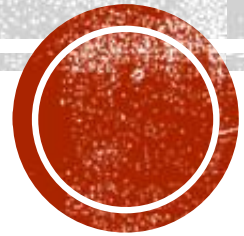
COVID-19

VISHAL DIDWANIA, MD



- Transmission
  - Droplet. Similar to Influenza. Cough, sneeze, talking
  - Surfaces
  - ? Airborne – less likely. Possible in closed space, poor ventilation
- Incubation – 14 days. 4-5 days on average
- Symptoms – mild in 80%. **Fever, fatigue, dry cough**, loss of smell/taste, diarrhea, headache, rhinorrhea, sore throat – COVID until proven otherwise
  - Dyspnea – 20-30% - 5-8 days after symptom onset
  - ARDS
- Fatality rate: Age dependent – as high as 5% age >70
- Risk factors: Age, cardiovascular disease, DM, HTN, chronic lung disease, Cancer, CKD, obesity BMI >30, smoking

COMPLICATIONS

- Cardiac – elevated troponin. 10-30% hospitalized patients. Usually no cardiac symptoms. NOT acute MI usually.
  - Arrythmia (usually asymptomatic), heart failure
- Thrombotic – hypercoagulable state
  - Venous – DVT/PT
  - Arterial – arterial thrombosis, CVA, MI, limb ischemia
- Rash – various types erythema multiforme, vesicular, urticarial, morbilliborm. **FYI can be seen in MIS-C and MIS-A**

Multisystem Inflammatory Syndrome

- Current or recent COVID-19
- Shares symptoms with Kawasaki disease (KD), KD shock, TSS
- Fever, multiorgan involvement, elevated inflammatory markers

▪ “Long hauler syndrome”

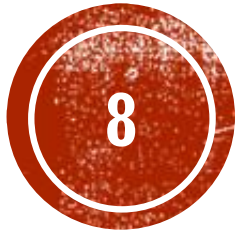
- Large percentage of patients with persistent, recurrent, or new sx
  - 87% - 1 sx
  - 55% - 3 sx
- No clear case definition. General continue for ≥ 12 weeks after acute COVID
- No alternative explanation
- Persistent cough, fatigue, dyspnea, chest pain most common
  - Headache, joint pain, insomnia, anxiety, cognitive dysfunction, myalgias, diarrhea

Clinical Evaluation

- Mild symptoms – home management
  - No clear indication for antibiotics or steroids
  - Consider outpatient treatment including monoclonal antibody through EEH
  - Also outpatient Remdesivir, plasma, monoclonal antibody available through MIDC
  - **CoVID Treatment Centers – CTC – www.ctcmedicine.com 844-227-MIDC**

Common Lab Findings

- Lymphopenia – 90%
- Elevated aminotransaminase
- Elevated LDH
- Elevated inflammatory markers (ferritin, CRP, ESR)
- D-dimer, procalcitonin, trop



TESTING

Diagnostic tests for COVID-19 [1,2]

Test category	Primary clinical use	Specimen type	Performance characteristics	Comments
NAATs (including RT-PCR)	Diagnosis of current infection	Respiratory tract specimens*	▪ High analytic sensitivity and specificity in ideal settings. ▪ Clinical performance depends on the type and quality of the specimen and the duration of illness at the time of testing. ▪ Reported false-negative rate ranges from <5 to 40%, depending on the test used.¶	▪ Time to perform the test ranges from 15 minutes to 8 hours.Δ ▪ Turnaround time is influenced by the test used and laboratory workflow. ▪ Some assays allow home collection of specimens that are mailed in.
Serology (antibody detection)	Diagnosis of prior infection (or infection of at least 3 to 4 weeks' duration)	Blood	▪ Sensitivity and specificity are highly variable. ▪ Detectable antibodies generally take several days to weeks to develop; IgG usually develops by 14 days after onset of symptoms. ▪ Cross-reactivity with other coronaviruses has been reported. ▪ Individual results should be interpreted with caution in settings of low seroprevalence; serologic tests that have high specificity still have a low positive predictive value.	▪ Time to perform the test ranges from 15 minutes to 2 hours. ▪ Turnaround time is influenced by the test used and laboratory workflow. ▪ It remains uncertain whether a positive antibody test indicates immunity against future infection.
Antigen tests	Diagnosis of current infection	Nasopharyngeal or nasal swabs	▪ Antigen tests are generally less sensitive than nucleic acid tests. ▪ Sensitivity is highest in symptomatic individuals within 5 to 7 days of symptom onset.	▪ Time to perform the test is <1 hour.

COVID-19: coronavirus disease 2019; NAAT: nucleic acid amplification test; RT-PCR: real-time polymerase chain reaction; IgG: immunoglobulin G; CDC: United States Centers for Disease Control and Prevention.

* Nasopharyngeal swabs, nasal swabs (from the mid-turbinate area or from both anterior nares), nasal or nasopharyngeal washes, oropharyngeal swabs, and saliva are recommended by the CDC. Nasal swabs can be self-collected by the patient on-site or at home. Mid-turbinate swabs and saliva can be collected by the patient while supervised. Lower respiratory tract specimens can be collected in hospitalized patients with suspected lower respiratory tract infection if an upper respiratory tract specimen tests negative.

¶ A single positive test generally confirms the diagnosis. If initial testing is negative and clinical suspicion remains, performing a second test can enhance diagnostic yield.

Δ Low-complexity rapid tests can be performed at the point of care and provide results in less than 1 hour. Most moderate- to high-complexity laboratory-based tests result in several hours. However, the time for a clinician or patient to receive a result depends on how frequently the test is run and other processing factors.

References:

1. *Cheng MP, Papenburg J, Desjardins M, et al. Diagnostic Testing for Severe Acute Respiratory Syndrome-Related Coronavirus 2: A Narrative Review. Ann Intern Med 2020; 172:726.*
2. *Weissleder R, Lee H, Ko J, Pittet MJ. COVID-19 Diagnostics in Context. Sci Transl Med 2020; 12:eabc1931.*

Testing

- NAAT – RT-PCR
  - Positive – confirms diagnosis
  - Negative – true negative vs false negative
    - If clinically consistent – consider positive
  - Testing after exposure in asymptomatic person – 5-7 days after exposure
    - If negative – quarantine based on CDC guidelines

HOME CARE

- In the United States, two monoclonal antibody therapies targeting SARS-CoV-2 (bamlanivimab and casirivimab-imdevimab (Regeneron)), each administered as a single intravenous dose, have received emergency use authorization from the US Food and Drug Administration (FDA) for non-hospitalized patients who have mild to moderate COVID-19 and certain risk factors for severe disease. These risk factors for adults (≥18 years) include any of the following:
- Body mass index (BMI) ≥35 kg/m^2
- Chronic kidney disease
- Diabetes mellitus
- Immunosuppression (immunosuppressive disease or treatment)
- ≥65 years of age
- ≥55 years of age **and** who have cardiovascular disease, **and/or** hypertension, **and/or** chronic obstructive pulmonary disease (or other chronic respiratory disease)

https://www.covid19treatmentguidelines.nih.gov/

Isolation vs Quarantine

Isolation – keeps someone home who is infected with the virus away from others

Quarantine – keeps someone who might have been exposed to the virus away from others

Standard **isolation**:

At least 10 days passed since symptom onset AND

At least 24h passed since resolution of fever WITHOUT fever reducing medications AND

There is **improvement** in symptoms (eg, cough, SOB)

If no symptoms and tested positive: 10 days from positive testing assuming no sx

Options to reduce quarantine

- After day 10 without testing
  - With this strategy, residual post-quarantine transmission risk is estimated to be about 1% with an upper limit of about 10%.

- After day 7 after receiving a negative test result (test must occur on day 5 or later)
  - With this strategy, the residual post-quarantine transmission risk is estimated to be about 5% with an upper limit of about 12%.

- After stopping quarantine: watch for sx for 14 days post-exposure, self isolate if symptoms, wear mask, social distancing, wash hands, avoid crowds, etc.
- CDC continues to endorse quarantine for 14 days and recognizes that any quarantine shorter than 14 days balances reduced burden against a small possibility of spreading the virus.

https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

Re-positive cases

- SARS-CoV-2 RNA in upper respiratory tract can be detected for weeks
  - Does NOT indicate prolonged infectiousness
  - Ok to return to work if meet previous criteria

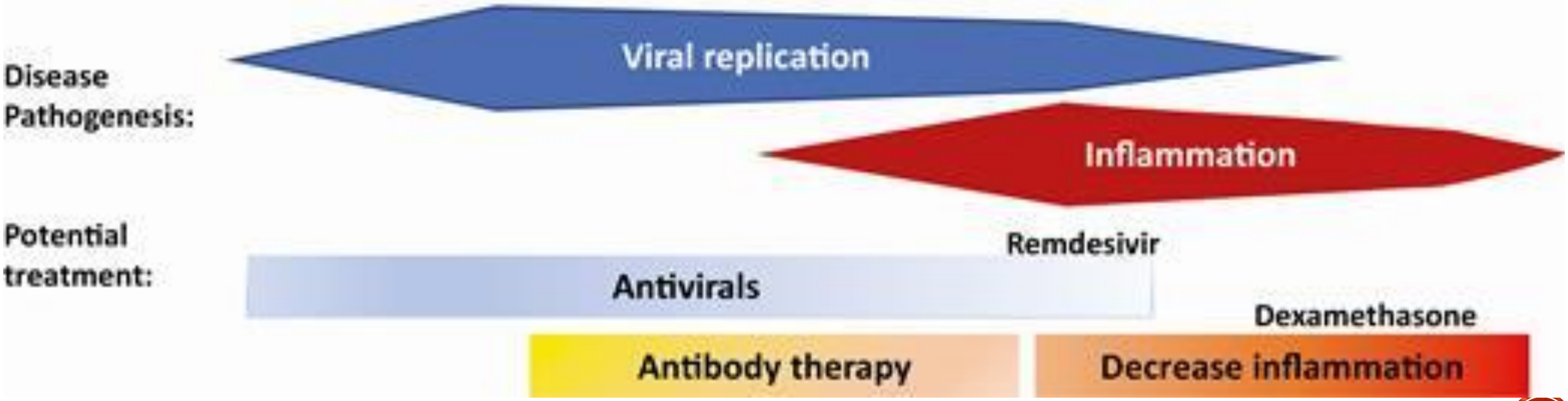
https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030&act=view&list_no=367267

16

TREATMENT

Multidimensional Challenge of Treating COVID-19

Stage/ Severity:	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (eg fever, cough, taste/smell changes); no dyspnea	O_2 saturation >=94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure



https://doi.org/10.1093/cid/ciaa1132

Early Virologic Phase

- Remdesivir
- Convalescent Plasma
- Steroids
- Monoclonal antibody cocktail

Inflammatory Phase

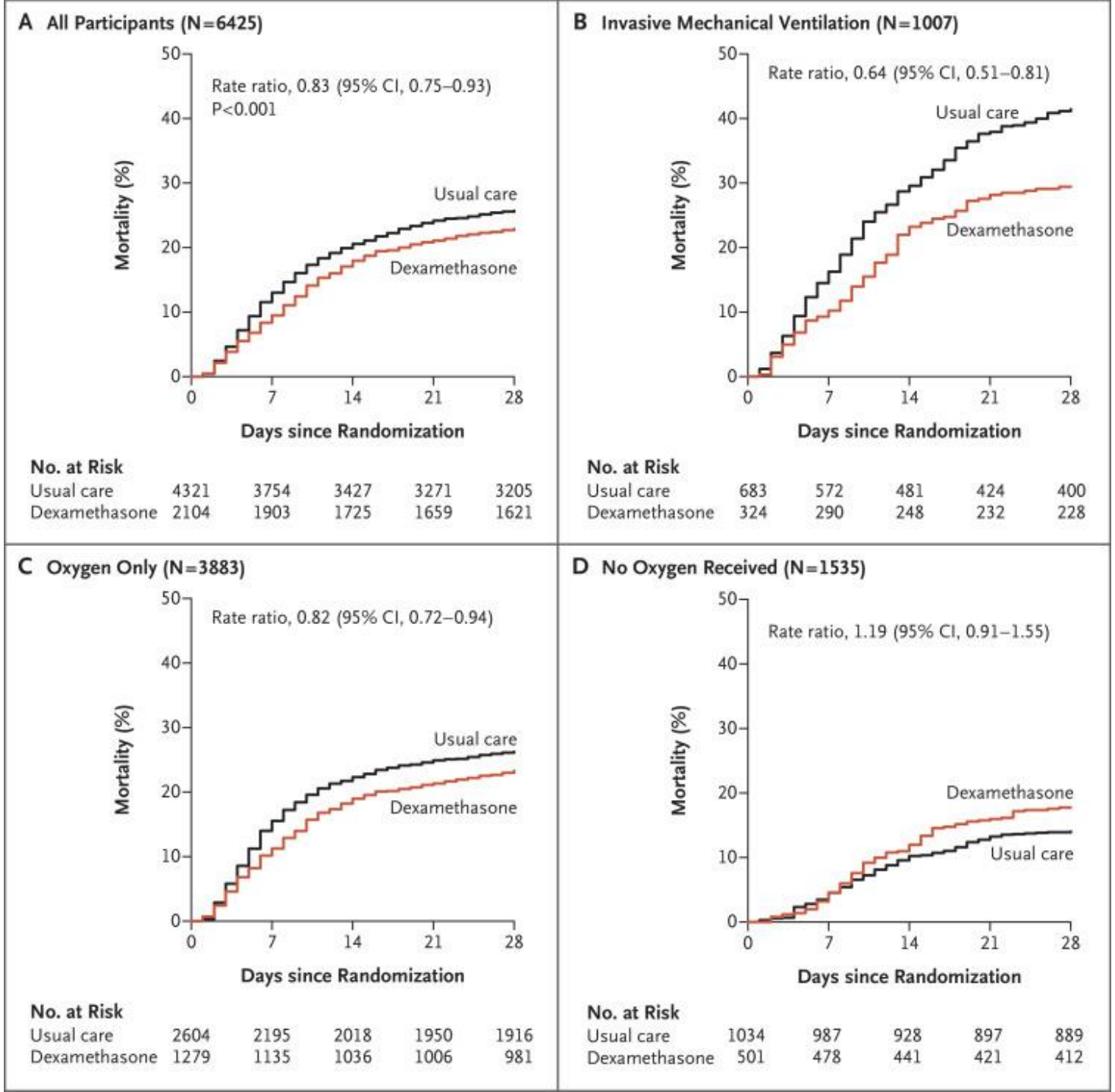
- Tocilizumab
- Baracitinib
- Steroids
- Convalescent plasma

RECOVERY Trial

Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report

- **Methods:** open label trial. Randomly assigned patients to receive IV/PO dexamethasone at 6 mg daily for up to 10 days vs usual care – 28 day mortality
- **Results:** 2104 patients in dexa and 4321 in usual care. Mortality:
  - All patients: 22.9% vs 25.7%
  - Vent: 29.3% vs 41.4%
  - O2: 23.3% vs 26.2%
  - No respiratory support: 17.8% vs 14.0% (not significant)
- **Conclusions:** In patients **hospitalized** with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.

RECOVERY Trial: https://pubmed.ncbi.nlm.nih.gov/32678530/


A All Participants (N=6425)
Rate ratio, 0.83 (95% CI, 0.75–0.93)
P<0.001
Usual care
Dexamethasone
Mortality (%)
Days since Randomization
No. at Risk
Usual care 4321 3754 3427 3271 3205
Dexamethasone 2104 1903 1725 1659 1621
B Invasive Mechanical Ventilation (N=1007)
Rate ratio, 0.64 (95% CI, 0.51–0.81)
Usual care
Dexamethasone
Mortality (%)
Days since Randomization
No. at Risk
Usual care 683 572 481 424 400
Dexamethasone 324 290 248 232 228
C Oxygen Only (N=3883)
Rate ratio, 0.82 (95% CI, 0.72–0.94)
Usual care
Dexamethasone
Mortality (%)
Days since Randomization
No. at Risk
Usual care 2604 2195 2018 1950 1916
Dexamethasone 1279 1135 1036 1006 981
D No Oxygen Received (N=1535)
Rate ratio, 1.19 (95% CI, 0.91–1.55)
Dexamethasone
Usual care
Mortality (%)
Days since Randomization
No. at Risk
Usual care 1034 987 928 897 889
Dexamethasone 501 478 441 421 412

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5

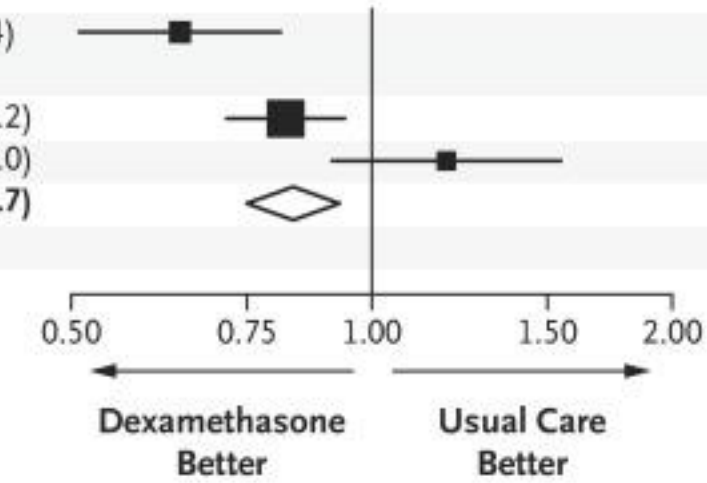
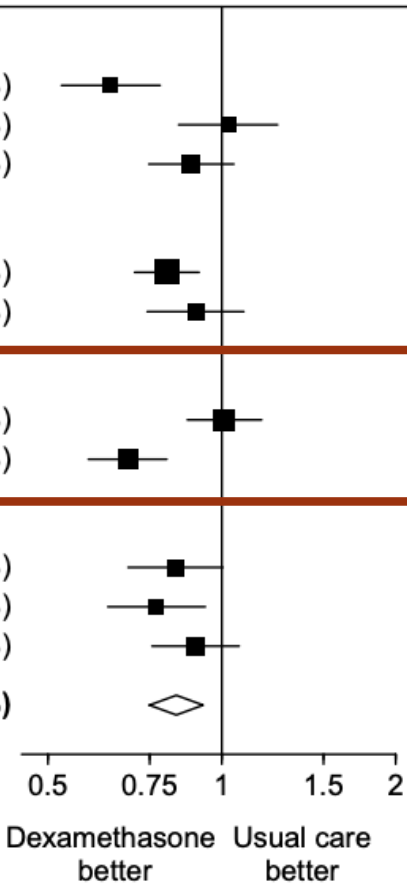


Figure S1: Effect of allocation to dexamethasone on 28−day mortality by other pre−specified baseline characteristics

Subgroup	Dexamethasone	Usual care	RR (95% CI)	Het/trend
Age, years				
<70	129/1141 (11.3%)	428/2504 (17.1%)	0.64 (0.53−0.78)	χ^2_1=4.9
≥70 <80	155/469 (33.0%)	271/859 (31.5%)	1.03 (0.84−1.25)	
≥80	198/494 (40.1%)	411/958 (42.9%)	0.89 (0.75−1.05)	
Sex				
Men	331/1338 (24.7%)	782/2749 (28.4%)	0.80 (0.71−0.91)	χ^2_1=0.9
Women	151/766 (19.7%)	328/1572 (20.9%)	0.90 (0.74−1.09)	
Days since symptom onset				
≤7	269/916 (29.4%)	500/1801 (27.8%)	1.01 (0.87−1.17)	χ^2_1=12.3
>7	212/1184 (17.9%)	604/2507 (24.1%)	0.69 (0.59−0.80)	
Baseline risk				
<30%	150/1268 (11.8%)	377/2682 (14.1%)	0.83 (0.69−1.00)	χ^2_1=0.4
≥30% <45%	146/464 (31.5%)	334/878 (38.0%)	0.77 (0.63−0.94)	
≥45%	186/372 (50.0%)	399/761 (52.4%)	0.90 (0.76−1.07)	
All participants	**482/2104 (22.9%)**	**1110/4321 (25.7%)**	**0.83 (0.75−0.93) p<0.001**	



RR=age−adjusted (or age−specific) rate ratio (with the exception of RR estimates by baseline−predicted risk, which are not adjusted for age).
CI=confidence interval. Chi−squared statistics correspond to tests for heterogeneity (or trend) in the log RRs across levels of each subgroup.
There was a clear trend towards greater proportional benefit among patients with symptoms for more than 7 days. Subgroup−specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% confidence intervals. For each of the four subgroups shown, the RRs and CIs are estimated from a regression model that includes a relevant interaction term enabling the effect of allocation to dexamethasone on mortality to be estimated separately at each level of the subgroup.
Baseline−predicted risk is calculated as exp(a)/(1 + exp(a)), where a = −1.23 − 2.85 (if age <50) − 2.03 (if age 50−59) − 1.21 (if age 60−69) − 0.51 (if age 70−79) + 0.42 (if male) − 0.34 (if >7 days since symptom onset) + 0.86 (if on oxygen only) + 2.18 (if on invasive mechanical ventilation) − 0.01 (if history of diabetes) + 0.22 (if history of heart disease) + 0.21 (if history of chronic lung disease) + 0.50 (if history of kidney disease).

RESEARCH SUMMARY

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

F.P. Polack, et al. DOI: 10.1056/NEJMoa2034577

CLINICAL PROBLEM

Safe and effective vaccines to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 are urgently needed. No vaccines that protect against betacoronaviruses are currently available, and mRNA-based vaccines have not been widely tested.

CLINICAL TRIAL

A randomized, double-blind study of an mRNA vaccine encoding the SARS-CoV-2 spike protein.

43,548 participants ≥16 years old were assigned to receive the vaccine or placebo by intramuscular injection on day 0 and day 21. Participants were followed for safety and for the development of symptomatic Covid-19 for a median of 2 months.

RESULTS

Safety:
Vaccine recipients had local reactions (pain, erythema, swelling) and systemic reactions (e.g., fever, headache, myalgias) at higher rates than placebo recipients, with more reactions following the second dose. Most were mild to moderate and resolved rapidly.

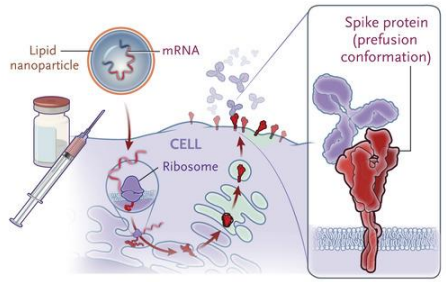
Efficacy:
The vaccine showed protection 7 days after the second dose; 95% efficacy was observed.

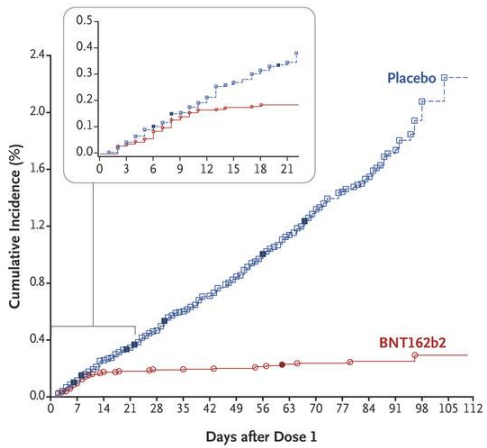
LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- Safety and efficacy beyond 2 months and in groups not included in this trial (e.g., children, pregnant women, and immunocompromised persons).
- Whether the vaccine protects against asymptomatic infection and transmission to unvaccinated persons.
- How to deal with those who miss the second vaccine dose.

Links: Full article | Quick Take | Editorial





Vaccine efficacy of 95% (95% credible interval, 90.3 –97.6%)

CONCLUSIONS

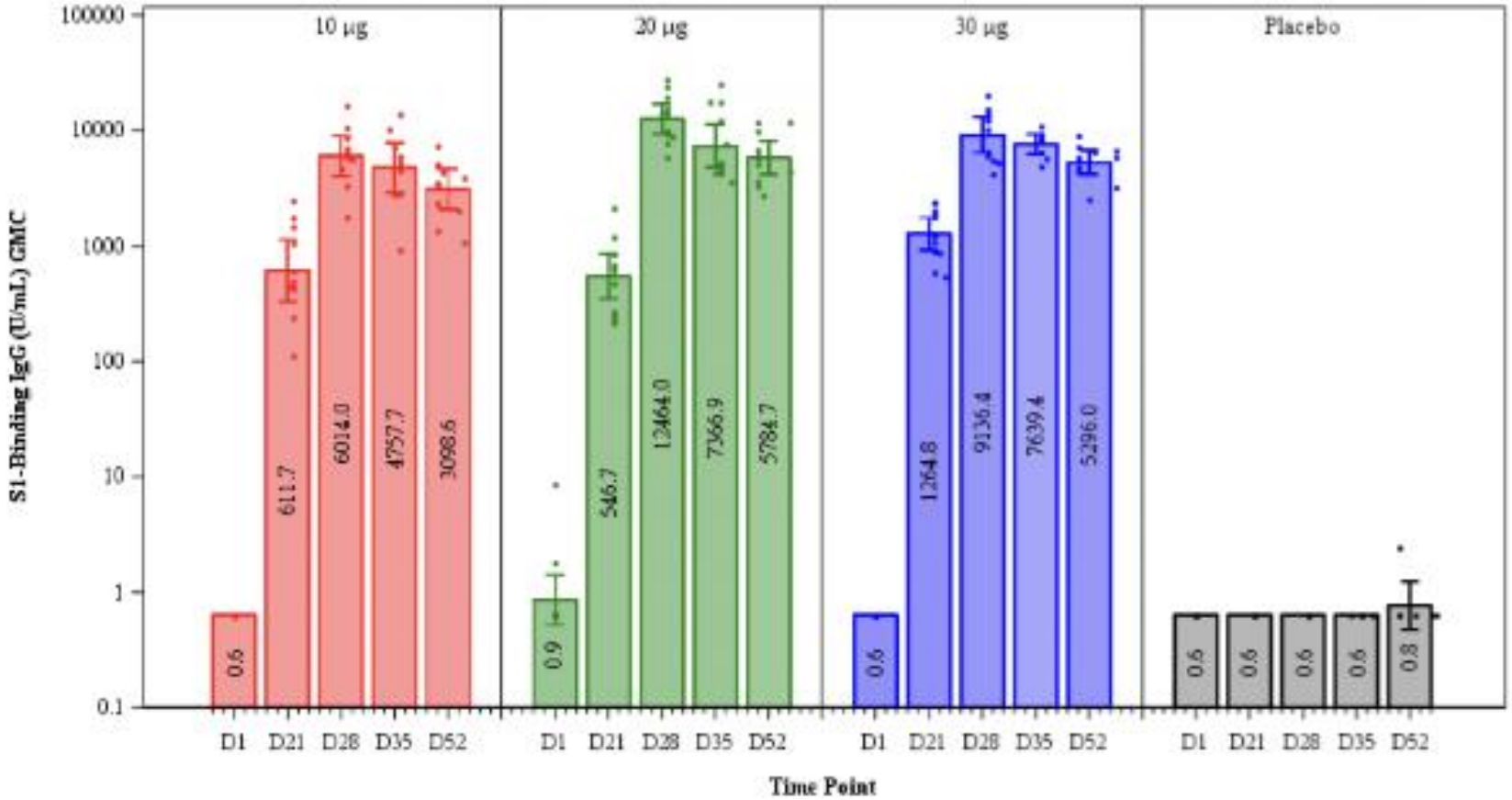
Two doses of an mRNA-based vaccine were safe over a median of two months and provided 95% protection against symptomatic Covid-19 in persons 16 years of age or older.

FP POLACK ET AL. N ENGL J MED 2020;383:2603-2615.

WHAT POPULATIONS WERE VACCINATED?

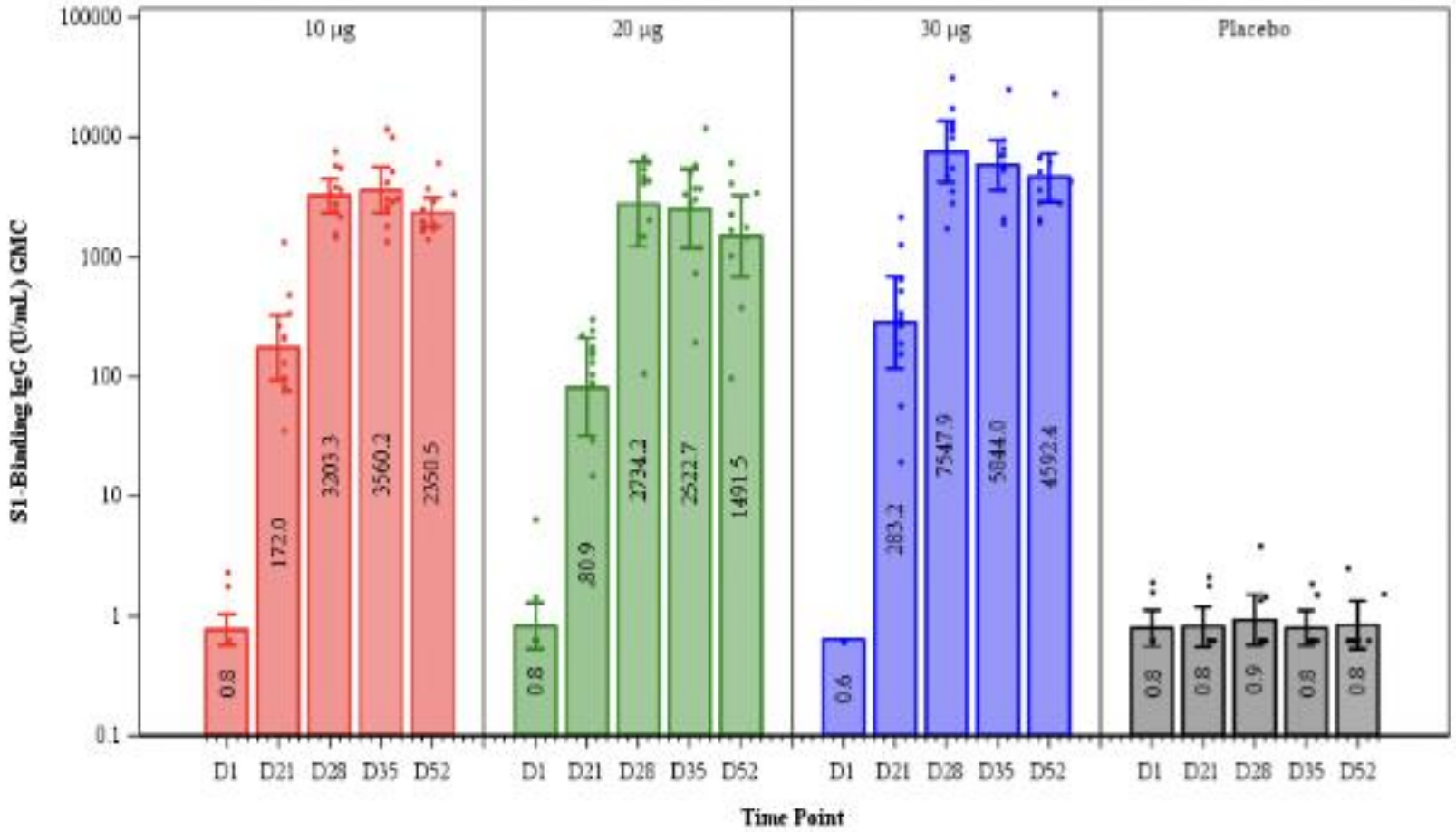
Total Randomized	43, 651 patients	
vaccinated	21,823	
Ages -	16-55 and > 55	
Demographics-	Black	- 9%
	Hispanic	- 28%
	Obese	- 35%
	HIV	120 patients

GMCs and 95% CI – S1-Binding IgG – Phase 1 – 18-55 Years – BNT162b2 – Evaluable Immunogenicity Population



Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; S1 = spike protein S1 subunit.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nda3/C4591001_IA_P1_Serology/adva_f002_s1_18_b2_p1

GMCs and 95% CI – S1-Binding IgG – Phase 1 – 65-85 Years – BNT162b2 – Evaluable Immunogenicity Population



Abbreviations: GMC = geometric mean concentration; IgG = immunoglobulin G; S1 = spike protein S1 subunit.
Note: Dots present individual antibody levels.
Note: Number within each bar denotes geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 17SEP2020 (22:01) Source Data: adva Table Generation: 17SEP2020 (23:29)
(Cutoff Date: 24AUG2020, Snapshot Date: 17SEP2020) Output File: /nda3/C4591001_IA_P1_Serology/adva_f002_s1_65_b2_p1

RESEARCH SUMMARY

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

L.R. Baden, et al. DOI: 10.1056/NEJMoa2035389

CLINICAL PROBLEM

The Covid-19 pandemic continues and expands. Additional data regarding vaccines to prevent symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are needed. The mRNA-1273 vaccine is a lipid-encapsulated mRNA vaccine encoding the prefusion stabilized spike protein of SARS-CoV-2.

CLINICAL TRIAL

A randomized, double-blind trial to evaluate the efficacy and safety of mRNA-1273.

30,420 participants ≥18 years old were assigned to receive either the vaccine or placebo in two intramuscular injections 28 days apart. Participants were followed for safety and the development of laboratory-confirmed, symptomatic Covid-19 over a median of 2 months after the second dose.

RESULTS

Safety:
Vaccine recipients had higher rates of local reactions (e.g., pain, erythema, swelling) and systemic reactions (e.g., headache, fatigue, myalgia) than placebo recipients. Most reactions were mild to moderate and resolved over 1–3 days.

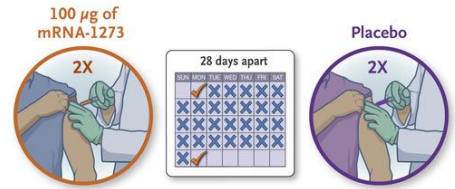
Efficacy:
The incidence of Covid-19 was lower among vaccine recipients than among placebo recipients as early as 14 days after the first dose. Protection in the vaccine group persisted for the period of follow-up.

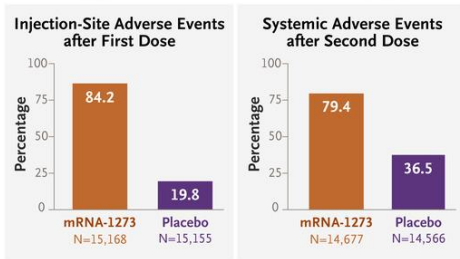
LIMITATIONS AND REMAINING QUESTIONS

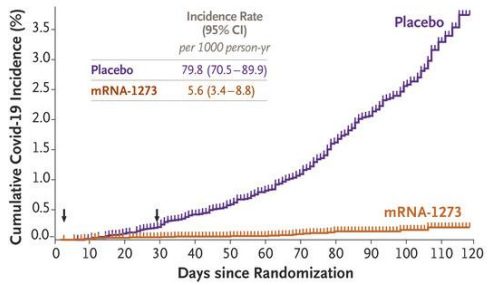
Further study is required to understand the following:

- Safety and efficacy over a longer period of time, in a larger population, and in pregnant women and children.
- Whether the vaccine protects against asymptomatic infection and transmission to unvaccinated persons.
- How to care for those who miss the second vaccine dose.

Links: Full article | NEJM Quick Take | Editorial







	mRNA-1273 Vaccine N=14,550	Placebo N=14,598
Symptomatic Covid-19	11	185
Severe Covid-19	0	30

Vaccine efficacy of 94.1% (95% CI, 89.3–96.8%; P<0.001)

CONCLUSIONS

Two doses of a SARS-CoV-2 mRNA-based vaccine were safe and provided 94% efficacy against symptomatic Covid-19 in persons 18 or older.

ADVERSE EVENTS

	Pfizer	Moderna
Pain at site w/i 7d	80%	85%
Fatigue	50	69
Headache	50	63
Fever	16	15
LAN	64	>200

Bell's Palsy – 3 in vacc grp; 1 in placebo (same as Pfizer)

Deaths – 6 total; 7 in vacc grp (same as Pfizer)

WHAT INFECTIONS ARE PREVENTED? PFIZER

	Vaccinated	Unvaccinated
Infections	8	162
Severe	1	9
after dose 1	0	4
betw 1 and 2	0	1
after dose 2	1	4

Suggestive that vaccination prevents severe disease

WHAT INFECTIONS ARE PREVENTED? MODERNA

	Vaccinated	Unvaccinated
Infections	11	185
Severe	0	30

Suggestive that vaccination prevents severe disease

UNKNOWNS/CONCERNS

Efficacy against asymptomatic infections

Efficacy in previously infected patients

Minimal data in HIV patients

No data in children <18 y/o, or pregnant pts.

No data on long term side effects

Minimal data on duration of immunity

Benefit of single dose of vaccine

THANK YOU!