Twitter Thread by Rajeev Venkayya MD



Rajeev Venkayya MD
@rvenkayya

THREAD

I created a simple table to illustrate the individual impact of the "flexible second dose timing" now recommended in the UK.

Coincidentally, @bob_wachter & @ashishkjha just tackled the US policy question in this important piece. 1/
https://t.co/n5bHkdIo0c

Person	Interval (weeks)	Dose #1	Dose #2	Protection before April	Protection after April	Comments
A	4	January	February	++	++	
B	12	January	April	+	+++	See notes 1&2
C	4	April	May	-	++	
		Comparison of protection		**A>B>C**	**B>A=C**	

This table provides a qualitative assessment of individual protection at different points in time based on a 4 or 12 week schedule for the AZ vaccine. It is based on statements of UK authorities, AZ data and the expected benefit of a longer primary vaccine schedule

Note 1: JCVI: single dose appears to provide "high short-term protection against severe disease"
Note 2: "+++" given expected benefit of longer interval between doses and immunogenicity data

References:
JCVI statement: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/759357623956
UK CMOs statement: https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines

> In @washingtonpost, @ashishkjha & I argue for the 2nd-shot-deferred strategy, partly by invoking the Mike Tyson principle. https://t.co/ZxrgVj3TJe We both came to this view because of the slow rollout & the new variant. But it's a tough call and reasonable people will disagree.
>
> — Bob Wachter (@Bob_Wachter) January 3, 2021

I based this on recent statements from the UK chief medical officers, JCVI, and what we know from prior vaccine development. 2/

JCVI: https://t.co/6FQ25d6MFE

UK Chief Medical Officer (CMO) statement: https://t.co/RTpAIqgE1i

CMO letter to the profession: https://t.co/4WeexrVYWX

This table and thread focuses on the AZ vaccine, where more data on a delayed second dose is available than with the Pfizer vaccine. It is not intended to address questions about single-dose regimens or mix & match approaches. 3/

Person	Interval (weeks)	Dose #1	Dose #2	Protection before April	Protection after April	Comments
A	4	January	February	++	++	
B	12	January	April	+	+++	See notes 1&2
C	4	April	May	-	++	
		Comparison of protection		**A>B>C**	**B>A=C**	

This table provides a qualitative assessment of individual protection at different points in time based on a 4 or 12 week schedule for the AZ vaccine. It is based on statements of UK authorities, AZ data and the expected benefit of a longer primary vaccine schedule

Note 1: JCVI: single dose appears to provide "high short-term protection against severe disease"
Note 2: "+++" given expected benefit of longer interval between doses and immunogenicity data

References:

JCVI statement: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/759357623956

UK CMOs statement: https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines

In the table, persons “A” and “B” both receive their first dose in January. “A” receives their second dose in February (4 weeks later), and “B” receives their second dose in April (12 weeks later). “C” receives their first dose in April and second dose in May (4 weeks later). 4/

Person	Interval (weeks)	Dose #1	Dose #2	Protection before April	Protection after April	Comments
A	4	January	February	++	++	
B	12	January	April	+	+++	See notes 1&2
C	4	April	May	-	++	
		Comparison of protection		**A>B>C**	**B>A=C**	

This table provides a qualitative assessment of individual protection at different points in time based on a 4 or 12 week schedule for the AZ vaccine. It is based on statements of UK authorities, AZ data and the expected benefit of a longer primary vaccine schedule

Note 1: JCVI: single dose appears to provide "high short-term protection against severe disease"
Note 2: "+++" given expected benefit of longer interval between doses and immunogenicity data

References:

JCVI statement: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/759357623956

UK CMOs statement: https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines

I made a qualitative comparison the potential efficacy during the two months between “A” and “B’s” second dose, as well as the potential longer-term efficacy after “B” receives their second dose. 5/

Person	Interval (weeks)	Dose #1	Dose #2	Protection before April	Protection after April	Comments
A	4	January	February	++	++	
B	12	January	April	+	+++	See notes 1&2
C	4	April	May	-	++	
		Comparison of protection		**A>B>C**	**B>A=C**	

This table provides a qualitative assessment of individual protection at different points in time based on a 4 or 12 week schedule for the AZ vaccine. It is based on statements of UK authorities, AZ data and the expected benefit of a longer primary vaccine schedule

Note 1: JCVI: single dose appears to provide "high short-term protection against severe disease"
Note 2: "+++" given expected benefit of longer interval between doses and immunogenicity data

References:

JCVI statement: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/759357623956

UK CMOs statement: https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines

For the two-month period between the timing of “A” and “B’s” second dose, the level of protection for “A” may be greater than “B,” as “A” has received their second dose, although JCVI suggests that most of this early protection is provided by the first dose. 6/

Person	Interval (weeks)	Dose #1	Dose #2	Protection before April	Protection after April	Comments
A	4	January	February	++	++	
B	12	January	April	+	+++	See notes 1&2
C	4	April	May	-	++	
		Comparison of protection		**A>B>C**	**B>A=C**	

This table provides a qualitative assessment of individual protection at different points in time based on a 4 or 12 week schedule for the AZ vaccine. It is based on statements of UK authorities, AZ data and the expected benefit of a longer primary vaccine schedule

Note 1: JCVI: single dose appears to provide "high short-term protection against severe disease"
Note 2: "+++" given expected benefit of longer interval between doses and immunogenicity data

References:
JCVI statement: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/759357623956
UK CMOs statement: https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines

JCVI says first-dose protection against hospitalization is high, so for that two month interval, I've assumed "B" is expected to be protected against the more severe forms of COVID-19 ("+"). 7/

Person	Interval (weeks)	Dose #1	Dose #2	Protection before April	Protection after April	Comments
A	4	January	February	++	++	
B	12	January	April	+	+++	See notes 1&2
C	4	April	May	-	++	
		Comparison of protection		**A>B>C**	**B>A=C**	

This table provides a qualitative assessment of individual protection at different points in time based on a 4 or 12 week schedule for the AZ vaccine. It is based on statements of UK authorities, AZ data and the expected benefit of a longer primary vaccine schedule

Note 1: JCVI: single dose appears to provide "high short-term protection against severe disease"
Note 2: "+++" given expected benefit of longer interval between doses and immunogenicity data

References:
JCVI statement: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/759357623956
UK CMOs statement: https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines

After "B's" second dose in April, we expect a more robust, higher quality and longer-lasting immune response than "A," as is often seen with longer intervals in a primary vaccination series and supported by AZ's data immunogenicity data. 8/ https://t.co/cqKIpomUHg

Person	Interval (weeks)	Dose #1	Dose #2	Protection before April	Protection after April	Comments
A	4	January	February	++	++	
B	12	January	April	+	+++	See notes 1&2
C	4	April	May	-	++	
		Comparison of protection		**A>B>C**	**B>A=C**	

This table provides a qualitative assessment of individual protection at different points in time based on a 4 or 12 week schedule for the AZ vaccine. It is based on statements of UK authorities, AZ data and the expected benefit of a longer primary vaccine schedule

Note 1: JCVI: single dose appears to provide "high short-term protection against severe disease"
Note 2: "+++" given expected benefit of longer interval between doses and immunogenicity data

References:

JCVI statement: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/759357623956

UK CMOs statement: https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines

> 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

The bottom line is that “A” may see some protective benefit over “B” for two months (although “B” is expected to be protected against severe COVID during that time), but “B” is expected to have better long-term protection after they receive their second dose at 12 weeks. 9/

Person	Interval (weeks)	Dose #1	Dose #2	Protection before April	Protection after April	Comments
A	4	January	February	++	++	
B	12	January	April	+	+++	See notes 1&2
C	4	April	May	-	++	
		Comparison of protection		**A>B>C**	**B>A=C**	

This table provides a qualitative assessment of individual protection at different points in time based on a 4 or 12 week schedule for the AZ vaccine. It is based on statements of UK authorities, AZ data and the expected benefit of a longer primary vaccine schedule

Note 1: JCVI: single dose appears to provide "high short-term protection against severe disease"
Note 2: "+++" given expected benefit of longer interval between doses and immunogenicity data

References:

JCVI statement: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/759357623956

UK CMOs statement: https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines

In other words, for the two months between “A” and “B’s” second dose: A>B>C

For the longer term, after “B” receives their second dose: B>A=C

10/

Person	Interval (weeks)	Dose #1	Dose #2	Protection before April	Protection after April	Comments
A	4	January	February	++	++	
B	12	January	April	+	+++	See notes 1&2
C	4	April	May	-	++	
		Comparison of protection		**A>B>C**	**B>A=C**	

This table provides a qualitative assessment of individual protection at different points in time based on a 4 or 12 week schedule for the AZ vaccine. It is based on statements of UK authorities, AZ data and the expected benefit of a longer primary vaccine schedule

Note 1: JCVI: single dose appears to provide "high short-term protection against severe disease"
Note 2: "+++" given expected benefit of longer interval between doses and immunogenicity data

References:

JCVI statement: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/759357623956

UK CMOs statement: https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines

At a population level, this strategy could double the number of people immunized immediately while production ramps up. Many in category “C” could shift to “B.”

This assumes immunization programs are keeping up with the number of doses available. 11/

A few important caveats: (1) the assumption of sustained efficacy after the first dose is based on an exploratory analysis in the age 18-55 population. This needs to be confirmed in the older adult population. Exploratory analyses have limitations, esp if not pre-specified. 12/

(2) the assumption that a longer schedule (“B”) will result in a higher-quality, more durable immune response is based on immunogenicity data and experience with other vaccines. The efficacy impact will have to be confirmed. 13/

(3) we need to confirm that vaccine protection against the new strain is comparable after the first and second doses, given the affinity maturation expected with a second dose. 14/

Some virologists have raised the theoretical concern that a change in schedule could promote emergence of vaccine escape mutants. This is an important consideration that has implications for single-dose vaccine development and WHO’s minimum vaccine efficacy threshold of 50%. 15/

Again, this illustration is based on statements from UK authorities, AZ’s published data, and what is known from prior vaccine development. It is not a prediction of the future or what will happen to any individual, and is subject to updates as new data becomes available. 16/

Person	Interval (weeks)	Dose #1	Dose #2	Protection before April	Protection after April	Comments
A	4	January	February	++	++	
B	12	January	April	+	+++	See notes 1&2
C	4	April	May	-	++	
		Comparison of protection		**A>B>C**	**B>A=C**	

This table provides a qualitative assessment of individual protection at different points in time based on a 4 or 12 week schedule for the AZ vaccine. It is based on statements of UK authorities, AZ data and the expected benefit of a longer primary vaccine schedule

Note 1: JCVI: single dose appears to provide "high short-term protection against severe disease"
Note 2: "+++" given expected benefit of longer interval between doses and immunogenicity data

References:

JCVI statement: https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/759357623956

UK CMOs statement: https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines

I hope this helps people understand the practical ramifications of the UK recommendations and the pros/cons at individual and population levels. The urgency of the question is driven by the emergence of the new variant in the UK as well as the

limited supply of vaccine. 17/

Thanks to our vaccine CMO, Dr. Gary Dubin for his input. More thoughts and links to others' views in the thread below.

I went through this exercise to clarify my own views and thought others might find it useful. Please take it in that spirit! 18/ https://t.co/2vzJ9Sdfc4

> THREAD
> There\u2019s 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/https://t.co/IFOC9M6vkq
>
> — Rajeev Venkayya MD (@rvenkayya) January 1, 2021