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instituto de investigación sanitaria

# Jornada X (+I) Aniversario

## Instituto Investigación Sanitaria BIODONOSTIA

San Sebastián, 19 noviembre de 2021

Osakidetza
DONOSTIALDEA ESI
OSI DONOSTIALDEA

# Update COVID-19
# Dónde estamos y a dónde vamos


## Dr. José Mª Miró

Infectious Diseases Service
Hospital Clinic - IDIBAPS
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Barcelona (Spain)

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CLÍNIC
BARCELONA
Hospital Universitari

UNIVERSITAT DE BARCELONA

# Potential conflict of interest

**Dr. José M Miró has received honoraria for speaking or participating in Advisory Boards and/or research grants from the following Pharmaceutical Companies:**

- Abbvie
- Angelini-Allergan
- Bristol-Myers Squibb
- Contrafect
- Genentech
- Gilead Sciencies
- Jansen
- Merck
- Medtronic
- Novartis
- Pfizer
- Roche
- Theravance
- ViiV Healthcare

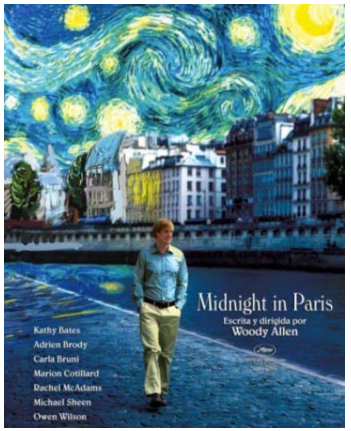
# Spanish Working Group on AIDS (GESIDA)
# Executive Committee, 1997-1998

# Biodonostia Health Research Institute
# Tenth (+1) Anniversary (2010-2021)


www.biodonostia.org



# 2010-2019
# Decade



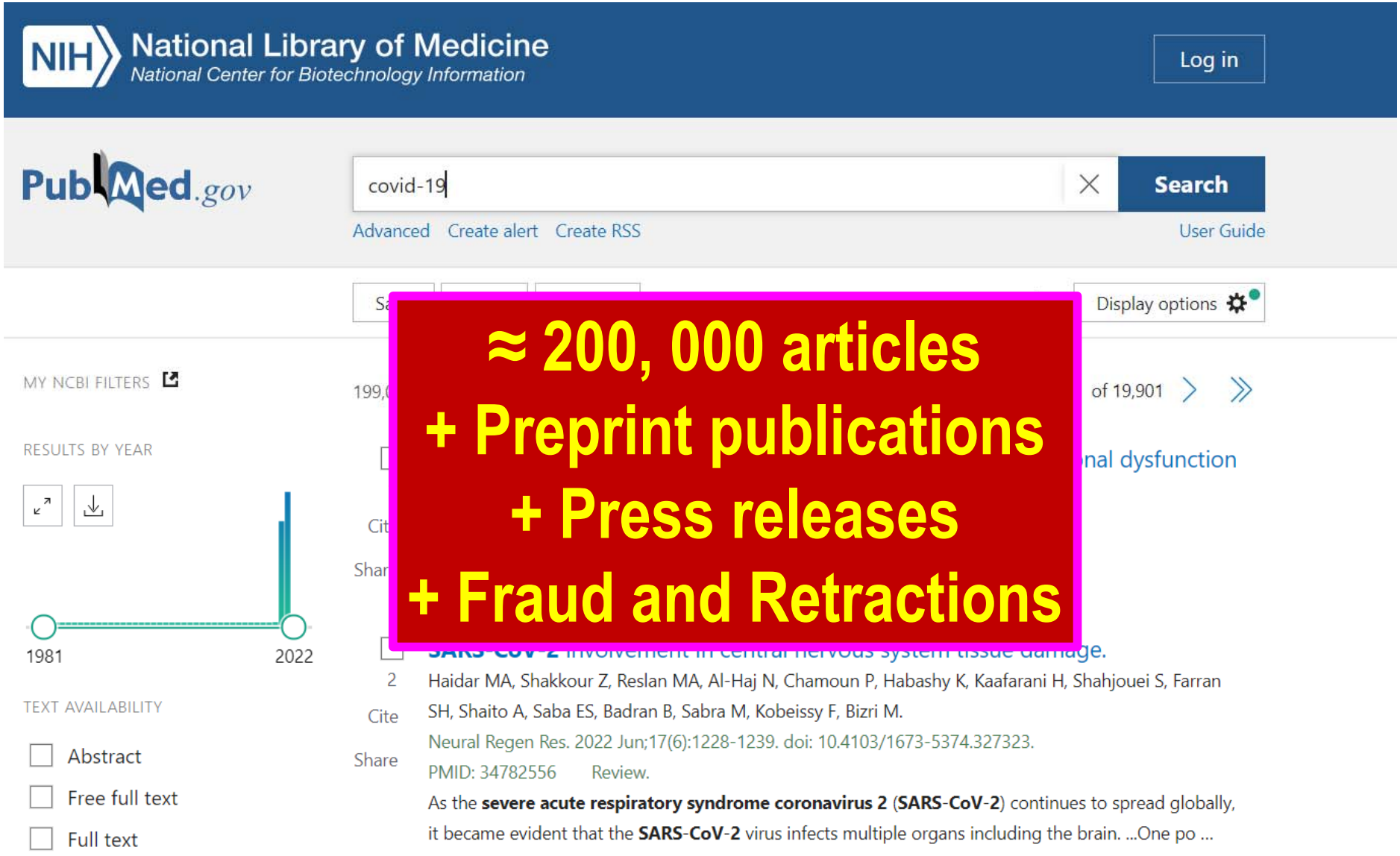

# In Wuhan, China started the outbreak of a novel Coronavirus (COVID-19) in Dec. 2019

Normile D. Science. Jan. 3, 2020 , 10:35 AM

# Widespread rapid dissemination in our hyper-connected world creates real-time challenges to prediction analyses

# 2020-2021


VACCINE
Pfizer
BIONTECH
Coronavirus COVID-19
VACCINE
moderna


National Library of Medicine
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Advanced
Create alert
Create RSS
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Display options
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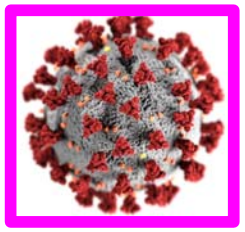
1981
2022
TEXT AVAILABILITY
Abstract
Free full text
Full text
of 19,901
≈ 200, 000 articles
+ Preprint publications
+ Press releases
+ Fraud and Retractions
Haidar MA, Shakkour Z, Reslan MA, Al-Haj N, Chamoun P, Habashy K, Kaafarani H, Shahjouei S, Farran SH, Shaito A, Saba ES, Badran B, Sabra M, Kobeissy F, Bizri M.
Neural Regen Res. 2022 Jun;17(6):1228-1239. doi: 10.4103/1673-5374.327323.
PMID: 34782556 Review.
As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread globally, it became evident that the SARS-CoV-2 virus infects multiple organs including the brain. ...One po ...



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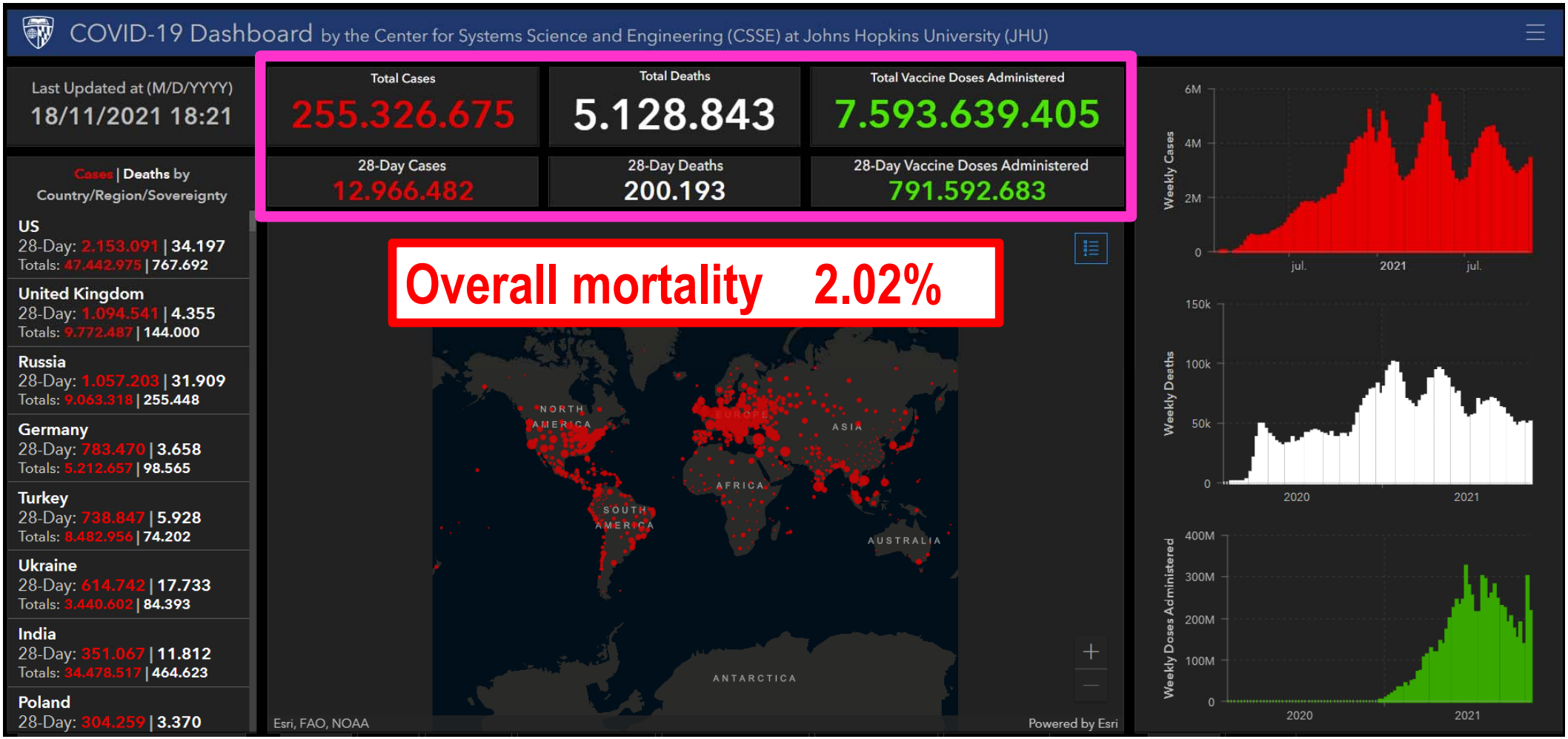
*Vaccine-induced Thrombotic Thrombocytopenia; ** Guillain-Barré syndrome

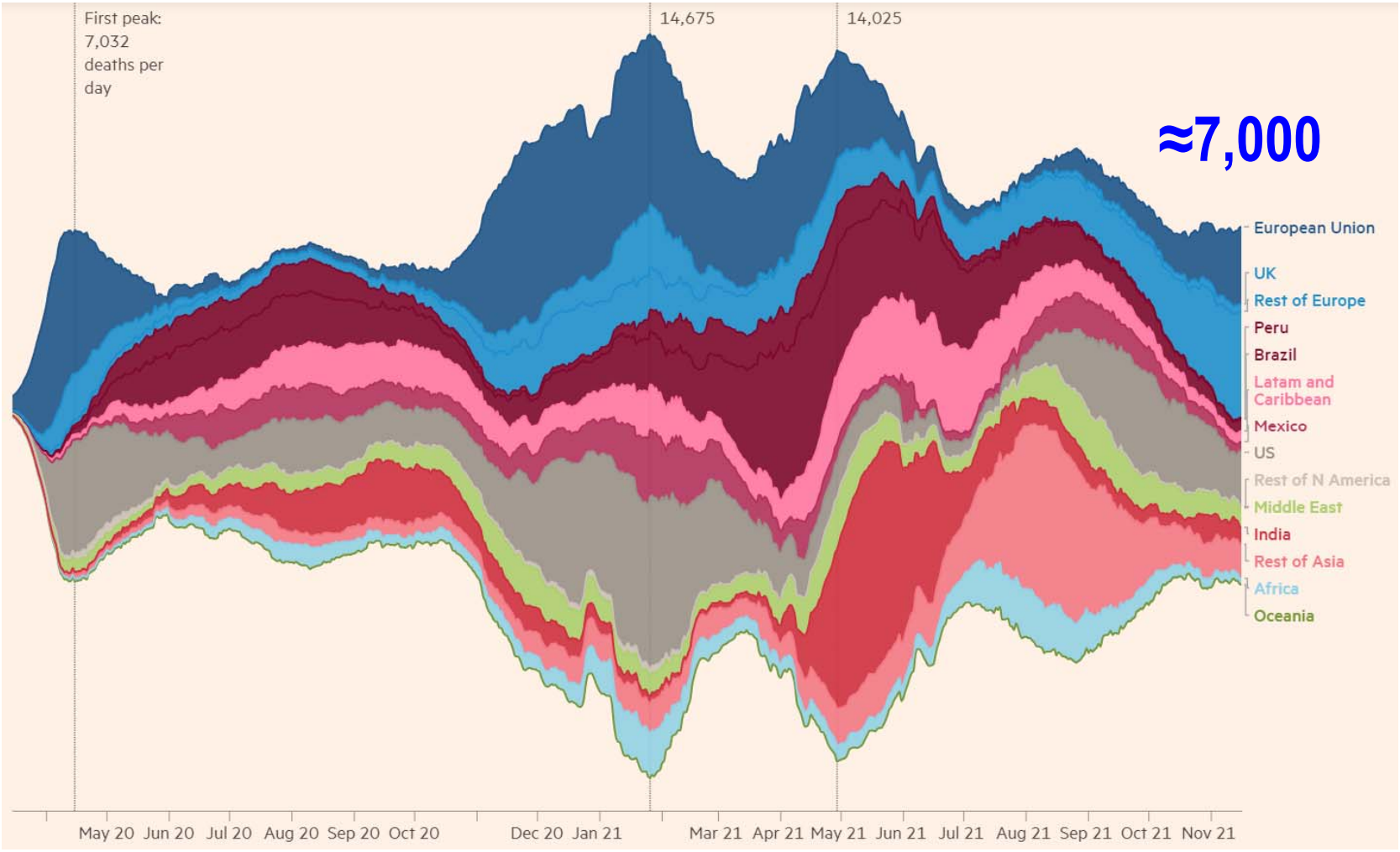
November 19th 2021

# COVID-19 Global Cases (Nov 19th 2021)

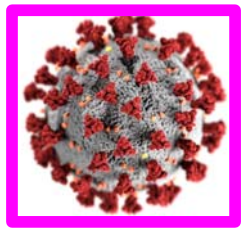



https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6; accessed on November 19th 2021

# Global COVID-19: Still more than 7,000 daily deaths!




https://www.ft.com/content/a2901ce8-5eb7-4633-b89c-cbdf5b386938?shareType=nongift – Nov 19th 2021



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# SARS-CoV-2 Variants & Key Mutations

## Variants Being Monitored (VBM)

→ Alpha (B.1.1.7 and Q lineages); Beta (B.1.351 and descendent lineages): Gamma (P.1 and descendent lineages); Epsilon (B.1.427 and B.1.429); Eta (B.1.525); Iota (B.1.526); Kappa (B.1.617.1) 1.617.3; **Mu (B.1.621, B.1.621.1);** Zeta (P.2); **Delta plus (AY.4.2) variant.**

## Variants of Interest (VOI)

→ Multiple mutations, rapid increase in incidence, spread in areas of high immunity. e.g. Currently none.

## Variants of Concern (VOC)

→ Increased transmission, virulence, immune escape. e.g., Delta (B.1.617.2 and AY lineages)

## Variants of Highly Consequence (VOHC)

→ Diagnostic, prevention measures or medical countermeasures failed. None described.

## Spike mutations associated with increased transmission

→ D614G; N501Y; K417

## Spike mutations associated with "antibody resistance"

→ E484K or Eek

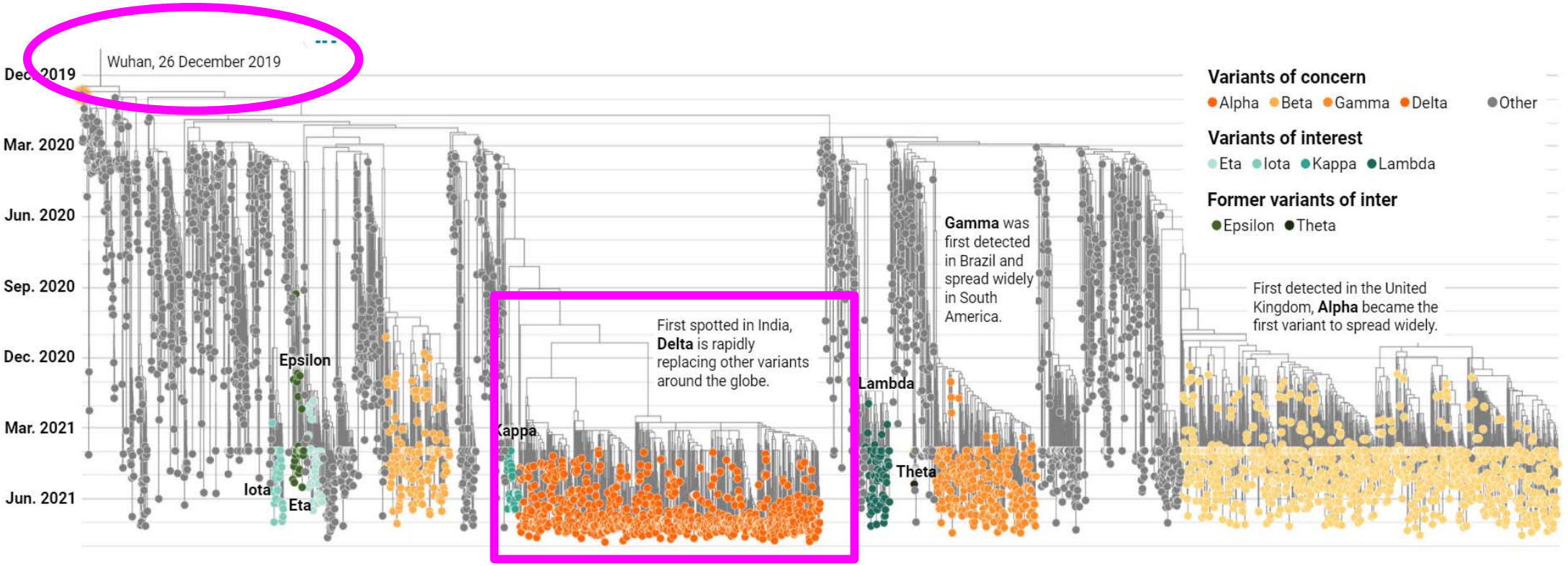
**Schematic of SARS-CoV-2 S and the mutation landscape in each VOC/VOI.**

Del, deletion; ins, insertion.

| | NTD | RBD | S1/S2 | S2 |
|---|---|---|---|---|
| B.1.1.7 (UK) | 69-70del/144-del | N501Y/±(E484K or S494P) | A570D/D614G/P681H | T716I/S982A/D1118H |
| B.1.351 (South Africa) | L18F/D80A/D215G/R246I/±242-244del | K417N/E484K/N501Y | D614G | A701V |
| P.1 (Brazil) | L18F/T20N/P26S/D138Y/R190S | K417T/E484K/N501Y | D614G/H655Y | T1027I/V1167F |
| B.1.427/B.1.429 (California) | S13I/W152C | L452R(±E484K) | D614G | |
| B.1.1.258 (Scotland) | ±69-70del | N439K | D614G | |
| B.1.525 (Nigeria) | Q52R/A67V/69-70del/144del | E484K | D614G/Q677H | F888L |
| B.1.526 (New York) | L5F/T95I/D253G | E484K | D614G | A701V |
| A.23.1(Liverpool) | R102I/F157L | V367F±E484K | Q613H/P681H | |
| A.27 | L18F | L452R/N501Y(±S494P) | A653V/A655Y | D796Y/G1219V |
| B.1.1.318 | T95I/144del | E484K | D614G/P681H | D796H |
| R.1 | W152L | E484K | D614G | G769V |
| B.1.1.298 (Denmark) | ±69-70del | Y453F | D614G | |
| B.1.617.1 (India) | E154K±(T95I/G142D) | L452R/E484Q | D614G/P681R | Q1071H or H1101D |
| B.1.1.519 (Mexico/US) | | T478K | D614G/P681H | T732A |
| B.1.214.2 (Belgium) | L5F/ins214TDR | Q414K/N450K | D614G | T716I |
| A.VOI.V2 (Tanzania) | D80Y/144del/210del/D215G /246-248del/L249M/W258L | R346K/T478R/E484K | H655Y/P681H | Q957H |

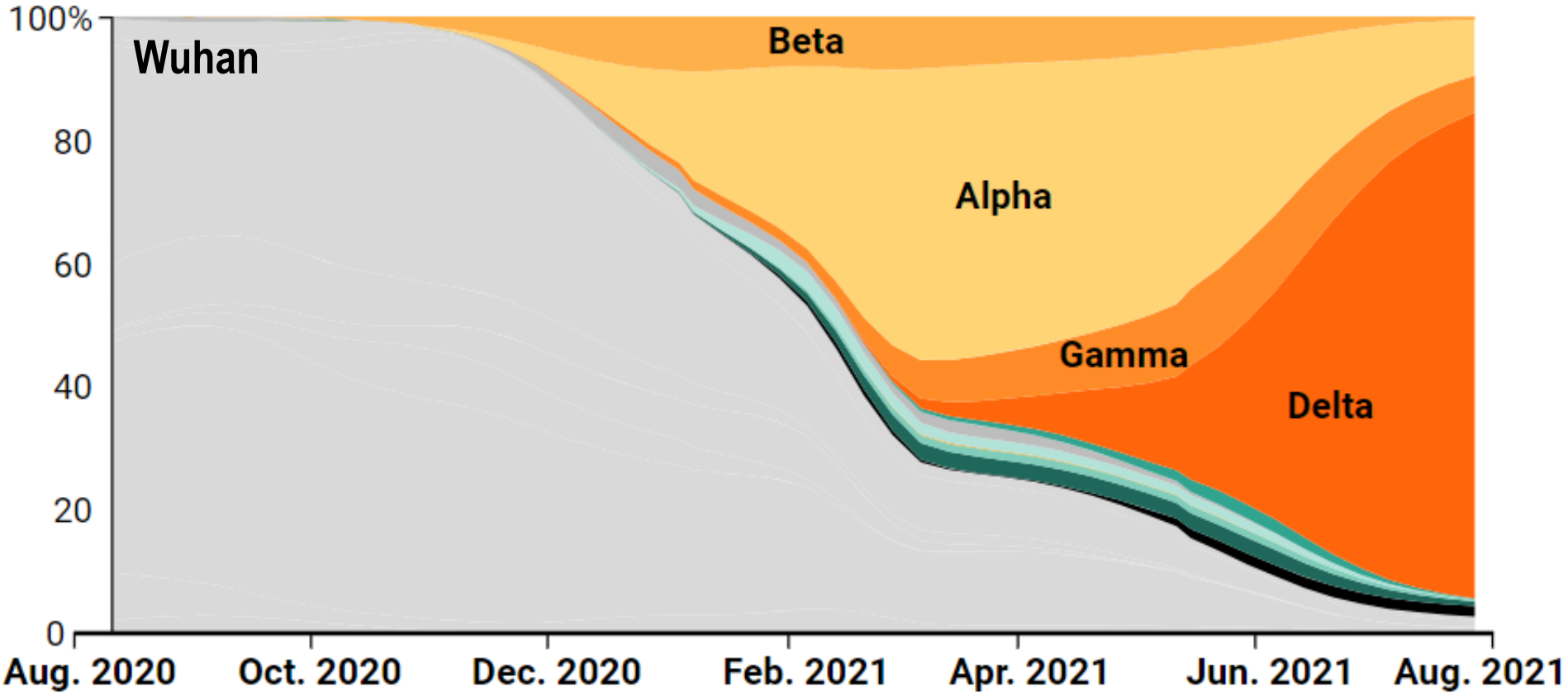
Corti D et al., Cell. Aug 19th 2021;184:4593-4595; https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html.

# SARS-CoV-2 Evolution in the World




Kupferschmidt K. Science, Aug 20th 2021; 373:844-849.

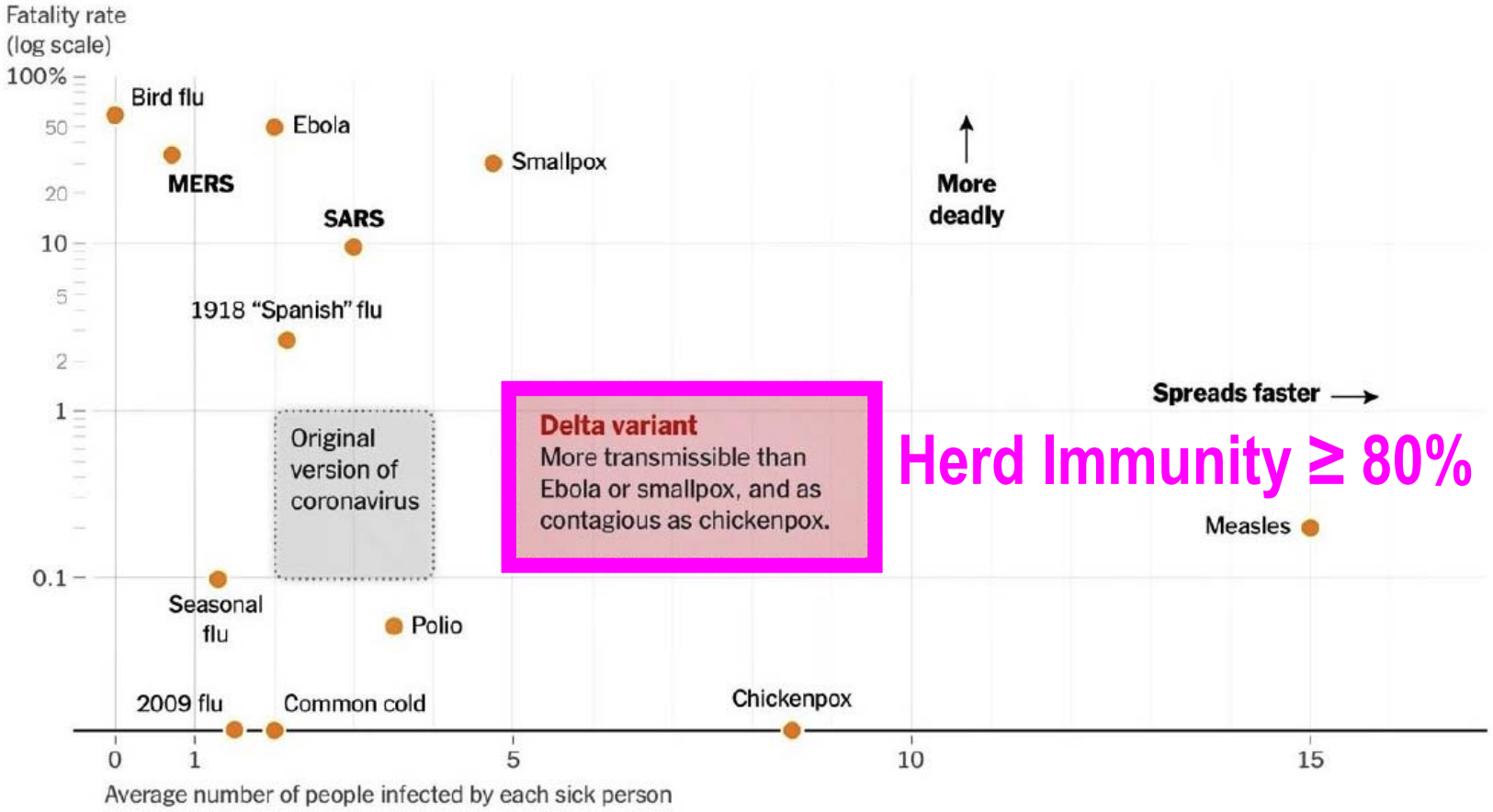
# SARS-CoV-2 Variants of Concern in the World




SARS-CoV-2 variants began to emerge in 2020. Alpha surged in many countries in early 2021, then was largely replaced by Delta. Two other variants of concern, Beta and Gamma, account for a smaller number of cases.

Kupferschmidt K. Science, Aug 20th 2021; 373:844-849.

# Delta variant ($R_0$= 5): More transmissible than Ebola or Smallpox and as contagious as Chickenpox



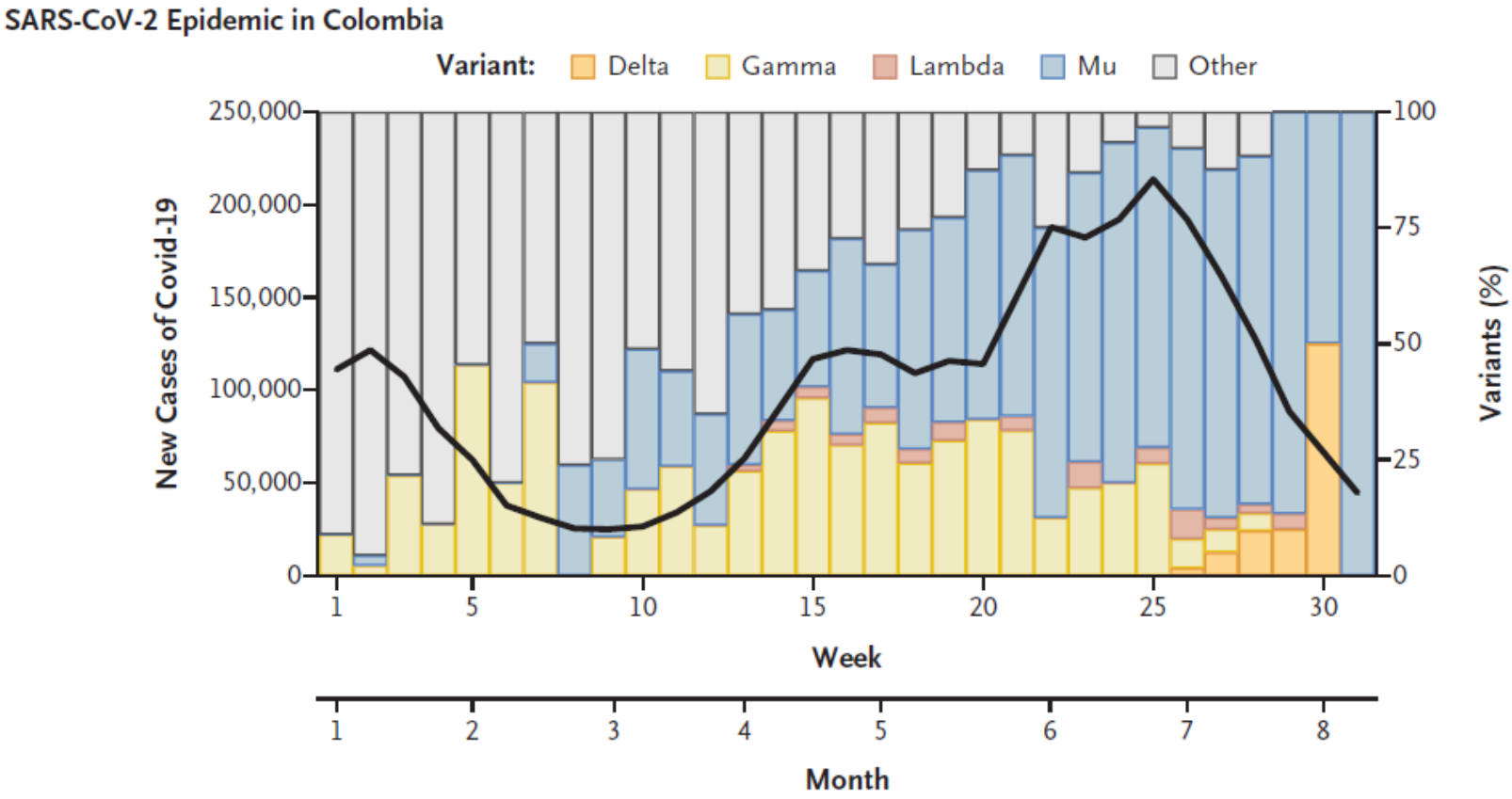

https://www.nytimes.com; https://www.nature.com/articles/d41586-021-02259-2; Liu Y et al,. J Travel Med. Oct 11 2021

# What we know about the Delta plus variant (AY.4.2.)

- **Delta plus (AY.4.2.) accounts for a slowly increasing proportion of cases in the UK (11%).** It is also present in other countries. It is not clear where it originated or when.
- This lineage has the **mutations of Delta and AY.4, and in addition S: A222V and Y145H**. These mutations are in the N terminal domain (NTD).
- **Delta plus (AY.4.2.) appears to have a modestly increased growth rate compared to Delta**. The **secondary attack rate for household contacts of cases** was **12.4% (95% CI: 11.9% to 13.0%)**, **10% higher** than that observed for other Delta cases where it was 11.1% (95% CI: 11.0% to 11.2%).
- A preliminary rapid **vaccine effectiveness** analysis does not suggest a significant reduction in vaccine effectiveness for AY.4.2 compared to Delta
- Based on these considerations and the high level of uncertainty, Delta plus (AY.4.2) was designated a new **Variant Under Investigation, VUI-21OCT-01.**

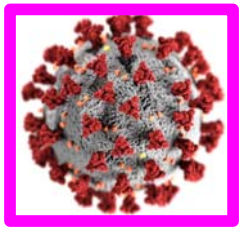
UK Health Security Agency. Technical briefing 27. October 29th 2021

# The Mu variant was first isolated on January 11, 2021, predominates in Colombia and had been detected in 39 countries




The **black line** reflects the number of new weekly cases, and the colored bars indicate the percentage of each variant of SARS-CoV-2 among the cases.

Uriu K et al. N Engl J Med. November 3 2021.



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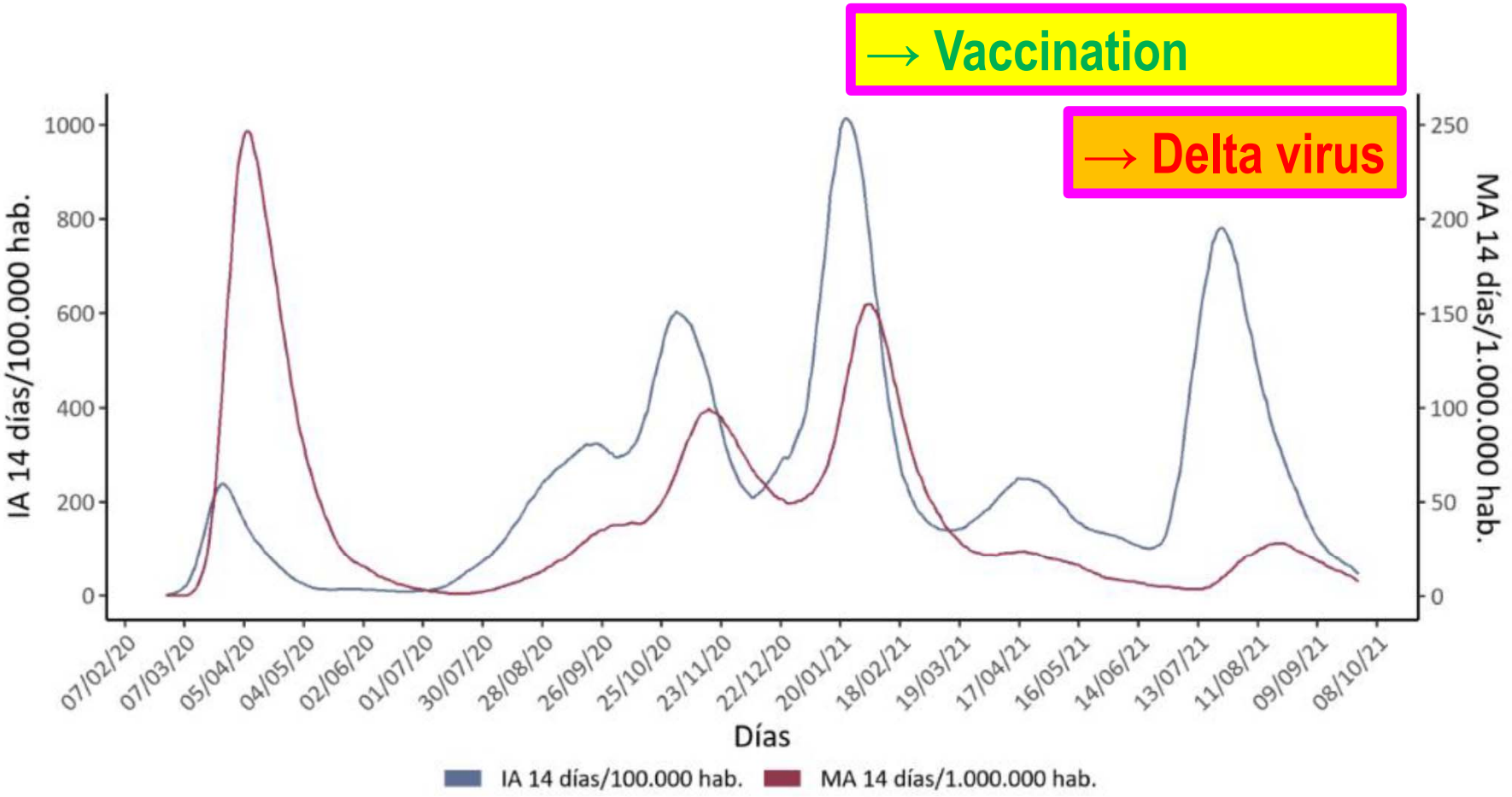
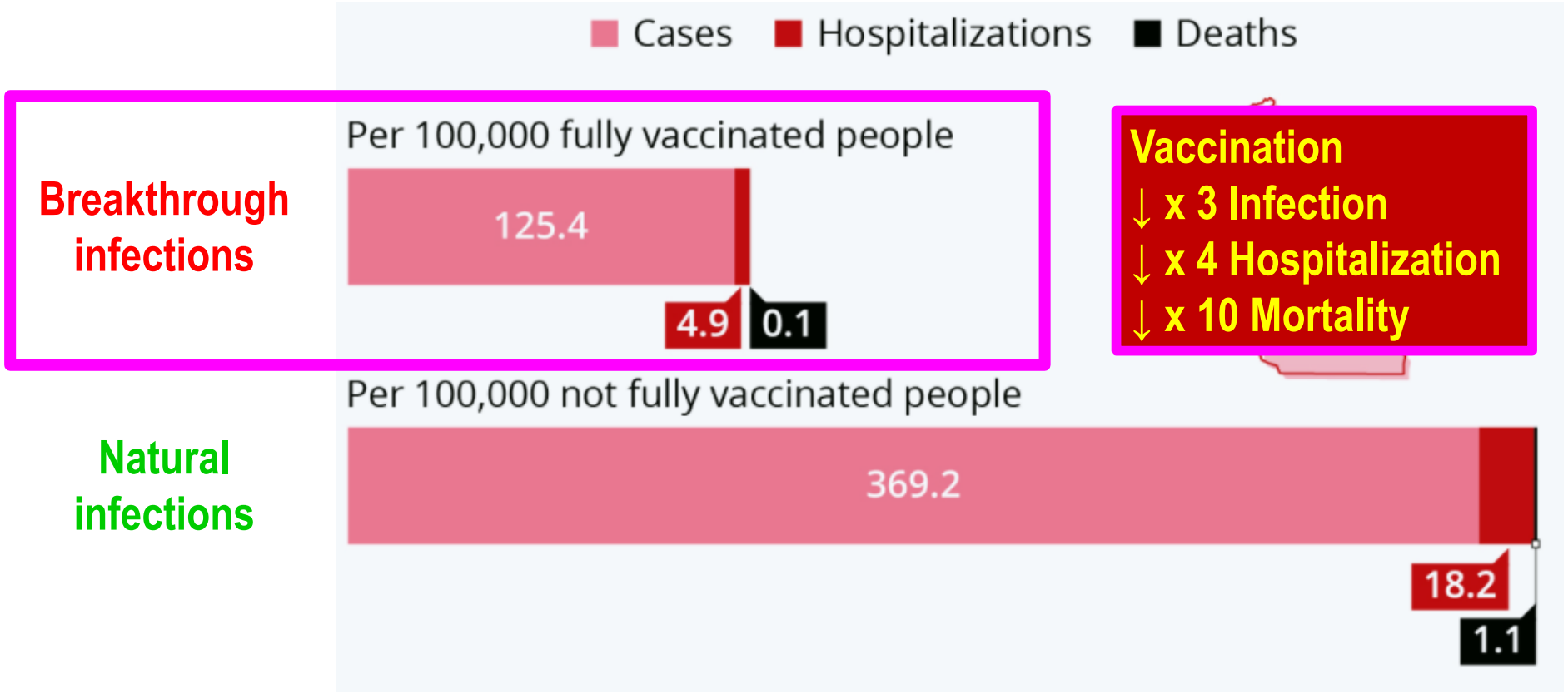
November 19th 2021

# COVID-19 in Spain: Cases and Deaths




Spanish Ministry of Health, Madrid, Spain. October 10th 2021

# How COVID-19 Affects Vaccinated and Unvaccinated People in Wisconsin, USA




Buchholz K, Statista. Aug 20th 2021. https://www.statista.com/chart/25589/covid-19-infections-vaccinated-unvaccinated/

# Less than 20% of Hospitalization occurred in vaccinated people in New Haven, USA

**172 (18%) breakthrough infections**

- 103 had received a partial vaccine course
- 15 had received a full course ≤14 days before symptom onset or a positive PCR
- **54 (6%) were fully vaccinated (>14 days)**

**Severity of COVID-19 in 54 fully vaccinated**

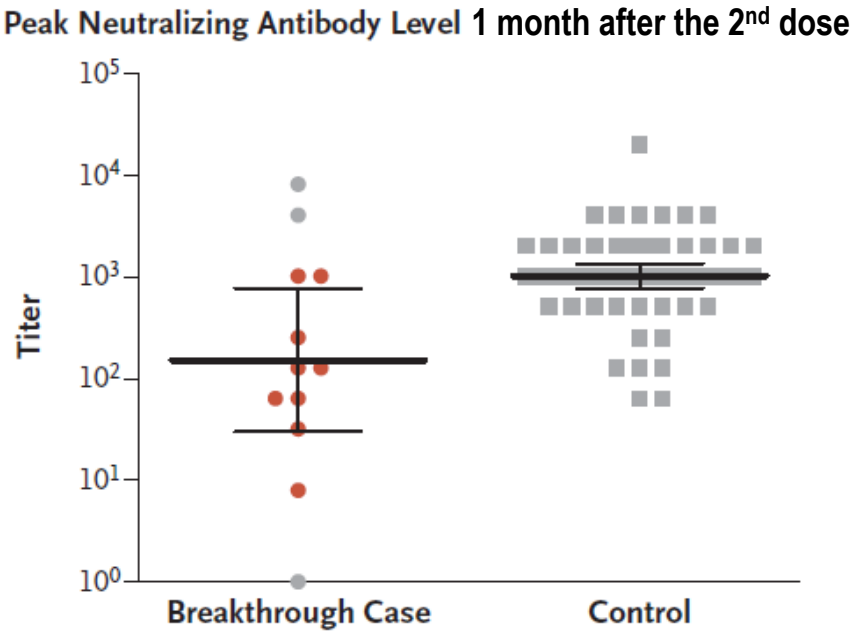
- Asymptomatic, 25 (46%)
- Mild/Moderate, 15 (27%)
- **Severe/Critical, 14 (26%)***
- **Mortality, 3 (6%)**

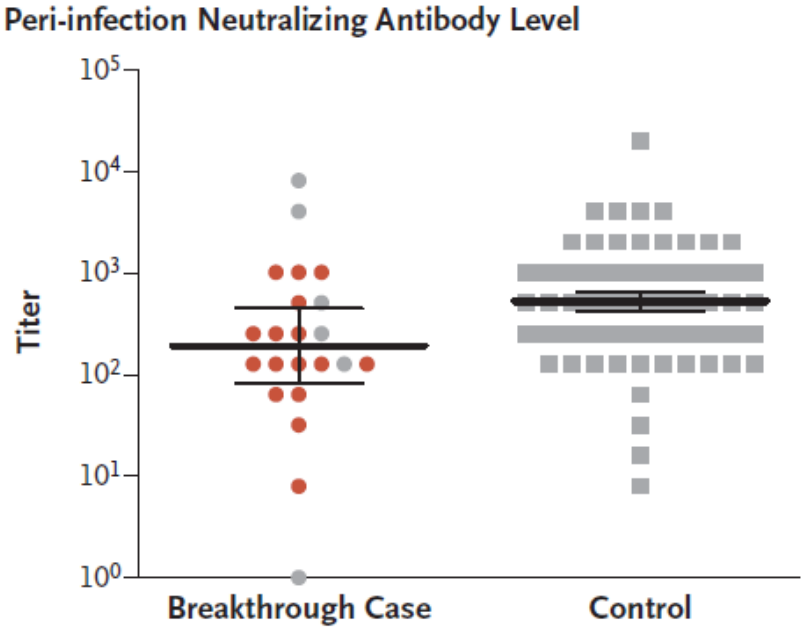
*__Median age__ was __80·5 years__ (IQR 76·5–85·0); __Median of 3 comorbidities per patient.__ __Comorbidities__ included overweight (BMI>25 kg/m²; n=9), cardiovascular disease (n=12), lung disease (n=7), malignancy (n=4), type 2 diabetes (n=7), and immunosuppressive agents (n=4).

Juthani PV et al. Lancet Infect Dis, September 7th 2021

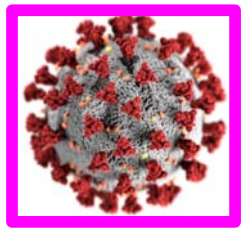
# Low neutralizing antibody titers in Covid-19 Breakthrough Infections in Vaccinated HCW

- **Most breakthrough infections in 39 health care workers (HCW) were mild or asymptomatic,** although persistent symptoms did occur.
- The B.1.1.7 (alpha) variant was found in 85% of samples tested.
- Among fully vaccinated HCW, **breakthrough infections were correlated with neutralizing antibody titers during the peri-infection period**.




Bergwerk M et al. N Engl J Med Oct 14th 2021;385:1474-84.



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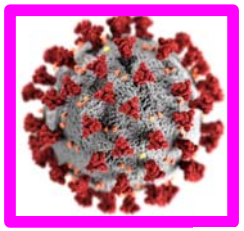
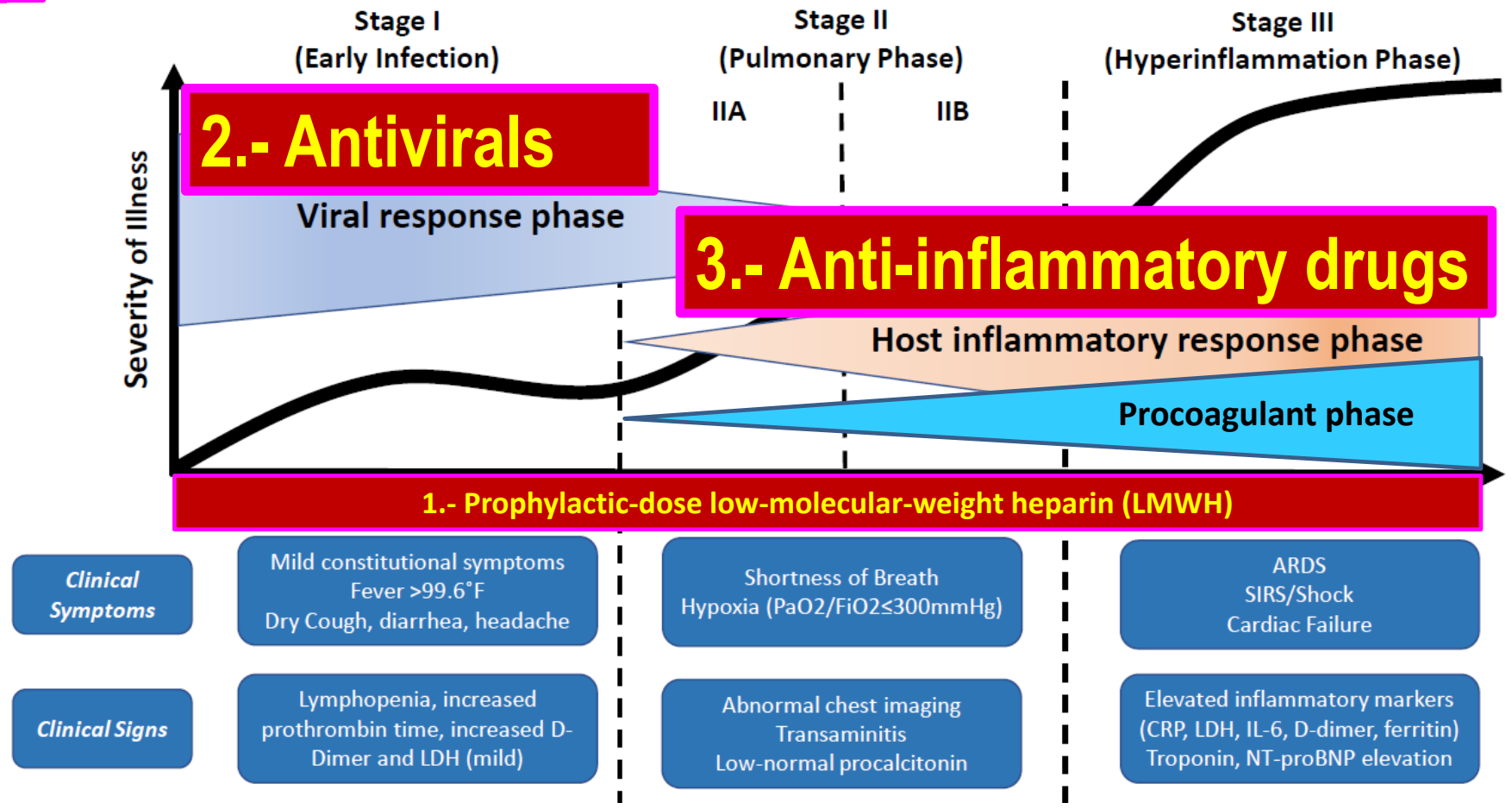


# Bases of COVID-19 treatment

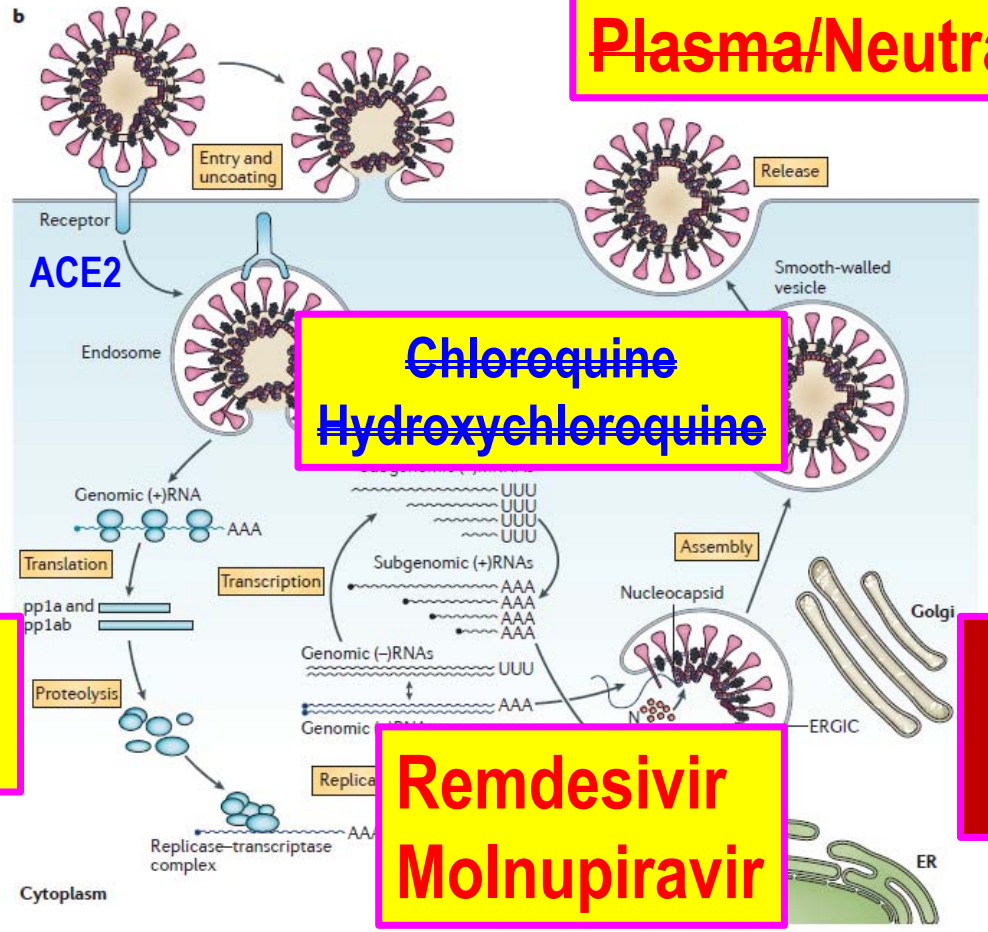



Siddiqu HK, Mehra MR. J Heart Lung Transplant. 2020 doi: 10.1016/j.healun.2020.03.012; Pericas JM, Hernandez-Meneses M et al. Eur Heart J. June 8th 2020.

# SARS-CoV-2 life cycle: Potential targets for antivirals

**Entry inhibitors**
**hrACE2 – APN01**

**~~Plasma/~~Neutralizing Antibodies**




**~~Chloroquine~~**
**~~Hydroxychloroquine~~**

**~~Interferon-beta~~**

**~~Ivermectin~~**

**~~Lopinavir/rtv~~**
**PF-07321332/rtv**

**Remdesivir**
**Molnupiravir**

**Potential for combining several antiviral drugs**

* Interferon induces hundreds of genes which can act on various parts of the lifecycle from potentially degrading viral RNA (OAS, RNASL) to inhibiting virus egress (BST-2)

De Wit Nature Rev Microbiol, 2016; Sanders JM, et al. JAMA. 2020 Apr 13. doi: 10.1001/jama.2020.6019.

# Coronavirus Drug and Treatment Tracker (November 7th 2021)

## New additions and recent updates

| | |
|---|---|
| Nov. 16 | Pfizer asks the F.D.A. to authorize its **Paxlovid** pill for emergency use. |
| Nov. 10 | Pfizer's **Paxlovid** moves to "promising evidence." |
| Nov. 4 | The United Kingdom is the first country to authorize **molnupiravir** for emergency use. |
| Oct. 26 | Expanded **monoclonal antibodies** and **antivirals** into their own sections. |
| Oct. 11 | Merck applies for emergency authorization for **molnupiravir**. |
| Oct. 1 | A trial showed **molnupiravir** reduced the risk of hospitalization and death by half. |

https://www.nytimes.com/interactive/2020/science/coronavirus-drugs-treatments.html

# There was a need for antivirals for the treatment of COVID-19 in the community to avoid hospitalization


Rambla de Catalunya, Barcelona, Spain

# There was a need for antivirals for the treatment of COVID-19 in the community to avoid hospitalization

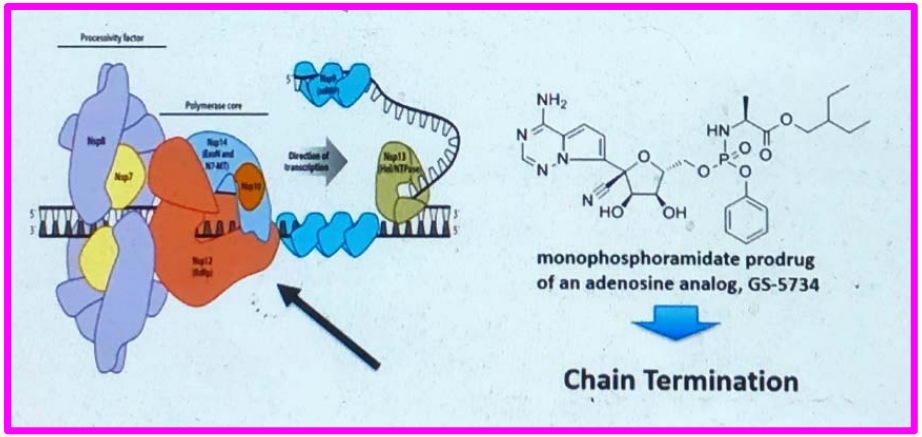
**We already have them here!**

- Remdesivir, IV (OPAT)
- Molnupiravir, oral
- PF-07321332/ritonavir, oral
- Parenteral monoclonal antibodies (OPAT)

OPAT: Outpatient parenteral antibiotic therapy

# IV Remdesevir (GS-5734)

- RNA-dependent RNA polymerase inhibitor.
- **Effective *in vitro* and in animal models against zoonotic and epidemic SARS-CoV, MERS-CoV and SARS-CoV-2 as both prophylactic and therapeutic agent**.
- PK: Renal excretion. **Not recommended eGFR ≤30 ml/min**. Few DDI.
- Dosage: 200 mg IV, then 100 mg/24 h during 5-10 days.
- Safety: few side effects (hypotension during infusion).




Sheahan TP et al. Sci Transl Med, 2017; De Wit ET al. Proc Natl Acad Sci U S A, 2020; Sheahan TP et al. Nat Commun; 2020;
Williamson BN et al. bioRxiv preprint doi: https://doi.org/10.1101/2020.04.15.043166.

# Remdesivir - Outpatient COVID-19 Treatment Trial

- Phase 3 (GS-US-540-9012) double-blind, randomized, placebo-controlled trial compared the efficacy and safety of **3 days of remdesivir (N=279)** to standard of care (N=283) in **non-hospitalized, high-risk participants with confirmed COVID-19**
- 562 participants were randomly assigned 1:1 to receive intravenous (IV) RDV (200 mg on day 1, 100 mg on days 2 to 3) or placebo.
- **The primary efficacy endpoint was composite COVID-19 hospitalization or all-cause death by day 28**.
- Overall, 52% were male, 44% were Hispanic/Latino ethnicity and **30% were ≥ 60 years old**. **The most common comorbidities were diabetes mellitus** (62%), **obesity** (56%; median BMI, 30.7) and **hypertension** (48%).

| | Remdesivir N=279 | Placebo N=283 | *P*-value |
|---|---|---|---|
| - Hospitalization/all-cause death | 0.7% | 5.3% | 0.008 |
| - Medical visits/all-cause death | 1.6% | 8.3% | 0.002 |
| - Grade ≥3 TRAEs | 3.6% | 7.1% | - |

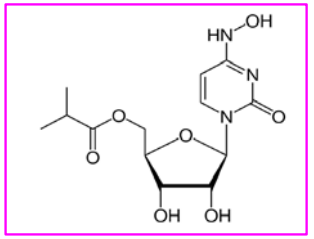
*Median baseline SARS-CoV-2 RNA nasopharyngeal viral load was 6.2 log copies/mL.
There was no difference between arms in time-weighted average change in nasopharyngeal viral loads from baseline up to day 7.

**No deaths occurred in either arm by day 28.**

**→ Remdesivir reduced hospital admission/death by 87%.**

Hill JA et al. IDWeek 2021 #LB1

# Molnupiravir, First Oral Drug for COVID-19




- Molnupiravir has **potent *in vitro* activity** against a broad range of coronaviruses, including SARS-COV-2 (including remdesivir-resistant mutants).
- Demonstrated **activity in *in vivo* models** (ferret and mouse) of SARS-CoV-2 disease, including prophylaxis, treatment, and prevention of transmission.
- It is rapidly absorbed and distributed after **oral administration** and subsequently converted intracellularly to active form.
- **Inhibits SARS-COV-2 viral RNA replication by incorporation of triphosphate metabolite in the viral genome, leading to viral error catastrophe**.
- It is not mutagenic or genotoxic in mammals.

Painter W, et al. CROI 2021 Poster #777; Sheahan TP et al. Sci Transl Med 2020.

# MOVe-OUT RCT in Outpatients showed promising results

| | Molnupiravir N=385 | Placebo N=377 | *P*-value |
|---|---|---|---|
| **Outcomes at 29 days** | | | |
| - Hospitalization/death | 7.3% | 14.1% | <0.001 |
| - Mortality | No deaths | 8 deaths | |

→ **Molnupiravir reduced the risk of hospitalization/death by 50%.**

Caraco Y et al. 31st ECCMID July 9-12 2021 P#4700; MSD Press release October 1st 2021

# PF-07321332/rtv, Second Oral Drug for COVID-19

- **PF-07321332-ritonavir (Paxlovid)** has **potent *in vitro* activity** against SARS-COV-2.
- **Inhibits SARS-COV-2-3CL viral protease** at a stage know as proteolysis, which occurs before viral RNA replication.
- It is absorbed and distributed after **oral administration** and ritonavir at low dose inhibits its metabolism and increase the concentrations.
- It is not mutagenic in preclinical studies.
- **Ritonavir may cause pharmacokinetic interactions** (DDI).

https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate

Pfizer press release, November 5th 2021

# Oral PF07321332/ritonavir (Paxlovid) – Phase 2/3 EPIC-HR

- **EPIC-HR** (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) is a multinational randomized, double-blind study of **non-hospitalized adult patients** with COVID-19, who are at high risk of progressing to severe illness.
- Eligible participants with at least **One underlying medical condition** and a **mild/moderate confirmed diagnosis of SARS-CoV-2 infection (within 5 days)** were randomized (1:1) to receive PF-07321332/ritonavir or placebo orally **every 12 hours** for **5 days.**
- **The primary efficacy endpoint was composite COVID-19 hospitalization or all-cause death by day 28**.
- **The study was stopped** after the first interim analysis with 1,219 adults enrolled by September 29, 2021 was performed.

| **At 28 days** | **PF07321332** N=607 | **Placebo** N=612 | *P*-value |
|---|---|---|---|
| - Hospitalization/death | 1.0% | 6.7% | <0.001 |
| - Death | No deaths | 10 deaths | - |
| - D/C due to TRAEs | 2.1% | 4.1% | - |

**→ PF07321332/ritonavir reduced hospital admission/death by 85%.**

**A Phase 2/3 EPIC-SR (Standard-Risk Patients) RCT started in August 2021.**

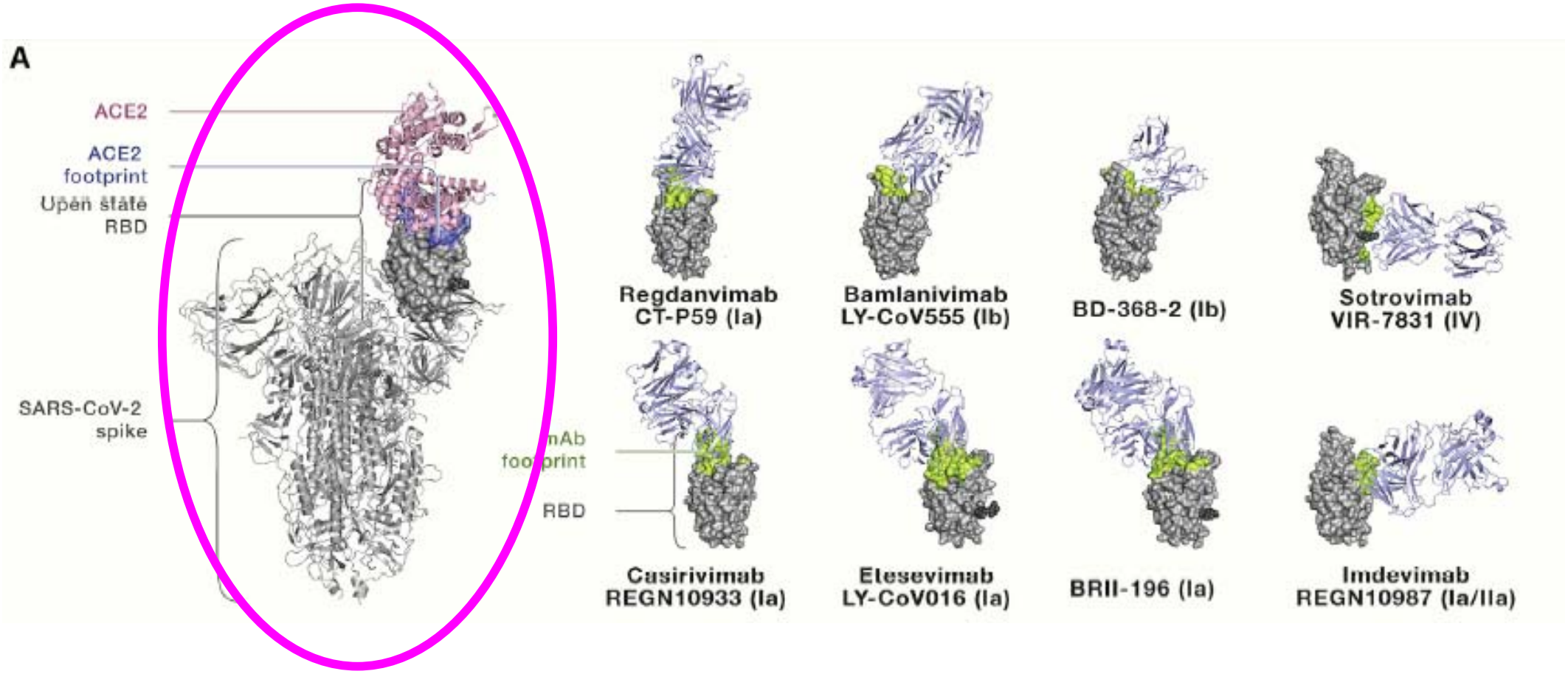
https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate

Pfizer press release, November 5th 2021

# Monoclonal Antibodies for COVID-19

- Bamlanivimab (Eli Lilly)
- Bamlanivimab and etesevimab (Eli Lilly)
- Casirivimab and imdevimab [REGEN-COV](Regeneron)
- Sotrovimab (GSK and Vir Biotechnology)
- AZD7442 (AstraZeneca)
- Others in development
- → Prevention (PEP) & Treatment COVID-19

# SARS-CoV-2 RBD complexes of mAbs (in green)




Corti D et al. Cell. Aug 19th 2021;184:4593-4595.

# Monoclonal Antibodies (mAbs) in Non-Hospitalized Patients

## Early Treatment in Patients with High Risk of Progression

| | mAb | PBO | *P*-value |
|---|---|---|---|
| | Hospitalization rates at 28 days | | |
| **Bamlanivimab** (iv single dose) - Chen P et al (N=552; 3:1)* | 1.6% | 6.3% | 0.017 |
| **Casirivimab plus Imdevimab** (iv single dose) - Weinreich DM et al. (N=799; 2:1)** | 3% | 9% | <0.001 |
| **Bamlanivimab plus Etesevimab** (iv single dose) - Dougan M et al. (N=1,035; 1:1)*** | 2.1% | 7% | <0.001 |
| **Sotrovimab** (im single dose) - Gupta A et al. (N=1,057; 1:1)**** | 1.1% | 5.7% | <0.001 |

* 452 patients were assigned to receive a single IV infusion of neutralizing antibody LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo

** 266 patients received a single IV infusion of 2,400 milligrams casirivimab and imdevimab (1,200 mg of each), 267 received 8,000 mg casirivimab and imdevimab (4,000 mg of each), and 266 received a placebo, within three days of obtaining a positive SARS-CoV-2 viral test.

*** 1,035 patients were randomized to a single IV infusion of either a neutralizing monoclonal-antibody combination agent (2800 mg of bamlanivimab and 2800 mg of etesevimab, administered together) or placebo within 3 days after a laboratory SARS-CoV-2 infection.

**** Single IV infusion of 500 mg or placebo. Sotrovimab has a double mechanism of action: neutralization plus inducing ADCC (NK cells) and ADCP (macrophages).

Chen P et al. NEJM Oct 28 2020; Weinreich DM et al. NEJM, Sep 29 2021; Dougan M et al. NEJM July 14, 2021; Gupta A et al. NEJM Oct 27, 2021.

# Risk reduction of hospital admission (and death) according to the treatment used in mild/moderate COVID-19 in high risk patients

| | Rates |
|---|---|
| Remdesivir, IV three days | 87% |
| Molnupiravir, oral 5 days | 50% |
| PF-07321332/ritonavir, oral 5 days | 85% |
| Single dose monoclonal antibodies | 65%-80% |

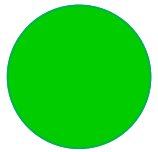
Most studies did not include vaccinated patients.

There are no data on the efficacy of monoclonal antibodies in vaccinated patients.

# What do we know about anti-inflammatory and anticoagulant treatment in the community?

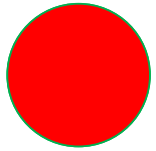
## Anti-inflammatory treatment

- Colchicine, oral
- Fluvoxamine, oral
- Budesonide, inhaled



## Anticoagulant treatment

- Aspirin, oral
- Apixaban, oral

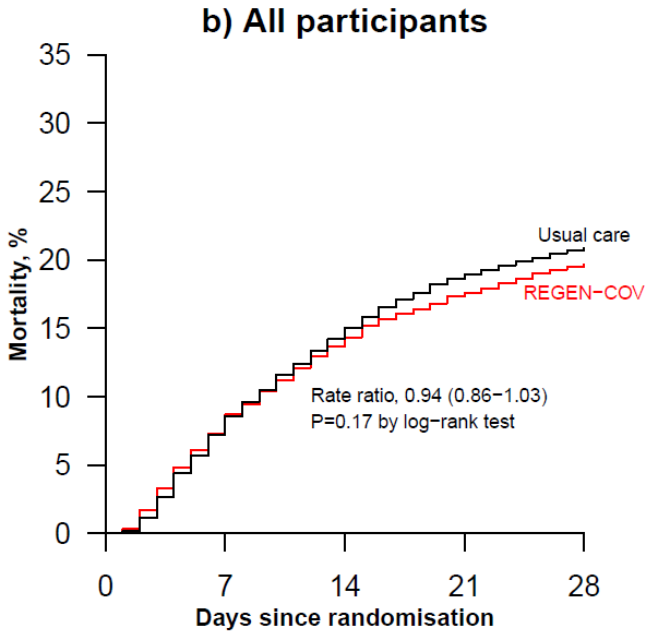


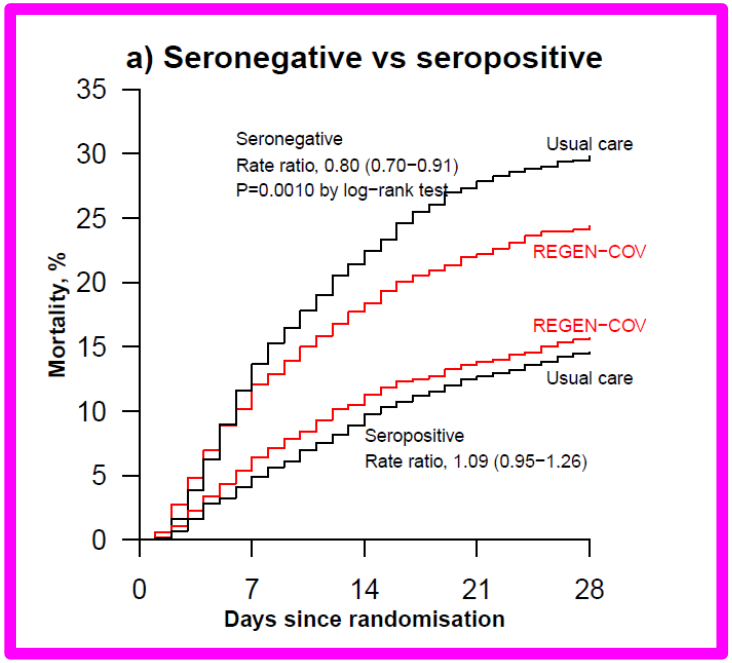
# What's new in antiviral, anti-inflammatory and anticoagulant treatment in hospitalized patients with severe COVID-19?

Hospital Clínic and U.B. School of Medicine, Barcelona, Spain

# Casirivimab & Imdevimab Reduced 28-day Mortality in Hospitalized Baseline Seronegative Patients: RECOVERY RCT

- Randomized, controlled, open-label platform trial. Eligible and consenting patients were randomly allocated (1:1) to either usual SoC (usual care group) or usual care plus a single dose of **REGEN-COV 8g (casirivimab 4g and imdevimab 4g) by IV infusion (REGEN-COV group).**
- Primary endpoint was **28-day mortality** assessed first among patients without detectable antibodies to SARS-CoV-2 at randomisation (seronegative) and then in the overall population.
- Between 18 September 2020 and 22 May 2021, **9785 patients were randomly allocated to receive usual care plus REGEN-COV or usual care alone**, including 3153 (32%) seronegative patients 5272 (54%) seropositive patients and 1360 (14%) patients with unknown baseline antibody status.




RECOVERY RCT. medRxiv June 16, 2021 (NCT04381936)

# RECOVERY Trial: Low-dose Dexamethasone Reduced Death

- RECOVERY was established as a randomized clinical trial to test a range of potential drugs for COVID-19, including dexamethasone.
- The trial has proceeded at unprecedented speed, enrolling over 11,000 patients from 175 NHS hospitals in the UK.
- The Independent Data Monitoring Committee (IDMC) has reviewed the emerging data about every two weeks to determine if there is evidence that would be strong enough to affect national and global treatment of COVID-19.
- **Dexamethasone: 6 mg once per day (either by mouth or by intravenous injection) for 10 days *vs.* Standard of Care (SoC).**
- **On June 8 IDMC concluded that dexamethasone reduced deaths in hospitalized patients with severe COVID-19.**

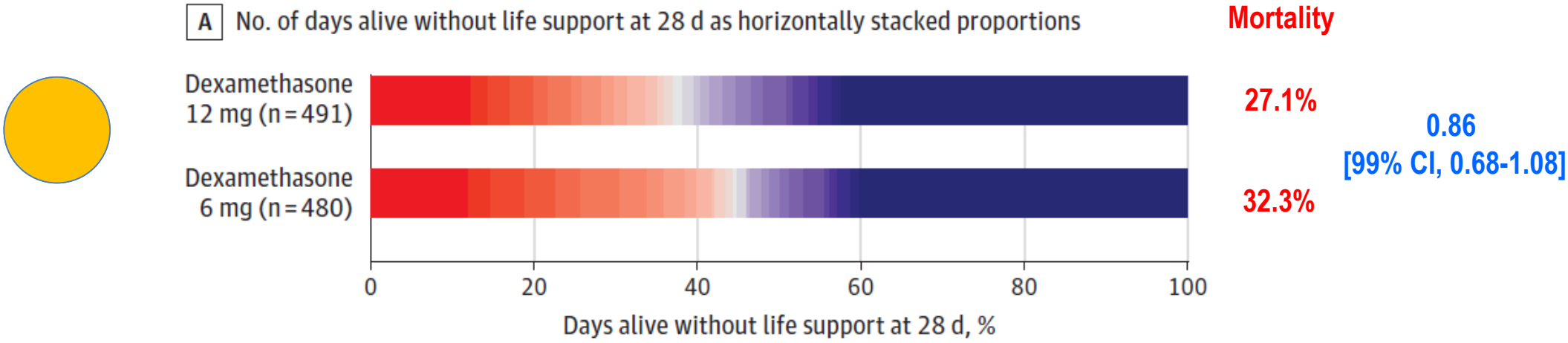
| **Recovery trial** | **Dexamethasone** | **SoC** | RR (95%CI) |
|---|---|---|---|
| Number of patients | 2104 | 4321 | |
| **28-day mortality** | **22.9%** | **25.7%** | **0.83 (0.75;0.93)** |
| **- Mechanical ventilation*** | **29%** | **41%** | **0.64 (0.51;0.81)** |
| **- Oxygen supply*** | **23%** | **26%** | **0.82 (0.72;0.94)** |
| **- No respiratory intervention*** | **18%** | **14%** | **1.19 (0.91;1.55)** |

*Rate Ratio (95% confidence interval)

RECOVERY Trial press release, June 16 2020; Horby PW et al. medRxiv. June 22, 2020; The RECOVERY Collaborative Group. NEJM July 17 2020. DOI: 10.1056/NEJMoa2021436.

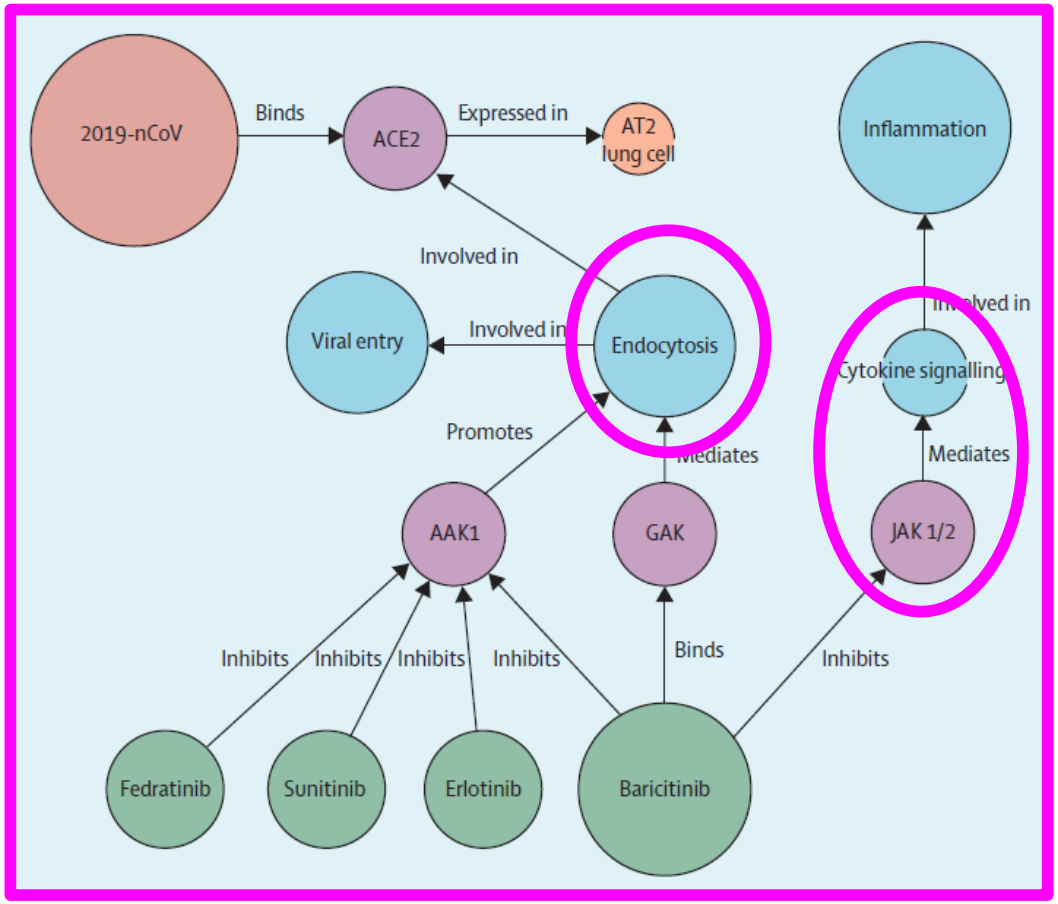
# COVID STEROID 2 RCT: 12 *vs.* 6 mg Dexamethasone

- Multicenter RCT conducted between August 2020 and May 2021 at 26 hospitals in Europe and India and included 1000 adults with confirmed COVID-19 requiring at least 10 L/min of oxygen or mechanical ventilation.
- **Patients were randomized 1:1 to 12 mg/d of intravenous dexamethasone (n = 503) or 6 mg/d of intravenous dexamethasone (n = 497) for up to 10 days.**
- The **primary outcome** was the **number of days alive without life support** (invasive mechanical ventilation, circulatory support, or kidney replacement therapy) at 28 days and was adjusted for stratification variables.
- Among patients with COVID-19 and severe hypoxemia, 12mg/d of dexamethasone compared with 6mg/d of dexamethasone did not result in statistically significantly more days alive without life support at 28 days.
- **However, the trial may have been underpowered to identify a significant difference.**




The COVID STEROID 2 Trial Group. JAMA. Oct 21 2021. doi: 10.1001/jama.2021.18295.

# Baricitinib has antiviral and anti-inflammatory properties

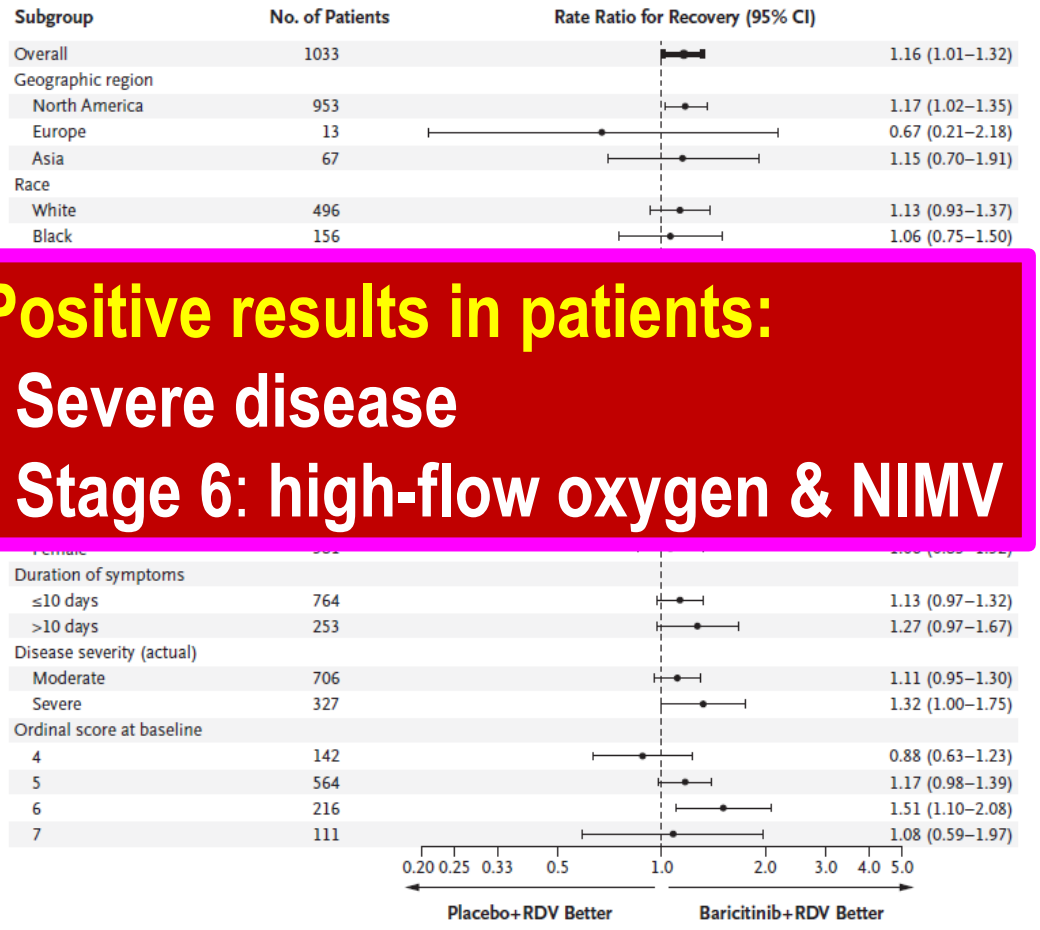



AAK1 = AP2-associated protein kinase 1; GAK = cyclin G-associated kinase; JAK1/2 = janus kinase 1/2 inhibitors

- There is a **high expression of TYK2 gene** in COVID-19 patients with poor outcome. **JAK 1/2 inhibitors (baricitinib)** could be useful to prevent inflammation.
- **Baricitinib** is indicated for the treatment of **moderate to severe active rheumatoid arthritis** in adult patients with an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs. The **recommended dose** is 4 mg QD orally.
- **The first pilot retrospective multicenter study** showed that baricitinib 4 mg/day used for 2 weeks (together with LPV/rtv) was not associated with SAEs, reduced SARS-CoV-2 viral burden in nasopharyngeal swabs and ICU admissions of patients with COVID-19 pneumonia*

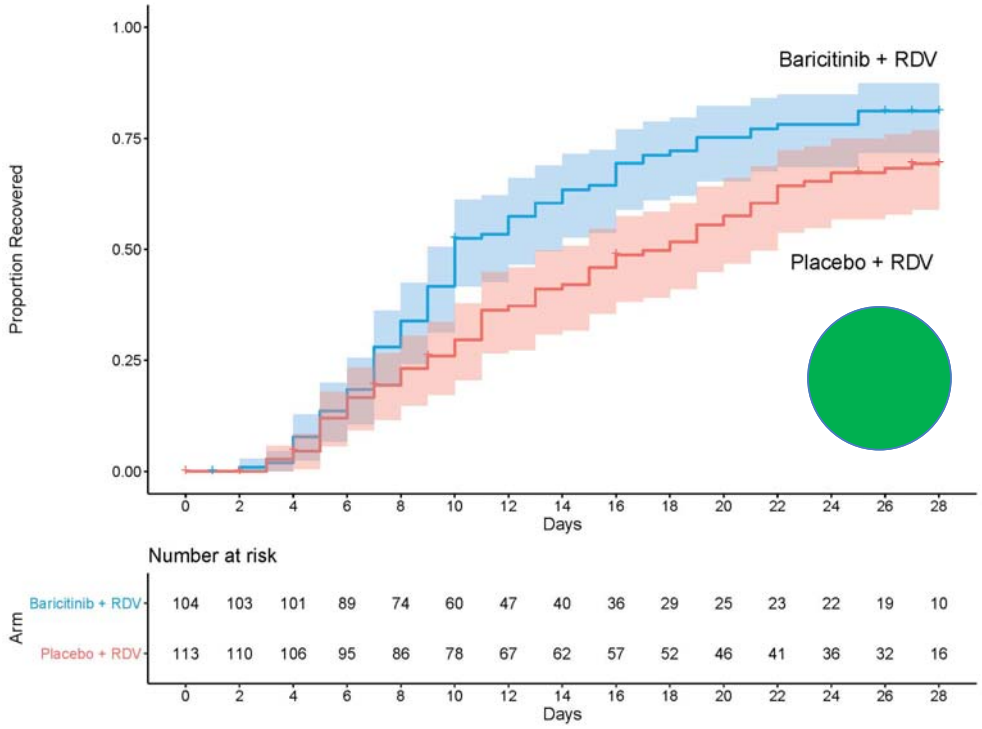
Richardson P et al. Lancet, February 3, 2020; Stebbing J et al. Lancet, Feb 27 2020; *Cantini F et al. J infect. Jun 242020 . doi: 10.1016/j.jinf.2020.06.052; Pairo-Castineira E. et al. Nature. 2020 Dec 11. doi: 10.1038/s41586-020-03065-y.

# Remdesivir plus Baricitinib – ACTT-2 (NIH): Stage 6




**Positive results in patients:**
- Severe disease
- Stage 6: high-flow oxygen & NIMV

**Baseline Ordinal Scale 6 (Stage 6)**




NIMV = Non-invasive mechanical ventilation

Kalil AC et al. N Engl J Med. March 4, 2021. DOI: 10.1056/NEJMoa2031994

# Baricitinib – Phase 3 RCT COV-BARRIER

- COV-BARRIER is a Phase 3 study evaluating **baricitinib 4 mg once daily** plus standard of care (SoC) vs. placebo plus SoC for **14 days**.
- **The trial did not meet statistical significance on the primary endpoint**, which was defined as a difference in the proportion of participants progressing to the first occurrence of **non-invasive ventilation including high flow oxygen or invasive mechanical ventilation (MV) including extracorporeal membrane oxygenation (ECMO) or death** by Day 28.
- Baricitinib-treated patients were 2.7 percent less likely than those receiving standard of care to progress to **ventilation (non-invasive or mechanical) or death**, a difference that was not statistically significant (**OR: 0.85; 95% CI 0.67, 1.08; p=0.1800**).

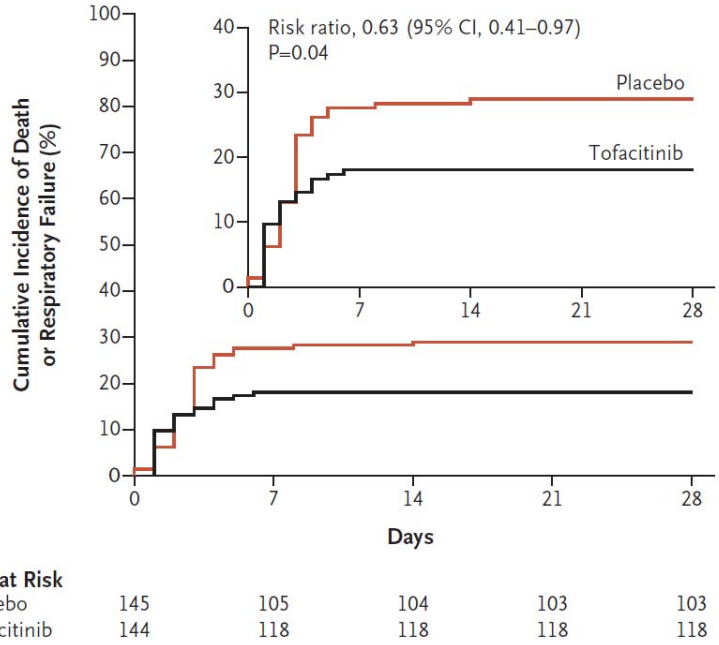
| | Baricitinib | Placebo | *P*-value |
|---|---|---|---|
| **Primary endpoint by day 28** | | | |
| - Number of patients | 764 | 761 | |
| **- Combined (MV, ECMO, death)** | **27.8%** | **30.5%** | **0.180** |
| **- 28-day mortality (secondary)** | **8.1%** | **13.1%** | **<0.001** |

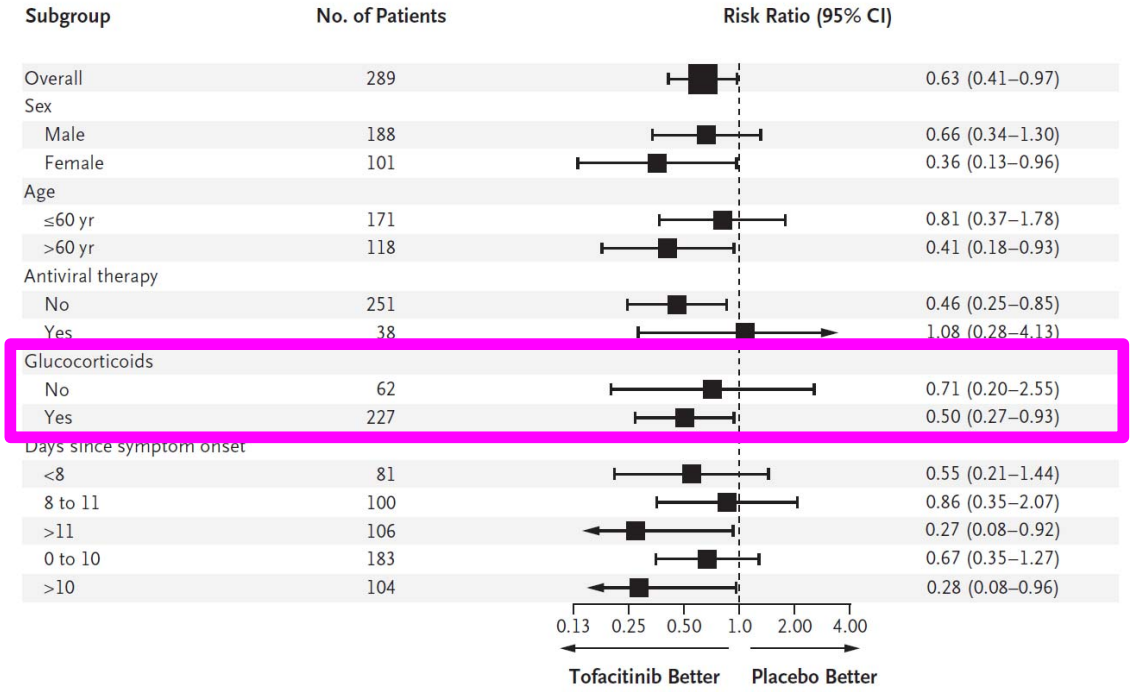
- **A reduction in mortality was also seen for the subgroups of patients being treated with or without corticosteroids at baseline**.
- Serious infections and venous thromboembolism (VTE) occurred in 8.5 percent and 2.7 percent of patients treated with baricitinib, respectively, versus 9.8 percent and 2.5 percent of patients treated with placebo.
- **NNT = 20 for saving one death.**

Marconi VC et al. Lancet Respir Med. 2021 Aug 31:S2213-2600(21)00331-3.

# Tofacitinib – STOP-COVID RCT for COVID-19

- Tofacitinib inhibits JAK1, JAK2, JAK3 and, to a lesser extent, TyK2. Hospitalized adults with Covid-19 pneumonia were randomly assigned, in a 1:1 ratio, to receive either tofacitinib at a dose of 10 mg or placebo twice daily for up to 14 days or until hospital discharge. The **primary outcome** was the occurrence of **death or respiratory failure through day 28** as assessed with the use of an eight level ordinal scale (with scores ranging from 1 to 8 and higher scores indicating a worse condition). All-cause mortality and safety were also assessed.



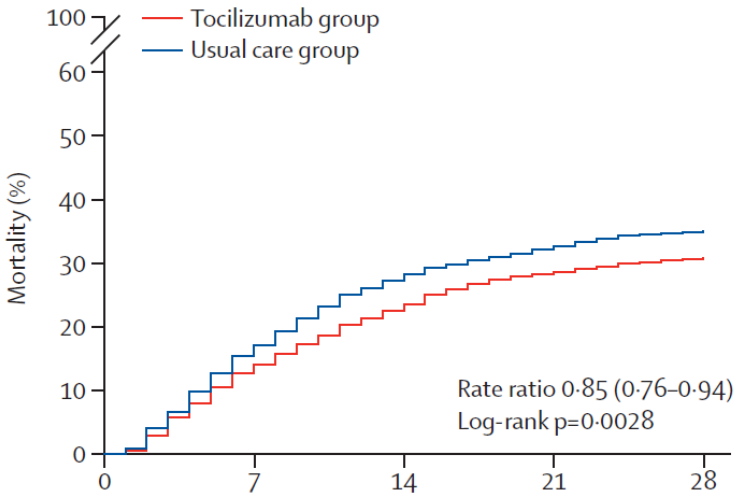

**→ Among patients hospitalized with Covid-19 pneumonia, tofacitinib led to a lower risk of death or respiratory failure through day 28 than placebo.**

Guimaraes PO et al. N Engl J Med. 2021; 385:406-415.

# Tocilizumab plus dexamethasone – RECOVERY Trial

- Randomized, controlled, open-label, platform trial, including **4,116 patients**.
- **Inclusion criteria**: patients with hypoxia (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein [CRP] ≥75 mg/L)
- RCT: **Standard of care alone** (**dexamethasone**) vs. usual **standard of care plus tocilizumab at a dose of 400 mg to 800 mg** (depending on weight) given intravenously. A second dose could be given 12-24 h.
- **The primary outcome was 28-day mortality**, assessed in the intention-to-treat population.

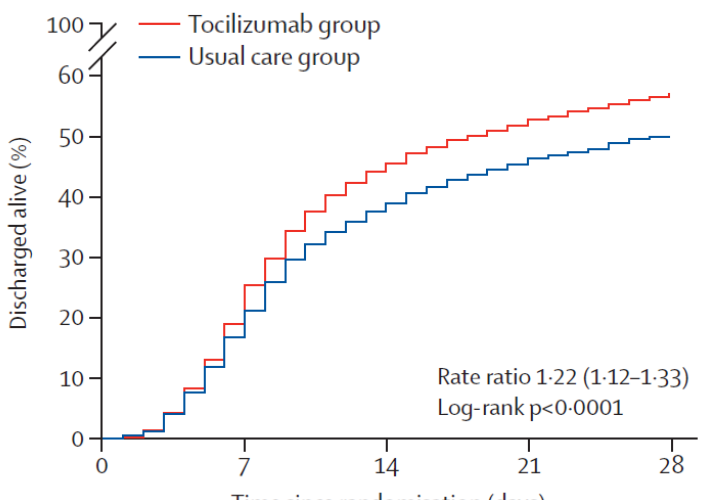
**A** **↓ by 15% 28-day Mortality**




Number at risk

| | | | | | |
|---|---|---|---|---|---|
| Tocilizumab | 2022 | 1736 | 1547 | 1445 | 1398 |
| Usual care | 2094 | 1735 | 1503 | 1410 | 1361 |

**B** **↑ 28-day Discharge from hospital by 22%**




Number at risk

| | | | | | |
|---|---|---|---|---|---|
| Tocilizumab | 2022 | 1509 | 1101 | 956 | 869 |
| Usual care | 2094 | 1653 | 1278 | 1124 | 1046 |

RECOVERY Collaborative Group (Horby PW). Lancet 2021; 397: 1637–45.

# Tocilizumab plus dexamethasone – RECOVERY Trial

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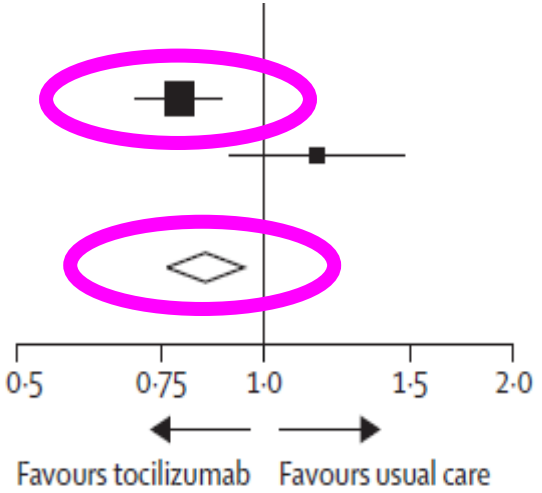
- **The primary outcome was 28-day mortality**, assessed in the intention-to-treat population.

| | | | |
|---|---|---|---|
| **Use of corticosteroids§ ($\chi^2_1$=7·7; p=0·01)** | | | |
| Yes | 482/1664 (29%) | 600/1721 (35%) | 0·79 (0·70–0·89) |
| No | 139/357 (39%) | 127/367 (35%) | 1·16 (0·91–1·48) |
| Unknown | 0/1 (0%) | 2/6 (33%) | .. |
| **All participants** | **621/2022 (31%)** | **729/2094 (35%)** | **0·85 (0·76–0·94)** |
| | | | **p=0·0028** |




*Rate Ratio (95% confidence interval)

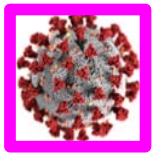
RECOVERY Collaborative Group (Horby PW). Lancet 2021; 397: 1637–45.

# WHO's Solidarity PLUS clinical trial enters a new phase with three new candidate drugs

- The World Health Organization (WHO) has announced the next phase in its Solidarity trial: **Solidarity PLUS** will enroll hospitalized patients in **52 countries** to test three new drugs in hospitalized COVID-19 patients.
- These therapies - artesunate, imatinib and infliximab – were selected by an independent expert panel for their potential in reducing the risk of death in hospitalized COVID-19 patients. They are already used for other indications: artesunate is used for severe malaria, imatinib for certain cancers, and infliximab for diseases of the immune system such as Crohn's Disease and rheumatoid arthritis.

- **IV Artesunate**, 7 d (anti-inflammatory properties)
- **Oral Imatinib**, 14 d (tyrosine kinase inhibitor that reverses pulmonary capillary leak)
- **IV Infliximab,** single dose (TNF alpha inhibitor)

WHO Press release, August 8th 2021
https://www.who.int/news/item/11-08-2021-who-s-solidarity-clinical-trial-enters-a-new-phase-with-three-new-candidate-drugs
For more information on the trial, see the trial registry https://www.isrctn.com/ISRCTN18066414



| | Community | Hospital - Ward | Hospital - ICU |
|---|---|---|---|
| **Disease stages** | Asymptomatic/Mild<br>Stages 1-2 | Moderate/Severe<br>Stages 3-5 | Critical (MV, ECMO)<br>Stages 6-7 |

Isolation, at least 10-14 days

**Treatment**

- Early antiviral therapy
- Proper timing anti-inflammatory drugs
- Prophylactic heparin

Symptomatic treatment
Close monitoring for early detection of progression. In older and high risk persons consider:

- **Parenteral mAbs* (OPAT)**
- **Oral molnupiravir**
- **Oral PF-07321332/ritonavir**
- **IV remdesivir (OPAT)**

**Remdesivir**, IV, 5 days
Stages 4 (no oxygen) & 5 (low-flow oxygen supply)
Stage 6 plus **Baricitinib/Tofacitinib**, oral, 14 days

**Dexamethasone**, IV/oral, 10 days.
Stages 5-7, low/high-flow oxygen supply, MV and ECMO
**Tocilizumab**, single IV dose

**Low molecular weight heparin, SC**
During the entire hospitalization period

Dr. JM Miro, personal opinion. November 2021.
* No experience in vaccinated patients.

# Post-Exposure Prophylaxis (PEP) against SARS-CoV-2

# PEP trials with Monoclonal Antibodies (mABs)

- **Randomized, double-blind, placebo-controlled trials for prevention of SARS-COV-2 infection** in **residents and staff** of skilled nursing and assisted living facilities where at least 1 case of SARS-CoV-2 infection had been confirmed in the previous 7 days or in asymptomatic **household contacts** of people with COVID-19 documented within the previous 4 days and returning home.
- **mABs can offer immediate protection** for exposed or **unvaccinated, partially vaccinated or IS individuals in high risk settings** (in contrast to vaccines that take 7-14 days after 2nd dose to offer protection).

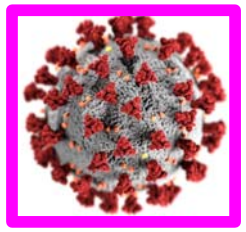
| | mAB | PBO | *P*-value |
|---|---|---|---|
| **BLAZE-2**<br>- Bamlanivimab (4,200 mg IV) | **57% (80%*) reduction**<br>symptomatic COVID-19 | | <0.001 |
| **R10933-10987-COV-2069A****<br>- Casirivimab/imdevimab (1,200 mg **SC**) | **81% reduction**<br>symptomatic COVID-19 | | <0.001 |

*Nursing home residents; **Reduction of SARS-CoV-2 infection, shortened time of viral shedding and shortened time of high viral load (>$10^4$ copies/mL) shedding **suggesting a benefit for reduced transmission**.

Lilly press release, January 27, 2021; REGENERON press release, April 12, 2021; Cohen MS et al. JAMA. 2021 Jul 6; 326:46-55.

# New PEP trials with oral antivirals

- Molnupiravir, oral
- PF-07321332/ritonavir, oral



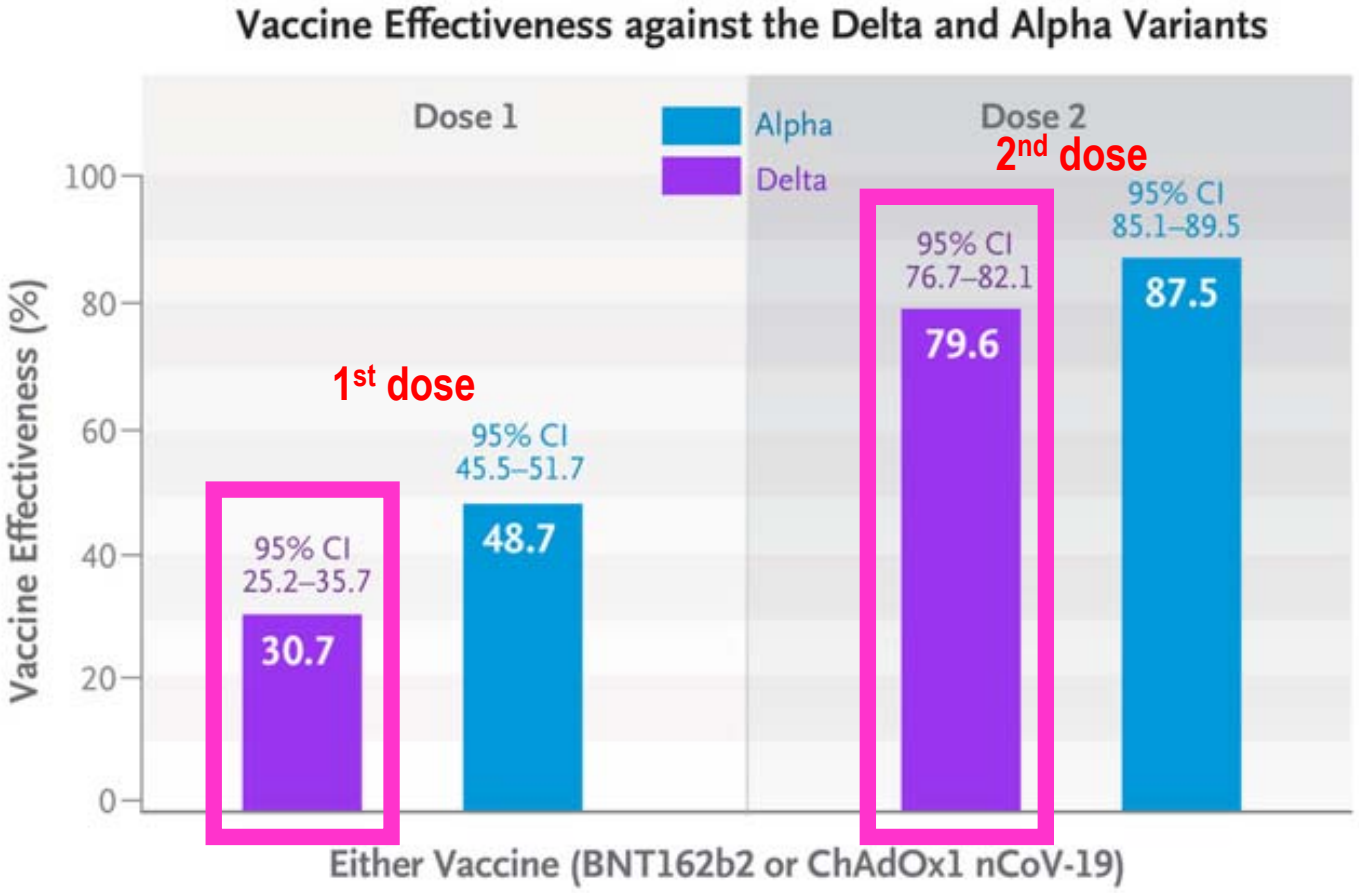
# Update COVID-19
# Where we are and where we are going

- Current epidemiological and mortality data
- SARS-CoV-2 variants of concern: Delta, Delta plus, and more
- COVID-19 Vaccine Breakthrough Infections
- What's new in medical treatment?
- **Vaccines efficacy on new SARS-CoV-2 variants of concern**
- Vaccine third booster dose: When and to whom?
- Vaccines safety new data: VITT*, Myocarditis and GBS**
- Take-home messages

*Vaccine-induced Thrombotic Thrombocytopenia; ** Guillain-Barré syndrome

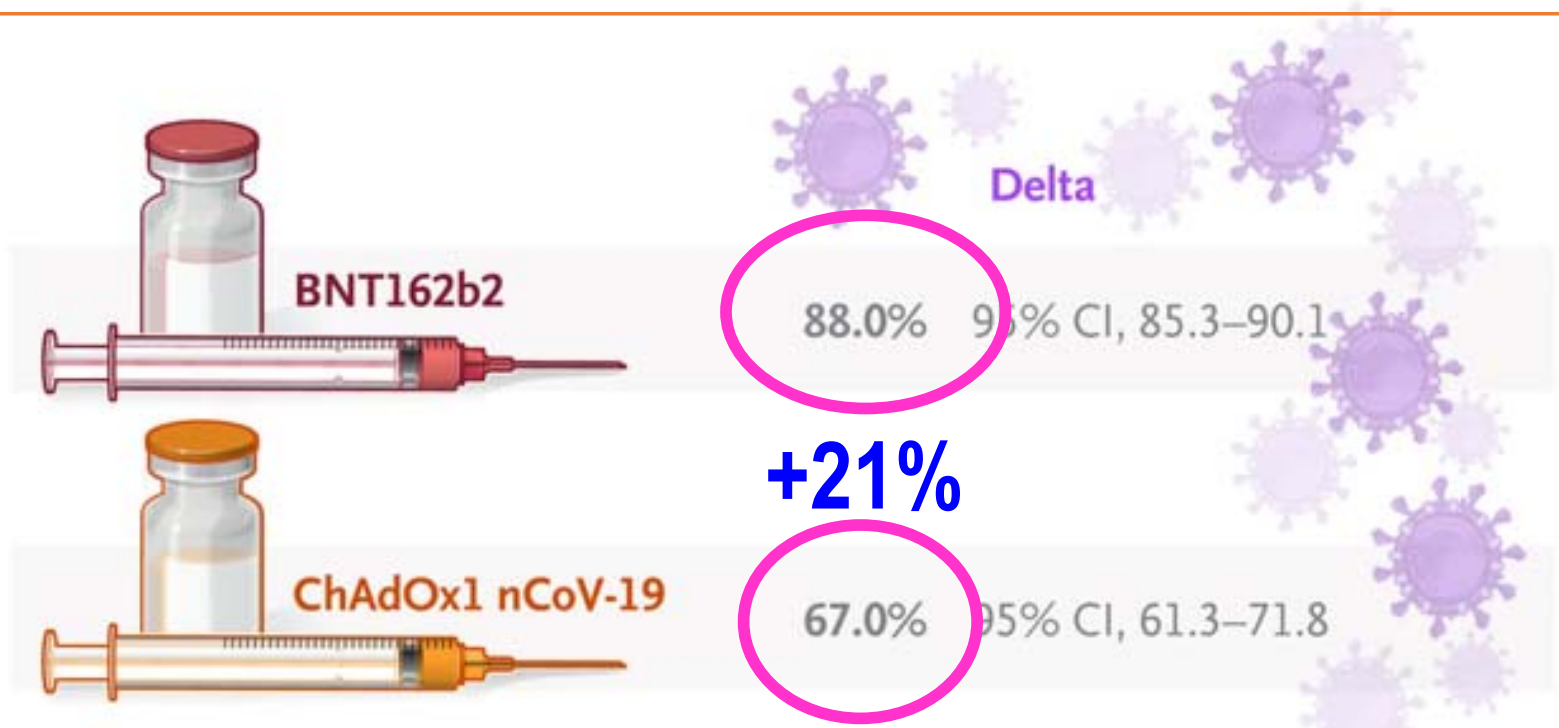
November 19th 2021

# BNT162b2 and ChAdOx1 nCoV-19 vaccine efficacy against Alpha & Delta variants




Lopez-Bernal J et al. N Engl J Med. August 12, 2021; 385:585-594.

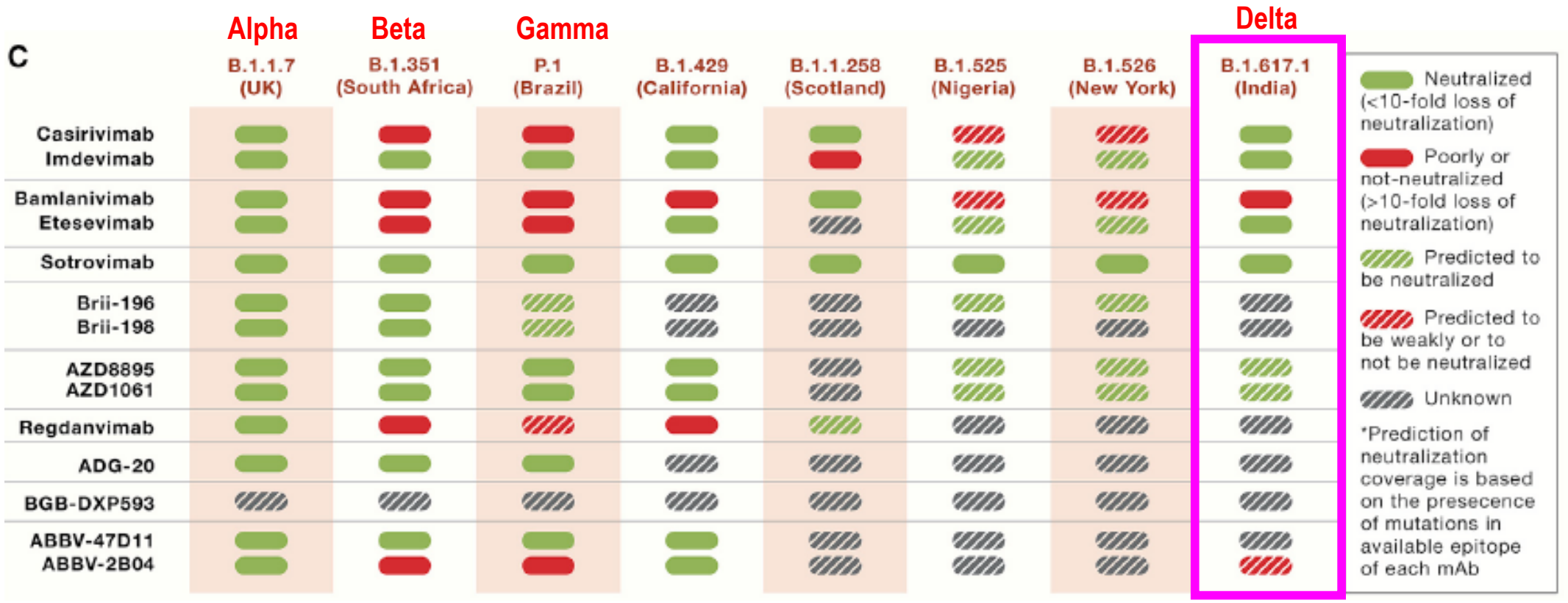
# BNT162b2 & ChAdOx1 nCoV-19 vaccine efficacy against Delta variant after the 2nd dose




- Vaccination reduces the risk of delta variant infection and accelerates viral clearance.
- Fully vaccinated individuals with breakthrough infections have peak viral load similar to unvaccinated cases and can efficiently transmit infection in household settings, including to fully vaccinated contacts.

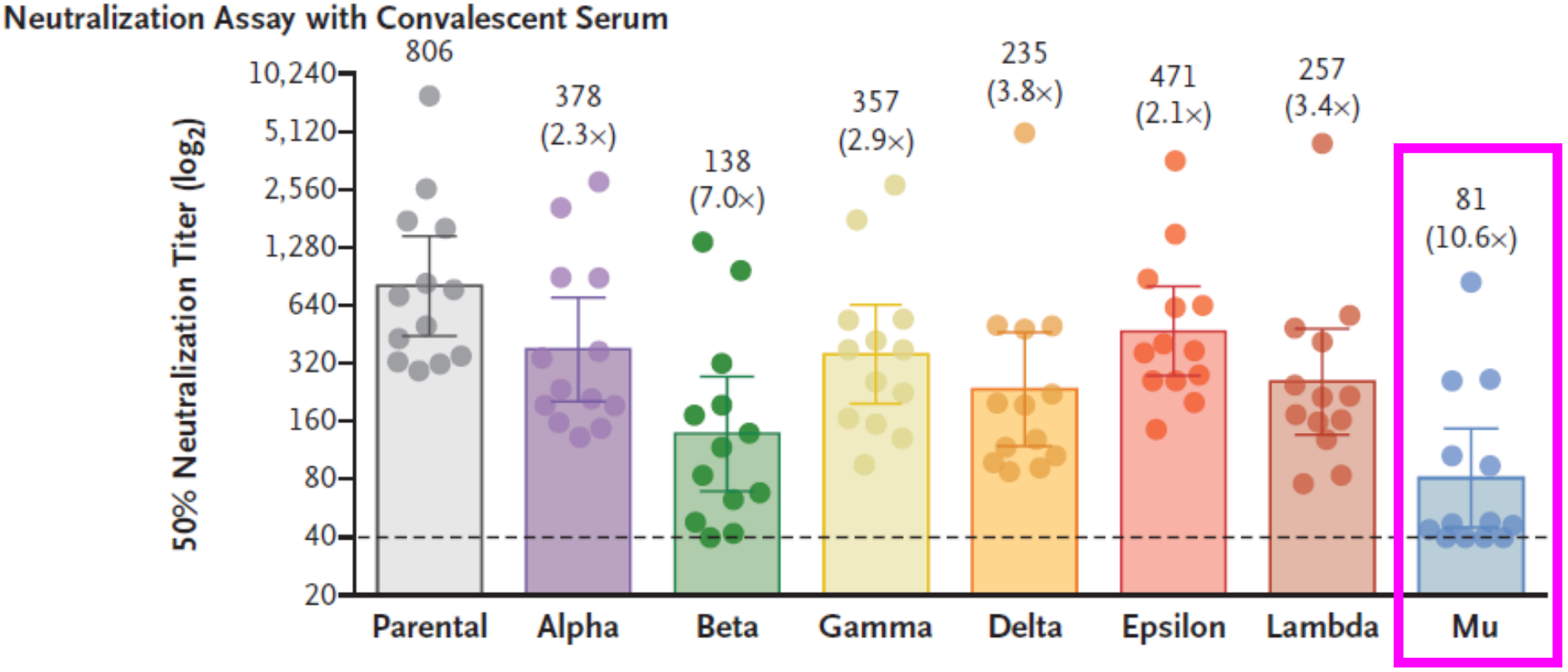
Lopez-Bernal J et al. N Engl J Med. August 12, 2021; 385:585-594; Singanayagam A et al,. Lancet Infect Dis. October 28, 2021.

# Neutralization of current monoclonal Antibodies (mAbs) against Variants of Concern (VoC) and Interest (VOI)




Corti D et al. Cell. August 19th 2021;184:4593-4595.

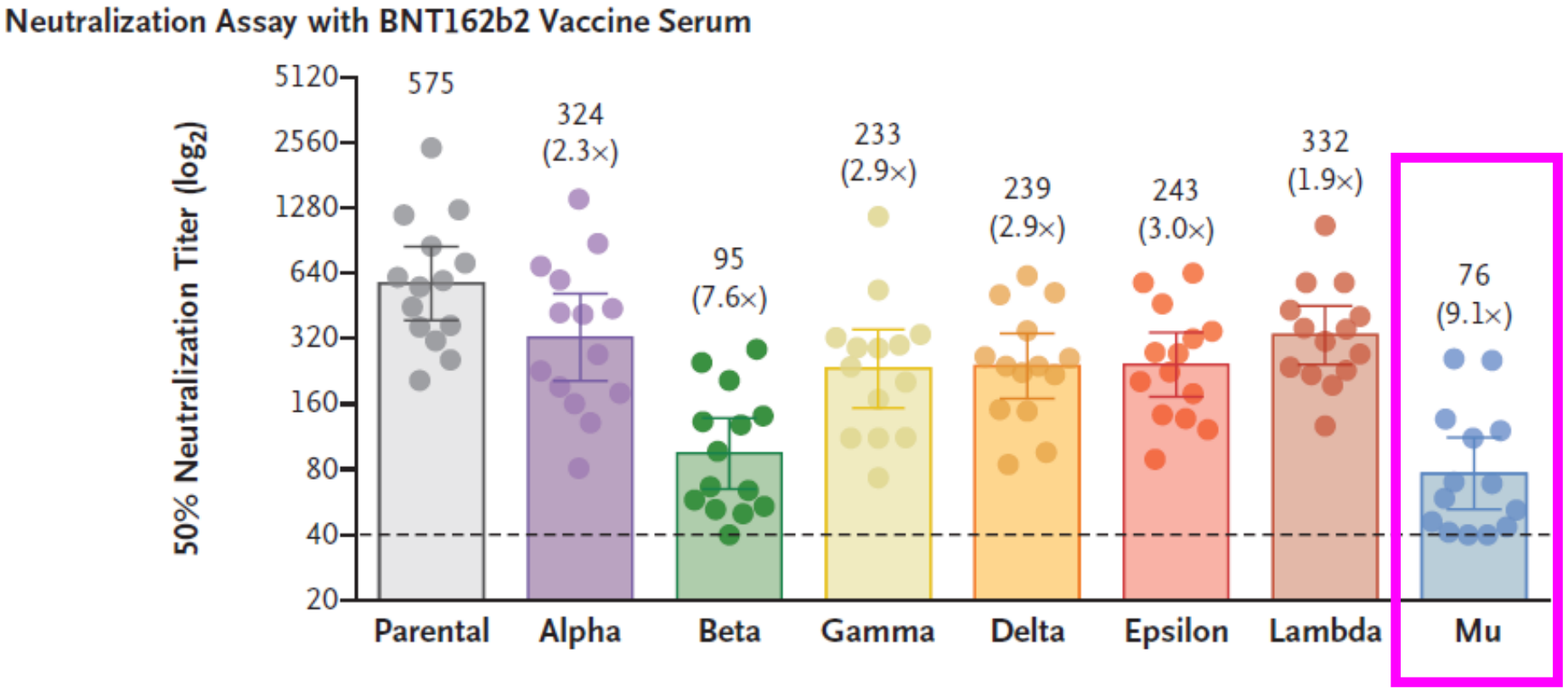
# Neutralization of the SARS-CoV-2 Mu Variant by Convalescent Serum (Colombia)




**The Mu variant is the most resistant variant to date.**

Uriu K et al. N Engl J Med. November 3 2021.

# Neutralization of the SARS-CoV-2 Mu Variant by mRNA Vaccine Serum (Colombia)

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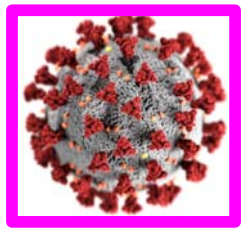

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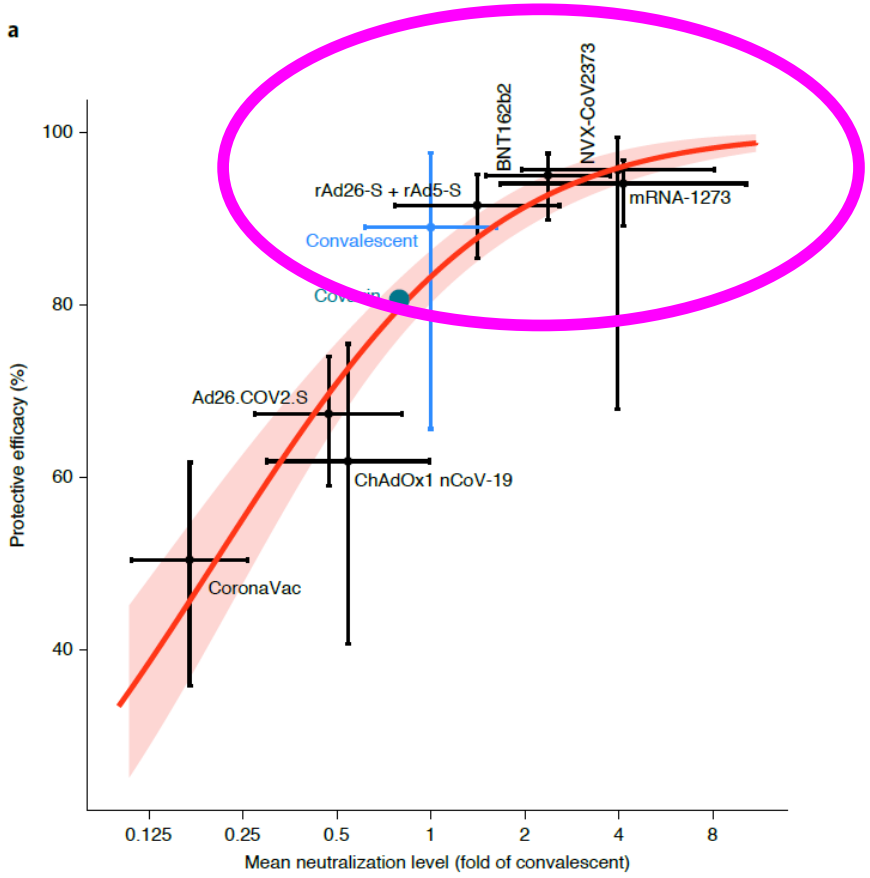
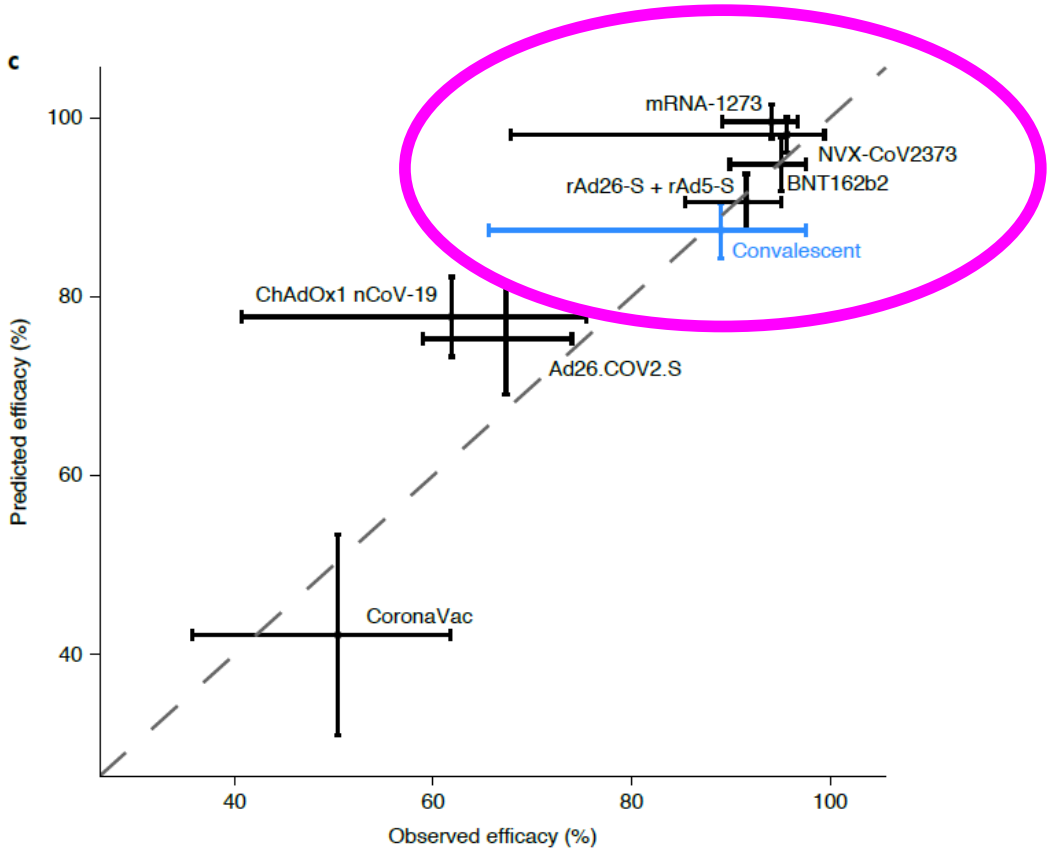
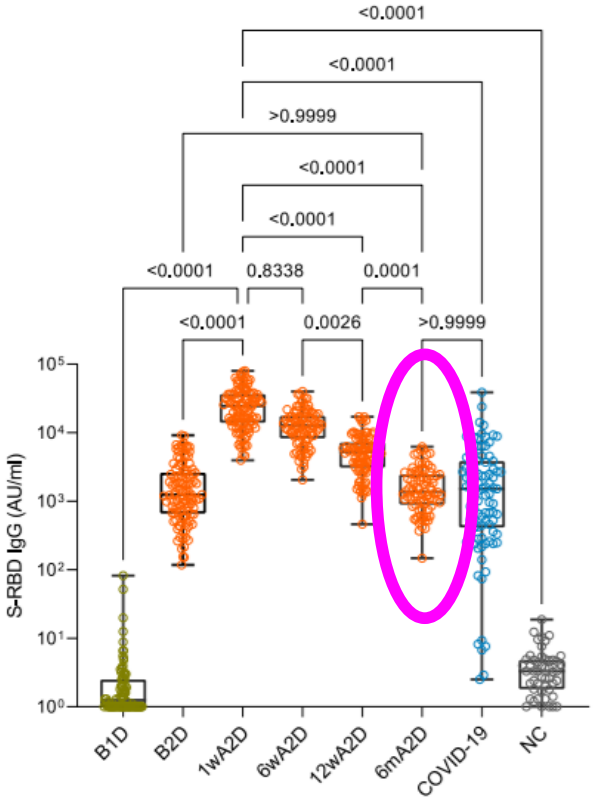
# Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection

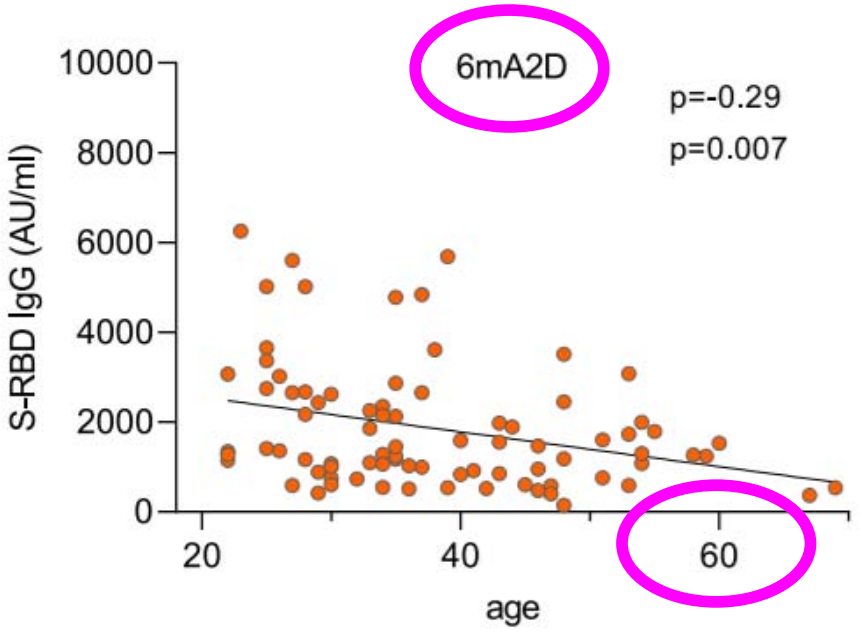



Khoury DS et al,. Nat Med. July 2021; 27:1205-1211.

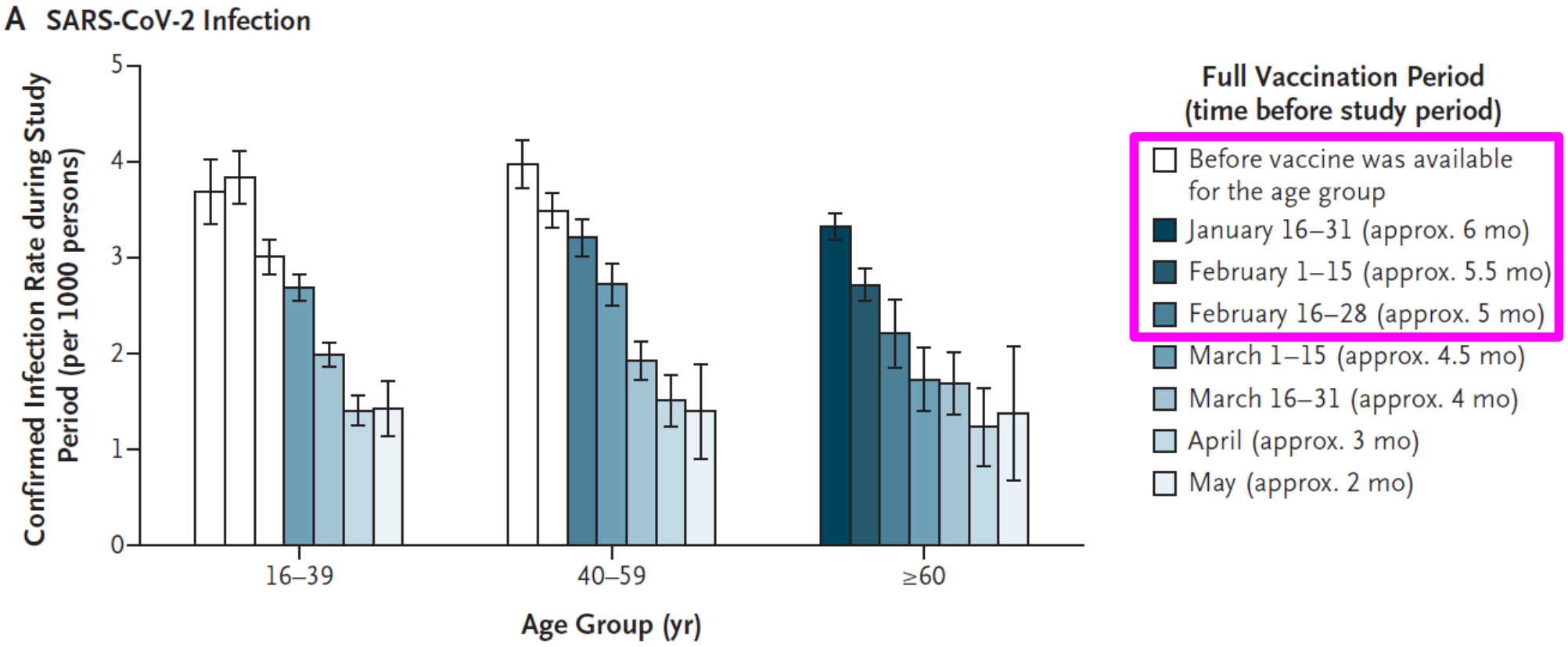
# Waning antibody responses in individuals vaccinated with Pfizer-BioNTech vaccine is more pronounced at 6 mo. and in those over 60 years of age




Naaber P et al. The Lancet Regional Health - Europe. 6 September 6 2021.

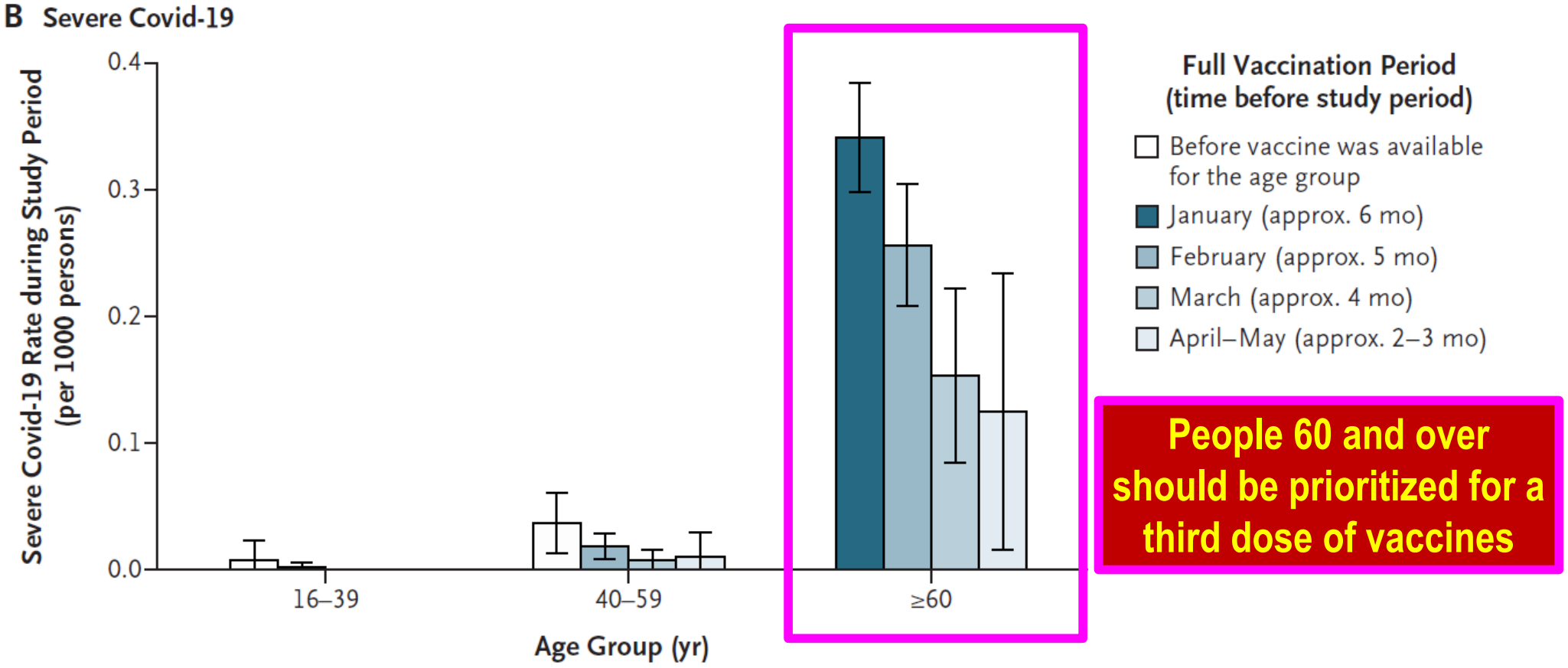
# The effects of waning antibodies neutralization titer on clinical outcomes: SARS-CoV-2 infection increased regardless age




Most infections were due to the Delta variant

Goldberg Y et al., NEJM October 27, 2021.

# The effects of waning antibodies neutralization titer on clinical outcomes: Severe COVID-19 mainly diagnosed ≥60 yr.




**People 60 and over should be prioritized for a third dose of vaccines**

Most infections were due to the Delta variant

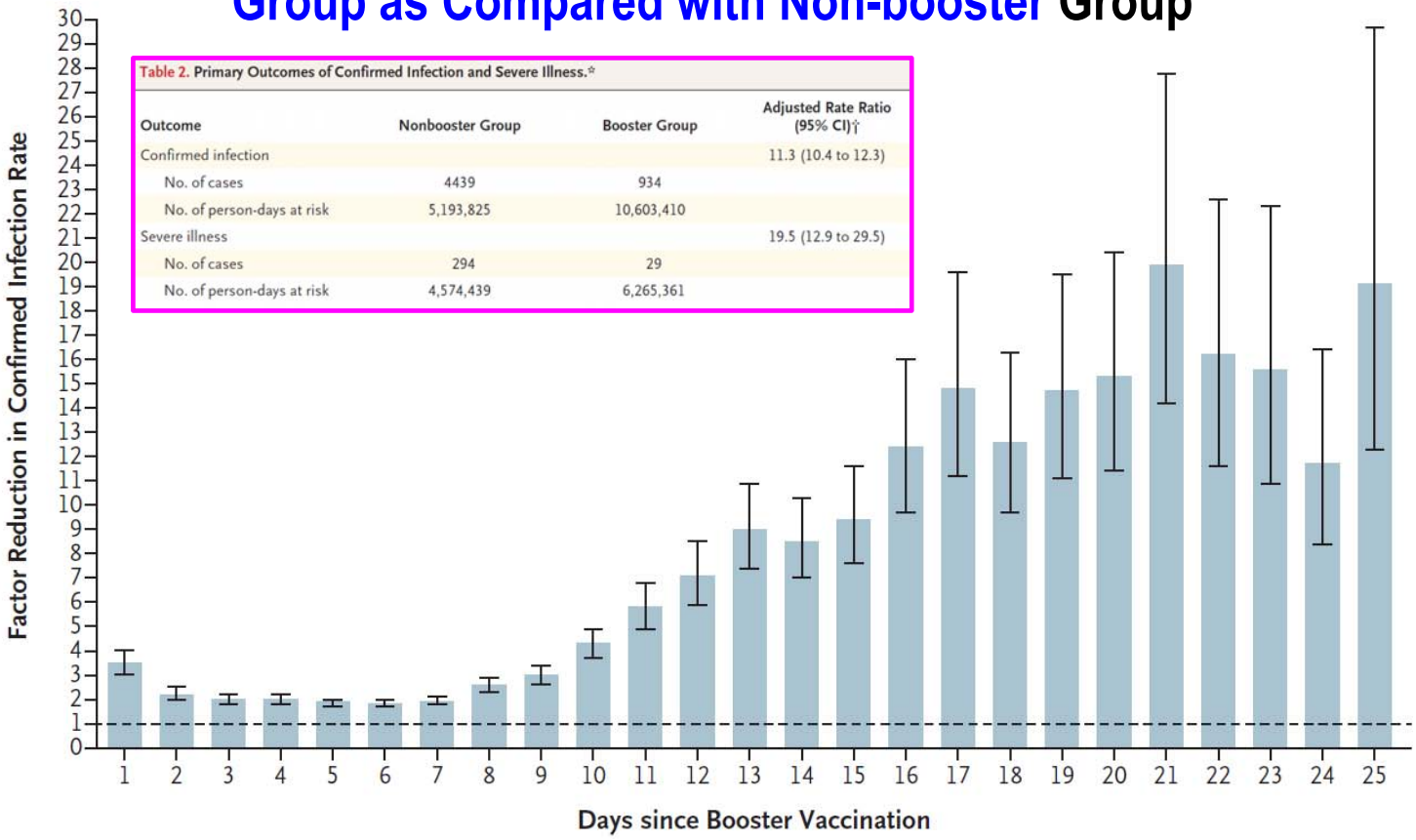
Goldberg Y et al., NEJM October 27, 2021.

# A 3rd booster dose of BNT162b2 vaccine protected against Covid-19 in persons who were ≥60 yr. of age in Israel

## Reduction in Rate of Confirmed Infection in Booster Group as Compared with Non-booster Group

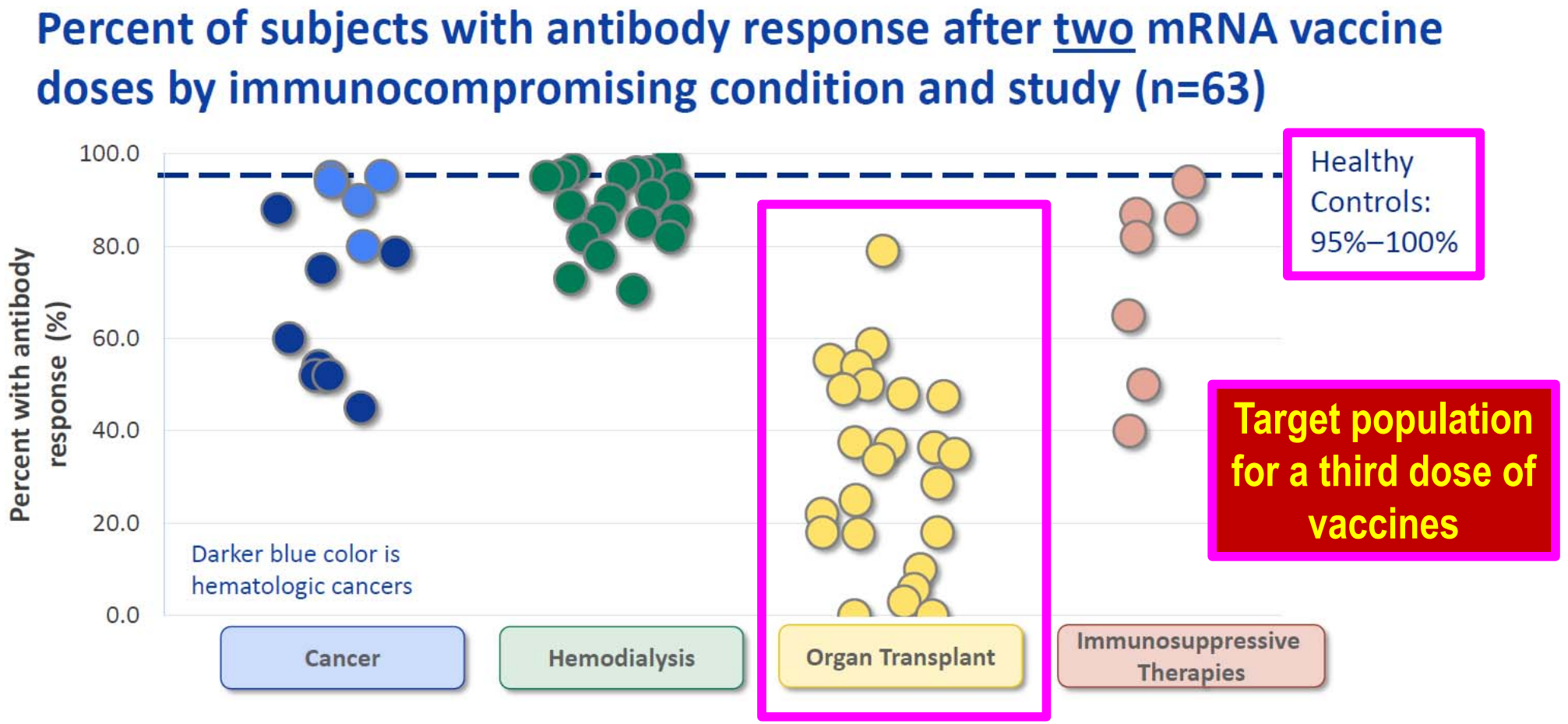
Table 2. Primary Outcomes of Confirmed Infection and Severe Illness.*

| Outcome | Nonbooster Group | Booster Group | Adjusted Rate Ratio (95% CI)† |
|---|---|---|---|
| Confirmed infection | | | 11.3 (10.4 to 12.3) |
| No. of cases | 4439 | 934 | |
| No. of person-days at risk | 5,193,825 | 10,603,410 | |
| Severe illness | | | 19.5 (12.9 to 29.5) |
| No. of cases | 294 | 29 | |
| No. of person-days at risk | 4,574,439 | 6,265,361 | |



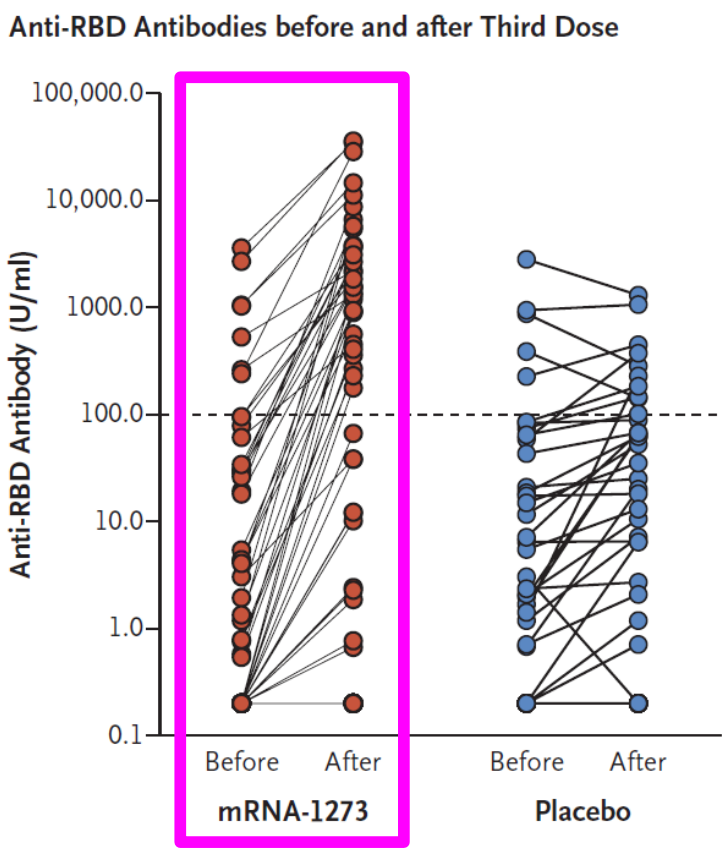

Bar-On YM et al., NEJM. September 15, 2021.

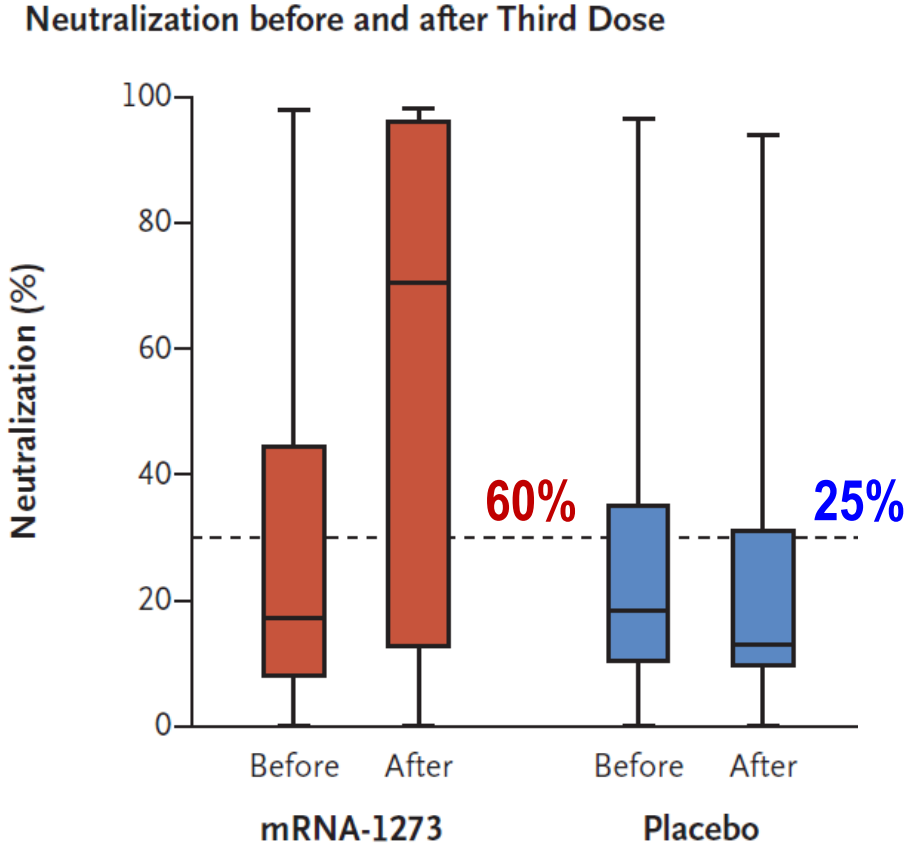
# Immunosuppressed patients have a much worse immune response to COVID-19 vaccines than healthy individuals




Oliver S. ACIP Meeting. July 22, 2021. https://www.cdc.gov/coronavirus.

# A Third Dose of mRNA-1273 Vaccine Increased Immune Responses in 120 Organ-Transplant Recipients: A RCT

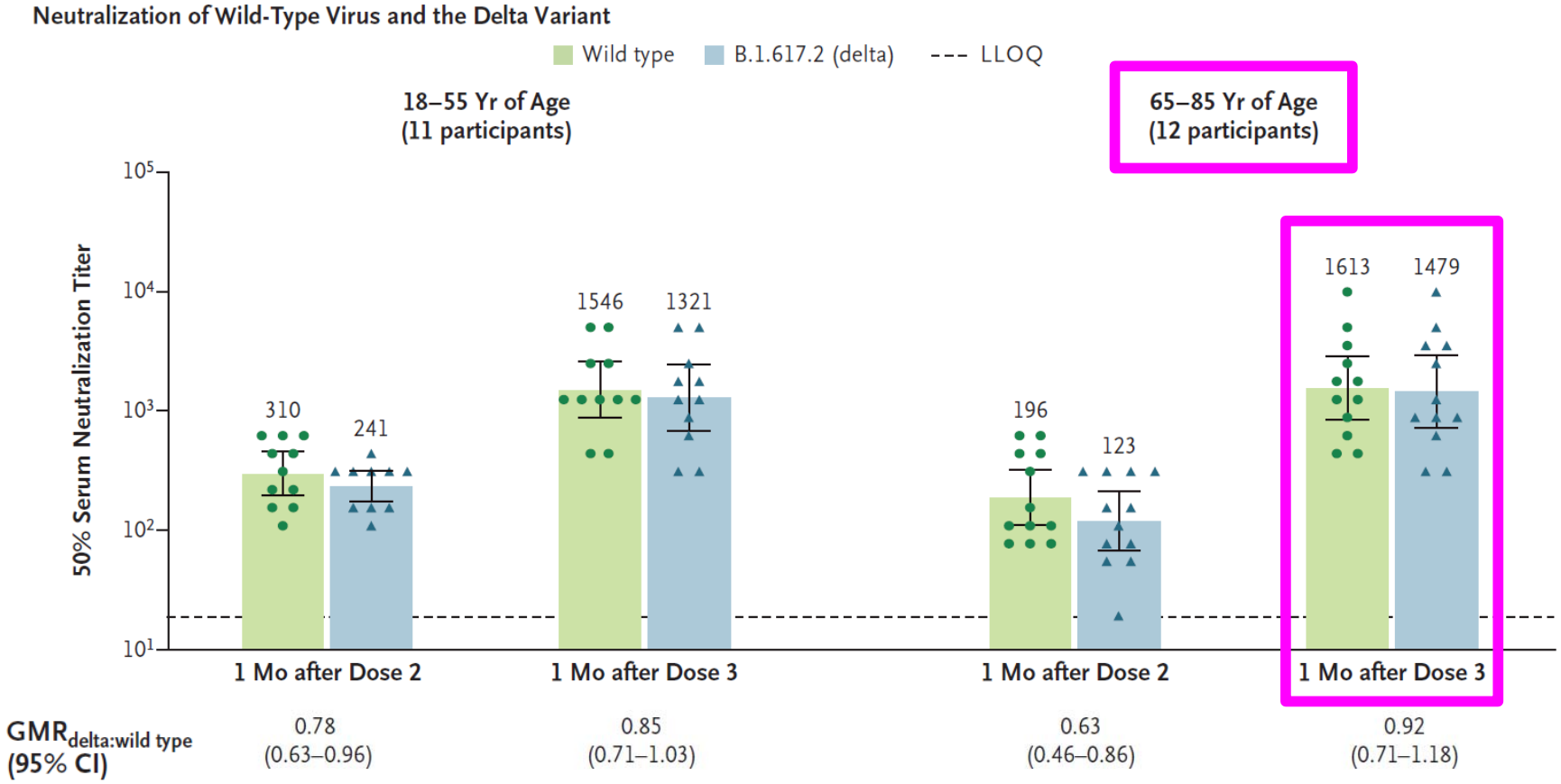



Median SARS-CoV-2-specific T-cell counts were greater after the third dose in the mRNA-1273 group than in the placebo group (432 vs. 67 cells per $10^6$ CD4+ T cells; 95% CI, 46 to 986).

Hall VG et al., NEJM. September 23, 2021.

# Neutralization of the Delta Variant Increased with a Third mRNA BNT162b2 Vaccine Dose



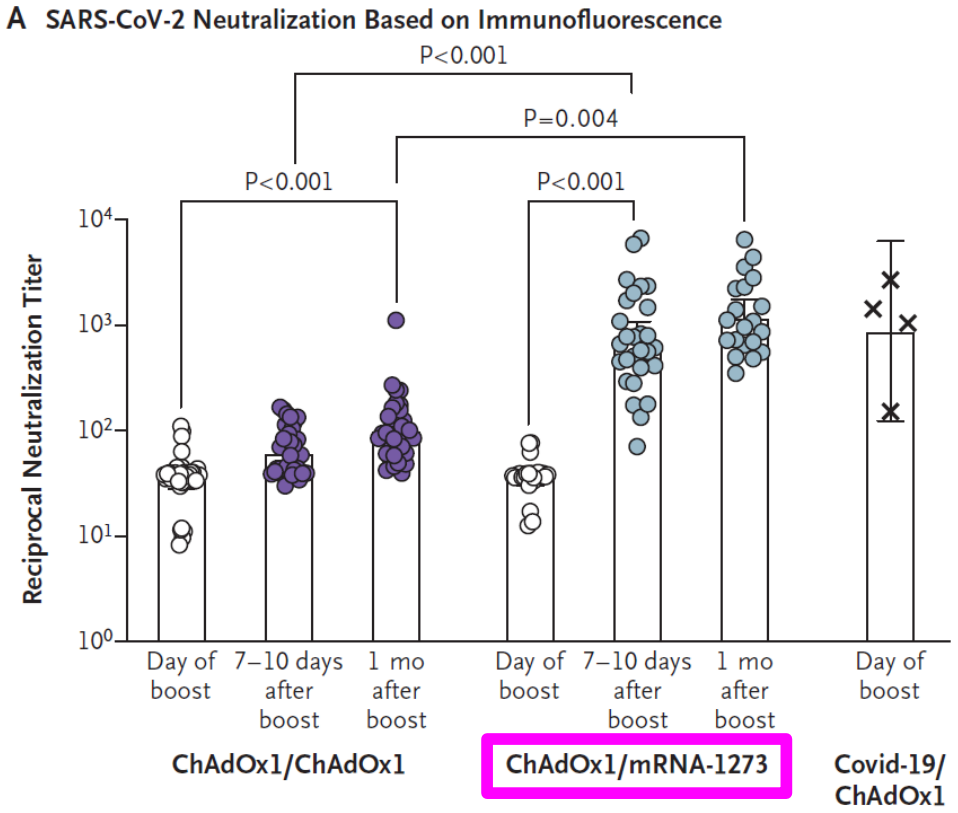

GMFR = Geometric mean fold rises in titers

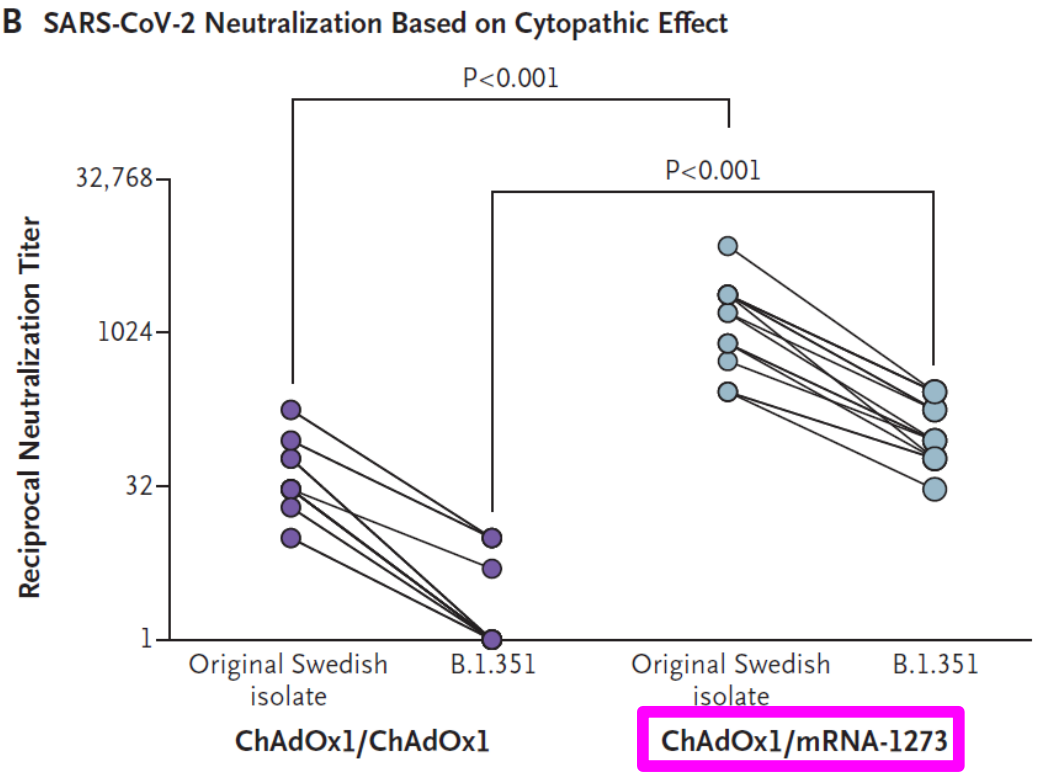
Falsey AR et al., N Engl J Med. Oct 21 2021; 385:1627-1629.

# What vaccine do we use for the third dose? mRNA vaccine !!!

## Results of Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination

### *In Vitro* Neutralization of Original SARS-CoV-2 Isolate from Sweden and the Beta Variant



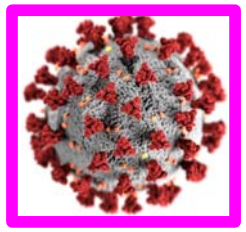




Normark J et al., N Engl J Med. 2021 Sep 9 2021; 385:1049-1051.

# Prioritization of the third dose

- Age ≥ 60 years
- Patients with comorbidities
- Immunosuppressed patients

- Last group general population



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# Vaccine Severe Adverse Events (SAE)

## Adenovirus-vector vaccines

- Thrombosis with Thrombocytopenia Syndrome (TTS)
- Guillain–Barré syndrome (GBS)

## mRNA vaccines

- Myocarditis/Pericarditis

# Thrombosis with Thrombocytopenia Syndrome (TTS) Rates

## Adenovirus-vector vaccines

- **Oxford-Astra Zeneca**
  **- After 1st dose: 10 cases per million**
  **→ After 2nd dose: 1 case per million**
- **Jansen: 2-4 cases per million**
- Sputnik V: no information

## mRNA vaccines

- Pfizer-BioNTech, 0.2 cases per million
- Moderna, 0.4 cases per million

Blanco J on behalf the Multidisciplinary Collaborative Group for the Scientific Monitoring of COVID-19 (GCMSC); https://www.isglobal.org/documents

# Guillain–Barré syndrome (GBS)

## Incidence after:

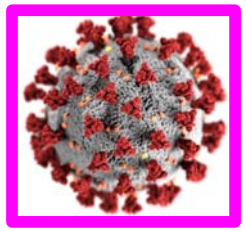
- ChAdOx1nCoV-19 vaccination, 3.8 cases per million
- Ad26.COV2.S COVID-19 vaccination, 5.1 cases per million
- SARS-CoV-2 infection, 14.5 cases per million !!!

Patone M et al,. Nat Med. October 25th 2021;
https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-guillain-barre-syndrome-listed-very-rare-side-effect.

# Myocarditis/Pericarditis

- **Incidence**: Moderna (100 µg), 33 cases per million
  Pfizer (30 µg), 13 cases per million
  → Highest incidence in males between 18 and 24 years:
  283 (Moderna) and 43 (Pfizer) cases per million.
- Almost 80% cases in males. Myocarditis was mild (76%) or moderate (22%) in most cases and severe in 2% (cardiogenic shock).
- Left ventricular dysfunction on echocardiography normalized in most cases during follow-up.
- Mortality was very rare.

Witberg G et al,. NEJM, October 6th 2021;
https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-myocarditis-pericarditis-vaccines-epi.pdf?sc_lang=en.



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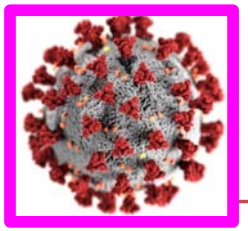
# Take-home messages

- The Delta variant is the one that currently predominates throughout the world.
- Vaccination reduces SARS-CoV-2 infection and severe COVID-19. These breakthrough infections are seen in patients who have made few neutralizing antibodies.
- **For the first time we have antiviral treatments that we will be able to give in the community to high-risk patients in order to avoid their hospitalization.**
- Treatment of severe COVID-19 has been standardized, with remdesivir, corticosteroids, tocilizumab, and prophylactic heparin being the standard of care.
- Immunity decreases over time and is lower in people over 60 years of age, with comorbidities and immunosuppression. The third dose should be prioritized in these groups.
- Thrombosis with thrombocytopenia and Guillain – Barré syndromes are rare and associated with Adenovirus-vector vaccines, while myocarditis/pericarditis with mRNA vaccines.



# Acknowledgements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A. Sarukhan
A. Vilella
A. Vallano

**To all front-line health-care workers**

**To our patients and their families**

Nov 19th 2021