Rapid Development of COVID-19 Vaccines

01/06/2020
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Disclosures

Sanofi
- Support for COVID-19 vaccine clinical trial

Altimmune
- Consultant for COVID-19 vaccine clinical development

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Outline

Treatment successes (focus on UAB)
- **Antivirals**
- **Immune modulators**
- **Monoclonal antibodies**

Effective vaccines
Upcoming vaccines in efficacy testing
Vaccine distribution
Anticipated questions

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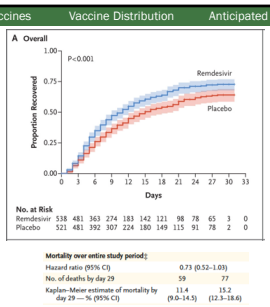
Remdesivir decreased the time to recovery



Mortality over entire study period‡		
Hazard ratio (95% CI)	0.73 (0.52–1.03)	
No. of deaths by day 29	59	77
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)

Beigel et al. NEJM 2020

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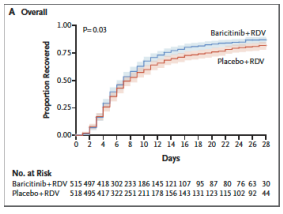
Baracitinib improved recovery



Kalil et al. NEJM 2020

Mortality over entire trial period‡		
Hazard ratio (95% CI)	0.65 (0.39–1.09)	
No. of deaths by day 28	24	37
Kaplan–Meier estimate of mortality by 28 — % (95% CI)	5.1 (3.5–7.6)	7.8 (5.7–10.6)

RECOVERY group. NEJM 2020

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)

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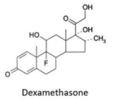
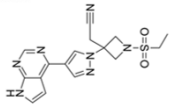
Anti-inflammatory drugs

Dexamethasone (steroids): RECOVERY Trial
- Decreased mortality rates



Dexamethasone

Baracitinib (UAB study by Drs. Erdmann and Goepfert)
- Improved patient outcome on top of Remdesivir



Are steroids better than baracitinib? ACTT4

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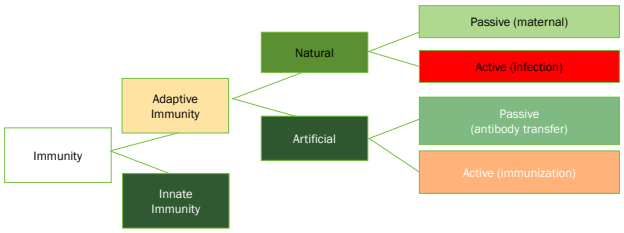
Overview of Immune Responses



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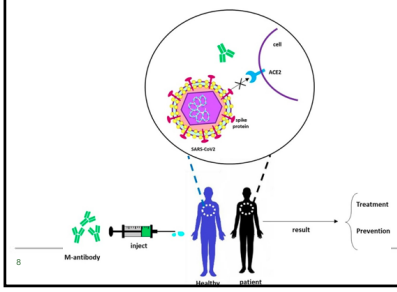
Monoclonal antibodies



Inpatient and Outpatient Treatment Studies at UAB:
Drs. Turner Overton and Sonya Heath
Outpatient Prevention Study:
Dr. Greer Burkholder

Eli Lilly: Outpatient and EUA
Regeneron: Inpatient

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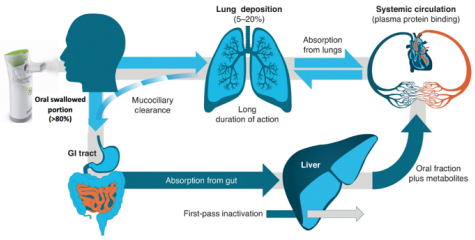
Inhalation of mAb enables rapid and efficient airway delivery



adopted from Strong et al. 2018 PMID: 29775668

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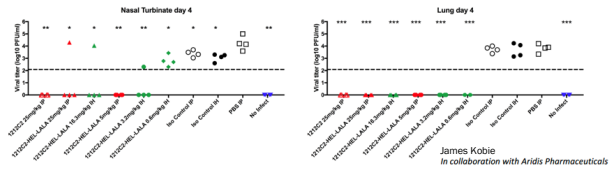
Inhaled SARS-CoV-2 monoclonal antibody decreases viral shedding in a hamster model



James Kobie
In collaboration with Aridis Pharmaceuticals

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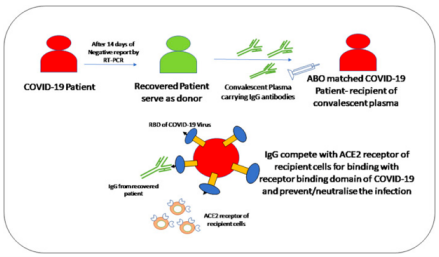
Plasma Donation



Dr. Sonya Heath
Outpatient
Inpatient
EUA

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A sample of other studies at UAB

ACTT3: Remdesivir vs Remdesivir with interferon-beta
ACTT4: Baracitinib vs Dexamethasone

IL-1 antagonist
- Anakinra (Drs. Randy Cron and Winn Chatham)
- Canakinumab (Dr. Turner Overton); did not work☹

I-Spy (Drs. Derek Russell and Sheetal Gandotra)
NRP2 modulator (Dr. Mike Wells)

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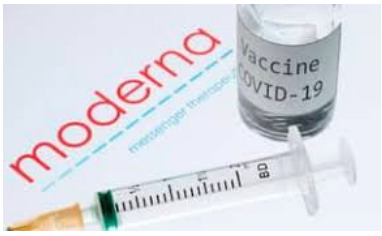
Treatments | Effective Vaccines | Upcoming Vaccines | Vaccine Distribution | Anticipated Questions

An ounce of prevention…Vaccines!



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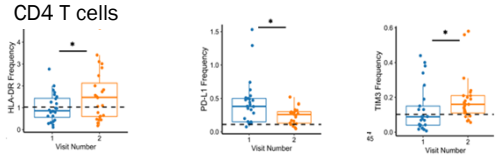
T cell activation increases into convalescence

CD4 T cells



Files et al. JCI 2020

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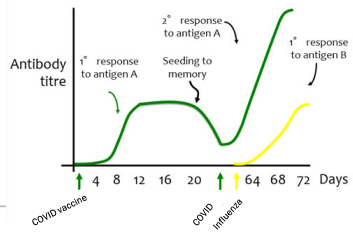
Clonal Nature of Adaptive immune Response Allows for Immunological Memory



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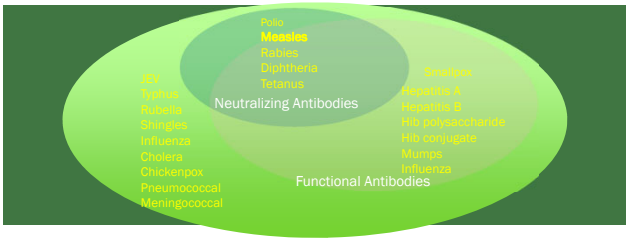
Antibodies are the Primary Correlates of Vaccine Protection



Adapted from Plotkin et al. Vaccine 2009

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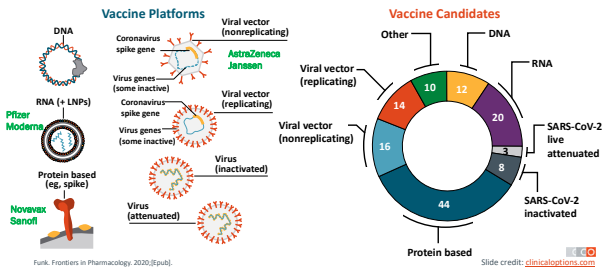
Vaccine Candidates in Development for SARS-Cov-2



Funk. Frontiers in Pharmacology. 2020;[Epub].

Slide credit: clinicaloptions.com

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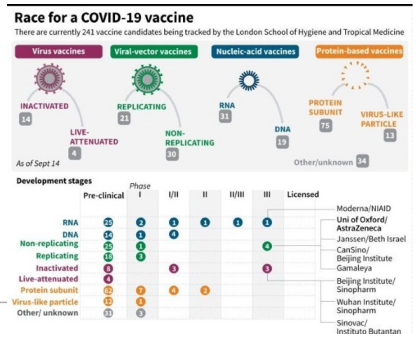
COVID Vaccine Development



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Moderna COVID-19 Vaccine Timeline

How so fast?

1. Targeting the Spike protein (2003)
2. Rapid identification and sequencing
3. Rapid mRNA vaccine development
4. Combined phases 1&2
5. Rapid enrollment (>30,000)
6. Large numbers of infections

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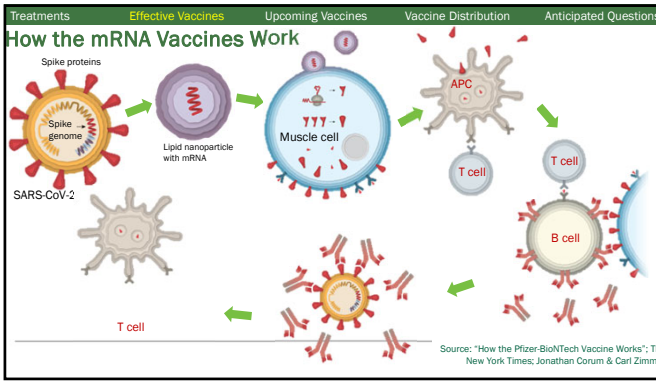
How the mRNA Vaccines Work



Source: "How the Pfizer-BioNTech Vaccine Works"; The New York Times; Jonathan Corum & Carl Zimmer

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

L.A. Jackson, E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene, R.N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens, A.J. Pruijssers, A. McDermott, B. Flach, N.A. Doria-Rose, K.S. Corbett, K.M. Morabito, S. O'Dell, S.D. Schmidt, P.A. Swanson II, M. Padilla, J.R. Mascola, K.M. Neuzil, H. Bennett, W. Sun, E. Peters, M. Makowski, J. Albert, K. Cross, W. Buchanan, R. Pikaart-Tautges, J.E. Ledgerwood, B.S. Graham, and J.H. Beigel, for the mRNA-1273 Study Group*

Jackson et al. NEJM 2020

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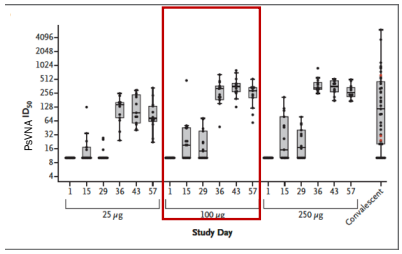
mRNA-1273 COVID vaccine induces neutralizing antibodies



Jackson et al. NEJM 2020

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

Baden et al. NEJM 2020

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mRNA-1273 phase 3 vaccine schedule

Vaccine vs placebo at day 1 and day 28

30,420 randomized

- **15,210 100mcg mRNA**
- **15,210 placebo**

~28,000 included in per protocol analysis

Baden et al. NEJM 2020

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Demographic and Clinical Characteristics at baseline

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Sex — no. of participants (%)			
Male	8,062 (53.1)	7,923 (52.2)	15,985 (52.7)
Female	7,108 (46.9)	7,258 (47.8)	14,366 (47.3)
Mean age (range) — yr	51.3 (18–85)	51.4 (18–85)	51.4 (18–85)
Age category and risk for severe Covid-19 — no. of participants (%)†			
18 to <65 yr, not at risk	8,886 (58.6)	8,888 (58.5)	17,774 (58.6)
18 to <65 yr, at risk	2,535 (16.7)	2,530 (16.7)	5,065 (16.7)
≥65 yr	3,749 (24.7)	3,763 (24.8)	7,512 (24.8)
Hispanic or Latino ethnicity — no. of participants (%)‡			
Hispanic or Latino	3,114 (20.5)	3,121 (20.6)	6,235 (20.5)
Not Hispanic or Latino	11,917 (78.6)	11,918 (78.5)	23,835 (78.5)
Not reported and unknown	139 (0.9)	142 (0.9)	281 (0.9)
Race or ethnic group — no. of participants (%)‡			
White	11,995 (79.1)	12,029 (79.2)	24,024 (79.2)
Black or African American	1,527 (10.1)	1,565 (10.3)	3,092 (10.2)
Asian	731 (4.8)	651 (4.3)	1,382 (4.6)
American Indian or Alaska Native	121 (0.8)	112 (0.7)	233 (0.8)
Native Hawaiian or Other Pacific Islander	32 (0.2)	35 (0.2)	67 (0.2)
Multiracial	321 (2.1)	315 (2.1)	636 (2.1)
Other	316 (2.1)	321 (2.1)	637 (2.1)
Not reported and unknown	127 (0.8)	155 (1.0)	282 (0.9)

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Baseline SARS-CoV-2 status — no. of participants (%)‖			
Negative	14,598 (96.2)	14,550 (95.8)	29,148 (96.0)
Positive	537 (3.5)	543 (3.6)	680 (3.5)
Missing data	235 (1.5)	288 (1.9)	523 (1.7)
Baseline RT-PCR test — no. of participants (%)			
Negative	14,923 (98.4)	14,917 (98.3)	29,840 (98.3)
Positive	95 (0.6)	87 (0.6)	182 (0.6)
Missing data	152 (1.0)	177 (1.2)	329 (1.1)
Baseline SAD anti-SARS-CoV-2 assay — no. of participants (%)			
Negative	14,726 (97.1)	14,690 (96.8)	29,416 (96.9)
Positive	303 (2.0)	305 (2.0)	608 (2.0)
Missing data	141 (0.9)	186 (1.2)	327 (1.1)
Risk factor for severe Covid-19 — no. of participants (%)			
Chronic lung disease	744 (4.9)	710 (4.7)	1,454 (4.8)
Significant cardiac disease	744 (4.9)	752 (5.0)	1,496 (4.9)
Severe obesity	1,021 (6.7)	1,025 (6.8)	2,046 (6.7)
Diabetes	1,446 (9.5)	1,435 (9.5)	2,875 (9.5)
Liver disease	96 (0.6)	100 (0.7)	196 (0.6)
Human immunodeficiency virus infection	87 (0.6)	92 (0.6)	179 (0.6)
Body-mass index¶			
No. of participants	15,007	14,985	29,992
Mean ±SD	29.3±6.7	29.3±6.9	29.3±6.8

Baden et al. NEJM 2020

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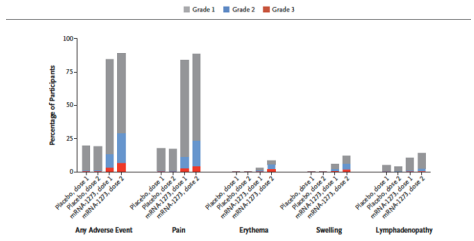
Local Events



Baden et al. NEJM 2020

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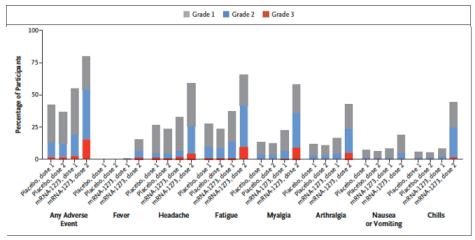
Systemic Events



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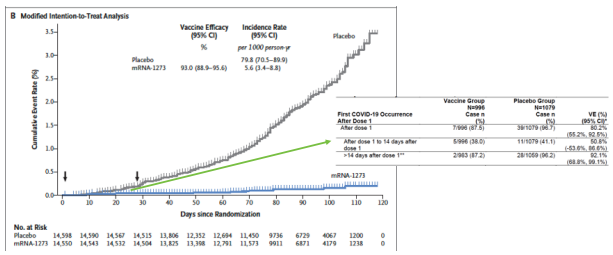
mRNA-1273 Vaccine Efficacy



First COVID-19 Occurrence	Vaccine Group N=996 Case n (%)	Placebo Group N=1079 Case n (%)	VE (%) (95% CI)*
After dose 1	7/996 (87.3)	39/1079 (96.7)	80.2% (55.2%, 92.6%)
After dose 1 to 14 days after dose 1	5/996 (38.0)	11/1079 (41.1)	50.6% (-53.8%, 88.6%)
>14 days after dose 1**	2/983 (87.2)	28/1059 (96.2)	92.1% (69.8%, 99.1%)

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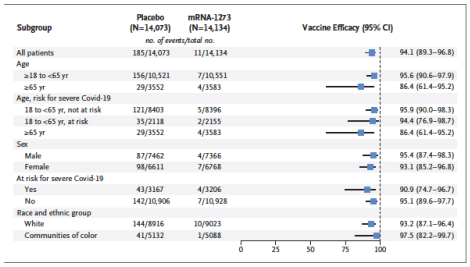
mRNA-1273 vaccine efficacy in subgroups



Baden et al. NEJM 2020

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mRNA-1273 vaccine in those with prior COVID infection

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
Baseline SARS-CoV-2			
Regardless of baseline SARS-CoV-2 status	6/15180	92/15170	93.5% (85.2, 97.2)
Positive	0/341	1/334 (0.3) 17.038	100%
Negative	6/14312 (<0.1) 2.154	90/14370 (0.6) 32.298	93.4% (84.8%, 97.1%)
Unknown or missing	0/527	1/465 (0.2)	100%

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mRNA-1273 vaccine efficacy with severe COVID risk

Subgroup	Vaccine Group Cases / N (%) Incidence rate per 1,000 person-years	Placebo Group Cases / N (%) Incidence rate per 1,000 person-years	VE % (95% CI)*
At risk for severe COVID-19 due to comorbidity, regardless of age			
Yes	1 / 3116 (<0.1) 1.604	24 / 3075 (0.8) 39.177	95.9% (69.7%, 99.4%)
Chronic Lung Disease	0/661	6/673 (0.9) 42.950	100%
Significant Cardiac Disease	0/686	3/678 (0.4) 21.463	100%
Severe Obesity (BMI ≥40 kg/m^2)	1/901 (0.1) 5.524	11/884 (1.2) 62.851	91.2% (32.0%, 98.9%)
Diabetes	0/1338	7/1309 (0.5) 27.148	100%
Liver Disease	0/93	0/90	
HIV infection	0/80	1/76 (1.3) 91.108	100%
No	4 / 10818 (<0.1) 1.911	66 / 10808 (0.6) 31.657	94.0% (83.5%, 97.8%)
Obesity (BMI >30 kg/m^2)**	2/5269 (<0.1%)	46/5207 (0.9)	95.8% (82.6, 99.0)

Baden et al. NEJM 2020

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Vaccines with the potential for rapid EUA

Chimp Ad recombinant from AstraZeneca

	Total number of cases	ChAdOx1 nCoV-19	Control	Vaccine efficacy (95% CI)	p value for interaction
COV002 (UK), age 18–55 years*	..	..	..	..	0·019
LD/SD recipients	33	3/1367 (0·2%)	30/1374 (2·2%)	90·0% (67·3 to 97·0)	..
SD/SD recipients	49	14/1879 (0·7%)	35/1922 (1·8%)	59·3% (25·1 to 77·9)	..
COV002 (UK), age 18–55 years with >8 weeks' interval between vaccine doses*	..	..	..	..	0·082
LD/SD recipients	33	3/1357 (0·2%)	30/1362 (2·2%)	90·0% (67·3 to 97·0)	..
SD/SD recipients	34	8/1407 (0·6%)	26/1512 (1·7%)	65·6% (24·5 to 84·4)	..
All SD/SD (UK and Brazil)†	..	..	..	..	0·557
<6 weeks' interval between vaccine doses	28	9/1702 (0·5%)	19/1698 (1·1%)	53·4% (−2·5 to 78·8)	..
≥6 weeks' interval between vaccine doses	70	18/2738 (0·7%)	52/2757 (1·9%)	65·4% (41·1 to 79·6)	..

Cohorts are all subsets of the primary efficacy population. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. BMI=body mass index. *Models adjusted for BMI (<30 vs ≥30 kg/m^2), health-care worker status (yes vs no), and ethnicity (white vs non-white). †Model adjusted for BMI (<30 vs ≥30 kg/m^2), health-care worker status (yes vs no), ethnicity (white vs non-white), age (<56 years vs ≥56 years), and study (COV002 vs COV003).

Table 3: Subgroup comparisons of efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population

Voysey et al. Lancet 2020

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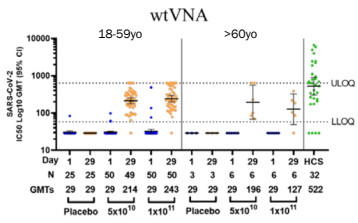
Vaccines with the potential for rapid EUA

Ad-26 recombinant from Janssen



- Fully enrolled 44,000 participants
- Better data in communities of color
  Better data for prevention of severe COVID?
- Efficacy read in the next week or 2
- EUA at the end of the month

Sadoff et al. NEJM 2021

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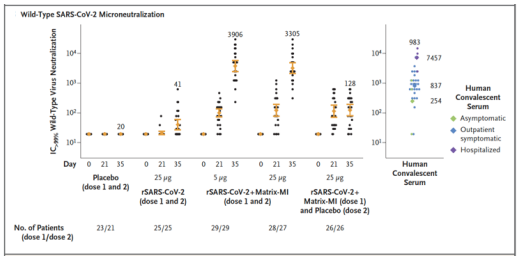
Recombinant protein vaccine efficacy study from Novavax just started!



Keech et al. NEJM 2020

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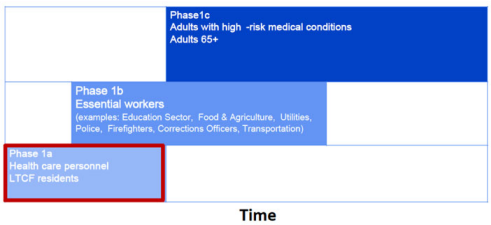
Treatments | Effective Vaccines | Upcoming Vaccines | Vaccine Distribution | Anticipated Questions

COVID Vaccine Allocation Plans

Work Group Proposed Interim Phase 1 Sequence



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Treatments | Effective Vaccines | Upcoming Vaccines | Vaccine Distribution | Anticipated Questions

UAB F

10,725 dc
9,713 dos
17,525 ne

UAB MEDICINE VACCINATION SEQUENCING PLAN

PHASE 1a.1	Phase 1a.2	Phase 1a.3	Phase 1a.4
COVID Care Units[1]	COVID Surge Units[2]	Remaining nursing units[2]	TKC Radiology
Emergency Departments	Anesthesia	Remaining providers	Maintenance
Labor and Delivery	Respiratory Therapy	Food and Nutrition Services	HSIS (patient-care focused)
Emergency Response Teams	Remaining GME	UAB Police (hospital-based)	Optometry
Nursing Pool Staff	Environmental Services	Care Transitions	Ambulatory/ Outpatient Clinics
Infectious Disease Faculty	Acute Care Rehab	Pastoral Care	Joint Health Sciences
Anesthesia	Inpatient Radiology Techs & Staff	Infection Prevention	Administration/Corporate Services
COVID Testing Team	Age > 65	Spain Rehabilitation Center	
COVID Vaccination Team	Infusion Therapy	Center for Psychiatric Medicine	
Key Emergency Management Personnel	Laboratory (including COVID Research)	Guest Services (includes Patient Transport)	
Pediatric COVID Unit and ED Faculty, Fellows, and Residents	Perioperative & Procedural Areas	Dentistry	
	Inpatient Advanced Practice Providers	Clinical Research	
	COVID Consulting Services		
	Pharmacy		

[1]Includes faculty, fellow, residents, nursing, EVS, and Respiratory Therapy Staff
[2]Includes corresponding provider groups

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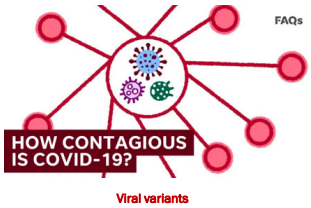
Do I need to be vaccinated every year?

Unknown



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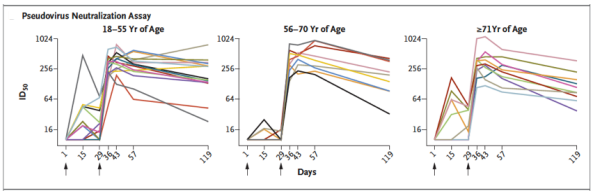
Do I need to be vaccinated every year? Durability

Antibody responses 4 months following mRNA-1273 vaccine



Widge et al. NEJM 2020

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I am pregnant or lactating, should I get the vaccine?

Pregnancy is a COVID high risk group
Not studied in these groups
Recommended by various organizations including ACOG

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I had an anaphylactic reaction to the influenza vaccine, should I get the COVID vaccine?

MAY PROCEED WITH VACCINATION	PRECAUTION TO VACCINATION	CONTRAINDICATION TO VACCINATION
ALLERGIES History of allergies that are unrelated to components of an mRNA COVID-19 vaccine[1], other vaccines, or injectable therapies, such as: • Allergy to oral medications (including the oral equivalent of an injectable medication) • History of food, pet, insect, venom, environmental, latex, etc., allergies • Family history of allergies **ACTIONS** • 30 minute observation period: Persons with a history of anaphylaxis (due to any cause) • 15 minute observation period: All other persons	**ALLERGIES** • History of any immediate allergic reaction[2] to vaccines or injectable therapies (except those related to component of mRNA COVID-19 vaccines[1] or polysorbate, as these are contraindicated) **ACTIONS:** • Risk assessment • Consider deferral of vaccination and/or referral to allergist-immunologist • 30 minute observation period if vaccinated	**ALLERGIES** History of the following are contraindications to receiving either of the mRNA COVID-19 vaccines[1]: • Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components • Immediate allergic reaction[2] of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components[3] (including polyethylene glycol)[4] • Immediate allergic reaction of any severity to polysorbate[4] **ACTIONS** • Do not vaccinate[5] • Consider referral to allergist-immunologist

CDC recommendations, December 2020

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I recovered from COVID infection, should I receive the vaccine?

YES but wait 90 days

- **Unlikely to get re-infected by then**
- **Allow more vaccine doses for others**
- **Less likely to develop systemic reactions?**

Immune responses may be better with vaccine

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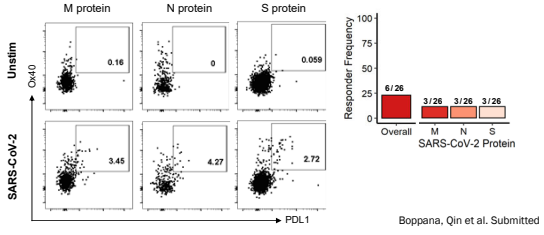
Poor induction of follicular helper T cells following infection



Boppana, Qin et al. Submitted

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Should I obtain an antibody test to see if I responded to the vaccine?

Unknown

Correlate of protection not known but unlikely to be protective if no antibodies are induced

Be sure you get the correct antibody test (S not N antibodies)

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I developed Guillain Barre Syndrome following a flu shot, should I receive the vaccine?

Prior GBS patients were excluded from most COVID vaccine efficacy studies

BUT

No cases of GBS have been reported in clinical trials

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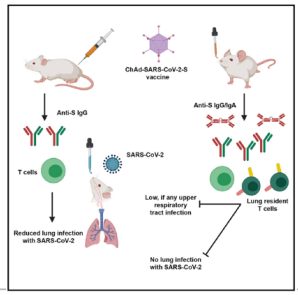
Do COVID vaccines protect against SARS-CoV-2 transmission?

Unknown!



Hassan et al. Cell 2020

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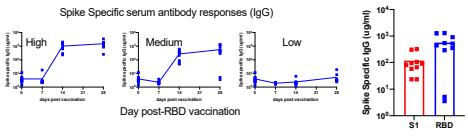
Testing the intranasal SARS-CoV-2 vaccine in mice

Intranasal Ad5 vaccine containing S1 domain from Spike or RBD domain from Spike



Randall and Lund labs

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Conclusions

COVID vaccines have been developed rapidly beating prior record by 4 years

- **SARS-1 knowledge**
- **New technology**
- **New trial design**
- **Rapid enrollment into large trials**
- **Growing pandemic**
- **Relatively low viral mutation rate**

Continued vigilance of vaccine side effects…

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Acknowledgements

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Unanticipated questions?

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