# Twitter Thread by Rajeev Venkayya MD

**Rajeev Venkayya MD**
@rvenkayya

## THREAD

## There’s much debate around the UK's recommended use of the AZ vaccine with a two-dose schedule and flexible timing of second dose. Some thoughts on the AZ recommendation (not Pfizer) based on available data with refs to some excellent threads.

> 1. It's a real pity the UK drug regulator, MHRA, doesn't hold public advisory committee meetings to assess #Covid vaccines, in the way @US_FDA does. Would have been fascinating to listen to a detailed analysis of the AstraZeneca-Oxford vaccine's emergency use application.
> Thread
>
> — Helen Branswell (@HelenBranswell) December 30, 2020

UK’s MHRA and JCVI are highly-experienced in vaccine assessments and recommendations, and they've surely weighed the benefits & risks of this recommendation carefully. That said, it would be good to see all the data underpinning their recommendation. 2/
https://t.co/NRcHbYxRIw

> AZ\u2019s new claim is that they achieve 95% efficacy by increasing dose interval to 3 months. I see no efficacy data to support it in the new UK approval but it appears true that immunogenicity is much higher with that regimen (antibody titer nearly 3x higher than short interval) pic.twitter.com/ZtxSPjHUot
>
> — Ed MD (@notdred) December 30, 2020

In general, vaccines should be taken on a schedule tested in an efficacy trial. But it wasn’t possible to conduct the typical dose and schedule optimization prior to these Ph3 trials, and those trials provided valuable data to inform these recommendations. 3/

The UK recommends a two-dose schedule, with the second dose between 4-12 weeks. This *is not* a single dose schedule. Given the data provided, and in the setting of limited supply, overstretched hospitals, and emergence of a more transmissible variant, this seems justifiable. 4/

The UK has important data on the AZ Vx that wasn’t available for Pfizer & Moderna at FDA's VRBPAC, including:
* single-dose efficacy through 4+ months; and

* single-dose immunogenicity (12+ weeks). 5/
https://t.co/vtbviE9VEx

> I've been seeing a lot of discussion around the dosage gaps recommended by government for the Astra/Oxford & Pfizer/BioNTech vaccines. My thoughts on the potential benefits & risks of such an approach, and the need for much greater transparency around these decisions. Thread. pic.twitter.com/mclqMDeMQ1
>
> — Deepti Gurdasani (@dgurdasani1) December 31, 2020

The data shows the AZ vaccine maintains efficacy in the setting of a delayed second dose, although it's not clear how fast this wanes over time. Delay of the second dose provides a better booster effect as measured by antibody levels, which is seen with other vaccines. 6/

> The level of protection gained from a single dose of COVID-19 Vaccine AstraZeneca was assessed in an exploratory analysis that included participants who had received one dose. Participants were censored from the analysis at the earliest time point of when they received a second dose or at 12 weeks post-dose 1. In this population, vaccine efficacy from 22 days post-dose 1 was 73.00% (95% CI: 48.79; 85.76 [COVID-19 Vaccine AstraZeneca 12/7,998 vs control 44/7,982]).

The second dose is important because it can drive a more robust and higher quality antibody response through a process called affinity maturation. It's well-understood that longer intervals can provide a better boost. 7/ https://t.co/cqKIpomUHg

> 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

In my view, the immediate priority is prevention of severe disease that drives deaths and the strain on health systems. Efficacy against severe disease is likely better than overall vaccine efficacy. Data after the first dose is promising although the numbers are small. 8/

**Table 2 COVID-19 Vaccine AstraZeneca efficacy against COVID-19**

| Population | COVID-19 Vaccine AstraZeneca | | Control | | Vaccine efficacy % (CI) |
|---|---|---|---|---|---|
| | N | Number of COVID-19 cases, n (%) | N | Number of COVID-19 cases, n (%) | |
| ***Primary (see above)*** | **5,807** | | **5,829** | | |
| COVID-19 cases | | 30 (0.52) | | 101 (1.73) | 70.42 (58.84, 80.63)[a] |
| Hospitalisations[b] | | 0 | | 5 (0.09) | - |
| Severe disease[c] | | 0 | | 1 (0.02) | - |
| ***Any dose*** | **10,014** | | **10,000** | | |
| COVID-19 cases after dose 1 | | 108 (1.08) | | 227 (2.27) | 52.69 (40.52, 62.37)[d] |
| Hospitalisations after dose 1[b] | | 2 (0.02)[e] | | 16 (0.16) | - |
| Severe disease after dose 1[c] | | 0 | | 2 (0.02) | |

N = Number of subjects included in each group; n = Number of subjects having a confirmed event; CI = Confidence Interval; [a] 95.84% CI; [b] WHO severity grading ≥4; [c] WHO severity grading ≥6; [d] 95% CI; [e] Two cases of hospitalisation occurred on Days 1 and 10 post vaccination.

There's nothing magic about the (short) 28d interval between doses, which was presumably chosen to ensure rapid onset of protection in Ph3. Vaccine efficacy won't disappear overnight with a delayed 2nd dose - it will wane over time, if at all. Ph3 data supports that concept. 9/

Yes there are risks of waning immunity, non-compliance with the second dose, confusion among the public, etc. Many are implementation considerations that can be addressed with planning and strong communication. 10/

It will be critically important to collect efficacy data around this "flexible second dose" schedule, esp in older adults & against severe disease, to inform licensure and recommendations in countries around the world that are counting on the introduction of this vaccine. 11/

Yes the AZ/Oxford studies had a number of issues, but we must remember that this highly-complex development program was executed in less than a year. And that Pfizer & Moderna's Ph3 execution & vaccine efficacy created very high expectations for all subsequent programs. 12/

The bottom line is that every country needs to make difficult policy decisions with the data they have, not what they'd like to have. There's no perfect answer here, but now that a decision has been taken, the UK can focus on maximizing the benefit and mitigating any risks. 13/