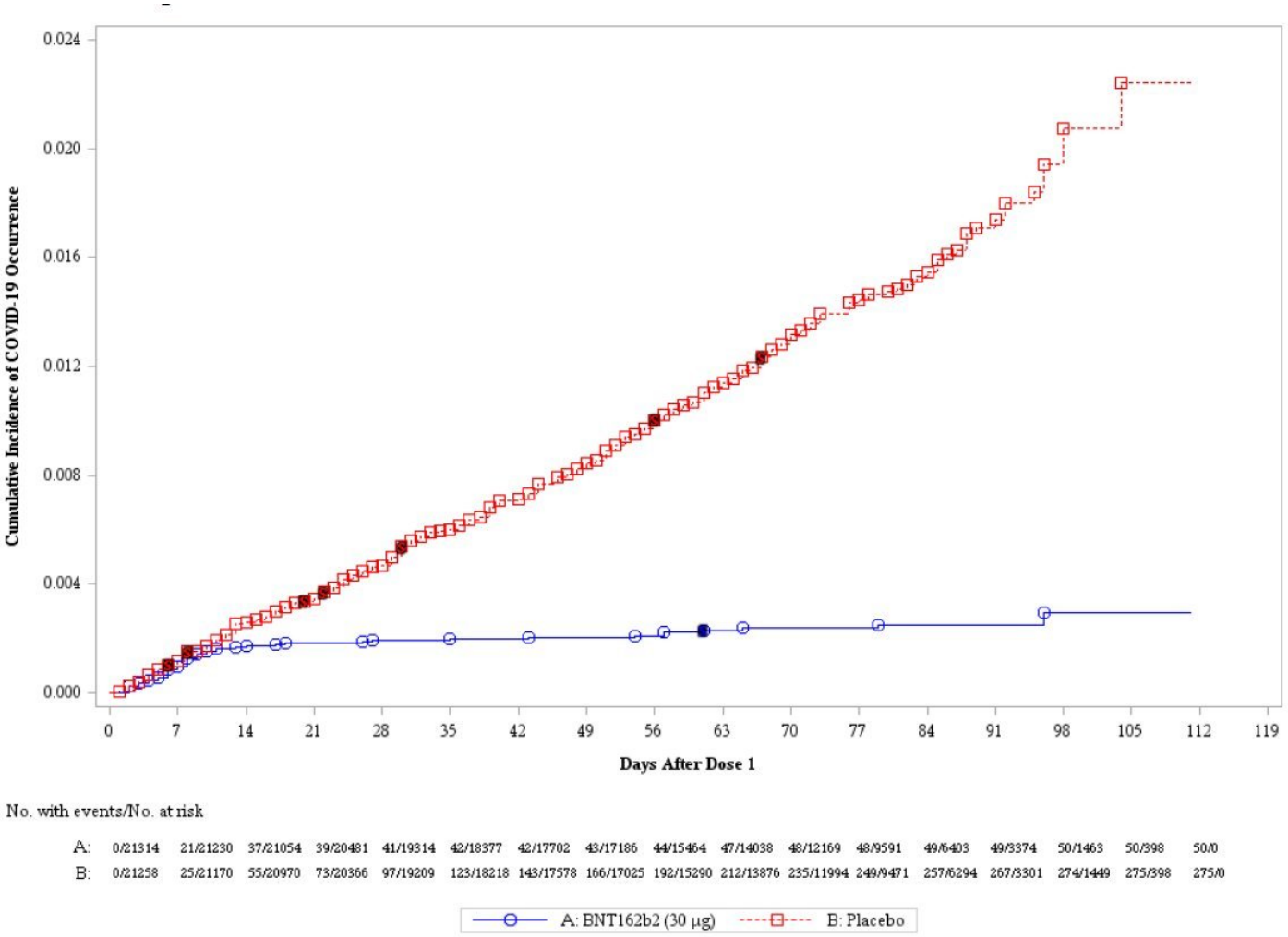
This issue is, appropriately, contentious. As a vaccinologist - & citizen & relative of people in at-risk groups - I fully support the UK decision to increase dose intervals of both our Ox/AZ product and the Pfizer product. I'd happily receive either with a >8w gap. Here's why ■

> 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

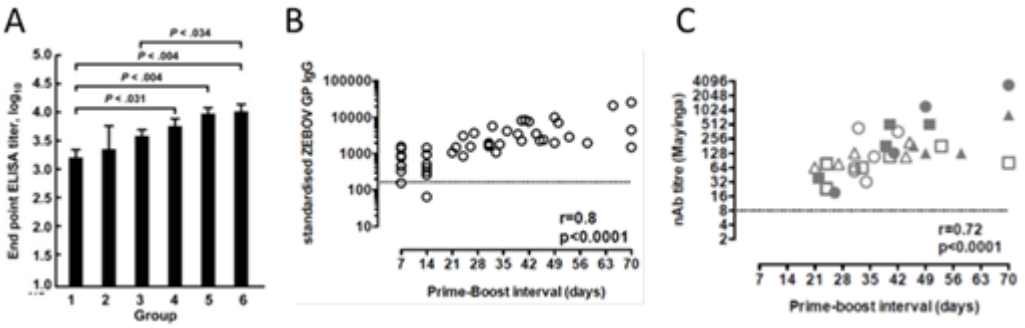
(so in response to @drmarkporter's point, higher immune responses with a longer interval is proven & now public. I haven't seen a similar analysis for efficacy against disease but the data exists and I suspect the regulators & JCVI committee have)

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.

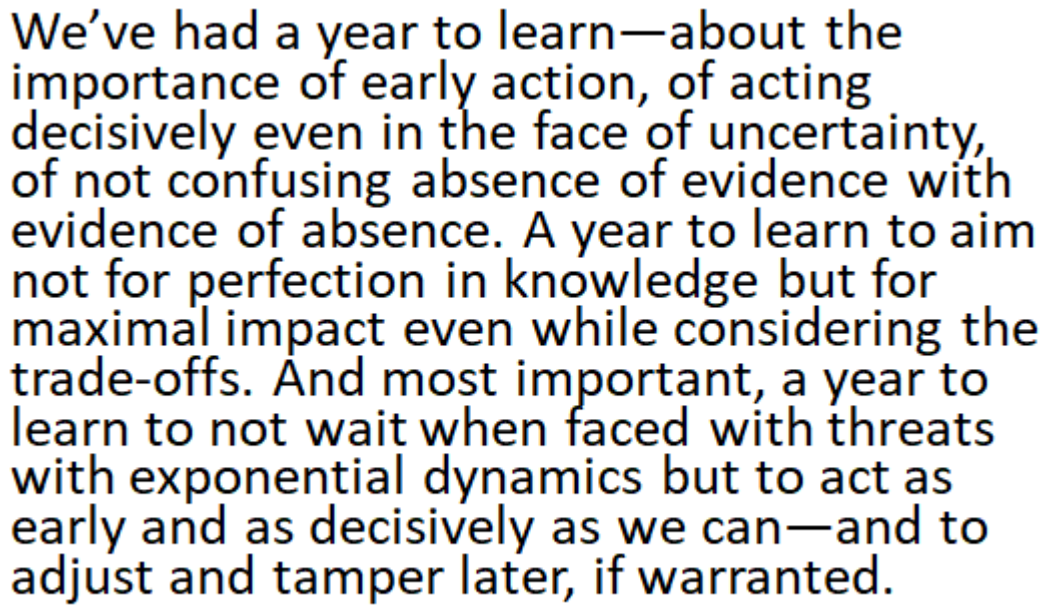
B & C are from Ewer, K., et al., N Engl J Med, 2016. 374(17): p. 1635-46
This was an Ebola vaccine study, using varying doses and intervals of an adenovirus prime and another viral vector (MVA) as the boost.

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 delivers 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



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...