COVID-19 Conversations

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COVID19Conversations.org
#COVID19Conversations
COVID-19 vaccines: Do they halt transmission? Do they protect against variants? From CDC guidance to clinical practice

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NAM-APHA Webinar: COVID-19 Conversations: Variants and Vaccines
March 17, 2021
Remember immunity - antibodies and cell-mediated immunity.

- **T cells** are the major immune defense against viruses.

**Memory T cells**
- **CD4+ T cell**: Th1 cells for intracellular pathogens; Th2 cells for extracellular pathogens.
- **CD8+ T cell**: Cytotoxic T cells.

**Memory B cells**
- **Plasma cell**: Makes antibodies.

- Of note, want Th1:Th2 ratio >>1 for viruses; Th2 CD4s block antiviral Th1-CD4s and CD8s.

Most vaccine trials measured antibodies and T cell responses.
<table>
<thead>
<tr>
<th>Company</th>
<th>Platform</th>
<th>Doses</th>
<th>Non-clinical results</th>
<th># who got vaccine</th>
<th>Protection from hospitalization from COVID-19</th>
<th>Protection from COVID severe dz (some at home)</th>
<th>Efficacy against milder COVID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderna</td>
<td>mRNA-1273 mRNA in lipid nanoparticle</td>
<td>2</td>
<td>Neutralizing Abs; Strong Th1 CD4+, CD8+; protection from challenge (macaques)</td>
<td>~15,000</td>
<td>97% (1 in vaccine arm after 2nd dose hospitalized)</td>
<td>97% (30 cases in placebo arm; 0 in vaccine reported but 1 severe per FDA)</td>
<td>94.1%</td>
</tr>
<tr>
<td>Pfizer</td>
<td>BNT162b2 mRNA in lipid nanoparticle</td>
<td>2</td>
<td>Neutralizing Abs; Strong Th1 CD4+, CD8+; protection from challenge (macaques)</td>
<td>~18,600</td>
<td>100%</td>
<td>100% (9 cases in placebo arm; 0 in vaccine - initially severe but not)</td>
<td>95%</td>
</tr>
<tr>
<td>Johnson &amp; Johnson</td>
<td>JNJ-78436725 Non-replicating human adenovirus/DNA</td>
<td>1</td>
<td>Neutralizing Abs; Strong Th1 CD4+ &gt; Th2; CD8+; challenge protection (macaque)</td>
<td>~22,000</td>
<td>100%</td>
<td>85.4% across 3 sites (7 deaths, 16 hospitalizations, all in placebo arm)</td>
<td>72% US; 61% Latin America; 64% S. Africa (96% B1.351)</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>AZD 1222 Non-replicating Chimpanzee Adenovirus-DNA</td>
<td>2</td>
<td>Neutralizing Abs; Strong Th1 CD4+ &gt; Th2; CD8+; protection from challenge (macaques)</td>
<td>~8588</td>
<td>100%</td>
<td>100% (15 in placebo – all hospitalized; 0 in vaccine)</td>
<td>70% overall; 76% 1 dose; S. Africa trial halted for mild</td>
</tr>
<tr>
<td>Novavax</td>
<td>NVX-CoV2373 Spike protein/RBD + Matrix M adjuvant</td>
<td>2</td>
<td>Neutralizing Abs; Strong Th1 CD4 &gt; Th2; challenge protection (macaques)</td>
<td>~8833</td>
<td>100%</td>
<td>100% (10 severe in placebo in UK/SA; 0 in vaccine)</td>
<td>96.4% UK; 89% B117 UK; 55% SA (94% B1351)</td>
</tr>
<tr>
<td>Sputnik V</td>
<td>Ad26 and Ad5 adenovirus/DNA</td>
<td>2</td>
<td>NAb; IFN-γ secretion PMBCs, cellular response</td>
<td>~14964</td>
<td>100%</td>
<td>100% (20 in placebo; 0 vaccine)</td>
<td>91.6%</td>
</tr>
</tbody>
</table>
How does functional T-cell response modulate severity of disease?

- T cell responses modulate the severity of disease
- Strong T cell responses in all of these trials seem to have led to prevention of severe disease
- Even prior to vaccines, data indicating cross T-cell immunity from other coronaviruses led to more mild SARS-CoV-2 infection
- If you get re-infected after natural infection or vaccine (likely rare), should be mild if mounted good T-cell response
- Fun fact: Study from 1918 survivors of influenza pandemic show durable B cell immunity (memory B-Ab) 90 years later!
Pfizer/BioNTech trial

- 2 shots, 30μg, 3 weeks apart
- Of 37,706 reported on in NEJM, 49.4% females, 82.9% White, 9.83% AA, 28% Hispanic/Latino
- 21.4% >65 years, Median age 51
- Obesity (35.1%), diabetes 8.4%; pulmonary disease 7.8%
- Of 170 who became infected with COVID-19, 162 in placebo arm and 8 in vaccine arm so 95% effective (same level across subsets)
- Severe disease from COVID-19 - 9 in placebo group; 0 in vaccine group (1 initially said severe, but FDA said not)
Modern vaccine trial

- Phase 3 enrolled 30,351 with data (15,170 in placebo, 15,181 in vaccine), >18 years of age
- 2 shots, 100μg, 4 weeks apart
- 47.3% female, 24.8%, ≥65 years of age, 36.5% of participants communities of color
- 22.3% participants high-risk (mean BMI 29.3)
- 196 final total symptomatic infections (e.g. 11 in vaccine group; 185 in placebo group), 94.1% efficacy
- Severe disease: 30 of the severe cases occurred in the placebo group (1 FDA reviewed in vaccine group)

![Graph showing vaccine efficacy and incidence rate](image)
Johnson and Johnson 1-dose phase 3 trial efficacy

- 468 cases symptomatic COVID
- 100% effective against hospitalization/death from COVID-19 (7 deaths & 14 hospitalizations in placebo)
- 85% effective against severe disease (could be O2 sat <93% but subset of severe disease included those hospitalized/died) across all 3 regions
- 89% efficacy against severe disease in South Africa where 95% of strains were B.1.351 (501Y.V2) variant
- 72% effective against moderate (>93% O2 sat) disease in U.S., 64% in South Africa, 61% Latin America (66% overall)

Immunogenicity data from NEJM phase I/II shows increases in immune responses over time, past 28 days

Press release: Phase 3 ENSEMBLE trial
Will vaccines halt transmission? Biological plausibility (4 main reasons)

1. IgG antibodies measured in trials found in high levels in nasal mucosa

2. Systemic vaccines induce IgA (mucosal immunoglobulin) and recent study shows mRNA COVID-19 vaccines induce IgA

3. Monoclonal antibodies hasten viral clearance from airways

4. Challenge experiments with macaques in pre-clinical trials show blocking of viral replication (or no/low viral RNA) in BAL and nasal swabs (Mercado Nature J&J vax, 2020; Guebre-Xabier Vaccine Novavax 2020)
March 11, 2021 - a year after WHO pandemic declared

- Real-world roll-out data from Ministry of Health Israel, Pfizer vaccine
- 94% of asymptomatic infection prevented
- 97% effective against symptomatic COVID-19 cases, hospitalizations, severe and critical hospitalizations, and deaths
- Unvaccinated individuals 44 times more likely to develop symptomatic COVID-19 and 29 times more likely to die from COVID-19
- 80% of circulating virus during roll-out was B117 variant
Swabbed pre-operative patients across the Mayo Clinic system

Risk of asymptomatic infection was 80% lower after even 1 dose (and still after 2 doses) of mRNA vaccine than those unvaccinated

As expected, symptomatic and asymptomatic infection reduced by vaccines
<table>
<thead>
<tr>
<th>Setting</th>
<th>Finding of xx% reduction in asymptomatic or infections that included asymptomatic</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare workers in England</td>
<td>86%</td>
<td>Hall SSRN, February 22, 2021</td>
</tr>
<tr>
<td>Healthcare workers in Israel</td>
<td>75%</td>
<td>Amit, Lancet, March 6, 2021</td>
</tr>
<tr>
<td>Patients in Mayo Clinic health system</td>
<td>88.7%</td>
<td>Pawlowski medRxiv, February 27, 2021</td>
</tr>
<tr>
<td>Israel Ministry of Health (nationwide)</td>
<td>94%</td>
<td>Pfizer press release, March 11, 2021</td>
</tr>
<tr>
<td>Israel general population (Pfizer)</td>
<td>90%</td>
<td>Dagan NEJM, February 24, 2021</td>
</tr>
<tr>
<td>Pre-surgical patients in Mayo Clinic health system</td>
<td>80%</td>
<td>Tande Clin Inf Dis, March 10, 2021</td>
</tr>
<tr>
<td>Healthcare workers in Cambridge University Hospitals</td>
<td>75%</td>
<td>Weekes Authorea, February 24, 2021</td>
</tr>
</tbody>
</table>

Moreover, nasal viral loads from post-vaccination exposures are low and likely noninfectious per CT values (use rapid Ag test)
Real-world data amazing (US, UK, Israel)

Shiloh Nature Immunology Review 3/12/21; CDC Tracker
Will vaccines work against variants?
Broad T cell repertoire (>19 CD4 epitopes; 17 CD8 epitopes) after infection. Means viral escape of T cell-immunity (from both natural infection and vaccination) unlikely, re-infection if happens mild
Negligible impact of SARS-CoV-2 variants on CD4+ and CD8+ T cell reactivity in COVID-19 exposed donors and vaccinees.

Alison Tarke, John Sidney, Nils Methot, Yun Zhang, Jennifer M Dan, Benjamin Goodwin, Paul Rubiro,

Then look at T-cell response to variants after vaccines- still intact

- Looked at SARS-CoV-2-specific CD4+ & CD8+ T cell responses from those with natural infection with non-variant, compared to variants B.1.1.7, B.1.351, P.1, CAL.20C
- No difference seen between pool of spike protein peptides corresponding to ancestral sequence & those from variants
- T cell reactivity against those pools from variants remained intact if you had mRNA vaccination (Pfizer/Moderna) (or natural infection)
Why not to worry clinically too much about variants

• This is what RNA viruses do, mutate more readily than DNA viruses
• SARS-CoV-2 doesn’t mutate that fast, it is just transmitted a lot
• Neutralizing Ab titer information from Moderna/ Pfizer vaccines reassuring
• T cell responses and B cells and antibodies all elicited by vaccines; reassuring data about no hospitalizations/deaths in J&J (Brazil, S. Africa UK) and AZ trial (included Brazil, South Africa) and Novavax (S. Africa) suggests T cells mediating protection against severe infection
• mRNA vaccines and DNA vaccines can be readily “tweaked” (as they are being) from companies to code for new variant ‘boosters’ in future
That said, we want to tamp down transmission to increase efficacy of vaccine—peel off restrictions slowly!

Fauci urges COVID vaccinations to stop new strains: 'Viruses cannot mutate if they don't replicate'
Want to Motivate Vaccinations? Message Optimism, Not Doom

Monica Gandhi

OPINION ESSAY | COVID-19

• Vaccine optimism can reduce vaccine hesitancy
• Public is savvy enough to understand tiered messaging
• Philosophy of “give an inch, they will take a mile” is not harm reduction
• Lessons from HIV (“serosorting”)—we (or least the good ones) never messaged abstinence

CDC guidelines – March 8, 2021

Vaccinated and vaccinated?

Importantly, no need to quarantine if exposed after vaccination if no symptoms

Vaccinated around unvaccinated and public?

Ok if privacy of home with non-susceptible persons; Keep masks, distancing in public; social norms

Unvaccinated and unvaccinated?

Feel free to mingle with each other without restrictions

Keep all usual restrictions
Vaccinated People Are Going to Hug Each Other

The vaccines are phenomenal. Belaboring their imperfections—and telling people who receive them never to let down their guard—carries its own risks.

JANUARY 27, 2021

Julia Marcus
Epidemiologist and professor at Harvard Medical School
Summary

- Vaccine trials show amazing efficacy and safety
- All vaccines reduce severe disease significantly, likely due to T-cell response – love the T cell
- Vaccines are almost certain to decrease transmission
- Variants can be managed - don’t worry
- Vaccine messaging can be tiered and optimistic