COVID-19
ONLINE EDUCATIONAL PROGRAM

COVID-19 Vaccines at Pandemic Pace: The Latest Results of Human Clinical Trials

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Conflicts of interest

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- I am a clinical investigator for trials funded by Regeneron, Gilead, and Johnson & Johnson
- I do not have any financial conflicts of interest

Natural Immune Responses to SARS-CoV-2

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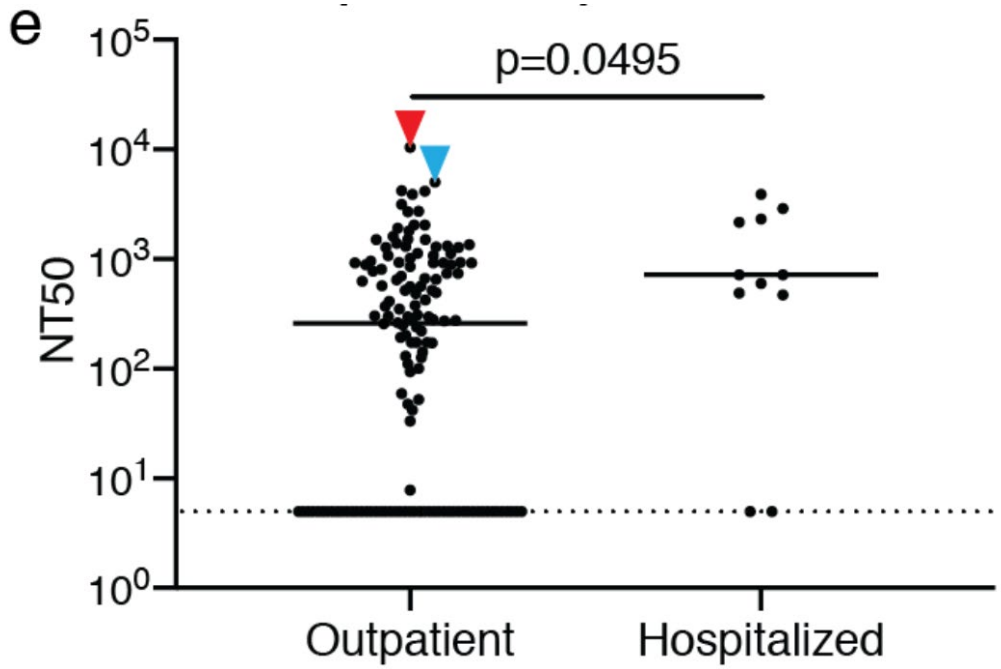
- 149 individuals who had recovered from COVID-19
- Wide range in neutralizing antibody titers
  - 1/3 of people had titers <50, but rare individuals with titers >5000
  - Geometric mean titer = 121
- Antibodies from different individuals were very similar, targeting same epitopes on Spike
- Even at low levels, potent neutralizing antibodies were found in all individuals
- Supports the concept that a vaccine could work in a broad spectrum of individuals

Neutralizing Antibody Titers in Recovered Individuals

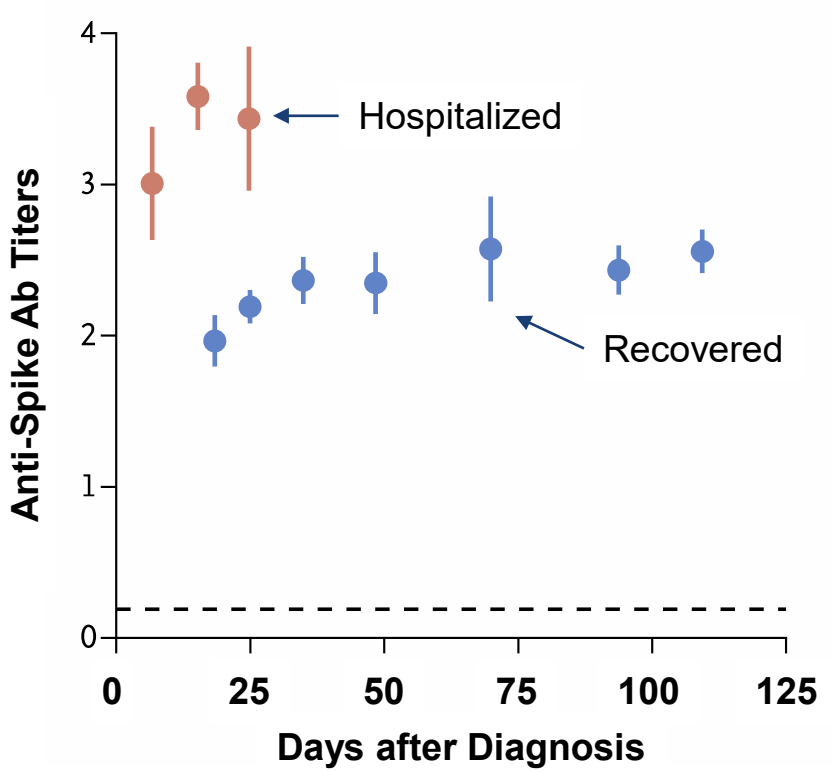


Robbiani *et al.* Nature 2020: Jun 18

Natural Immune Responses to SARS-CoV-2

- 1,237 persons with COVID-19 in Iceland, followed for 4 months
- 91% were seropositive by 25 days
- Ab titers increased over 2 months and then stayed steady
- No significant decrease in Ab titers at 4 months
- Hospitalized persons seroconverted more frequently and quickly
- Ab titers were most strongly associated with hospitalization and clinical severity
- Provides evidence that antibodies can persist, at least over a 4 month period

Binding Antibody Titers over Time



Gudbjartsson *et al.* NEJM 2020: Sep 01

Natural Immunity in Non-Human Primates

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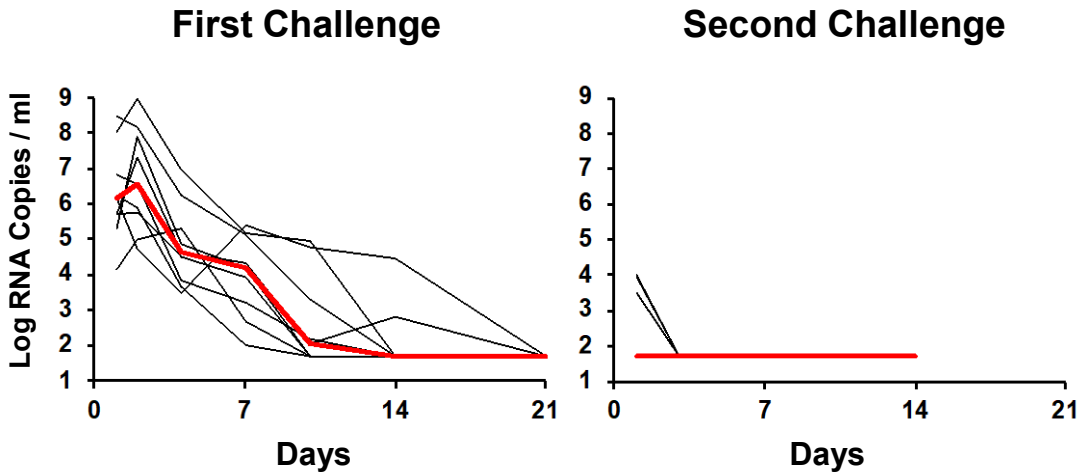
- 9 rhesus macaques were infected with SARS-CoV-2 via upper airway
  - All animals had high viral load in BAL
  - Median NAb titers **~100**
- At day 35, animals were re-challenged via upper airway again
  - 3 animals had low viral load in BAL on day 1, with no recoverable live virus
  - No viral RNA was detected in BAL at any other time-points
  - All animals had a rapid boost in immune responses, showing robust immune memory

Viral Load in Bronchoalveolar Lavage



Chandrashekar *et al.* Science 2020: May 20

Vaccine-Induced Immunity in Non-Human Primates

Ad26-Based Vaccine Experiment

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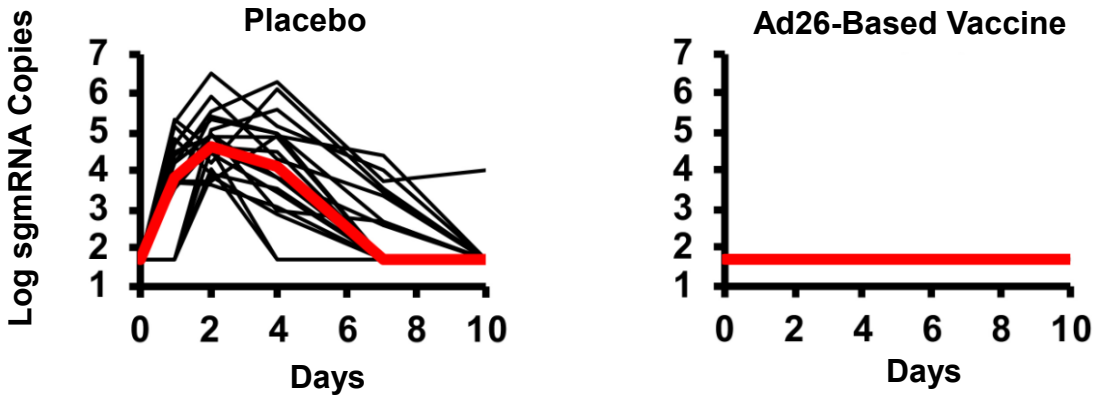
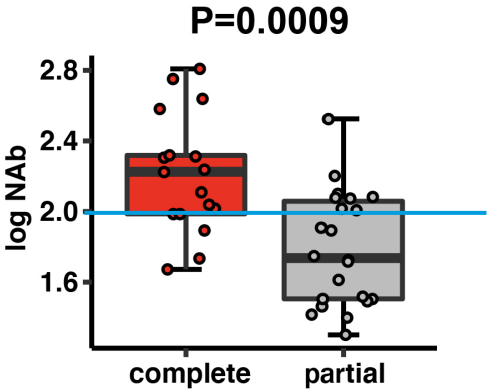
- 52 monkeys immunized with Ad26-based vaccines or placebo
- Median NAb titers in Ad26-S.PP monkeys were 4-fold higher than in convalescent humans
- Ad26-S.PP monkeys had nearly complete protection following challenge
- Vaccine-elicited serum NAb titers inversely correlated with protection
- Vaccine also protected against severe disease in hamsters

Viral Load in Bronchoalveolar Lavage in Monkeys



NAbs by Complete/Partial Protection

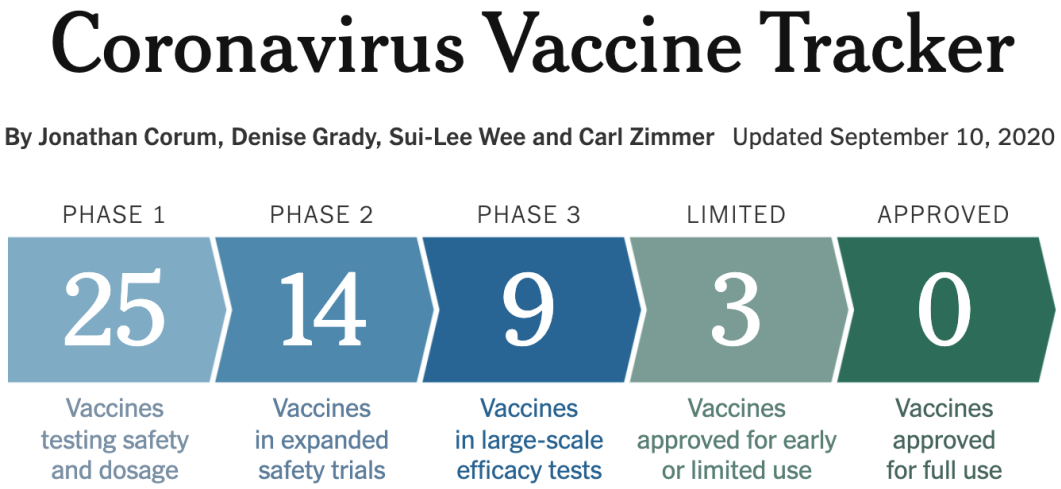


Mercado *et al.* Nature 2020: July 30; Tostanoski et al. Nat Med: Sep 3

Types of COVID-19 Vaccines

Same Spike Protein, Different Mechanisms of Delivery

- Vaccines in Phase 3 testing, with published clinical data:
  - Pfizer
  - moderna
  - AstraZeneca
  - NOVAVAX Creating Tomorrow's Vaccines Today
  - 康希诺生物 CanSinoBIO
  - THE GAMALEYA NATIONAL CENTER OF EPIDEMIOLOGY AND MICROBIOLOGY



BNT162b2 Vaccine – *Phase 1*

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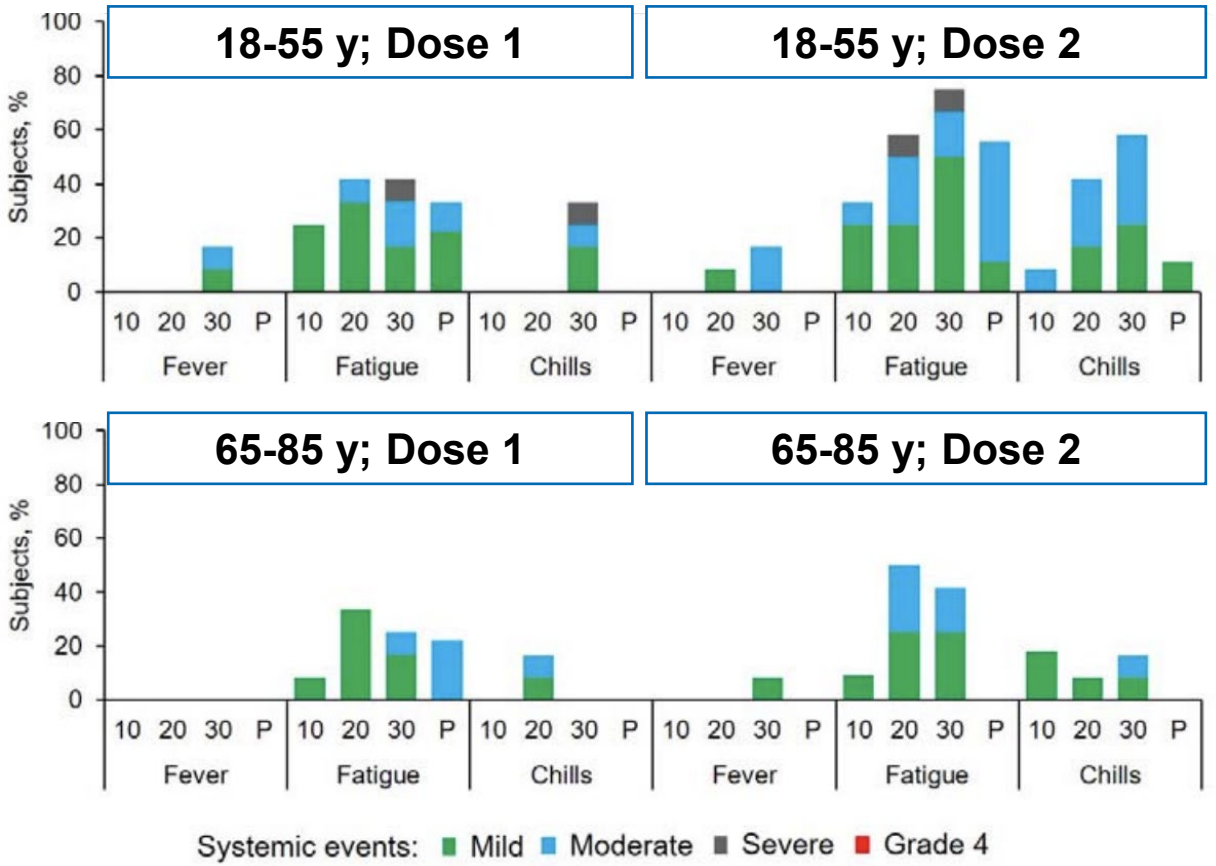
- **Platform:** lipid nanoparticle-formulated, nucleoside-modified RNA (modRNA)
- **Study Design**: Randomized, controlled trial (N=90 for BNT162b2 arm)
  - Two vaccinations, 21 days apart
  - Dose 10 µg, 20 µg, or 30 µg
- **Vaccine Safety**
  - No serious adverse events; no study pauses – but only 7 days f/u so far
  - Symptoms were dose-dependent, greater after the second dose and transient
  - Fevers were uncommon

Percentage of Participants with Systemic Symptom



Preprint - Walsh *et al.* medRxiv 2020: Aug 28

BNT162b2 Vaccine – *Phase 1*

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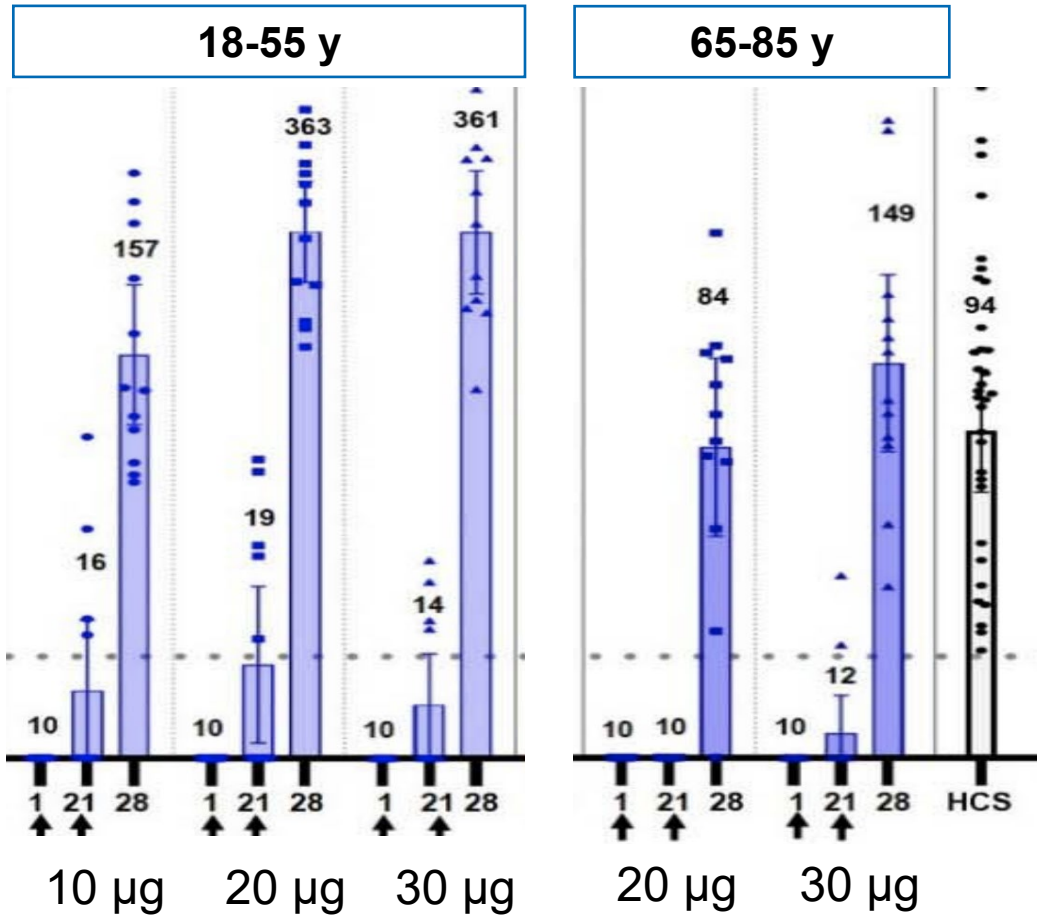
- **Antibody responses**
  - Anti-spike antibodies were generated in all participants after first dose
  - Neutralizing antibodies required two doses
  - Antibody responses were lower in older adults compared to younger
  - Lowest responses were in 10 µg group; 20 µg and 30 µg were similar
  - GMT of 30 µg were 2-4 times higher than convalescent serum
- **T cell responses**
  - Not analyzed at time of publication

Neutralizing Antibody Titers in Humans



Preprint - Walsh *et al.* medRxiv 2020: Aug 28

moderna mRNA-1273 Vaccine – *Phase 1*

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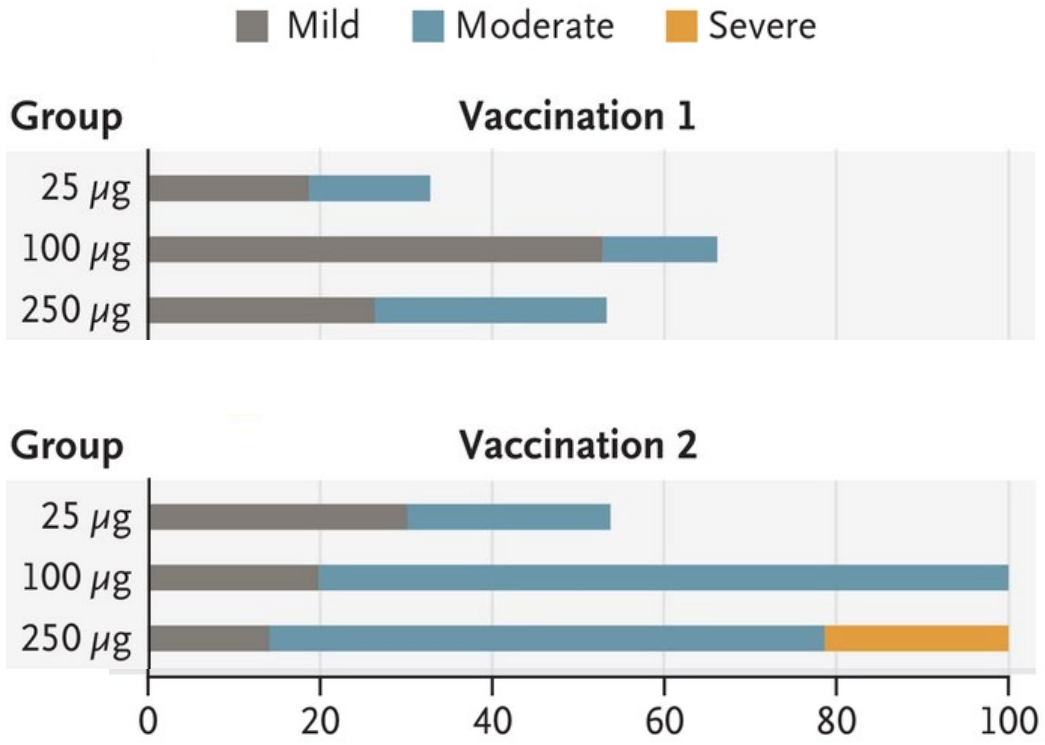
- **Platform:** nanoparticle encapsulating mRNA
- **Study Design**: Open-label trial (N=45)
  - Two vaccinations, 28 days apart
  - Dose 25 µg, 100 µg, or 250 µg
- **Vaccine Safety**
  - No serious adverse events; no study pauses
  - First dose led to mild/moderate symptoms
  - Second dose of 100 µg or 250 µg had marked increase in symptoms
    - 100% had systemic symptoms
    - 21% at 250 µg were severe
    - 40-60% had fever, 1 with T39.6 (T103.2)

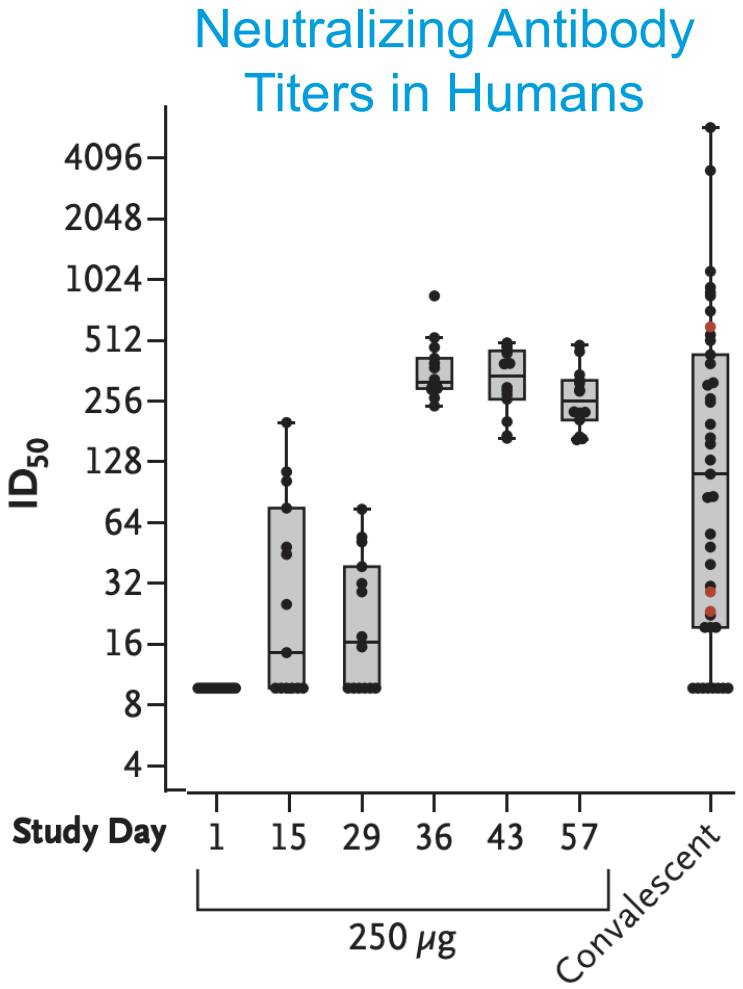
Percentage of Participants with Any Systemic Symptom



Jackson *et al.* NEJM 2020: July 14

mRNA-1273 Vaccine – *Phase 1*

- **Antibody responses**
  - Anti-spike antibodies were generated in all participants after first dose
  - Neutralizing antibodies required two doses
    - Lowest responses in 25 µg dose
    - 100 µg or 250 µg responses similar to higher end of convalescent sera
- **T cell responses**
  - CD4 T cell responses were elicited by lower doses; strongly biased toward Th1 phenotype
  - Minimal CD8 T cell responses



Jackson *et al.* NEJM 2020: July 14

AstraZeneca ChAd Vector Vaccine – *Phase 1/2*

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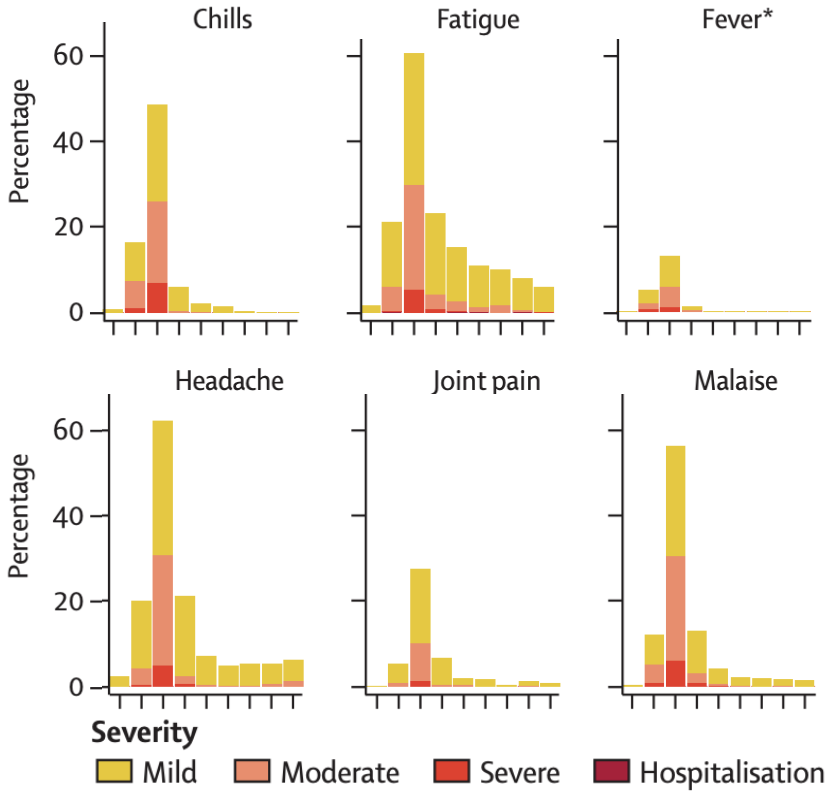
- **Platform:** Chimp adenovirus vector
- **Study Design**: Single-blind, randomized controlled trial (N=1077)
  - 5 x 10^{10} VP vs. meningococcal vaccine
  - One arm received prophylactic paracetamol
- **Vaccine Safety**
  - No serious adverse events; no study pauses
  - Systemic symptoms were common
    - ~60% muscle ache, malaise, and chills
    - ~20% with fever, 2% with T>39 (102.2)
  - Paracetamol prevented many symptoms
  - Symptoms after second dose were *less* severe

Percentage of Participants with Systemic Symptom



Folegatti *et al.* Lancet 2020: July 20

AstraZeneca ChAd Vector Vaccine – *Phase 1/2*

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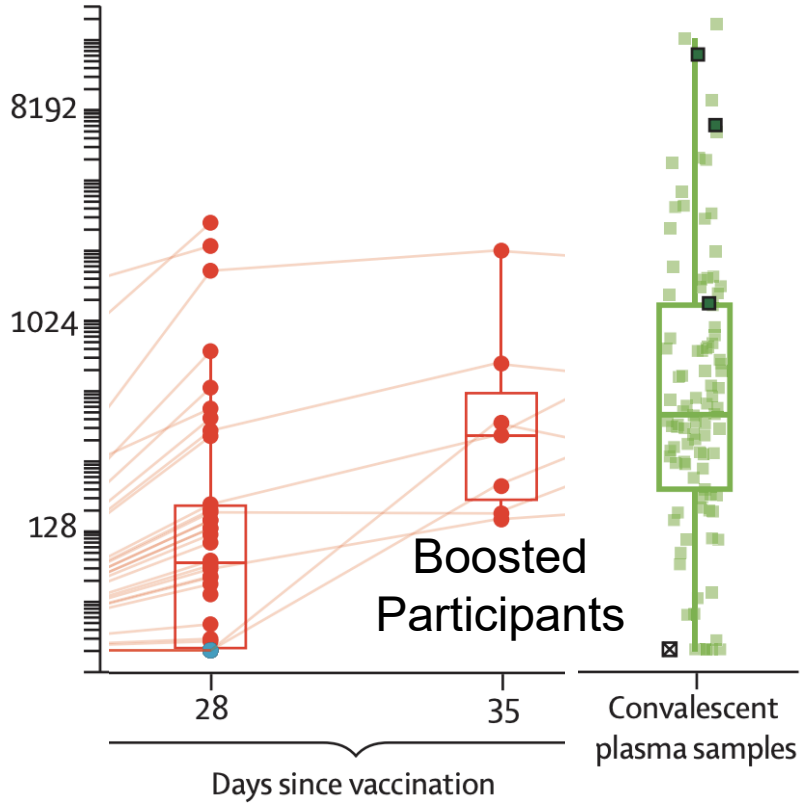
- **Antibody responses**
  - Anti-spike binding antibodies peaked by day 28 and remained elevated to day 56
  - Neutralizing Ab titers were relatively low after single dose
  - Pseudo NAb titers GMT <128 (lower than convalescent plasma)
  - Boosting increased NAb in small cohort
- **T cell responses**
  - T cell responses were detected, but cytokine profiles were not reported

Neutralizing Antibody Titers in Humans



Folegatti *et al.* Lancet 2020: July 20

NOVAVAX NVX-CoV2373 Vaccine – *Phase 1/2*

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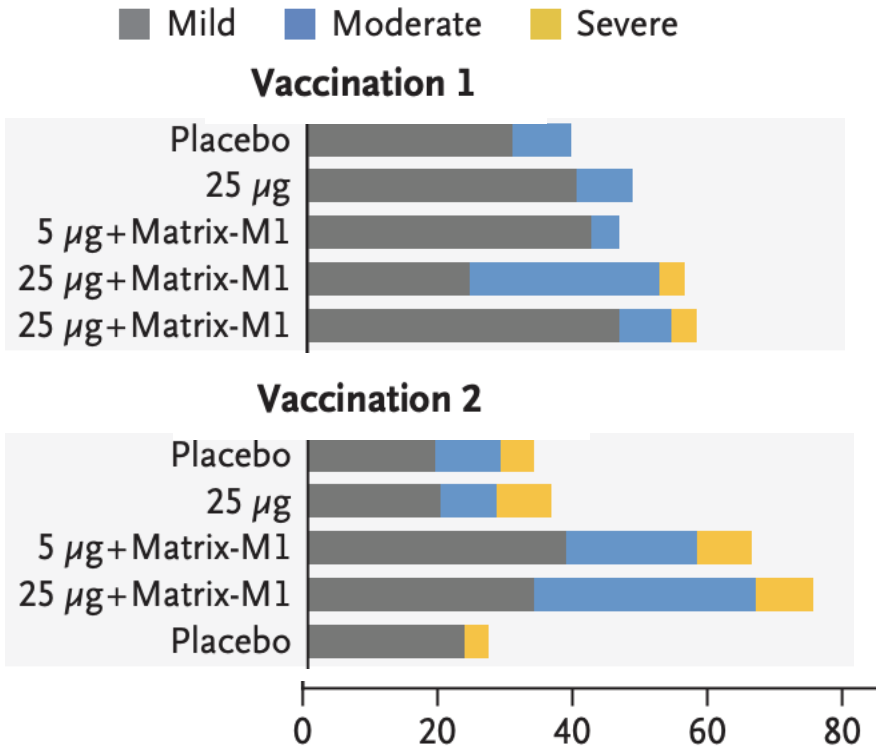
- **Platform:** nanoparticle encapsulating spike protein plus adjuvant
- **Study Design:** randomized placebo-controlled trial in Australia (N=131)
  - 5-µg and 25-µg with or without Matrix-M1
  - One or two doses
- **Vaccine safety**
  - No serious adverse events; no study pauses
  - Majority had no symptoms or mild; only one participant with fever
  - Slightly more symptoms after 2nd vaccine

Percentage of Participants with Any Systemic Symptom



Keech *et al.* NEJM 2020: Sep 2

NOVAVAX NVX-CoV2373 Vaccine – *Phase 1/2*

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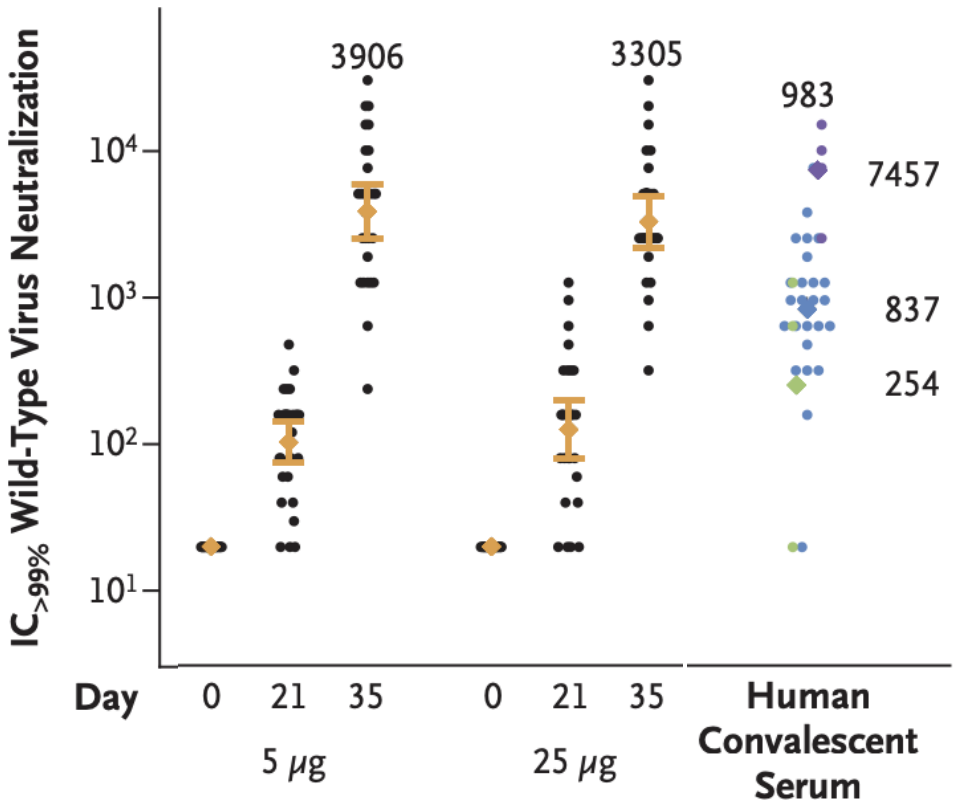
- **Antibody responses:**
  - Single shot elicited binding antibodies in nearly everyone, but boost significantly increased responses
  - Adjuvanted two-dose regimens were most immunogenic; dose made no difference
  - At day 35, neutralizing Abs were 4 to 6 times greater than convalescent serum GMT
- **T cell responses**
  - Adjuvanted regimens induced polyfunctional CD4+ T-cell responses with a Th1 phenotype

Neutralizing Antibody Titers in Humans

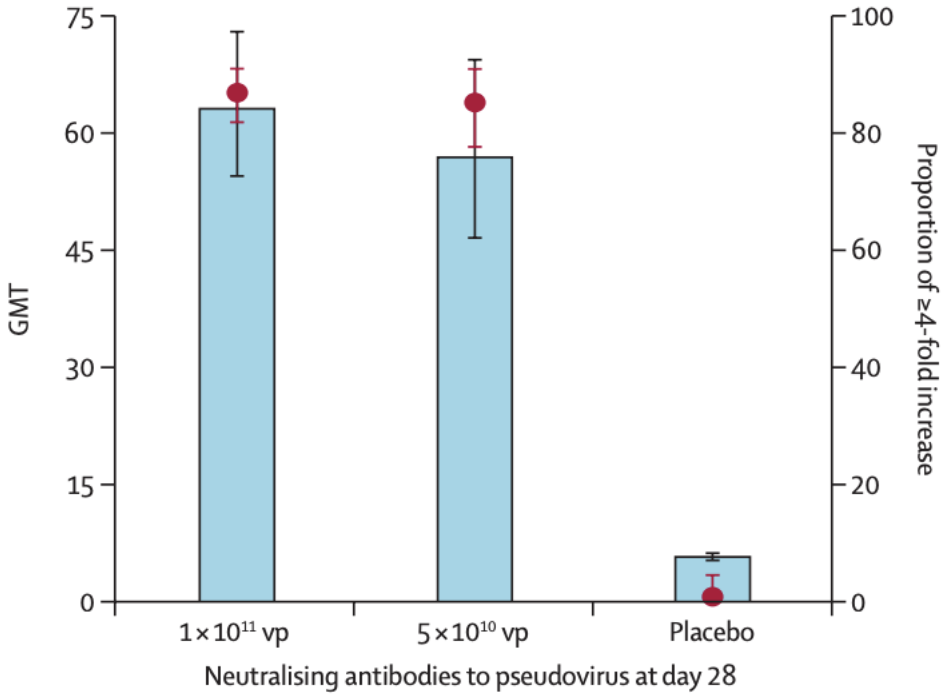


Keech *et al.* NEJM 2020: Sep 2

Ad5 Vector Vaccine – *Phase 1 & 2*

- **Platform:** Replication-defective Ad5 vector
- **Phase 1:** Open-label trial of low-middle-high doses (N=108) in Wuhan, China
  - High dose was not well tolerated
  - Low/moderate NAb titers after single shot
- **Phase 2:** RCT (N=508) in Wuhan, China
  - Middle dose was not well tolerated (9% had severe adverse events, mostly T>101.3 °F)
  - Low dose as immunogenic as high dose
- **Phase 3:** Underway in China, Saudi Arabia and Pakistan
- Limited Approval: Chinese military, unclear if mandatory or optional for soldiers

Neutralizing Antibody Titers in Humans

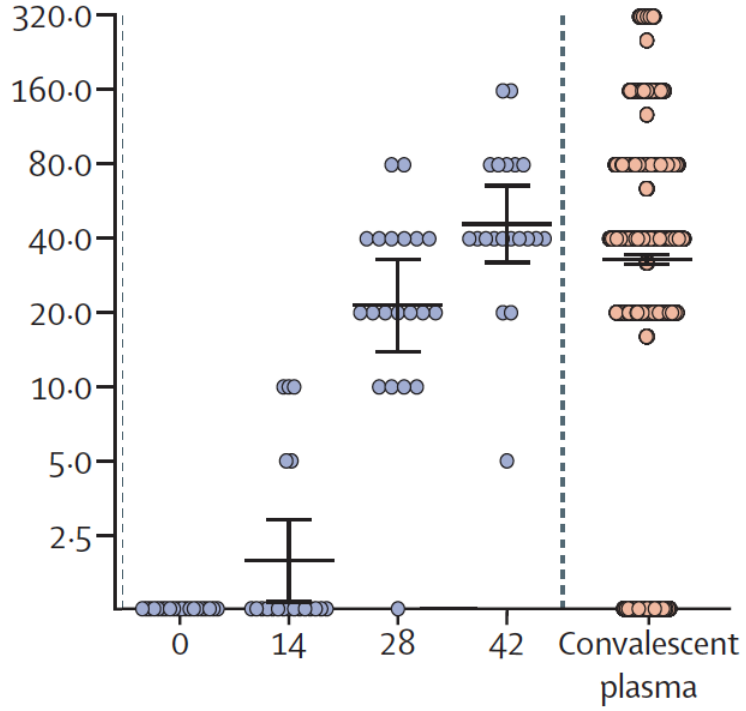


Zhu *et al.* Lancet 2020: May 22 & Jul 20

Ad26/Ad5 Vector Vaccine – *Phase 1/2*

- **Platform:** Ad26 prime at D0, Ad5 boost at D21
- **Phase 1:** Open-label trial of non-lyophilized vaccine combo in Moscow, Russia (N=20)
- **Phase "2":** Open-label trial of lyophilized vaccine combo in Moscow, Russia (N=20)
  - Generally well-tolerated; 50% with fevers
  - Neutralizing Ab (live virus) GMT ~46
  - *Very small sample size for a safety cohort*
- **Phase 3**: Underway per report, no details
- 'Approved' in Russia: Recommended for use; unclear uptake

Neutralizing Antibody Titers in Humans



Logunov *et al.* Lancet 2020: Sep 04

Summary (1)

- COVID-19 leads to neutralizing antibody responses in humans
  - There is a wide range in titers, likely related to severity of illness
  - NAbs target Spike protein
  - It is unknown if NAbs are protective in humans
- Animal studies suggest that immunity to COVID-19 is possible
  - Convalescent NAbs protect monkeys against re-infection
  - Vaccines protect animals from COVID-19 infection and severe disease
- Nearly all COVID-19 vaccine candidates use Spike protein
  - Only the delivery mechanism is different

Summary (2)

- Phase 1 & 2 clinical data are promising
  - Multiple platforms are safe and generally well-tolerated
  - Vaccines all elicited antibody responses
  - But, room for improvement: some participants with transient febrile syndrome; 2 doses are required for strong NAb responses

- **Finally: durability and protective efficacy are currently unknown for all COVID-19 vaccines at this time**

Thank You and Questions

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