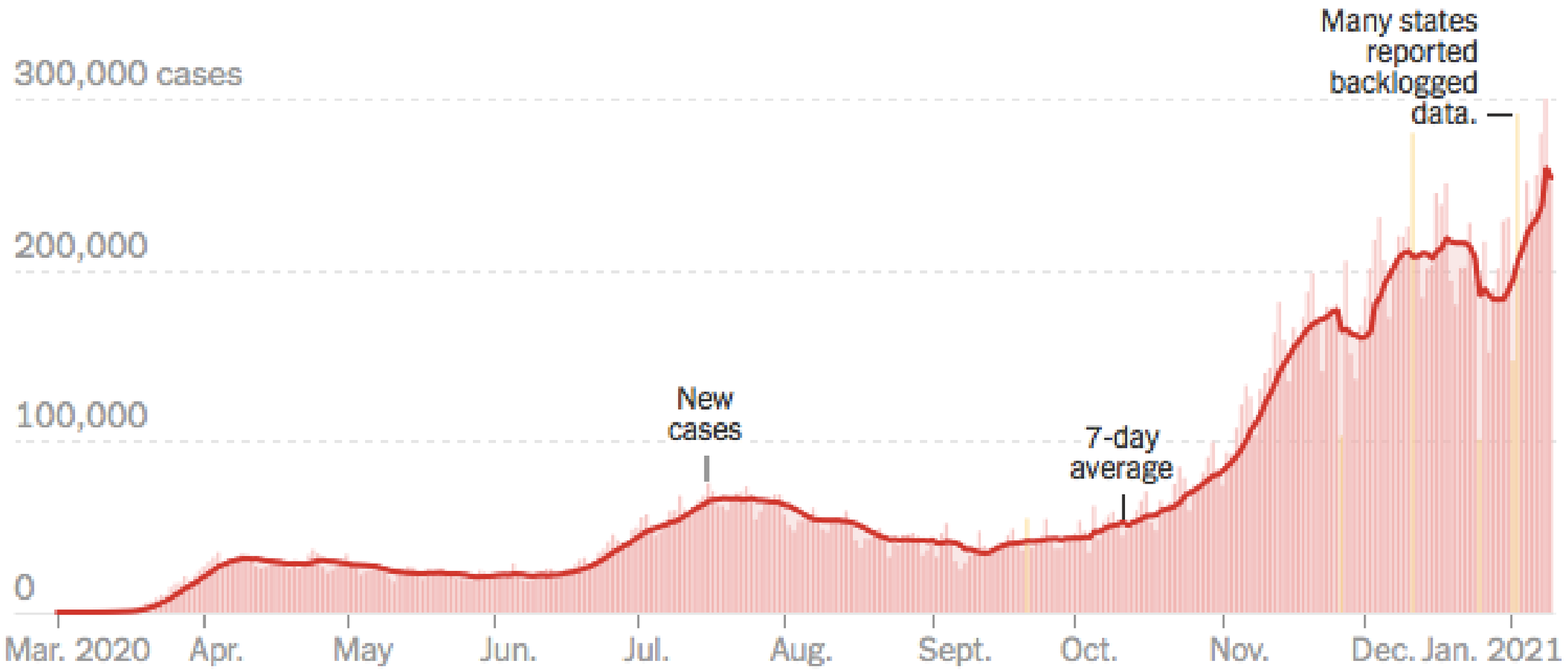
# SARS-CoV-2 Update

Rajeev Bais MD, MPH

1/14/21

# SARS-CoV-2 Outline

- Cases/Hotspots
- Current and novel treatment options
- Viral variants
- Vaccines
- Rollout
- Questions




| | TOTAL REPORTED | ON JAN. 9 | 14-DAY CHANGE |
|---|---|---|---|
| **Cases** | 22.4 million+ | 252,142 | +34% → |
| **Deaths** | 374,389 | 3,261 | +43% → |
| **Hospitalized** | | 130,781 | +11% → |

Day with reporting anomaly. Hospitalization data from the Covid Tracking Project; 14-day change trends use 7-day averages.

## Cases and deaths by state and county

This table is sorted by places with the most cases per 100,000 residents in the last seven days. Charts are colored to reveal when outbreaks emerged.

**Cases** | Deaths

Search counties

| | TOTAL CASES | PER 100,000 | DAILY AVG. IN LAST 7 DAYS | ▼ PER 100,000 | WEEKLY CASES PER CAPITA (FEWER – MORE; March 1 – Jan. 9) |
|---|---|---|---|---|---|
| + Arizona MAP » | 618,546 | 8,498 | 10,391 | 143 |  |
| + Rhode Island MAP » | 97,614 | 9,214 | 1,381 | 130 |  |
| + California MAP » | 2,728,139 | 6,905 | 41,309 | 105 |  |
| + Oklahoma MAP » | 331,362 | 8,374 | 4,117 | 104 |  |
| + South Carolina MAP » | 354,525 | 6,886 | 5,338 | 104 |  |
| + Utah MAP » | 305,999 | 9,545 | 3,139 | 98 |  |
| + Arkansas MAP » | 255,076 | 8,452 | 2,901 | 96 |  |
| + Tennessee MAP » | 641,123 | 9,388 | 6,402 | 94 |  |
| + Kentucky MAP » | 306,462 | 6,860 | 3,995 | 89 |  |
| + Massachusetts MAP » | 432,791 | 6,279 | 6,136 | 89 |  |

Original Investigation | Infectious Diseases

## SARS-CoV-2 Transmission From People Without COVID-19 Symptoms

Michael A. Johansson, PhD; Talia M. Quandelacy, PhD, MPH; Sarah Kada, PhD; Pragati Venkata Prasad, MPH; Molly Steele, PhD, MPH; John T. Brooks, MD; Rachel B. Slayton, PhD, MPH; Matthew Biggerstaff, ScD, MPH; Jay C. Butler, MD

- Decision analytical model
  - Assessed multiple scenarios for transmission
  - Estimated that **over 50% of overall transmission from asymptomatic individuals**
    - Pre-symptomatic individuals and asymptomatic

# COVID-19 rapid tests are inexpensive and fast but sometimes give incorrect results*

1 in 5 patients with symptoms and confirmed COVID-19 received a negative rapid antigen test result

* 1,098 paired nasal swabs collected at 2 universities in Wisconsin, September 28–October 9, were tested using Sofia SARS Antigen FIA and compared to rRT-PCR/viral culture results.

People with **symptoms** and a **negative rapid test** should

Get a confirmation (RT-PCR) test

Wear a mask

Stay home in a separate room

Compared PCR and antigen test results:
In PCR + symptomatic people, antigen test missed 1 in 5
In PCR + asymptomatic people, antigen test missed 3 in 5

| DISEASE SEVERITY | PANEL'S RECOMMENDATIONS |
|---|---|
| Not Hospitalized, Mild to Moderate COVID-19 | There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (**bamlanivimab** or **casirivimab plus imdevimab**) are available through EUAs for outpatients who are at high risk of disease progression.[a] These EUAs do not authorize use in hospitalized patients.<br><br>**Dexamethasone** should not be used **(AIII)**. |
| **Hospitalized[a] But Does Not Require Supplemental Oxygen** | **Dexamethasone** should not be used **(AIIa)**.<br><br>There are insufficient data to recommend either for or against the routine use of **remdesivir**. For patients at high risk of disease progression, the use of remdesivir may be appropriate. |
| **Hospitalized[a] and Requires Supplemental Oxygen**<br><br>(But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO) | Use one of the following options:<br>• **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)**<br>• **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[e,f]<br>• **Dexamethasone**[d] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)** |
| **Hospitalized[a] and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation** | Use one of the following options:<br>• **Dexamethasone**[d,f] **(AI)**<br>• **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)**[e,f] |
| **Hospitalized[a] and Requires Invasive Mechanical Ventilation or ECMO** | **Dexamethasone**[d] **(AI)**[g] |

ORIGINAL ARTICLE

# Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

| | Dexamethasone 6 mg daily + SOC | Standard care |
|---|---|---|
| Number of patients | 2104 | 4321 |
| 28 day all cause mortality | 21.6% | 24.6% |
| Those requiring mechanical ventilation | 29.3 % | 41.4% |
| Discharged from hospital within 28 days | 67.2 % | 63.5% |

ORIGINAL ARTICLE

# Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

- The benefit was greatest in:
  - patients with symptoms > 7 days
  - patients who required mechanical ventilation.
- No benefit among patients with shorter symptom duration or no supplemental O2

ORIGINAL ARTICLE

# Remdesivir for the Treatment of Covid-19 — Final Report

John H. Beigel, M.D., Kay M. Tomashek, M.D., M.P.H., Lori E. Dodd, Ph.D., Aneesh K. Mehta, M.D., Barry S. Zingman, M.D., Andre C. Kalil, M.D., M.P.H., Elizabeth Hohmann, M.D., Helen Y. Chu, M.D., M.P.H., Annie Luetkemeyer, M.D., Susan Kline, M.D., M.P.H., Diego Lopez de Castilla, M.D., M.P.H., Robert W. Finberg, M.D., et al., for the ACTT-1 Study Group Members*

- November 5, 2020
- 1,062 patients
- 50% remdesivir, 50% to placebo

| | Remdesivir | placebo |
|---|---|---|
| Median recovery time | 10 | 15 |
| 15 day mortality (estimates) | 6.7% | 11.9% |
| 29 day mortality | 11.4% | 15.2% |
| SAE | 24.6% | 31.6% |

# Convalescent Plasma

- NIH Update - October 9, 2020
  - **There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.**

ORIGINAL ARTICLE

# A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

Ventura A. Simonovich, M.D., Leandro D. Burgos Pratx, M.D., Paula Scibona, M.D., María V. Beruto, M.D., Marcelo G. Vallone, M.D., Carolina Vázquez, M.D., Nadia Savoy,

- Published NEJM Nov 24, 2020
  - Randomized multicenter trial in Argentina
  - Hospitalized adult patients with severe Covid-19 pneumonia
- Inclusion Criteria: At least one of the following
    - $SaO_2$ below 93% on room air
    - $PaO_2/FiO_2$ <300 mm Hg
    - SOFA or modified SOFA (mSOFA) score of two or more points above baseline status
    - 228 patients were assigned to receive CP & 105 to receive placebo.
    - The median time from the onset of symptoms to enrollment in the trial - 8 days
    - Infused convalescent plasma had a median titer of 1:3200 of total SARS-CoV-2 antibodies
- **Overall mortality**
  - **CP arm- 10.96%**
  - **Placebo- 11.43%**
- Adverse events and serious adverse events were similar in the two groups.

ORIGINAL ARTICLE

# Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

Romina Libster, M.D., Gonzalo Pérez Marc, M.D., Diego Wappner, M.D., Silvina Coviello, M.S., Alejandra Bianchi, Virginia Braem, Ignacio Esteban, M.D., Mauricio T. Caballero, M.D., Cristian Wood, M.D., Mabel Berrueta, M.D., Aníbal Rondan, M.D., Gabriela Lescano, M.D., et al., for the Fundación INFANT–COVID-19 Group*

- January 6, 2021
- Randomized, double-blind, placebo-controlled study in Argentina b/w June 4 - October 25, 2020
- Convalescent Plasma with high antibody titers (1:1000) was given within 72 hrs of onset of symptoms
- 160 patients randomized: over 75yo or b/w 65-74 with significant co-morbidities
- Stopped early because of a decrease in COVID patients
- **Progression to Severe Respiratory Disease was 16% in pts receiving CP vs 31% of placebo**
- Patients receiving plasma with titers > 1:3200 reduced the risk of progression to severe disease by 73%

# Tocilizumab

- **Studies Showing No Benefit:**
  - RCT-TCZ-COVID-19 (n=126)
    - Primary end point- hypoxia, ICU admission or death- Stopped early due to lack of benefit
  - CORIMUNO-19-TOCI(n=131)
    - Toci may have reduced need for mechanical ventilation but no impact on mortality
  - BACC Bay Trial(n=243)- 7 Boston hospitals
    - Placebo controlled
    - Toci did not reduce requirement for intubation or reduce mortality
  - Empacta (n=389)
    - Placebo controlled
    - Toci reduced need for mechanical ventilation but mortality did not improve
  - COVACTA trial
    - First global, randomized, double-blind, placebo-controlled phase III study
    - Primary endpoint - clinical status in hospitalized patients with severe infection
    - Did not meet its primary endpoint of improved clinical status
    - No difference in patient mortality at week 4

- **NIH Recommendations - August 27,2020**
  - **The Panel recommends against the use of IL-6 receptor monoclonal antibodies (sarilumab, tocilizumab) or anti-IL-6 monoclonal antibody (siltuximab) for the treatment of COVID-19, except in a clinical trial.**

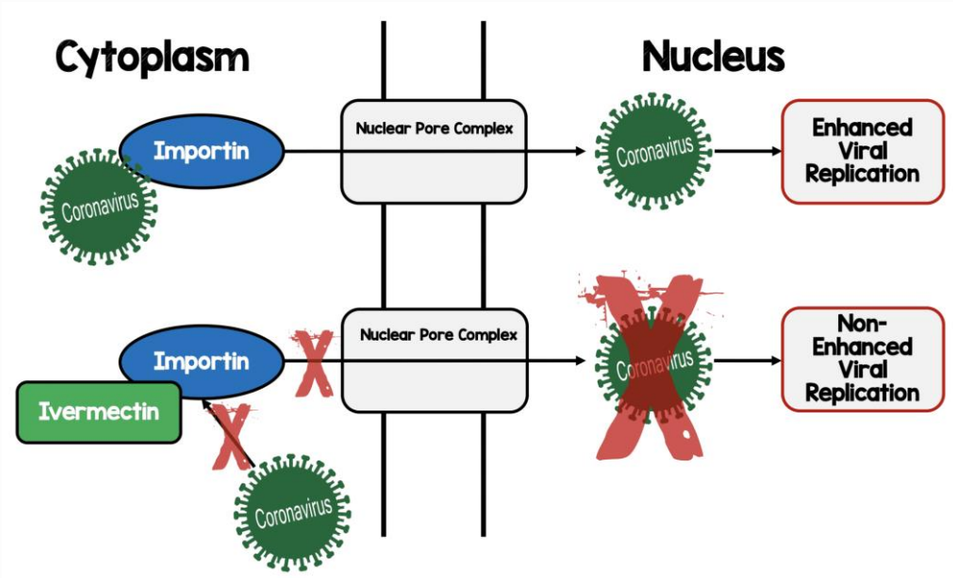
ORIGINAL ARTICLE

# Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

Carlos Salama, M.D., Jian Han, Ph.D., Linda Yau, Ph.D., William G. Reiss, Pharm.D., Benjamin Kramer, M.D., Jeffrey D. Neidhart, M.D., Gerard J. Criner, M.D., Emma Kaplan-Lewis, M.D., Rachel Baden, M.D., Lavannya Pandit, M.D., Miriam L. Cameron, M.D., Julia Garcia-Diaz, M.D., et al.

- Randomly Assigned hospitalized patients with COVID-19 who were not receiving mechanical ventilation to receive standard of care plus 1 or 2 doses of either tocilizumab or placebo.
- **More ethnic diversity**: 56% Hispanic/Latino; 14.9% Black; 12.7% American Indian or Alaska Native; 12.7% were non-Hispanic White, 3.7% other
- More than 25% of patients were older than 65 years; More than 75% had at least 1 coexisting condition
- 55.4% of pts in the toci arm **received dexamethsone** vs 67.2% of pts in the placebo group
- 52.6% of pts in the toci arm **received remdesivir** vs 58.6% of pts in the placebo group
- **Percentage of pts who had received mechanical ventilation or who had died by day 28 was 12% in the tocilizumab group and 19.3% in the placebo group**

# Ivermectin




- Ivermectin is an FDA approved antiparasitic drug - used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies
  - Ivermectin inhibits the host importin alpha/beta-1 nuclear transport proteins
- ICON Study: Retrospective cohort study of consecutive patients hospitalized at four Broward Health hospitals in South Florida with confirmed SARS-CoV-2.
  - Ivermectin was associated with lower mortality during treatment of COVID-19
- **NIH Recommendation**
- The COVID-19 Treatment Guidelines Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

# Hydroxychloroquine

- NIH Recommendations:
  - The Panel **recommends against** the use of chloroquine or hydroxychloroquine with or withour azithromycin for the treatment of COVID-19 in hospitalized patients (AI)
  - In non-hospitalized patient, the Panel **recommends against** the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19, except in a clinical trial (AI)
  - The Panel **recommends against** the use of high-dose chloroquine (600mg twice daily for 10 days) for the treatment of COVID-19 (AI).

# MONOCLONAL ANTIBODY: Bamlanivimab

- A neutralizing monoclonal antibody that targets the receptor-binding domain of the spike protein of SARS-CoV-2
- Blocks viral entry into cells
- November 9, 2020, the FDA issued an Emergency Use Authorization (EUA) to make bamlanivimab available for the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at risk for progressing to severe disease and/or hospitalization.
- Criteria:
  - BMI>35
  - Chronic Kidney Disease
  - Diabetes mellitus
  - Immuno-compromising condition
  - Aged >65 years
  - Aged 55 years and have:
    - cardiovascular disease, or
    - hypertension, or
    - Chronic obstructive pulmonary disease/other respiratory disease

ORIGINAL ARTICLE

# SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., et al., for the BLAZE-1 Investigators*

- 452 participants were randomized to receive one of three doses of bamlanivimab (700 mg, 2,800 mg, or 7,000 mg) or placebo
- Within 3 days of having a positive SARS-CoV-2 virologic test result
- Excluded if they had a saturation of oxygen (SpO2) ≤93% on room air, respiratory rate ≥30 breaths/minute, or heart rate ≥125 beats/minute
- median age was 45 years (range: 18–86 years) in the pooled bamlanivimab groups and 46 years (range: 18–77 years) in the placebo group
    - only a small percentage of participants aged >65 years (10.7% [33/309] in the bamlanivimab groups vs. 14.0% [20/143] in the placebo group)
- median time from symptom onset to infusion of bamlanivimab or placebo was 4 days across the groups
- COVID-19-related hospitalization, emergency department visit, or death within 28 days of treatment was lower in those who received bamlanivimab (1.6%) than in those who received placebo (6.3%)
    - In a post hoc analysis of participants at high-risk for progression to severe COVID-19 (defined as aged ≥65 years or having a body mass index [BMI] ≥35), four of 95 participants (4.2%) in the combined bamlanivimab arms versus seven of 48 (14.6%) participants in the placebo group were hospitalized or had emergency department visits.

# MONOCLONAL ANTIBODY:Casirivimab Plus Imdevimab

- 2 recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the spike protein receptor binding domain of SARS-CoV-2
- Blocks binding of the binding of the spike protein to the host cell
- November 21, 2020, the FDA issued an Emergency Use Authorization (EUA) to make casirivimab plus imdevimab combination available for the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at risk for progressing to severe disease and/or hospitalization.
- Criteria:
  - BMI>35
  - Chronic Kidney Disease
  - Diabetes mellitus
  - Immuno-compromising condition
  - Aged >65 years
  - Aged 55 years and have:
    - cardiovascular disease, or
    - hypertension, or
    - Chronic obstructive pulmonary disease/other respiratory disease

# MONOCLONAL ANTIBODY

- Criteria:
  - Aged >12 years and have
    - BMI>35
    - Chronic Kidney Disease
    - Diabetes mellitus
    - Immuno-compromising condition or on Immuno-compromising medications
  - Aged 55 years and have:
    - cardiovascular disease, or
    - hypertension, or
    - Chronic obstructive pulmonary disease/other respiratory disease
  - Aged > 65 years
  - Aged 12-17 years and have:
    - BMI > 85th percentile for their age, or
    - Sickle cell disease, or
    - Congential or acquired heart disease, or
    - Neurodevelopmental disorders (i.e cerebral palsy), or
    - Asthma or other chronic lung disease requiring daily medication, or
    - A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)

ORIGINAL ARTICLE

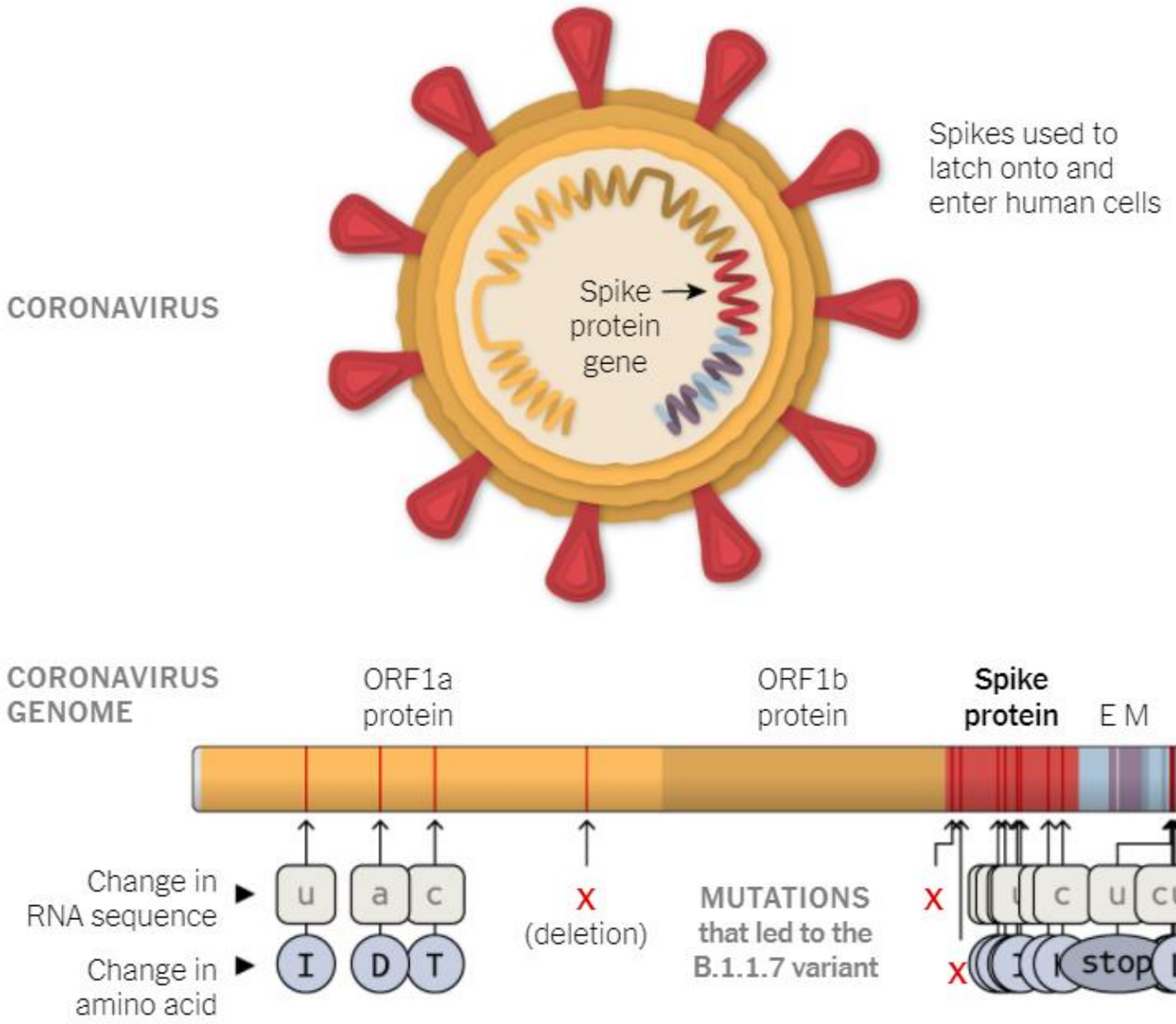
# Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

Andre C. Kalil, M.D., M.P.H., Thomas F. Patterson, M.D., Aneesh K. Mehta, M.D., Kay M. Tomashek, M.D., M.P.H., Cameron R. Wolfe, M.B., B.S., M.P.H., Varduhi Ghazaryan, M.D., Vincent C. Marconi, M.D., Guillermo M. Ruiz-Palacios, M.D., Lanny Hsieh, M.D., Susan Kline, M.D., Victor Tapson, M.D., Nicole M. Iovine, M.D., Ph.D., et al., for the ACTT-2 Study Group Members*

- Oral Janus kinase inhibitor that is selective for JAK1 and JAK2 which may prevent cellular immune activation and inflammation.
- FDA approved to treat moderate to severe rheumatoid arthritis.
- On November 19, 2020 the FDA issued an EUA for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged >2 year with COVID who require supplemental O2, invasive mechanical ventilation, or ECMO.
- 1033 hospitalized patients randomized to receive baricitinib  or placebo (both grps received remdesivir)
- Excluded if patients were receiving dexamethsone
- In pts who required high-flow O2 the time to recovery in the baricitinib arm was 10 days vs 18 days in the placebo group
- Patients who received glucocorticoids after randomization had a higher incidence of serious or nonserious new infection than those who did not (56 of 223 patients [25.1%] vs. 44 of 793 patients [5.5%])
- In the rare circumstances **where corticosteroids cannot be used**, the Panel recommends using baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, nonintubated patients who require oxygen supplementation (BIIa).

## A New Variant

A series of tiny mutations found in many British samples of the coronavirus may help the virus spread more easily. The coronavirus variant is known as B.1.1.7.




By Jonathan Corum | Source: Andrew Rambaut et al., Covid-19 Genomics Consortium U.K.

# New Variants

- What we know:
  - RNA viruses frequently mutate; not all are important
  - UK (September) variant ~60% recent infections in London
  - Mutation in receptor binding domain of spike protein
    - (S:N501Y) + other mutation (deletion at 69,70)
  - UK variant identified in the US, not travel-associated
  - Preprint estimates UK variant **56% more transmissible**
  - **No evidence of increased severity of illness**
  - South African strain also S:N501Y but not related
  - Both UK and SA variants **associated with higher viral load**

- https://cmmid.github.io/topics/covid19/uk-novel-variant.html

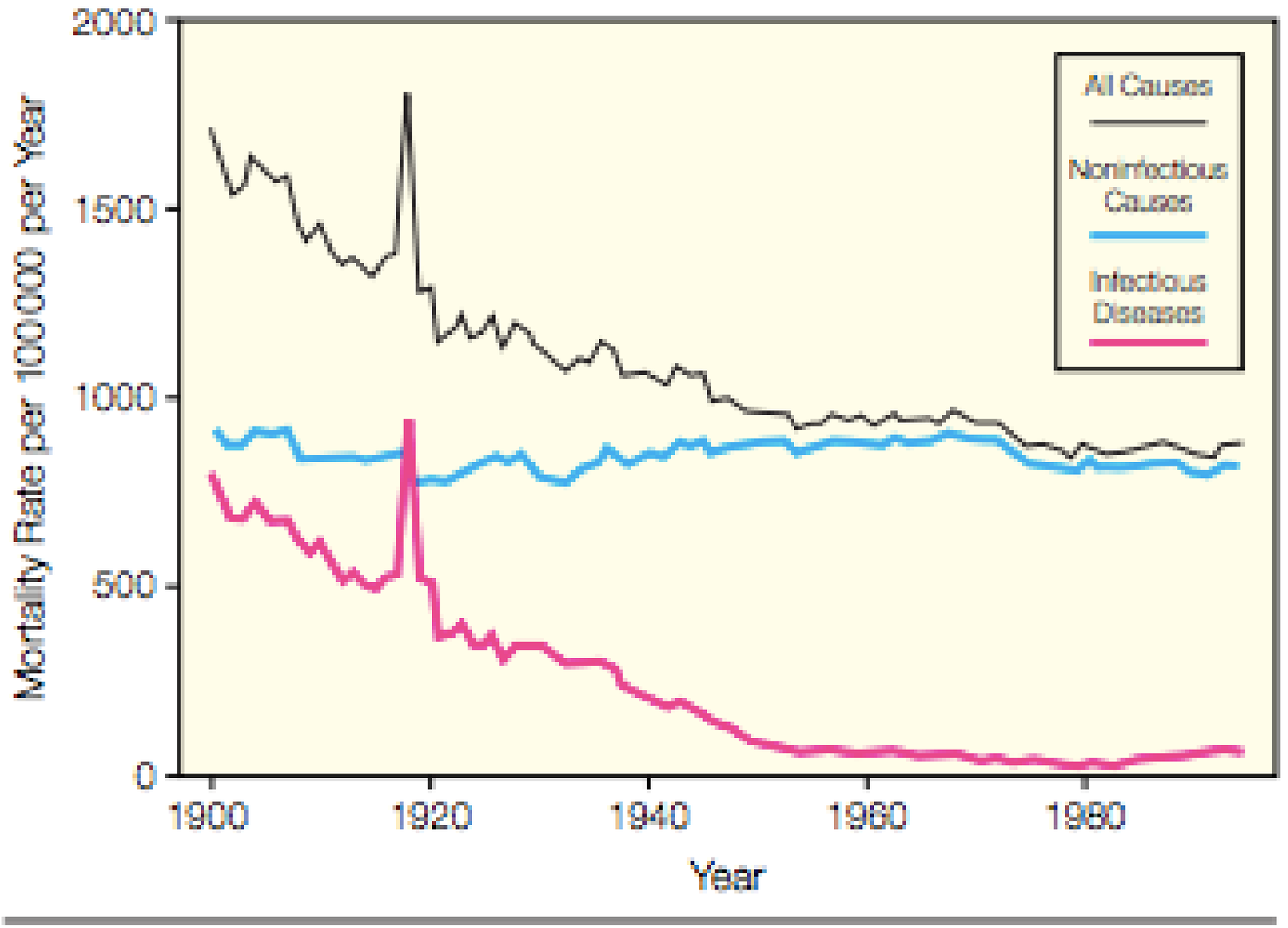
# New Variants

- What we know:
  - Public Health England stated that there is **no evidence that current vaccines would not protect against UK variant**
  - South African variant has more mutations to spike protein
  - Pfizer/BioNTech and University of Oxford scientists are testing vaccines against new variants
  - If need, we could make tweaks to the mRNA

- https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-emerging-variant.html

# New Variants

- What we don’t know:
  - Increased spread because of biology or behavior
    - Study from Center for Mathematical Modeling of Infectious Diseases at the London School of Hygiene and Tropical Medicine
  - How widely spread
  - Differences in response to drugs, including monoclonal antibody
    - Monoclonal ab target a specific epitope, whereas natural or vaccine-induced immunity is polyclonal (against several parts of the spike protein)
  - Ability to evade detection by specific diagnostic tests
    - Most PCR tests have multiple targets to detect the virus, so even if a mutation impacts one, the other PCR targets will still work
  - https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-emerging-variant.html

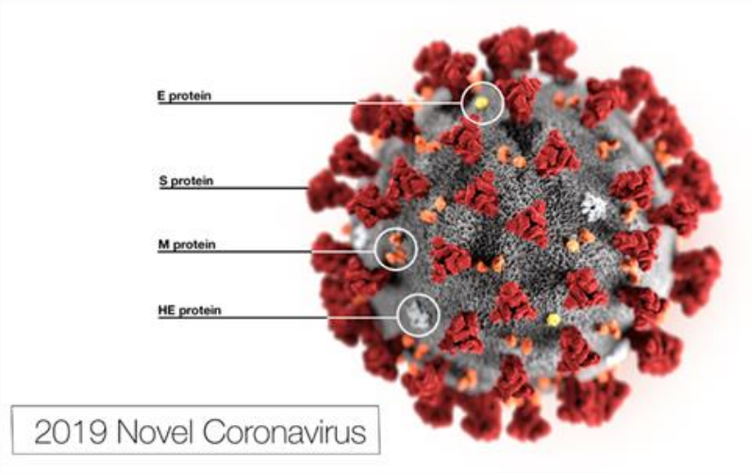


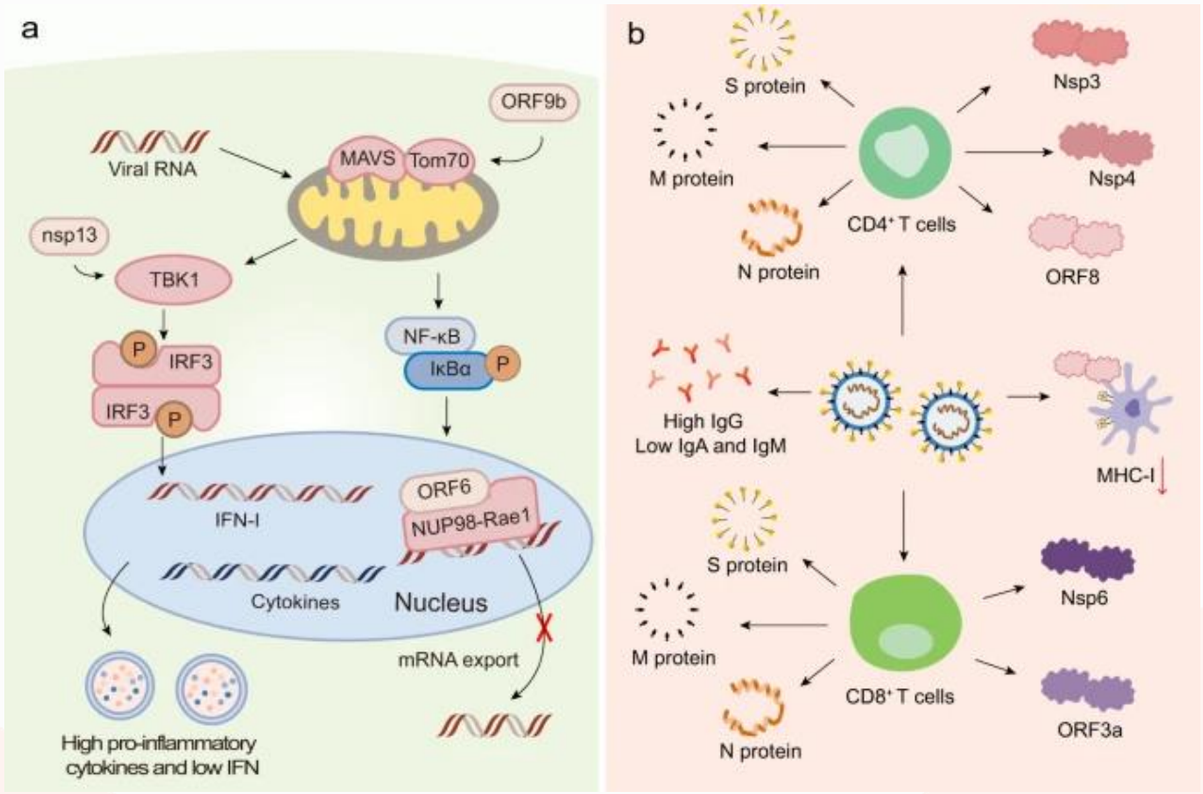

# Trends in Infectious Disease Mortality in the United States During the 20th Century

# SARS-CoV-2 Vaccines: How Did We Get Here?

- Usually a very deliberate process but stakes were too high
- Operation Warpspeed
- Modern Science
- Experiences from MERS/SARS
- A LOT OF LUCK!

# Immunity



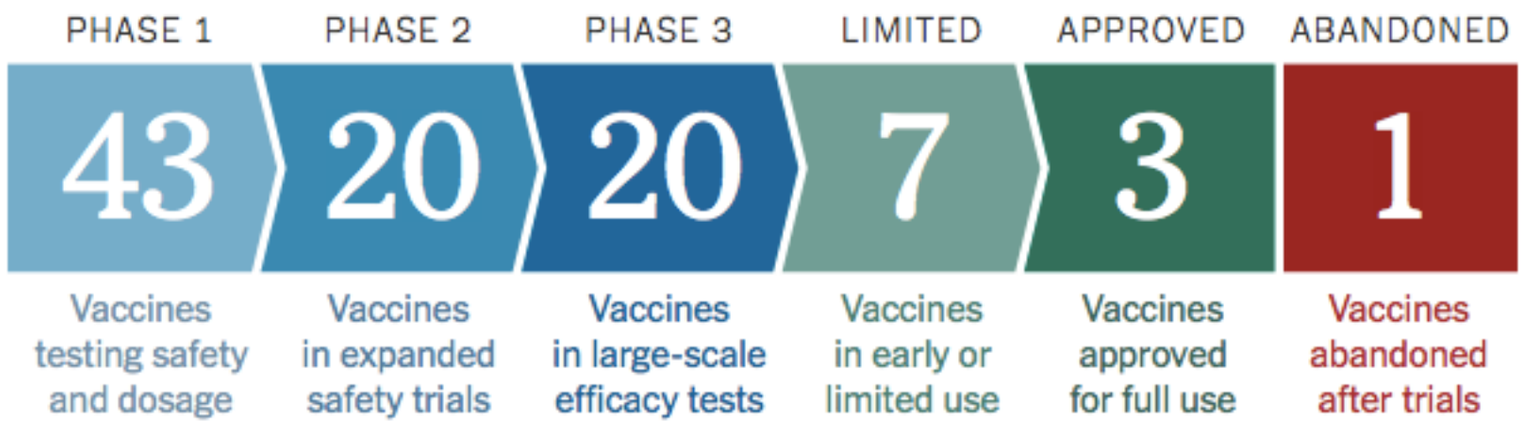




Travel Med Infect Dis. 2021 January-February; 39: 101911. PMCID: PMC7654327
Published online 2020 Nov 10. doi: 10.1016/j.tmaid.2020.101911 PMID: 33186686

Protective immunity against COVID-19: Unravelling the evidences for humoral *vs.* cellular components

# Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee Updated Jan. 9, 2021

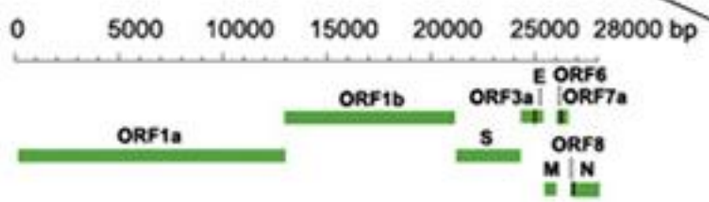


## Leading vaccines

| Developer | How It Works | Phase | Status |
|---|---|---|---|
| Pfizer-BioNTech | mRNA | 2 3 | Approved in Canada, other countries.<br>Emergency use in U.S., other countries. |
| Moderna | mRNA | 3 | Approved in Canada.<br>Emergency use in U.S., E.U., Israel. |
| Gamaleya | Ad26, Ad5 | 3 | Early use in Russia.<br>Emergency use in Belarus, other countries. |
| Oxford-AstraZeneca | ChAdOx1 | 2 3 | Emergency use in Britain, India, other countries. |
| CanSino | Ad5 | 3 | Limited use in China. |
| Johnson & Johnson | Ad26 | 3 | |
| Vector Institute | Protein | 3 | Early use in Russia. |
| Novavax | Protein | 3 | |
| Sinopharm | Inactivated | 3 | Approved in China, U.A.E., Bahrain.<br>Emergency use in Egypt. |
| Sinovac | Inactivated | 3 | Limited use in China. |
| Sinopharm-Wuhan | Inactivated | 3 | Limited use in China, U.A.E. |
| Bharat Biotech | Inactivated | 3 | Emergency use in India. |

## Nucleotide based vaccine candidates

Genomic RNA




DNA sequence of
S,M and N genes as vaccine target

mRNA -1273 and BNT162
encoding S protein

## Subunit vaccine candidates

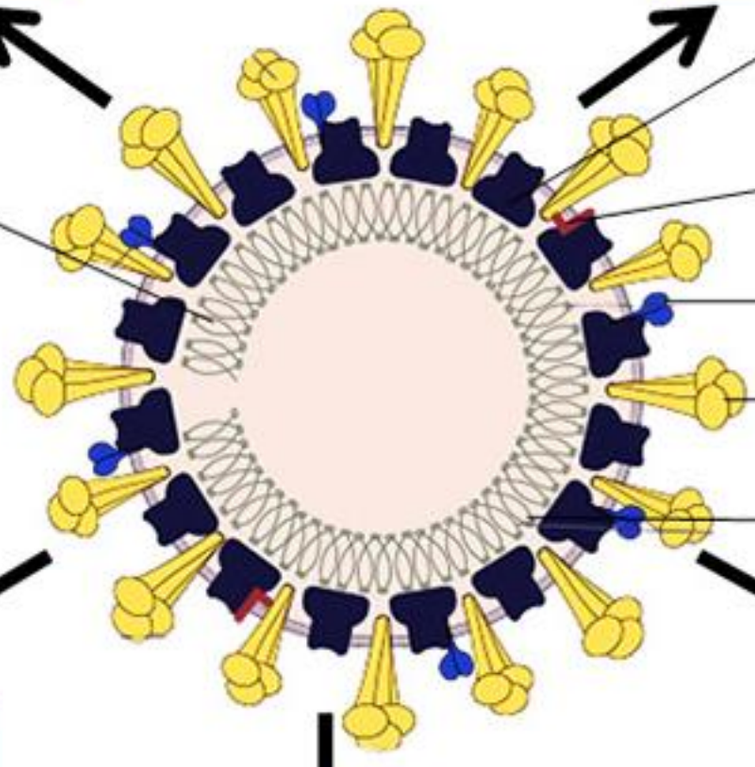
Membrane protein (M)

Envelope small
membrane protein (E)

Hemagglutinin Estrase (HE)

Spike Glycoprotein (S)

Nucleoprotein (N)



## Inactivated vaccines candidates

Inactivated or
whole killed virus (WKV)

## Viral vector based vaccine candidates

Coronavirus proteins/glycoproteins
expressed by attenuated adenovirus/poxvirus/
newcastle disease virus

## Attenuated vaccines candidates

Gene deletion of various
essential genes (S,N,E genes),
Nonstructural proteins (nsp) encoding genes

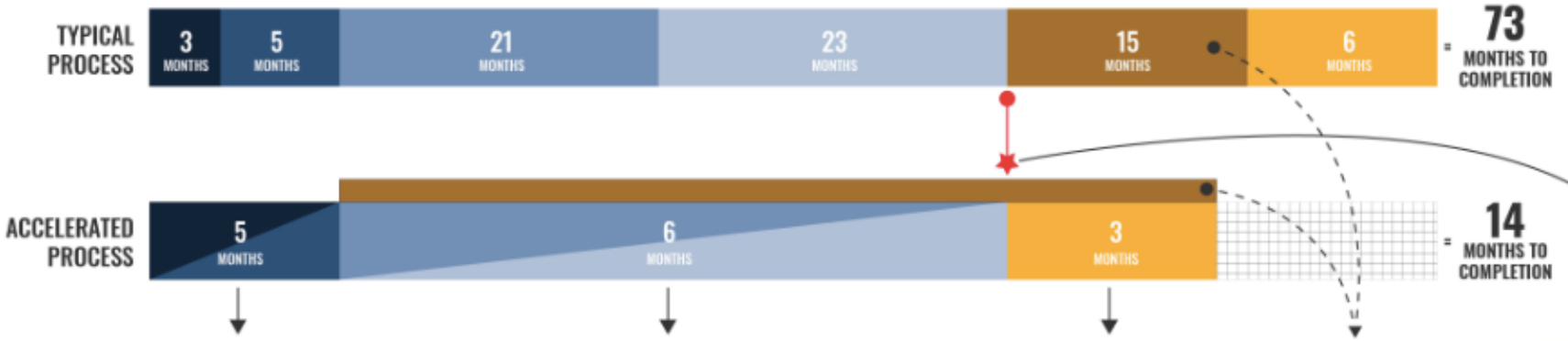
Review article

# Vaccination strategies to combat novel corona virus SARS-CoV-2

Satish Chandra Pandey [a, b], Veni Pande [a, b], Diksha Sati [a], Shobha Upreti [a], Mukesh Samant [a]

# OPERATION WARP SPEED
## ACCELERATED VACCINE PROCESS

**MISSION:** Deliver 300 million doses of safe and effective vaccine by 1 January 2021.




**1**

A typical 8-month process is accelerated by:

- Creating vaccine candidates immediately after viral genome sequence is available.
- Using vaccine platforms developed for other diseases.

**2**

A typical 42-month process is accelerated by:

- Large scale Phase III clinical trials of 30,000 volunteers allowing for rapid collection and earlier analysis of safety and efficacy data of demographically diverse populations by the FDA, reducing the typical 12-month approval process to three months.
- Two promising candidates began Phase III clinical trials in July, with others to follow quickly in coming months. Before beginning Phase III, candidates must show safety data from animal and human studies.
- The U.S. Government funding at-risk, large-scale manufacturing of the most promising vaccine candidates during Phase III clinical trials to ensure any vaccine proven to be safe and effective is available immediately upon FDA Emergency Use Authorization (EUA) approval or licensure.

**4**

A typical 6-month process is accelerated by:

- A tiered approach based on CDC recommended allocation methodology used as part of pandemic flu planning and the COVID-19 response will be used to determine vaccine distribution.

**3**

A typical 15-month process is accelerated by:

- Planning for infrastructure and distribution before the vaccines are approved or authorized.
- CDC leading distribution planning with DoD augmentation.

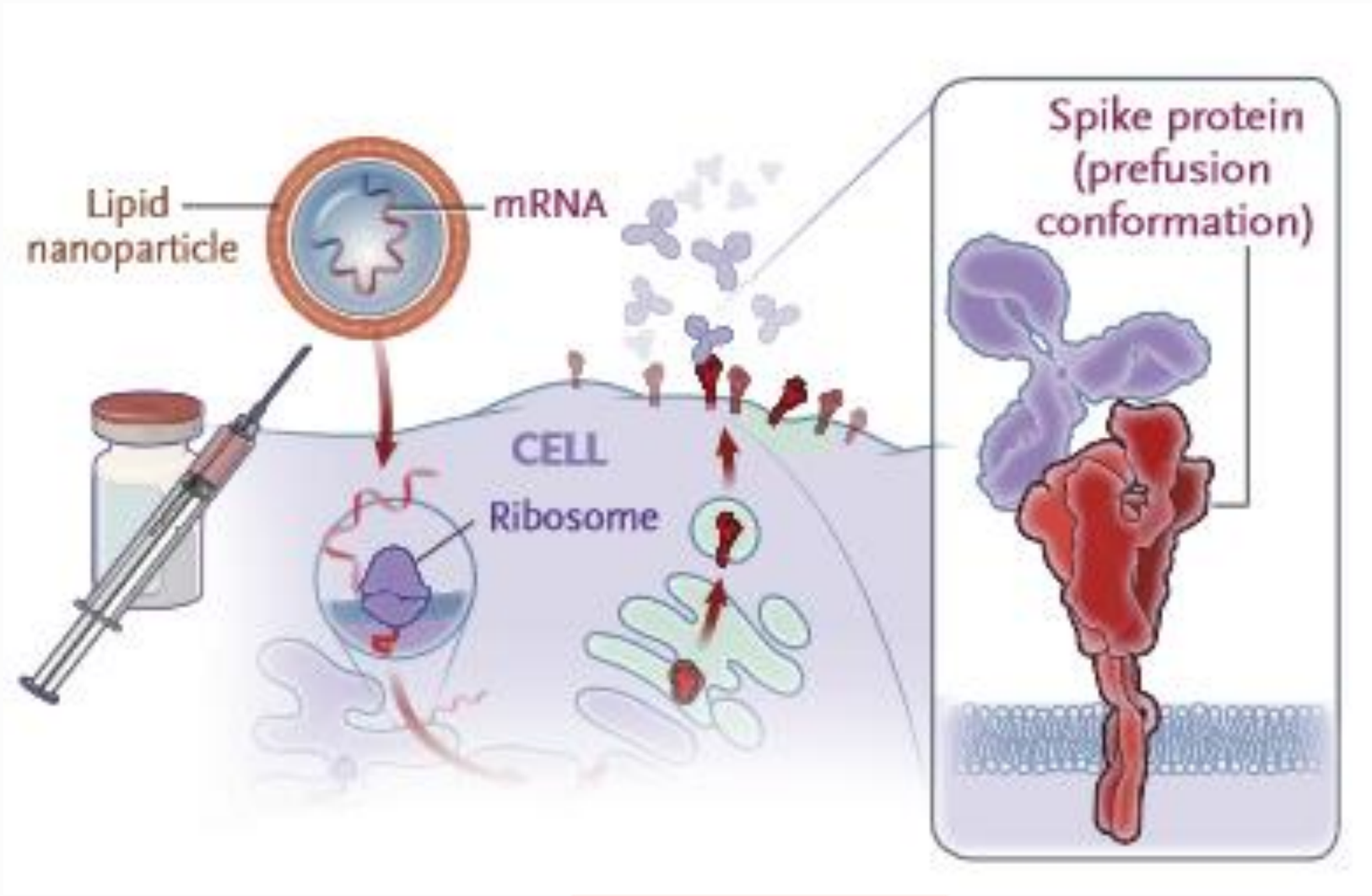
**5**

A typical 12-month FDA review for EUA approval or licensure is accelerated by:

- Providing continuous safety and efficacy data collected in large Phase III clinical trials.

R&D + Preclinical Trials Vaccine Candidate/s Identified
Phase I Clinical Trials
Phase II Clinical Trials
Phase III Clinical Trials
Manufacturing
Distribution

- mRNA Vaccines



| | BNT 162b2 | mRNA-1273 |
|---|---|---|
| FDA Approved | No | No |
| EUA | 16+ | 18+ |
| Prevention symptomatic disease | 95% (8 vs 162 cases) | 94% (11 vs 185 cases) |
| Prevention asymptomatic disease | ? No data yet | Yes, swab at 2nd vaccine<br>15 vs 39 asymptomatic |
| Prevention of severe disease | Yes (1 vs 3 cases) or 1 vs 9 | Yes (0 vs 30 cases) |
| Prevention of death | ? (2 vs 4 deaths) | ? (6 vs 7 (1 COVID) death) |
| Minimum order | 975 doses (5 doses/vial) | 100 doses (10 doses/vial) |
| Storage | -94F | -4F |
| Stability | Thawed - 5 days | Fridge 5 days/Room Temp 12Hr |
| Dosing | 2 doses 21 days apart | 2 doses 28 days apart |
| Dose | mRNA 30ug (0.3ml) | MRNA 100ug (0.5ml) |

# BNT 162b2 (Pfizer/BioNTech)

- mRNA vaccine EU submitted 1/20/202
- Reviewed 1/30/2020 (92 pages)
- C45900 was started as a Phase /2 study in the US and amended to expand to a global Phase 2/3 study enrolling ~44,000 participants (1:1 randomization)
- 83% White, 28% Hispanic, 42% >55 yo
- 20% with comorbidity, 30% obese, 23 pregnancies (9 withdrew)
- Ediary in > 6,000 patients
- SAEs, deaths, **treatment limiting AEs (0.1%), same in both arms**

**Figure 8. Geometric Mean Titers: SARS-CoV-2 Neutralization Assay – NT50 – Evaluable Immunogenicity Population – Phase 2**

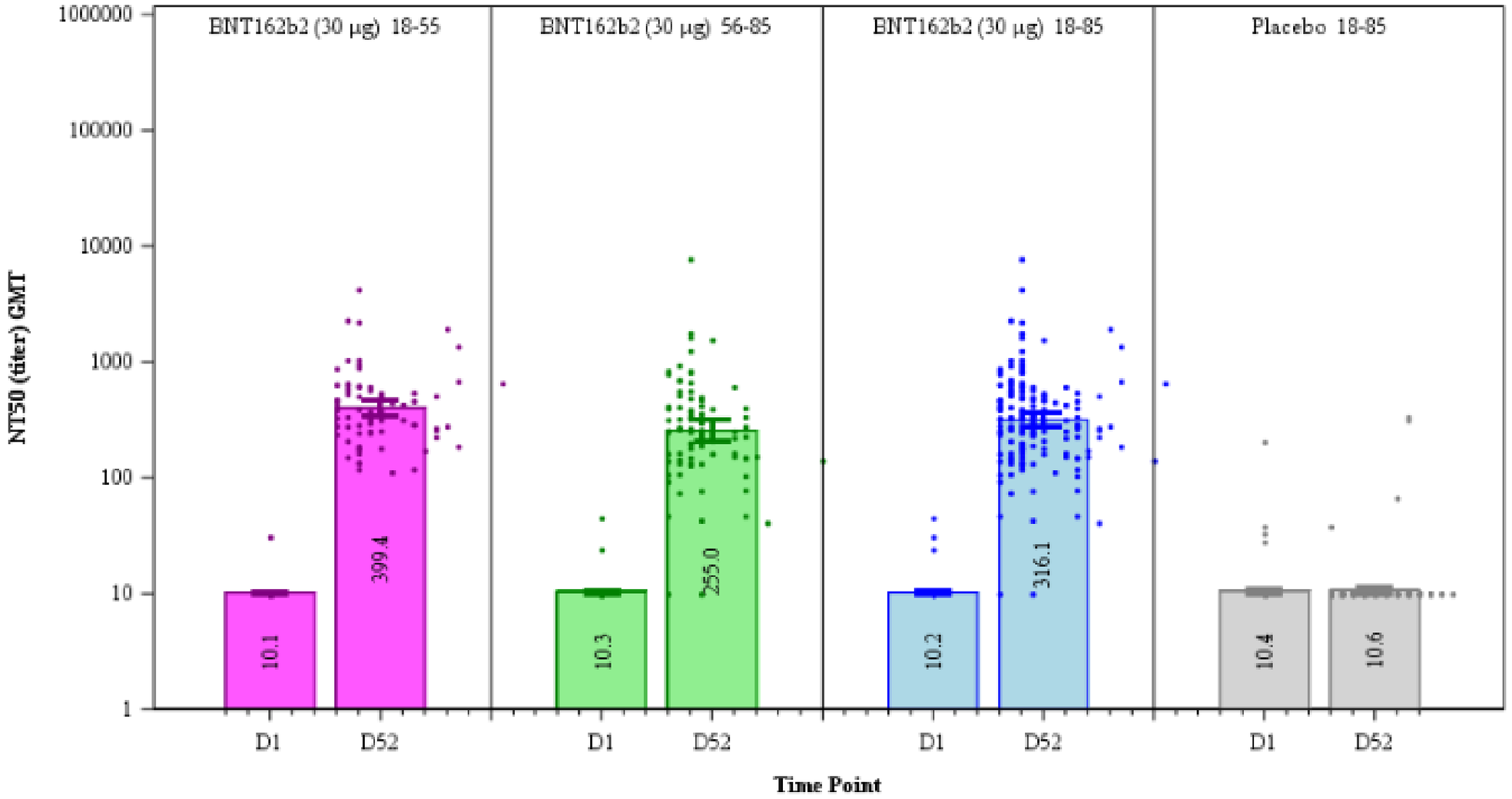


**Figure 9. Participants Reporting Local Reactions, by Maximum Severity, Within 7 Days After Each Dose, by Age Group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: 16-55 Years**

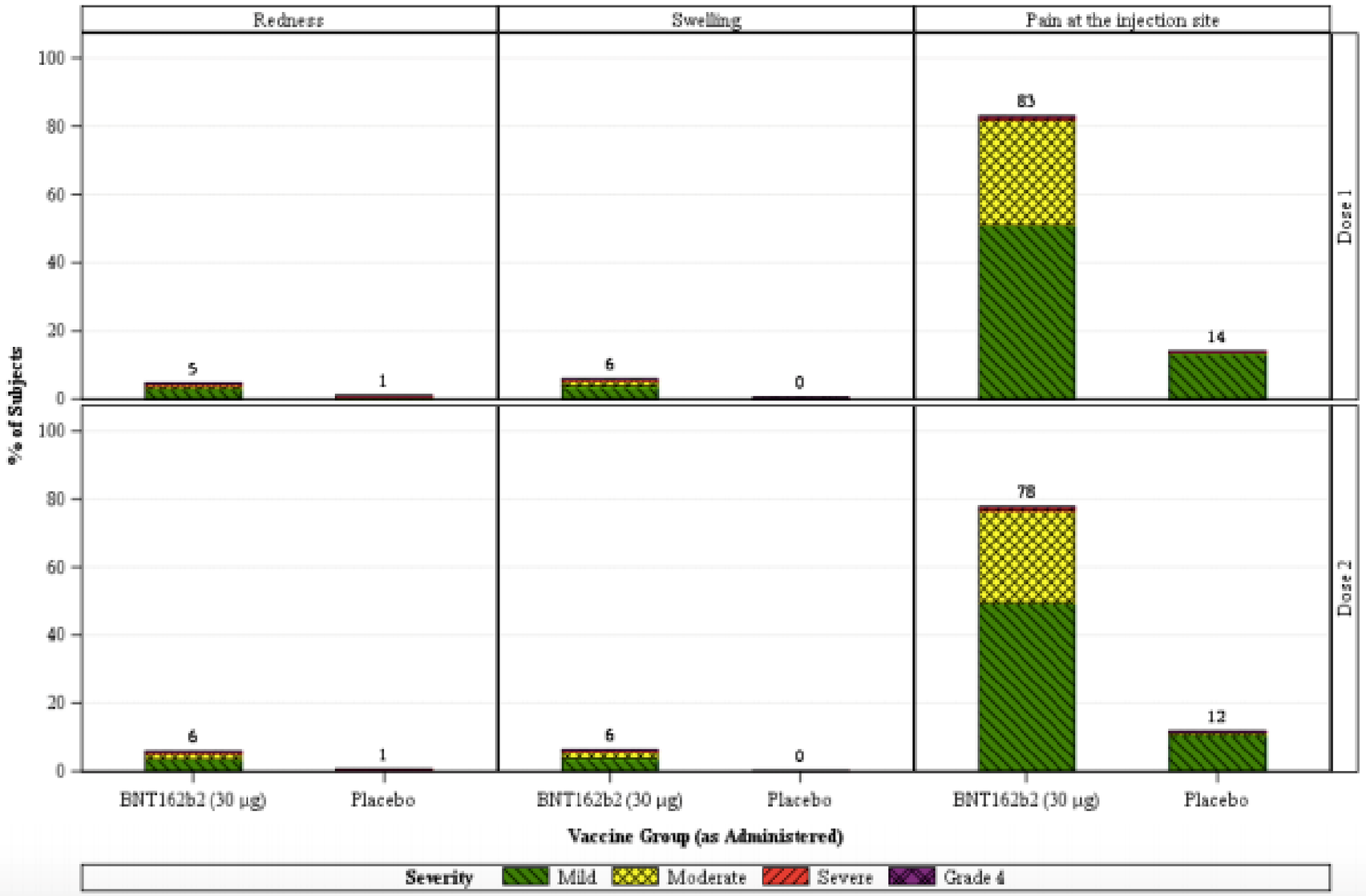


**Figure 11. Participants Reporting Systemic Events, by Maximum Severity, Within 7 Days After Each Dose, by Age Group – Reactogenicity Subset for Phase 2/3 Analysis – Safety Population Age Group: 16-55 Years**

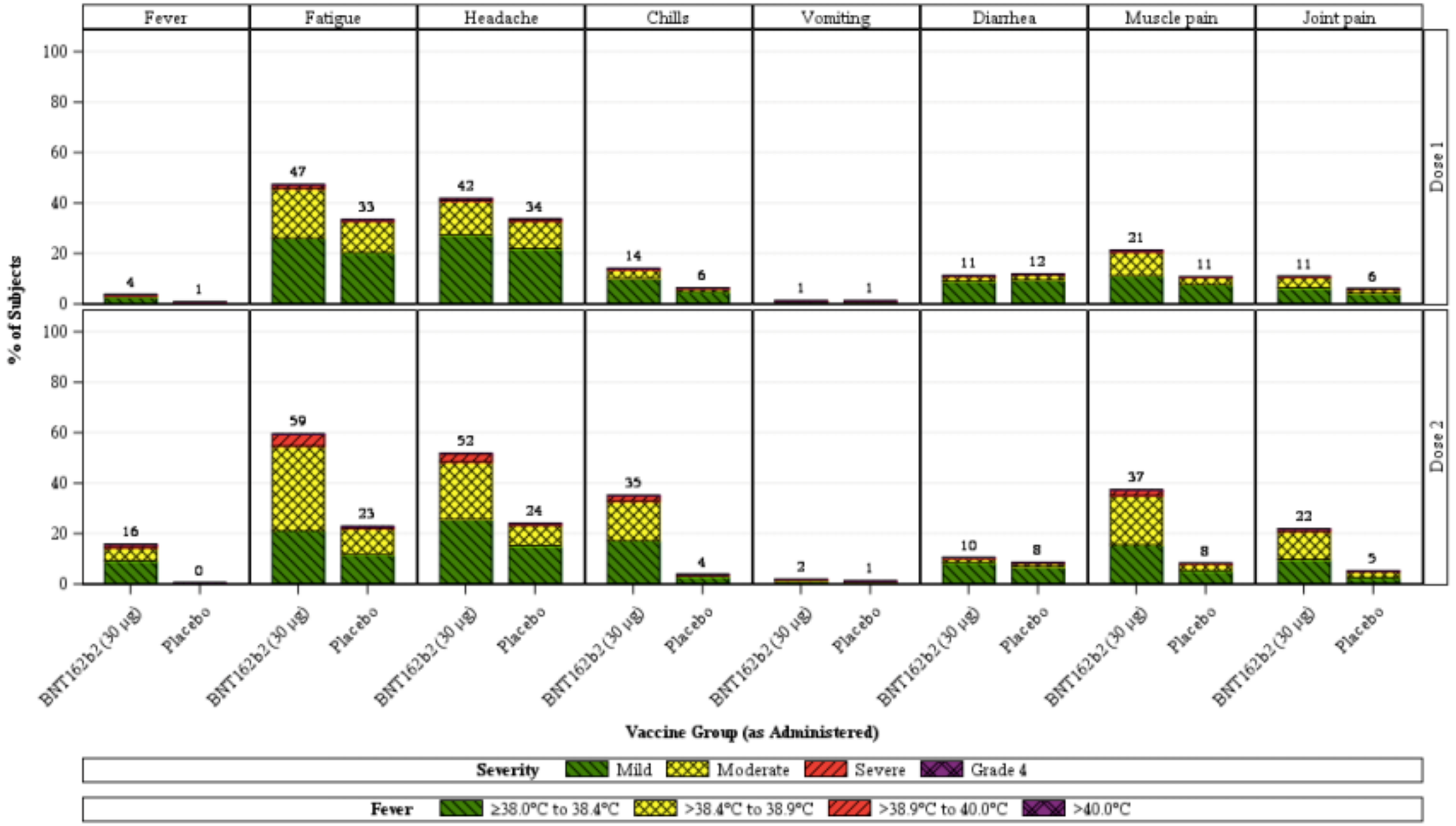


**Table 6. Number (%) of Subjects Reporting at Least 1 Adverse Event From Dose 1 to 1 Month After Dose 2 – ~38000 Subjects for Phase 2/3 Analysis – Safety Population**

| | Vaccine Group (as Administered) | |
|---|---|---|
| **Adverse Event** | **BNT162b2 (30 µg) (N[a]=18801) n[b] (%)** | **Placebo (N[a]=18785) n[b] (%)** |
| Any event | 5071 (27.0) | 2356 (12.5) |
| Related[c] | 3915 (20.8) | 953 (5.1) |
| Severe | 220 (1.2) | 109 (0.6) |
| Life-threatening | 18 (0.1) | 20 (0.1) |
| Any serious adverse event | 103 (0.5) | 81 (0.4) |
| Related[c] | 3 (0.0) | 0 |
| Severe | 57 (0.3) | 48 (0.3) |
| Life-threatening | 18 (0.1) | 19 (0.1) |
| Any adverse event leading to withdrawal | 34 (0.2) | 25 (0.1) |
| Related[c] | 14 (0.1) | 7 (0.0) |
| Severe | 13 (0.1) | 7 (0.0) |
| Life-threatening | 2 (0.0) | 4 (0.0) |

**Table 9. Vaccine Efficacy – First COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population**

| | Vaccine Group (as Randomized) | | | | | | |
|---|---|---|---|---|---|---|---|
| | BNT162b2 (30 µg) (N[a]=18198) | | Placebo (N[a]=18325) | | | | |
| Efficacy Endpoint | n1[b] | Surveillance Time[c] (n2[d]) | n1[b] | Surveillance Time[c] (n2[d]) | VE (%) | (95% CI[e]) | Pr (VE >30% \| data)[f] |
| First COVID-19 occurrence from 7 days after Dose 2 | 8 | 2.214 (17411) | 162 | 2.222 (17511) | 95.0 | (90.3, 97.6) | >0.9999 |

**Table 16. Vaccine Efficacy – First Severe COVID-19 Occurrence From 7 Days After Dose 2 – Subjects Without Evidence of Infection Prior to 7 Days After Dose 2 – Evaluable Efficacy (7 Days) Population**

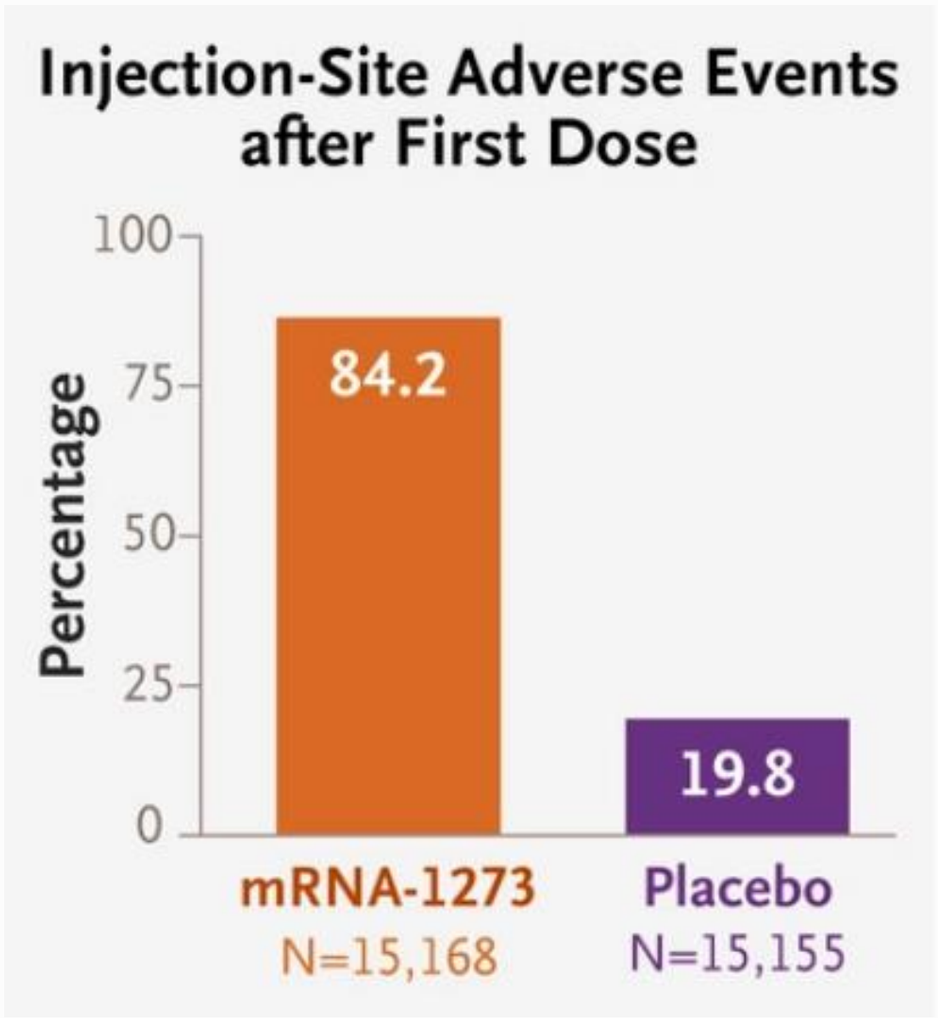
| | Vaccine Group (as Randomized) | | | | | | |
|---|---|---|---|---|---|---|---|
| | BNT162b2 (30 µg) (N[a]=18198) | | Placebo (N[a]=18325) | | | | |
| Efficacy Endpoint | n1[b] | Surveillance Time[c] (n2[d]) | n1[b] | Surveillance Time[c] (n2[d]) | VE (%) | (95% CI[e]) | Pr (VE >30% \| data)[f] |
| First severe COVID-19 occurrence from 7 days after Dose 2 | 1 | 2.215 (17411) | 3 | 2.232 (17511) | 66.4 | (-124.8, 96.3) | 0.7429 |

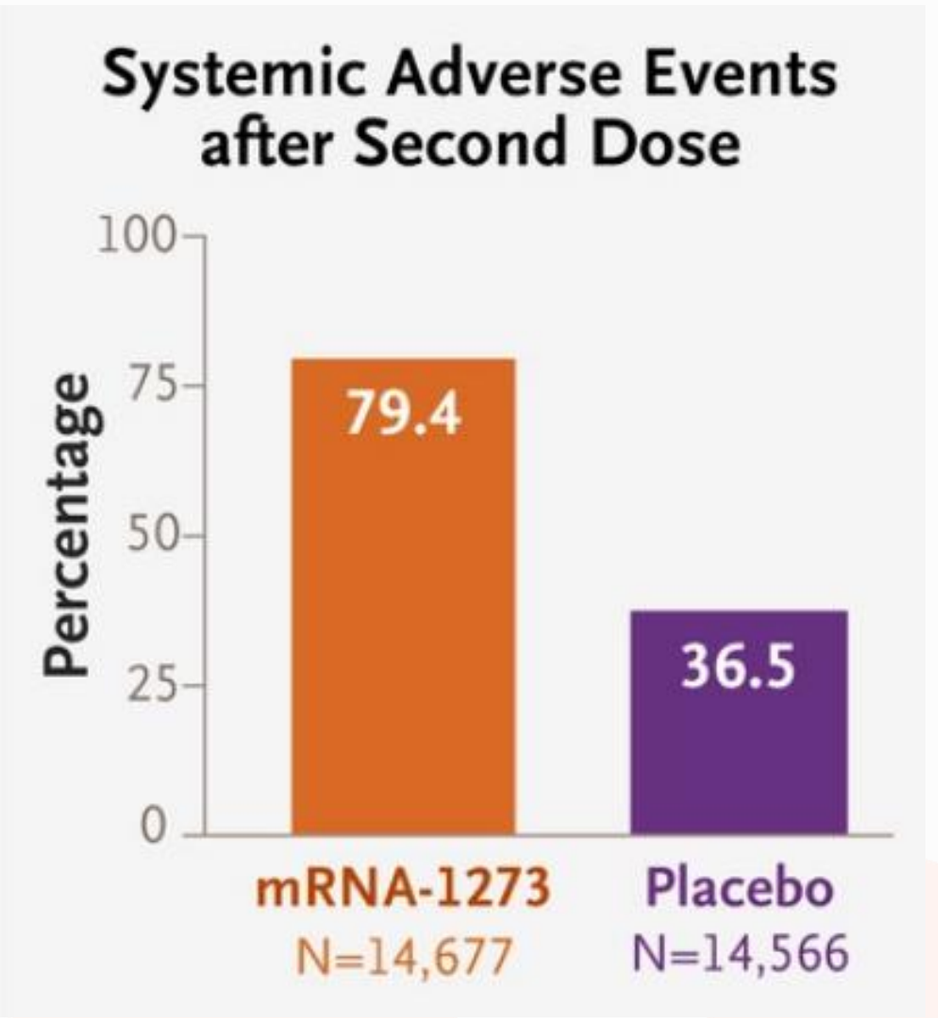
**Table 18. Vaccine Efficacy – First Severe COVID-19 Occurrence After Dose 1 – Dose 1 All-Available Efficacy Population**

| | Vaccine Group (as Randomized) | | | | | |
|---|---|---|---|---|---|---|
| | BNT162b2 (30 µg) (N[a]=21669) | | Placebo (N[a]=21686) | | | |
| Efficacy Endpoint Subgroup | n1[b] | Surveillance Time[c] (n2[d]) | n1[b] | Surveillance Time[c] (n2[d]) | VE (%) | (95% CI[e]) |
| First severe COVID-19 occurrence after Dose 1 | 1 | 4.021 (21314) | 9 | 4.006 (21259) | 88.9 | (20.1, 99.7) |
| After Dose 1 to before Dose 2 | 0 | | 4 | | 100.0 | (-51.5, 100.0) |
| Dose 2 to 7 days after Dose 2 | 0 | | 1 | | 100.0 | (-3800.0, 100.0) |
| ≥7 Days after Dose 2 | 1 | | 4 | | 75.0 | (-152.6, 99.5) |

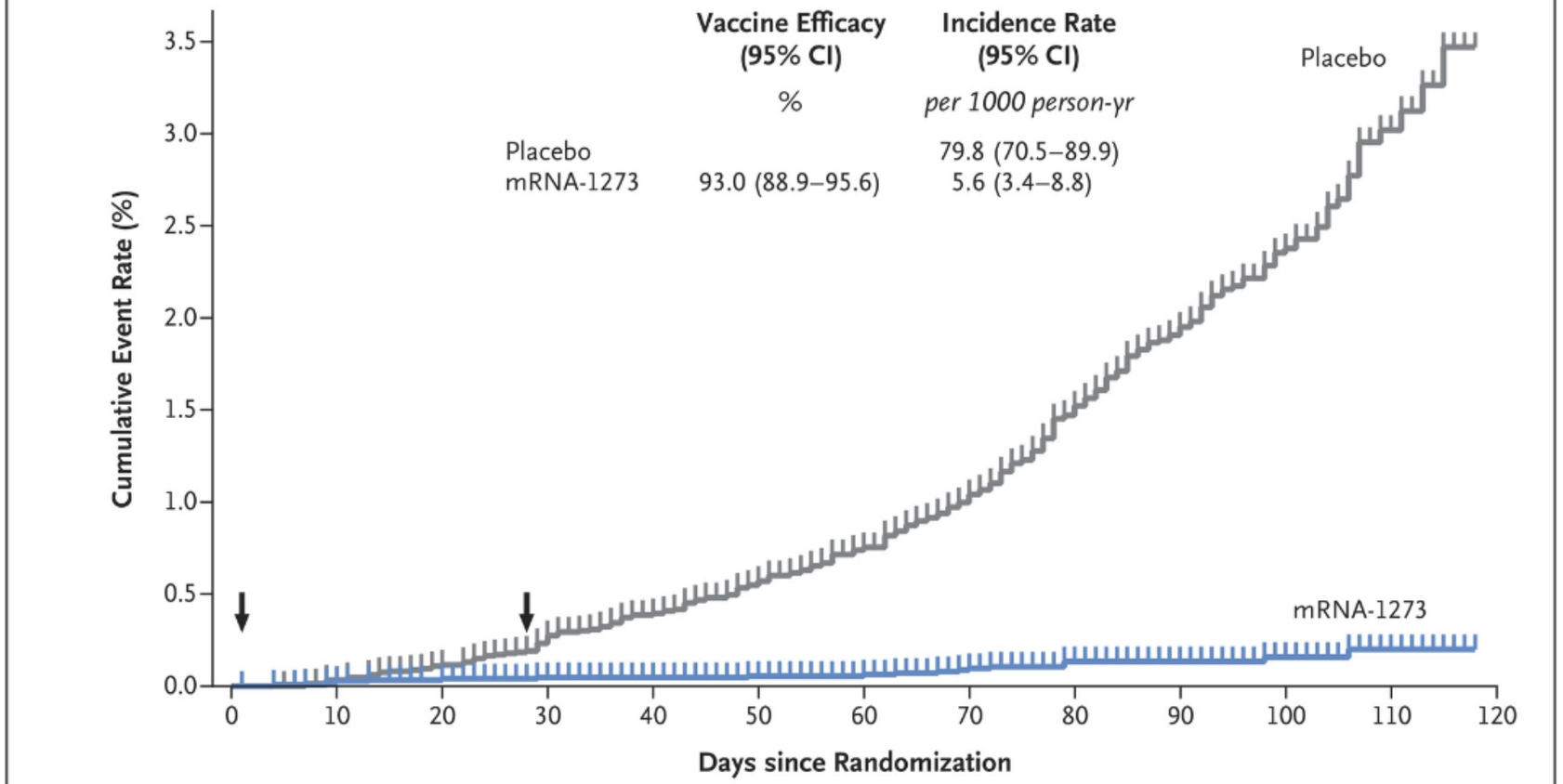
# mRNA-1273 (Moderna)

- mRNA vaccine EUA submitted 11/30/20
- Reviewed 12/17/20 (54 pages)
- mRNA -1273-P301 is a 30,000 participant study done at 99 sites in the US (1:1 randomization)
- 80% White, 20% Hispanic, 25% >65 yo
- 26% with comorbidity, 6.7% severely obese, 13 pregnancies (2 abortions: 1 spontaneous (both in placebo)
- Solicited AE in all patients
- SAE, deaths, **treatment limiting AEs (0.1%) - same in both arms**


Injection-Site Adverse Events after First Dose
Percentage
100
75
50
25
0
84.2
19.8
mRNA-1273
N=15,168
Placebo
N=15,155


Systemic Adverse Events after Second Dose
Percentage
100
75
50
25
0
79.4
36.5
mRNA-1273
N=14,677
Placebo
N=14,566

**B** Modified Intention-to-Treat Analysis




**No. at Risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 14,598 | 14,590 | 14,567 | 14,515 | 13,806 | 12,352 | 12,694 | 11,450 | 9736 | 6729 | 4067 | 1200 | 0 |
| mRNA-1273 | 14,550 | 14,543 | 14,532 | 14,504 | 13,825 | 13,398 | 12,791 | 11,573 | 9911 | 6871 | 4179 | 1238 | 0 |

| Covid-19 Onset | Placebo (N=14,598) | mRNA-1273 (N=14,550) |
|---|---|---|
| Randomization to 14 days after dose 1 | 11 | 5 |
| 14 Days after dose 1 to dose 2 | 35 | 2 |
| Dose 2 to 14 days after dose 2 | 19 | 0 |
| Starting 14 days after dose 2 | 204 | 12 |
| Total (any time after randomization) | 269 | 19 |

| Subgroup | Placebo (N=14,073) | mRNA-1273 (N=14,134) | Vaccine Efficacy (95% CI) |
|---|---|---|---|
| | *no. of events/total no.* | | |
| All patients | 185/14,073 | 11/14,134 | 94.1 (89.3–96.8) |
| Age | | | |
| ≥18 to <65 yr | 156/10,521 | 7/10,551 | 95.6 (90.6–97.9) |
| ≥65 yr | 29/3552 | 4/3583 | 86.4 (61.4–95.2) |
| Age, risk for severe Covid-19 | | | |
| 18 to <65 yr, not at risk | 121/8403 | 5/8396 | 95.9 (90.0–98.3) |
| 18 to <65 yr, at risk | 35/2118 | 2/2155 | 94.4 (76.9–98.7) |
| ≥65 yr | 29/3552 | 4/3583 | 86.4 (61.4–95.2) |
| Sex | | | |
| Male | 87/7462 | 4/7366 | 95.4 (87.4–98.3) |
| Female | 98/6611 | 7/6768 | 93.1 (85.2–96.8) |
| At risk for severe Covid-19 | | | |
| Yes | 43/3167 | 4/3206 | 90.9 (74.7–96.7) |
| No | 142/10,906 | 7/10,928 | 95.1 (89.6–97.7) |
| Race and ethnic group | | | |
| White | 144/8916 | 10/9023 | 93.2 (87.1–96.4) |
| Communities of color | 41/5132 | 1/5088 | 97.5 (82.2–99.7) |

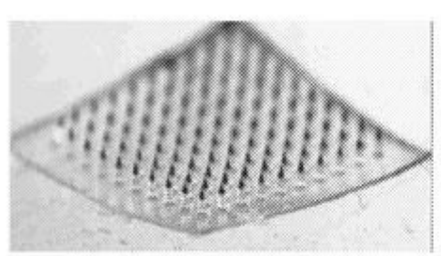
# ChAdOx1 (Oxford/Astra Zeneca)

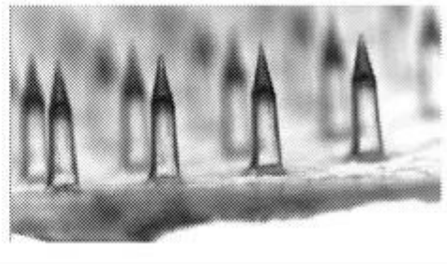
- Chimpanzee adenovirus chimeric vaccine
- Not reviewed by FDA, approved in Canada, UK
- ChAdOx1 combination of 5 studies in UK and Brazil (12k patients)
- 18-55 yo cohort planned as single-dose cohort.  The protocol was modified in July 2020 to offer a 2nd dose (after robust booster responses identified in early immunogenicity cohorts)
- >80% white, average BMI 25, female, >80% HCW

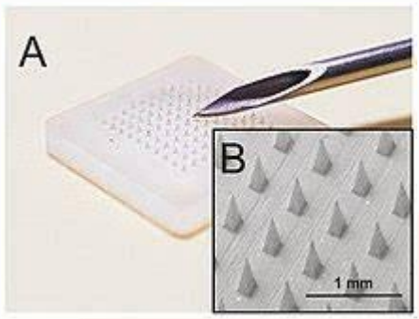
| | ChAdOx1 | Placebo | Vaccine Efficacy |
|---|---|---|---|
| All symptomatic | 30/5807 (0.5%) | 101/5829 (1.7%) | 70.4% (54.8 to 80.6) |
| LD/SD | 3/1367 (0.2%) | 30/1374 (2.2%) | 90.0% (67.4 to 97) |
| SD/SD | 15/2377 (0.6%) | 38/2430 (1.6%) | 60.3% (28.0 to 78.2) |
| Asymptomatic | 29/3288 (0.9%) | 40/3350 (1.2%) | 27.3% (-17.2 to 54.9) |
| LD/SD | 7/1120 (0.6%) | 17/1127 (1.5%) | 58.9% (1.0 to 82.9) |
| SD/SD | 22/2168 (1.0%) | 23/2223 (1.0%) | 3.8% (-72.4 to 46.3) |

# PittCoVacc (UPenn)

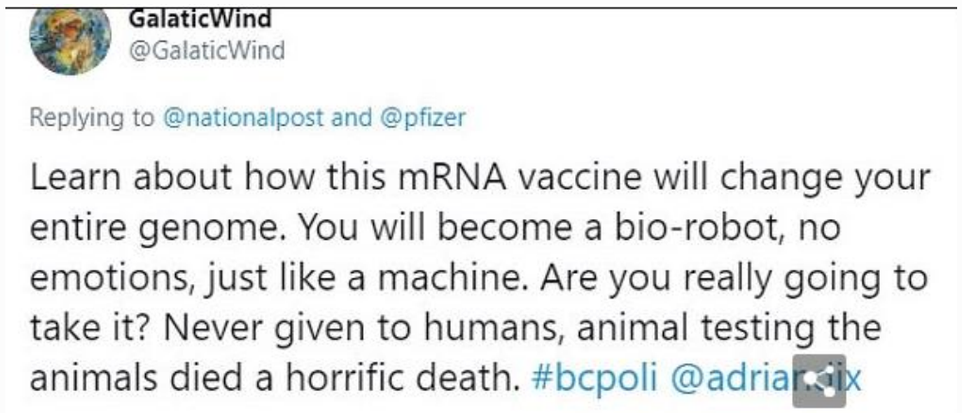
- S1 Spike protein delivered epidermally by sugar microneedles - stored at room temperature







# Vaccine Misinformation






# Cure for Vaccine Misinformation

- Information, information, information
- ‘Should I have my...parents, children…vaccinated?’: Only if you like them
- Vaccine hesitancy is curable with information
- Anti-vaxxers are not, don’t waste your time

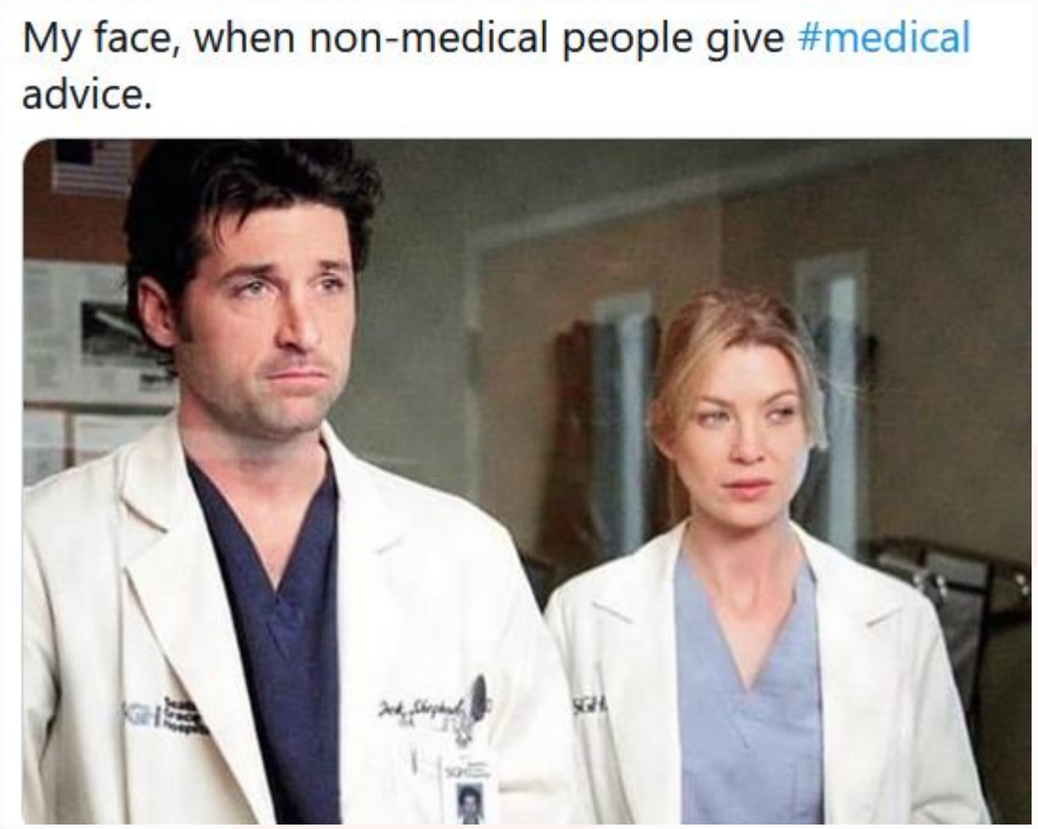

Love them. Protect them.
Never inject them.
There are NO safe vaccines!
Shaken Baby Syndrome
Chronic Ear Infections
Death
SIDS
Seizures
ADD
Allergies
Asthma
Autism
Diabetes
Meningitis
and polio are caused by adverse reactions to vaccine poisons.
Go to: VaccineTruth.com
or call Vaccination Liberation: 1-888-249-1421


WOULD YOU INJECT MATTER FROM ABORTED FETUSES INTO YOUR CHILD?
92% OF CHILDREN WHO ARE VACCINATED HAVE BEEN POTENTIALLY INJECTED WITH DNA FROM ABORTED FETUSES
INDEPENDENCEDECLARATION.ORG


Trust in God
not vaccines
#saynotobillgates


NO VACCINE
NEEDED
I HAVE
AN
IMMUNE
SYSTEM
MY BODY
MY CHOICE
FAKE
NEWS
RTE

- Internet: Gosh, I don’t know about these MRNA vaccines.
- Me and my physician friends: I want this vaccine so bad I would take it in my eye!



| Description | Pfizer-BioNTech COVID-19 vaccine | Moderna COVID-19 vaccine |
|---|---|---|
| **mRNA** | Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 | Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2 |
| **Lipids** | 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide | PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol |
| | 1,2-distearoyl-sn-glycero-3-phosphocholine | 1,2-distearoyl-sn-glycero-3-phosphocholine |
| | Cholesterol | Cholesterol |
| | (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) | SM-102: heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate |
| **Salts, sugars, buffers** | Potassium chloride | Tromethamine |
| | Monobasic potassium phosphate | Tromethamine hydrochloride |
| | Sodium chloride | Acetic acid |
| | Dibasic sodium phosphate dihydrate | Sodium acetate |
| | Sucrose | Sucrose |

# Where can we help?

- Difference between safety and tolerability
- Difference between vaccine safety and COVID disease risk
- Leading by example
- Debunking myths

# Would you take this vaccine?

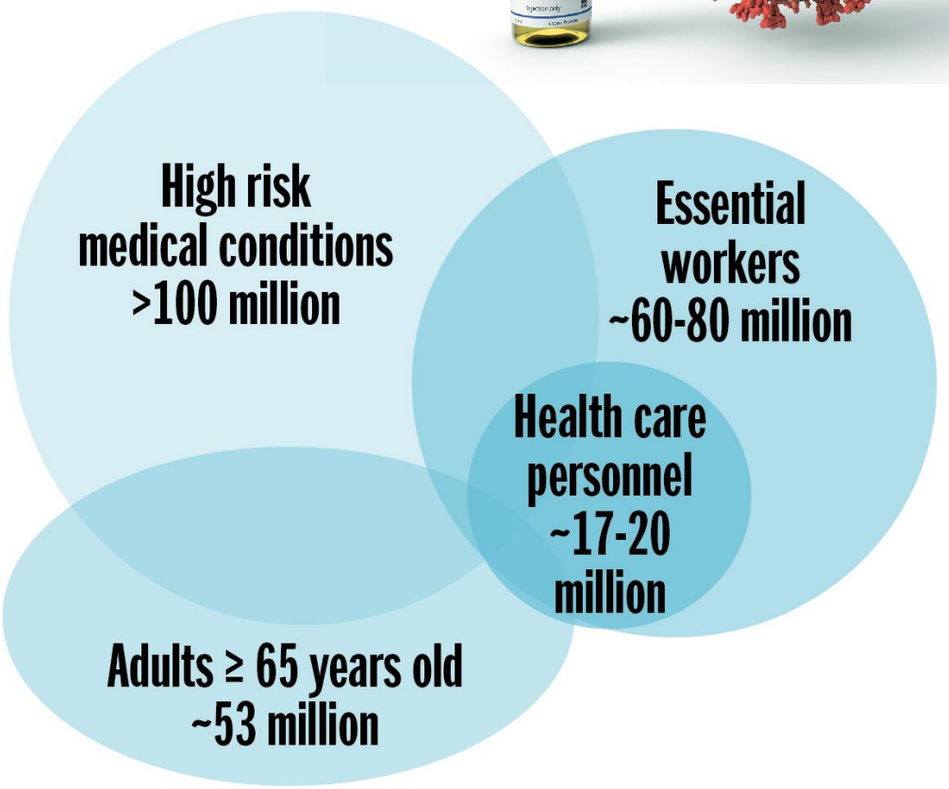
- Up to 3% mortality
- Bizarre neurological events
- Bizzare coagulation events including strokes, heart attacks, and amputations
- Myriad of short term and long term complications
- Destroyed lungs requiring lung transplants or life long oxygen therapy
- All at a cost of at least $16 trillion dollars

# Goals of Mass Vaccination

- Decrease Morbidity
  - Vulnerable, elderly, high risk,essential, socially mobile
- Decrease Mortality
  - Elderly, vulnerable, high risk
- **Decrease the Transmission/lower R0**
  - Socially mobile, essential, ‘anti-maskers/denialist/party animals’

# Groups for early phase vaccination

*Accounts for more than half of all U.S. adults*


SOURCE: Advisory Committee on Immunization Practices presentation, Aug. 26, 2020

# Relative Impact from the U.S. Population Stratification Model: Analysis 1

| Group vaccinated | Population -wide decrease in rate per 10 million courses | |
|---|---|---|
| | COVID-19 Infections | COVID-19 Deaths |
| Healthcare personnel | 3.5% | 3.3% |
| Essential workers | 3.1% | 3.1% |
| With underlying conditions | 3.8% | 4.3% |
| Persons ⩾65 years old | 0.7% | 6.1% |

Vaccine Efficacy (VE) assumptions

- 70% among persons 18-64 years old
- 50% among persons ≥65 years old

- Healthcare workers
  - Easy, experienced, buy in high, small sample, high exposure, important example but ineffective
- Nursing home staff/residents
  - high mortality with/without disease, prior infection
- Elderly (65 vs 75 years)
- High risk conditions (proof?)
- **Essential workers**
  - **Teachers and first responders**
- **Multigenerational families**
- **Social fabric (athletics, culture, leaders)**

# How about these?

- Pregnant patients
  - Real significantly increased risk of disease vs. theoretically low risk of vaccine
  - Pregnant women should not be excluded from standard of care
- Breastfeeding patients
  - No obvious issues with vaccines

- ACOG recommends that COVID-19 vaccines should not be withheld from pregnant individuals who meet criteria for vaccination based on ACIP-recommended priority groups.
- COVID-19 vaccines should be offered to lactating individuals similar to non-lactating individuals when they meet criteria for receipt of the vaccine based on prioritization groups outlined by the ACIP.

# How about these?

- Children (153 16-18 yo)
  - Do not need efficacy but some safety data
  - Mandatory inclusion in studies
- Previous COVID disease
  - CDC recommends vaccination after 90d
    - Prisma Health established 30d rule
  - Previous antibody therapy delay 90d?
- Can we create a tier 5?
  - 30ug of spike protein vs grams during the disease
  - Antibody titer is NOT helpful

# How do we roll this out?
# Not like this!

- Federal plans and numbers change at least weekly
- **Vaccines do not save lives, vaccinations save lives**
- Plan for roll out ‘let the states figure it out’ is naive at best
  - Federal guidance/support limited to ‘who’ and ignored the ‘how’
- Health Departments  (Testing, tracking, tracing, reporting, and why not add the vaccines as an unpaid mandate)
- Hospitals/Clinics to role out during a historic surge
- **Current role out rate will complete this in 2026**
- **To be done in October we need >1.5 million doses per day**

# COVID-19 Vaccinations in the United States

Overall US COVID-19 Vaccine Distribution and Administration

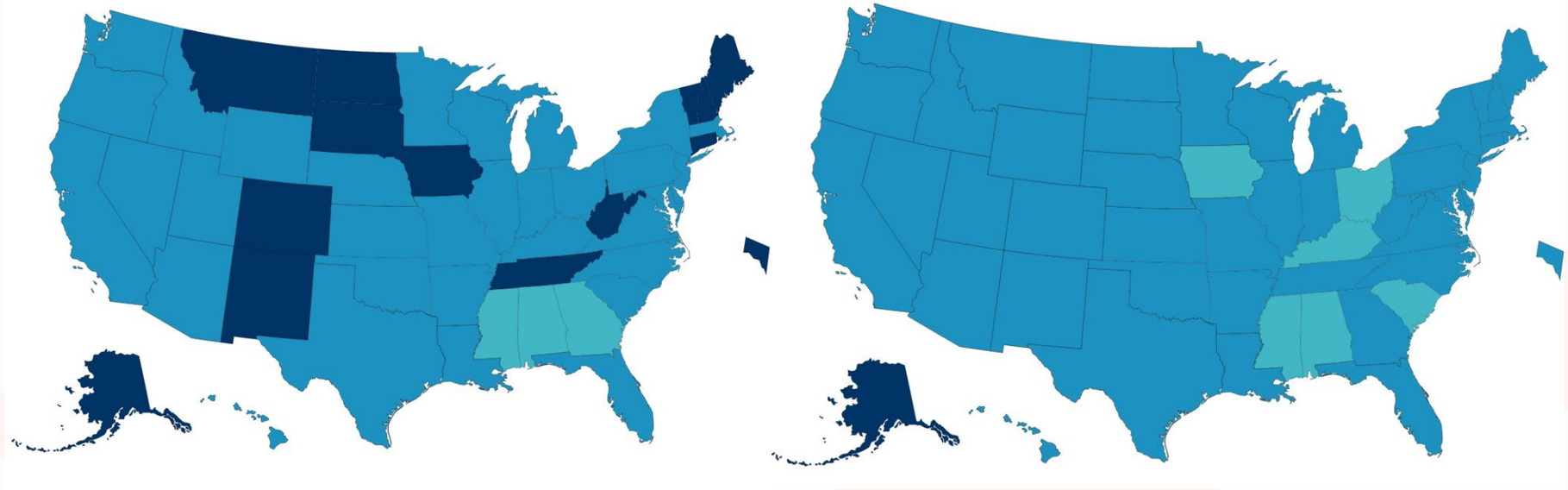
| Total Doses Distributed | Total Number of People Initiating Vaccination (1st Dose Received) |
|---|---|
| 17,288,950 | 5,306,797 |

CDC | Updated: Jan 06 2021 As of 9:00am ET

Federal Pharmacy Partnership for Long-Term Care Program (Subset of Overall Numbers)

| Doses Distributed for Use in Long-Term Care Facilities | Number of People Initiating Vaccination (1st Dose Received) in Long-Term Care Facilities |
|---|---|
| 3,416,875 | 511,635 |

CDC | Updated: Jan 06 2021 As of 9:00am ET



https://covid.cdc.gov/covid-data-tracker/#vaccinations

# Issues

- The baseline promise is actually pretty easy
  - No adult person who should be vaccinated
  - We are too concerned about shipping vaccines, we should be more worried about giving vaccines
  - We are too concerned about wasting vaccines, we should be more worried about wasting opportunities to vaccinate
- It is worrisome that the US is fumbling in the easy phase