Episode 169 Update on the Janssen or Johnson & Johnson vaccine

Dear colleagues,

First, if you want to retrieve the scientific literature ion this topic, use the term **Ad26.COV2.S**. In the text, I will use the more familiar terms: Janssen, J&J or Johnson and Johnson.

The literature on this vaccine consist for 2/3 on the wicked side effect of VITT (vaccine induced thrombocytosis and thrombocytopenia), which I will only briefly discuss and put into perspective.

It remains difficult to appreciate the true comparative efficacy of this vaccine, which has the big advantage of one dose. Let's look at the available evidence.

Phase 3 trial in perspective

Ep 169-1: Sadoff Phase 3 trial in three countries NEJM July 2021.

Table 3. Vaccine Efficacy against Covid-19 with Onset at Least 14 Days and at Least 28 Days after Administration of Vaccine or Placebo, According to Country (Per-Protocol at-Risk Population).*

Variable	≥14 Days after Administration†					≥28 Days after Administration‡				
	Ad26.COV2.S		Placebo		Vaccine Efficacy (95% CI)	Ad26.COV2.S		Placebo		Vaccine Efficacy (95% CI)
	no.	*person-yr*	*no.*	*person-yr*	%	*no.*	*person-yr*	*no.*	*person-yr*	%
Worldwide										
No. of participants	19,514		19,544			19,306		19,178		
Moderate to severe–critical Covid-19	173	3113.9	509	3089.1	66.3 (59.9 to 71.8)	113	3100.3	324	3065.9	65.5 (57.2 to 72.4)
Severe–critical Covid-19	19	3124.7	80	3121.0	76.3 (57.9 to 87.5)	8	3106.0	48	3082.0	83.5 (54.2 to 96.9)
United States										
No. of participants	9,119		9,086			8,958		8,835		
Moderate to severe–critical Covid-19	51	1414.0	196	1391.3	74.4 (65.0 to 81.6)	32	1403.4	112	1375.6	72.0 (58.2 to 81.7)
Severe–critical Covid-19	4	1417.2	18	1404.8	78.0 (33.1 to 94.6)	1	1405.2	7	1382.2	85.9 (–9.4 to 99.7)
Brazil										
No. of participants	3,370		3,355			3,354		3,312		
Moderate to severe–critical Covid-19	39	555.7	114	548.8	66.2 (51.0 to 77.1)	24	554.8	74	546.1	68.1 (48.8 to 80.7)
Severe–critical Covid-19	2	558.9	11	556.8	81.9 (17.0 to 98.1)	1	556.2	8	549.8	87.6 (7.8 to 99.7)
South Africa										
No. of participants	2,473		2,496			2,449		2,463		
Moderate to severe–critical Covid-19	43	377.6	90	379.2	52.0 (30.3 to 67.4)	23	376.1	64	376.9	64.0 (41.2 to 78.7)
Severe–critical Covid-19	8	380.2	30	382.9	73.1 (40.0 to 89.4)	4	377.0	22	379.0	81.7 (46.2 to 95.4)

So, the **efficacy against moderate-to-severe COVID is in the 52- 72 % range and 75- 85 % against the severe-critical disease**. There is a tendency of higher efficacy after > 28 days.

Clearly, for both South-Africa and Brazil, the more resistant E484K containing mutants **beta and gamma** were becoming dominant during the trial, making direct comparison with the Pfizer, Moderna and Astra-Zeneca trial difficult, as these were largely conducted before these variants appeared.

The efficacy in the well-represented older (> 60yrs) participants was equivalent and they presented fewer side effects. However, it is unclear whether the oldest, more vulnerable groups (> 80, > 90) were well represented.

Ep 169-2: Comments in NEJM it becomes clear that there is uncertainty protection beyond 3 months.

Ep 169-3: Short recap of the trial results of the main RNA and Adeno vaccines for those who lost track.

Ep 169-4: Montastruc et al argue that the **relative risk reduction**, as reported in most clinical trials, fails to take into account baseline risks and tend to exaggerate the positive results. They propose that **absolute risk reduction** (the arithmetic difference between the risk in the treatment group and the risk in the control group) is more clinically relevant. As can be seen in their table, while RR of the mRNA vaccines is 5-6 X lower than for Astra-Zeneca and Janssen, the **difference in absolute risk reduction (ARR) between both types of vaccines is rather small**, especially as compared with an EBOLA vaccine. Clearly, these calculations are based on the clinical trials with the caveats that the mRNA trials were conducted at a more "favorable time" (when no VOC were circulating).

TABLE 1 Risk of infections expressed as absolute risk (AR), absolute risk reduction (ARR), number needed to treat (NNT), and relative risk (RR) with its 95% confidence interval (CI) with the four COVID-19 vaccines (V), influenzae vaccine (V), and Ebola vaccine (V)

	Results in exposed patients	Results in control patients	AR in exposed patients	AR in control patients	ARR	NNT	RR	95% CI
Pfizer vaccine tozinameran Comirnaty®	8/21 720	162/21 728	0.04%	0.74%	0.71%	141	0.05	0.02–0.10
Moderna vaccine	11/15 210	185/15 210	0.07%	1.20%	1.13%	91	0.06	0.03–0.11
AstraZeneca vaccine	30/5807	101/5829	0.50%	1.70%	1.20%	83	0.30	0.19–0.44
Sputnik V vaccine	16/14 964	62/4902	O.10%	1.30%	1.20%	83	0.09	0.05–0.14
Janssen vaccine	66/19 306	193/19 178	0.34%	1.01%	0.67%	149	0.34	0.26–0.45
Influenzae vaccine	221/18 797	357/13 095	1.18%	2.73%	1.56%	64	O.43	0.35–0.50
Ebola vaccine	91/91 492	880/92 262	0.10%	9.50%	9.4%	11	0.11	0.08–0.11

As you may know, the same vector technology with the rare human Adenovirus type26 has also been used in the development§ of EBOLA and HIV vaccines, but in those cases an heterologous "boost" with either an MVA vector (for EBOLA) or envelope protein (for HIV) was used.

Ep 169-5: briefly describes the status of EBOLA vaccines. The vaccine developed by Merck, based on yetl another viral vector (vesiculo stomatitis virus or VSV) has been fully approved, while the Janssen vaccine has a provisional authorization, since the efficacy in phase 3 has not been proven.

Ep 169-6: A disappointing result has been obtained with the HIV vaccine in South-Africa with 25 % protection, but a wide confidence interval.

Real world data on efficacy

Ep 169-7: **Confirms the clinical trial data**: *Of the 1,779 vaccinated individuals with at least two weeks of follow-up, only 3 (0.17%) tested positive for SARS-CoV-2 15 days or more after vaccination compared to 128 of 17,744 (0.72%) unvaccinated individuals (4.34 fold reduction rate).*
However, this preprint was already published in April (during the alpha epidemic and before the delta) and I could not find follow-up in the US….

Ep 169-8: A recent article in the New York Times reports on the Sisonke study in South Africa, using the Janssen vaccine in 500,000 health care workers at high risk.

- The vaccine is **91-95 % effective against death and 65-66 % against hospitalization**.
- The effects against **delta were slightly better than against beta** (!).
- Protective effects were **durable** (similar between 1-3 months and 3-4 months.
- Breakthrough infections were mild in 96 % of cases and
- Only 2 cases of thrombosis were seen, both recovered.

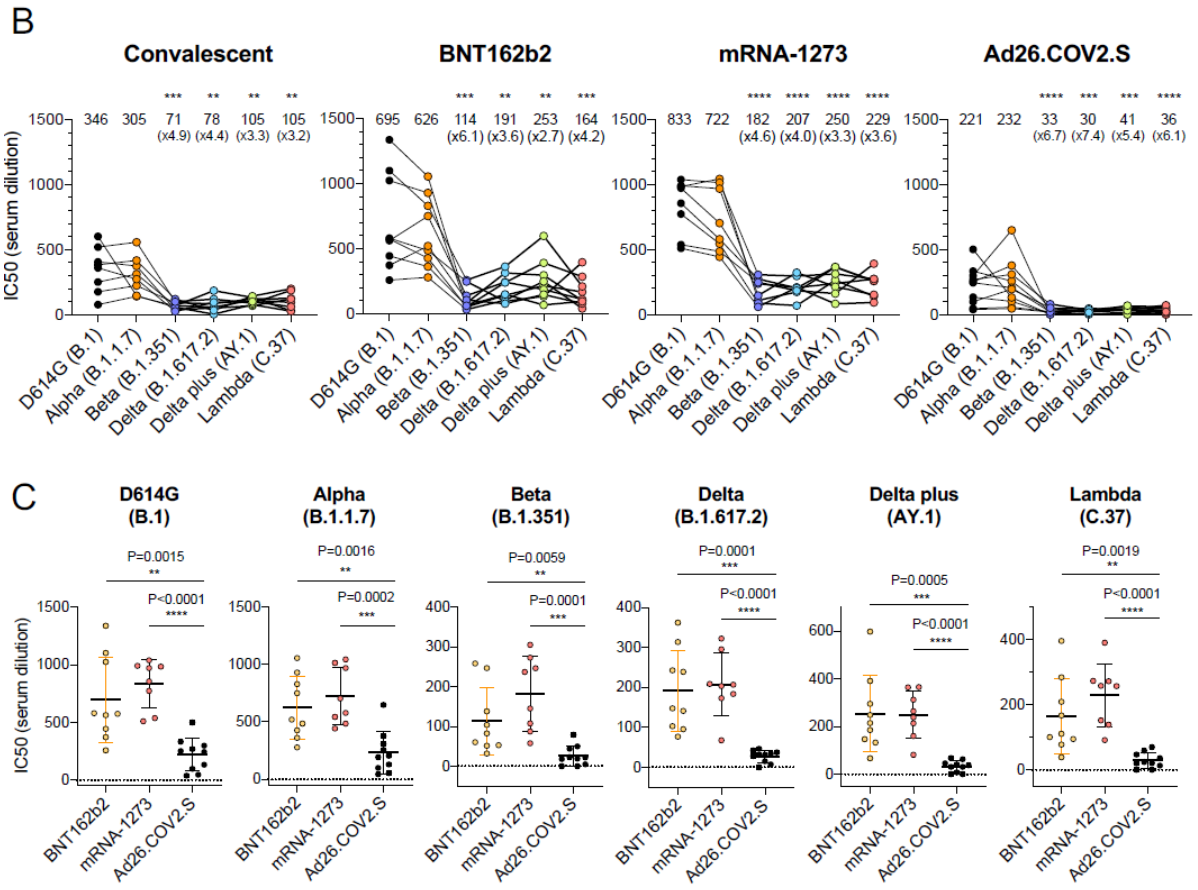
I could not find a reprint, but a nice slide show is provided.

Follow-up on immunogenicity: durability and breadth

Ep 169-9: According to Barouch et al (involved in the development) in NEJM, both T and B responses, including neutralizing antibodies against a range of variants (also beta, gamma and delta) are stable during 8 months.

Ep 169-10: Alter et al (also connected with J&J) reports on stable T cell responses up to 71 days after vaccination, but here lower titers of neutralizing antibodies against the gamma (3 fold) and beta (5 fold) were noted. Delta was not tested.

Ep 169-11: Tada et al (independent from J&J) compare convalescent plasma and sera from mRNA and Janssen vaccinated subjects. As you can see, **significantly lower titers of neutralizing antibodies in the Janssen vaccinees and especially very low titers against beta, delta and lambda VOC**



Boosting

Ep 169-12: "Natural boost": Comparison of HCW in South-Africa, either naïve or prior infection with D614G (1st wave) or with beta (2nd wave) and then vaccinated with Janssen.

- Vaccination after either infection induced much more (> 100 X) neutralizing antibodies than in naïve HCW (Fig 1 p. 24)
- Also > 100 X higher neut titers against beta and delta after infection + vaccination (Fig 2 p. 25)
- Prior infection was not required for the generation of high magnitude T cell responses
- No data on clinical protection against (re)infection) in this study.

Ep 169-13: Sadoff (for J&J)

- *A single dose of Ad26.COV2.S, which demonstrated protection in a Phase 3 efficacy trial, elicited durable neutralizing and binding antibodies for at least 8 and 6 months,*
- *A 5x1010 vp or 1.25x1010 vp booster dose at 6 months elicited rapid and robust increases in spike binding antibody levels.*

- *Even older adults in whom spike specific antibody titers had declined to undetectable levels at month 6 post primary vaccination showed similar strong responses to this low dose booster vaccination*.

These anamnestic responses even in individuals with undetectable antibodies may also occur in response to SARS-CoV-2 infection and hence these people are likely still protected against severe COVID-19.

In this study, only binding Ab were evaluated (no formal neut) and no data on variants.

Side effects

Ep 169-14: Eurosurveillance study on **thrombosis at unusual sites** after either of 4 COVID vaccines. Per million vaccinations for **Astra-Zeneca 21.6 > Janssen 12 >> Moderna 5.6 > Pfizer** 2

Ep 169-15: CDC risk/benefit evaluation for

- Janssen: mainly Guilain-Barré Syndrome (GBS increasing with age) and thrombosis and thrombocytopenia (TTS rather decreasing with age)
- Pfizer and Astra-Zeneca mainly myocarditis in young males (anaphylaxis not considered here)

→ **Very clear benefit >> risk,** see Table

TABLE 2. Estimated COVID-19 outcomes prevented during 120 days after 1-dose Janssen (Johnson & Johnson) COVID-19 vaccination and 2-dose mRNA (Pfizer-BioNTech or Moderna) COVID-19 vaccination, number of Guillain-Barré syndrome and thrombosis with thrombocytopenia syndrome cases expected per million Janssen vaccine doses administered, and number of myocarditis cases expected per million second mRNA vaccine doses administered, by sex and age group — United States, 2021*

Vaccine	Benefits: COVID-19 outcomes prevented				Harms: adverse events†	
Sex/Age group, yrs	Cases	Hospitalizations	ICU admissions	Deaths	GBS	TTS
Janssen (Johnson & Johnson) COVID-19 vaccine§						
Females						
18–29	8,900	700	50	5	1	4–5
30–49	10,100	900	140	20	6–7	8–10
50–64	12,100	1,600	350	120	7–8	3–4
≥65	29,000	5,900	1,250	840	8–10	0
Males						
18–29	6,600	300	60	3	2	2–3
30–49	7,600	650	150	25	7–8	1–2
50–64	10,100	1,800	480	140	14–17	1–2
≥65	36,600	11,800	3,300	2,300	7–8	0
mRNA (Pfizer-BioNTech or Moderna) COVID-19 vaccine¶					Myocarditis	
Females						
18–29	12,800	750	50	5	3–4	
30–49	14,600	950	140	20	1–2	
50–64	17,500	1,700	375	125	1	
≥65	32,000	6,200	1,300	900	<1	
Males						
18–29	9,600	300	60	3	22–27	
30–49	11,000	700	160	25	5–6	
50–64	14,700	1,900	500	150	1	
≥65	52,700	12,500	3,500	2,400	1	

Abbreviations: GBS = Guillain-Barré syndrome; ICU = intensive care unit; TTS = thrombosis with thrombocytopenia syndrome.
* Benefits and harms were calculated using case incidence and hospitalization data for the week ending June 19, 2021, and for harms using cases through June 30 (GBS and myocarditis) and through July 8 (TTS), projected for a 120-day period using methods described here: https://www.cdc.gov/vaccines/covid-19/info-by-product/janssen/risk-benefit-analysis.html
† Estimates for adverse events are based on an estimated risk of cases per million doses administered with a +/- 10% range.
§ Benefits and harms calculated per million doses of Janssen vaccine administered.
¶ Benefits and harms calculated per million second doses of mRNA (Pfizer-BioNTech and Moderna) vaccine administered.

Conclusions :

1) Single dose Janssen Ad26.COV2.S vaccine seems to provide **durable protection against COVID disease** at a level that is at least equivalent to 2 doses of Astra-Zeneca. Direct cohort comparisons with mRNA have not been reported.
2) There is preliminary evidence for **protection against COVID by beta, gamma and delta variants**. The protection against infection has not been studied well
3) **Neutralizing antibody levels**, induced by Janssen are lower than those induced by mRNA vaccines in an independent study. **Is T cell immunity important in protection?**
4) Janssen has certainly **a good risk/benefit profile**. Thrombosis occurs at a rate about half that in Astra-Zeneca and double that of Moderna.
5) A **booster** vaccine elicits a **strong anamnestic response** also in elderly with undetectable levels.

I leave it here for today. I have at least a dozen of other papers that I would like to discuss and share, but we will take a break to enjoy the late summer. So, episode 170 will be rather for next Tuesday or Wednesday.

Enjoy the weekend.
Guido