Janssen/Johnson & Johnson Adenovirus Vector Vaccine Summary 3.3.2021 0900

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Last reviewed: 3.3.21

- Ad26.COV2.S = recombinant replication incompetent human adenovirus type 26 encoded with Spike protein from SARS CoV-2
- Unlike mRNA vaccines, this study was for ONE dose
    - Ongoing study examining 2 doses, 57 days apart
- At time of analysis, median follow up from vaccination = 58 days
- Efficacy analysis based on 39,321 participants: 19,630 vaccinated & 19,691 placebo
- International study in eight countries:
    - Majority of participants: United States, South Africa, Brazil
    - Other included countries: Mexico, Chile, Argentina, Colombia, Peru
- Demographics (appear well balanced between both groups):
    - Race: 58.7% white, 19.4% Black/African American, 3.4% Asian, 9.5% American Indian/Alaskan Native
    - Ethnic groups: 45.1% Hispanic
    - ≥1 co-morbidity: 40.8%
    - Obese: 28.7%
    - HIV: 2.7%
- Excluded:
    - Pregnant and breastfeeding women
    - Persons younger than 18
    - Immunocompromised or on immunosuppressive meds within previous six months
    - Previous receipt of any coronavirus vaccine
- Study participants who become eligible for an EUA vaccine during study could request unblinding; as of Jan. 21:
    - Total unblinded: 2,257 participants
        - 1,080 vaccine group
        - 1,177 placebo group
    - Data collected up to unblinding included in EUA request

Epidemiological Setting—Important Differences From mRNA Studies

- Study conducted during period of very high transmission and emergence of new variants
    - ~96% cases in South Africa during study due to B.1.351 variant (20H/501Y.V2)
    - ~71% cases in Brazil during study due to P.2 variant
- Estimated COVID-19 incidence during course of study 19.8%

Vaccine Efficacy

- Co-primary endpoints: first occurrence of molecularly confirmed:
    1. Moderate COVID-19 ≥ 14 days or ≥ 28 days after vaccination
    2. Severe/critical COVID-19 ≥ 14 days or ≥ 28 days after vaccination
- Moderate to Severe/Critical COVID-19
    - ≥ 14 days after vaccination, overall efficacy = 66.9%
        - 116 cases in vaccine group
        - 348 cases in placebo group
    - ≥ 28 days after vaccination, overall efficacy = 66.1%
        - 66 cases vaccine group

        - 193 cases placebo group
    - *Cumulative incidence starts to separate about 14 days after vaccination*
- Severe/Critical COVID-19
    - ≥ 14 days after vaccination, overall efficacy = 76.7%
        - 14 cases in vaccine group
        - 60 cases in placebo group
    - ≥ 28 days after vaccination, overall efficacy = 85.4%
        - 5 cases in vaccine group
        - 34 cases in placebo group
    - *Cumulative incidence starts to separate around 7 days after vaccination*
    - Data of interest: As of day 42, only one case in vaccine group reported thus far vs. 13 cases in placebo group (92.4% efficacy for day 42 onwards) - preliminary data due to limited data available beyond 57 days
    - Cumulative incidence separation of any COVID-19 case (moderate or severe) with Ad26 vaccine is very similar to that seen with either mRNA vaccine, i.e protection appears to start around day seven and improves thereafter
- Hospitalizations and Deaths
    - Only two cases of COVID-19 in the vaccine arm (zero cases >28 days from vaccination) vs. 21 in placebo arm required medical intervention (i.e. hospitalization)
        - **Efficacy >14 days post-vaccination = 85.8%**
        - **Efficacy >28 days post-vaccination = 100%**
    - There was one additional hospitalization in vaccine group and 16 in placebo group after review of SAE forms (serious adverse event), adding further support to excellent efficacy of this vaccine against hospitalization
    - Deaths: 19 overall
        - Three in vaccine group (NONE associated with COVID-19 or attributable to vaccine)
        - 16 in placebo group (six due to COVID-19)

This vaccine KEEPS PEOPLE OUT OF THE HOSPITAL and PREVENTS DEATHS. These two points need to be repeated EVERY SINGLE time we talk about this vaccine.

- Vaccine efficacy against ANY symptomatic COVID-19 infection was 68.1% at 14 days & 69% at 28 days post-vaccination
- Vaccine efficacy against asymptomatic infection (no symptoms & seroconversion to +anti-nucleocapsid IgG) at day 71 = 100%
    - Based on limited subset, are preliminary and will need further assessment in larger subset but suggest possible protection against asymptomatic viral carriage
- Vaccinated participants who got infected with COVID-19 experienced fewer symptoms and had milder course of illness
- Vaccine efficacy by country
    - Another point of emphasis: ***this vaccine is highly effective against both the South Africa and Brazil variants at preventing severe disease***
    - While both mRNA vaccines suggest decreased efficacy in labs studies (again the SA variant, no data yet for Brazil variant), **neither mRNA vaccine has any real world clinical trial data against either of these variants**

Country	Onset	Mod to Severe	Severe/Critical
US	≥ 14 days ≥ 28 days	74.4% 72.0%	78.0% 85.9%
Brazil	≥ 14 days ≥ 28 days	66.2% 68.1%	**81.9%** **87.6%**
South Africa	≥ 14 days ≥ 28 days	52.0% 64.0%	**73.1%** **81.7%**

- Vaccine efficacy against any severity COVID-19 was maintained in all age groups (with and without co-morbidities), genders, race and ethnic groups
- At this point, there is too little data to make any definitive statements about protection in persons with HIV but available data does not suggest any negative impact

Adverse events

- Local adverse events
  - Pain (48.7%)
  - Erythema & swelling (<8%)
  - Vast majority pain grade 1-2, only 0.3% grade 3
  - Median duration 2 to 3 days
- Systemic adverse events
  - Most grade 1-2, grade 3 <2% & no grade 4 events reported
  - Median duration 1 to 2 days
  - Most common
    - Fatigue (38.2%)
    - Headache (39%)
    - Myalgia (33.2%)
  - Any grade fever uncommon (9.0%)
    - Median duration 1 day
  - Other systemic events reported (unsolicited)
    - Chills, malaise, arthralgia, cough, nasal congestion, diarrhea
- Medically Attended Adverse Events (MAAE)
  - 1.4% vaccine vs 1.9% placebo
  - Most MAAE due to COVID-19, as reflected by greater number reported in placebo group
  - Others reported include: UTI, URI, arthralgia (more common in vaccine group)
  - No MAAE led to study discontinuation
- Serious Adverse Events
  - Reported in 227 participants (0.4% vaccine vs 0.6% placebo)
  - Transverse sinus thrombosis with cerebral hemorrhage in vaccine recipient
    - Led to pause in study & after further investigation, cause was determined NOT due to vaccine
  - Events possibly related to vaccination
    - Pericarditis
    - Brachial radiculitis, onset immediate following vaccination & not resolved at time of report
    - Grade 3 post-vaccination syndrome, participant required brief hospitalization and symptoms completely resolved
    - Non-anaphylactic allergic reactions
      - Rash: 24 vaccine vs 16 placebo

        - Urticaria: 8 vaccine vs. 3 placebo
        - Hypersensitivity: 6 vaccine vs 4 placebo; further investigation majority due to seasonal allergies or meds other than vaccine
    - Anaphylactic allergic reactions
        - 15 vaccine vs 8 placebo
        - None actually met accepted criteria for anaphylaxis
        - NO severe allergic reactions with any temporal relation to vaccine
        - One case type IV hypersensitivity within 3 days vaccine felt to be due vaccine
    - Tinnitus
        - 6 vaccine vs 0 placebo
        - No temporal relation to vaccine & all participants found to have underlying medical conditions or used medications that were more likely cause than vaccine
    - Convulsions/seizures
        - 4 vaccine vs 1 placebo
        - None determined to be related to vaccine
    - DVT/PE
        - 14 vaccine vs 10 placebo
        - No cases in vaccine group considered related to vaccine
    - Demyelinating disorders
        - 4 vaccine group vs 5 placebo
        - One case Guillian-Barre syndrome in vaccine recipient occurred 16 days post-vaccination & was felt to be possibly related by Janssen
    - Bell's Palsy
        - 3 vaccine vs 2 placebo
        - Observed frequency felt to be consistent with expected background rate and none of the cases in vaccine group were felt to be due to the vaccine
- **Adverse events overall were no different across sex, race, ethnicity, geographics, co-morbidities, HIV serostatus**

- Deaths
    - 19 overall
        - Three in vaccine group (lung abscess, non-COVID-19 pneumonia, one of unknown cause)
        - 16 in placebo (6 due to COVID-19)
        - No deaths were considered related to vaccine nor were any deaths in vaccine group due to COVID-19
- Other relevant safety information
    - Unlike mRNA vaccine, Adenovirus vector vaccines have been extensively studied and used safely in clinical studies involving vaccines for Ebola virus, RSV, HIV, Malaria, HPV and Zika virus
    - As of Dec 21, 2020 >193,000 people have received an Ad26 vaccination of various types
    - Safety has been studied from 6 months up to 4.5 years and at this point, there has been no major safety concerns found with the use of any Ad26 vaccine platform
    - Ad26 based Ebola vaccine is currently given to pregnant women in the context of a large vaccination study in Democratic Republic of Congo
        - 1,522 pregnancies reported, none of the adverse pregnancy outcomes and serious adverse events were related to the study Ad26 vaccine
    - Eight pregnancies reported in COVID-19 vaccine trials
        - One spontaneous abortion and one elective abortion
        - None of reported adverse pregnancy outcomes considered related to vaccine

- Janssen/Johnson & Johnson is getting ready to launch COVID-19 vaccine trial in pregnant women

Vaccine benefits

- Substantially reduces risk of moderate to severe COVID-19
- Virtually eliminates risk for hospitalization & death related to COVID-19
- Appears very effective at preventing severe disease, hospitalization and death against South Africa and Brazil variants
  - Only vaccine thus far with CLINICAL data against these variants
- At this time, involves only ONE injection
  - Ongoing study evaluating efficacy of two injections
- Vaccine can be stored in regular freezer for up to 24 months and in refrigerator for three months, substantially easing storage requirements compared to mRNA vaccines
- Does not have any risk for vaccine enhanced associated disease or vaccine enhanced associate respiratory disease
- Immunogenicity study supportive of vaccine efficacy with antibody titers increasing up to 57 days post-vaccination with not waning at least 85 days post-vaccination; vaccine also induces robust Th1 CD4 & CD8 immune responses (this is likely to be very important for longer term immunity)

Vaccine risks

- Predictable mild to moderate local and systemic adverse reactions such as injection site pain, fatigue, headache & myalgias
- As with mRNA vaccines, serious adverse events are very uncommon and occurred in equal frequency between groups
- No specific safety concerns at this point but as with any vaccine or medication, once deployed to larger population continued active surveillance may reveal additional less frequent and/or more serious adverse events that were not detected in trial population
  - **Unlike mRNA vaccines, Ad26 has already been actively studied in >193,00 people for various other vaccine studies over the last 4 to 5 years and to date, NO serious safety concerns have been identified after follow up ranging from 6 months to 4.5 years**

Remaining questions—very similar to those involving mRNA vaccines

- Efficacy and safety in pregnancy women as they were excluded from trial
  - Trial getting ready to start
- Duration of protection—it's too early to tell, hopefully as the study proceeds we will have a better idea
- Effectiveness in immunocompromised persons—NONE included in trial
- Effectiveness in people with previous history of SARS-CoV2 infection---data not reported in FDA document
- Effectiveness in pediatric population—no participants under 18
  - Study getting ready to launch, Spectrum Health is a participating site
- Effectiveness against asymptomatic infection
  - Early preliminary data from study seems to indicate it is highly effective, but too early as of yet to draw firm conclusions
- Effectiveness against long-term effects of COVID-19

- Effectiveness against mortality—larger number of participants needed and will be part of ongoing observational trial
    - Data very encouraging thus far
- Effectiveness against transmission will require further study post-authorization to better assess

Bottom Line

- Despite “perceived” lower efficacy, vaccine is highly efficacious & will undoubtedly be invaluable to fight against COVID-19
- We need to consistently and clearly emphasize:
    - This vaccine’s effectiveness against
        - Moderate to severe disease and death
        - Preventing hospitalization
    - Emerging variants from South Africa and Brazil
    - Study was conducted at time of extremely high transmission at all study sites, including US and during time of emerging variants
        - The same cannot be said about the data reported by Pfizer and Moderna for their respective EUA applications
    - Already well-established safety record of Ad26 vaccine platform, particularly its use in the Ebola epidemics