Advances in COVID-19 Management

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Conflict of Interest: JKR

- **Honoraria for lectures and/or consultancies from Abivax, Galapagos, Gilead, Janssen, Merck, NPO Petrovax Pharm LLC, Theratechnologies and ViiV.**
- **Research grants from Dt. Leberstiftung, DZIF, Hectorstiftung, NEAT ID.**

» Epidemiology

COVID-19 Pandemic: anounced from WHO 11th March 2020 (118.000 confirmed infections in 114 countries)

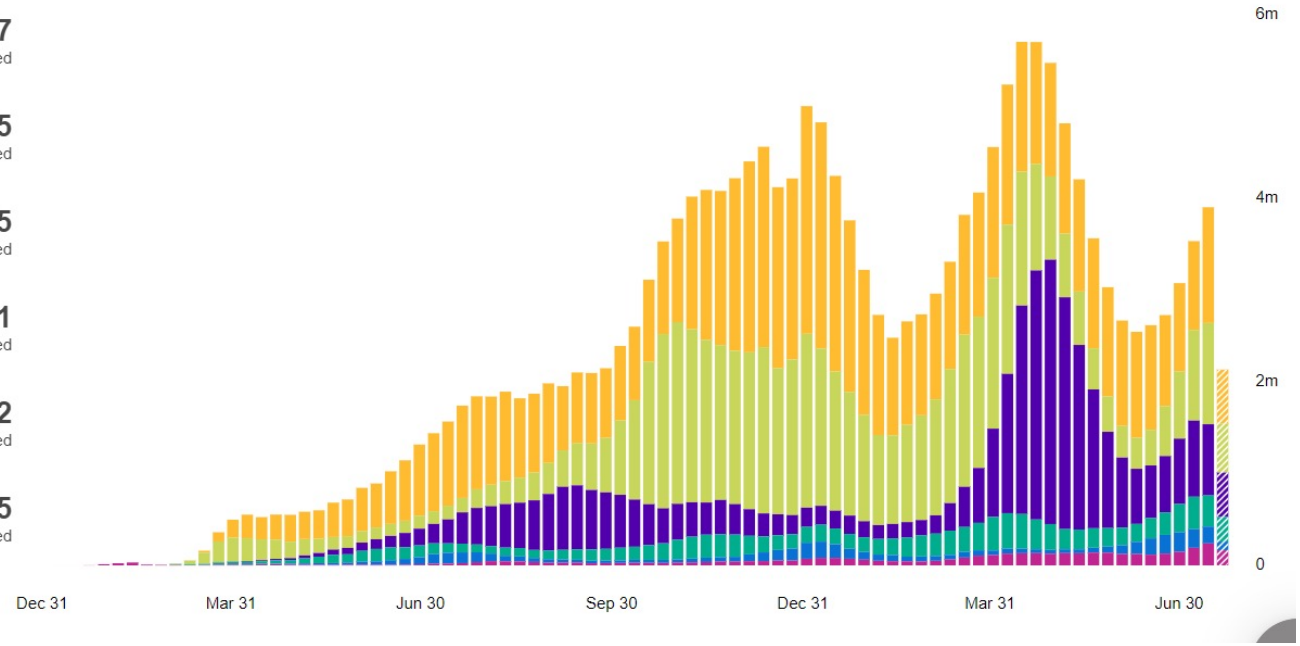
Globally, as of 6:17pm CEST, 29 July 2021, there have been 195.886.929 confirmed cases of COVID-19, including 4.189.148 deaths, reported to WHO.

WHO Dashboard

Americas	76,584,467 confirmed
Europe	59,638,715 confirmed
South-East Asia	38,018,705 confirmed
Eastern Mediterranean	12,401,911 confirmed
Africa	4,868,312 confirmed
Western Pacific	4,374,055 confirmed

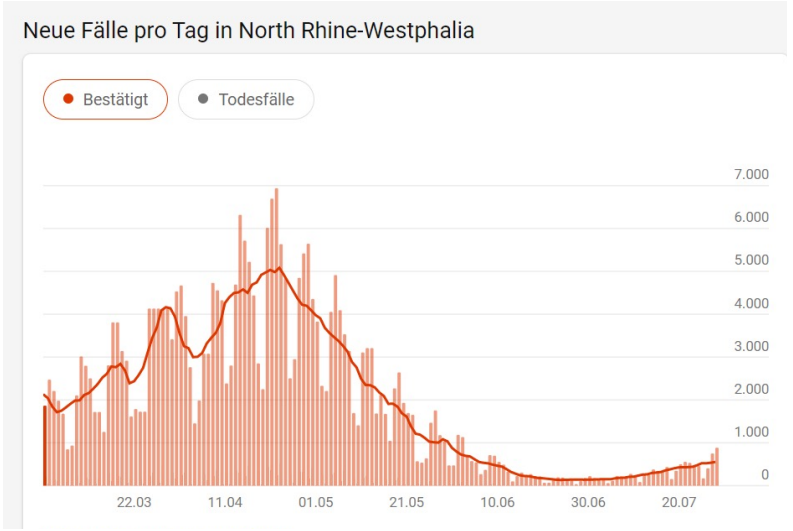
Source: World Health Organization

Data may be incomplete for the current day or week.



Worldometer

Country	Cases	Deaths	Region
United States	35,586,564	628,503	North America
India	31,572,344	423,244	Asia
Brazil	19,839,369	554,626	South America
Russia	6,242,066	157,771	Europe
France	6,079,239	111,764	Europe
United Kingdom	5,801,561	129,515	Europe
Turkey	5,682,630	51,184	Asia
Argentina	4,905,925	105,113	South America



How should we respond to the Coronavirus SARS-CoV-2 outbreak?

- Social distancing
- Face mask wearing
- Digital contact tracing (backward contact tracing up to 14 days, use of mobile phone signals)
- Serosurveillance studies
- High capability for coronavirus lab testing
- Sufficient amount of ICU beds
- Lockdown strategies
- School closing
- Vaccination

Guidance for Implementing COVID-19 Prevention Strategies in the Context of Varying Community Transmission Levels and Vaccination Coverage

- **CDC recommends five critical factors be considered to inform local decision-making:**
  - **1) level of SARS-CoV-2 community transmission**
  - **2) health system capacity**
  - **3) COVID-19 vaccination coverage**
  - **4) capacity for early detection of increases in COVID-19 cases**
  - **5) populations at increased risk for severe outcomes from COVID-19.**
- **Among strategies to prevent COVID-19, CDC recommends all unvaccinated persons wear masks in public indoor settings. Based on emerging evidence on the Delta variant (2), CDC also recommends that fully vaccinated persons wear masks in public indoor settings in areas of substantial or high transmission.**

Christie A et al. MMWR 2021, July 27th

» Testing

Coronavirus Disease 2019 Testing Basics

	MOLECULAR TEST	ANTIGEN TEST	ANTIBODY TEST
Also known as...	Diagnostic test, viral test, molecular test, nucleic acid amplification test (NAAT), RT-PCR test, LAMP test	Diagnostic test, viral test, rapid test	Serological test, serology, blood test, serology test
How the sample is taken...	Nasal swabs, either shallow or deep (most tests). Saliva (some tests)	Nasal or nasopharyngeal swab (most tests)	Blood from a fingerstick or vein
How long it takes to get results...	Less than an hour (at-home tests and some point-of-care locations), same day (some point-of-care locations) or 1-3 days (tests sent to a lab for processing). Some tests may take longer in some locations, depending on testing capacity.	Some may be very fast (15–30 minutes), depending on the test	Same day (some point-of-care locations) or 1-3 days (tests sent to a laboratory for processing)
Is another test needed...	Not usually. This type of test is typically highly accurate andmusually does not need to be repeated. Some may indicate the need to re-test in certain circumstances.	Maybe. Positive results are usually highly accurate, but false positives can happen, especially in areas where very few people have the virus. Negative results may need to be confirmed with a molecular test.	Sometimes a second antibody test is needed for accurate results.
What it shows...	Diagnoses active COVID-19 infection. (Some tests may also diagnose influenza or other respiratory viruses)	Diagnoses active COVID-19 infection. (Some tests may also diagnose influenza or other respiratory viruses)	Shows if you've been infected by the virus that causes COVID-19 in the past
What it can't do...	It cannot show if you ever had COVID-19 or were infected with the virus that causes COVID-19 in the past	It may not detect an early COVID-19 infection. Your health care provider may order a molecular test if your antigen test shows a negative result, but you have symptoms of COVID-19. It also cannot show if you ever had COVID-19 or were	It cannot diagnose COVID-19 at the time of the test or show that you do not have COVID-19

www.fda.gov (April 2021)

nature biotechnology ARTICLES
https://doi.org/10.1038/s41587-021-00966-9

LAMP-Seq enables sensitive, multiplexed COVID-19 diagnostics using molecular barcoding

Kerstin U. Ludwig[1], Ricarda M. Schmithausen[2], David Li[3,4,5,6], Max L. Jacobs[7,8], Ronja Hollstein[1], Katja Blumenstock[7], Jana Liebing[9], Mikołaj Słabicki[3,10,11], Amir Ben-Shmuel[12], Ofir Israeli[13], Shay Weiss[12], Thomas S. Ebert[7], Nir Paran[12], Wibke Rüdiger[7], Gero Wilbring[2], David Feldman[14], Bärbel Lippke[1], Nina Ishorst[1,15], Lara M. Hochfeld[1], Eva C. Beins[1], Ines H. Kaltheuner[16], Maximilian Schmitz[16], Aliona Wöhler[17], Manuel Döhla[2,18], Esther Sib[2], Marius Jentzsch[7], Jacob D. Borrajo[3,6], Jonathan Strecker[3,4,5,6], Julia Reinhardt[9], Brian Cleary[3], Matthias Geyer[16], Michael Hölzel[9], Rhiannon Macrae[3,4,5,6], Markus M. Nöthen[1], Per Hoffmann[1,19], Martin Exner[2], Aviv Regev[3,20,21,22,23,24], Feng Zhang[3,4,5,6,23] and Jonathan L. Schmid-Burgk[3,4,5,6,7]

- **Frequent testing of large population groups combined with contact tracing and isolation measures will be crucial for containing Coronavirus Disease 2019 outbreaks. Here we present LAMP-Seq, a modified, highly scalable reverse transcription loop-mediated isothermal amplification (RT–LAMP) method. Unpurified biosamples are barcoded and amplified in a single heat step, and pooled products are analyzed en masse by sequencing. Using commercial reagents, LAMP-Seq has a limit of detection of ~2.2 molecules per µl at 95% confidence and near-perfect specificity for severe acute respiratory syndrome coronavirus 2 given its sequence readout.**
- **Clinical validation of an open-source protocol with 676 swab samples, 98 of which were deemed positive by standard RT–qPCR, demonstrated 100% sensitivity in individuals with cycle threshold values of up to 33 and a specificity of 99.7%, at a very low material cost.**
- **With a time-to-result of fewer than 24 h, low cost and little new infrastructure requirement, LAMP-Seq can be readily deployed for frequent testing as part of an integrated public health surveillance program.**

Ludwig K et al. Nature Biotechnology 2021

» Clinical presentation

Watch for symptoms

» People with COVID-19 have had a wide range of symptoms reported – ranging from mild symptoms to severe illness. Symptoms may appear 2-14 days after exposure to the virus. Anyone can have mild to severe symptoms. People with these symptoms may have COVID-19:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

Delta variant Covid symptoms 'include headaches, sore throat and runny nose'

Researchers warn that UK's most widely established variant may be mistaken for milder illness

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Natalie Grover *Science correspondent*
@NatalieGrover
Mon 14 Jun 2021 16.20 BST

▲ Data suggests the Delta variant is at least 40% more transmissible than the Alpha variant first detected in Kent. Photograph: Leon Neal/Getty Images

Headaches, a sore throat and a runny nose are the most common symptoms associated with the UK's most widely established Covid variant, researchers have said.

The data, collected as part of the app-based Zoe Covid symptom study, suggests that the Delta variant first detected in India feels like a "bad cold", according to Tim Spector, a professor of genetic epidemiology at King's College London, who is leading the work.

"Covid is ... acting differently now, it's more like a bad cold," he said. "People might think they've just got some sort of seasonal cold, and they still go out to parties ... we think this is fuelling a lot of the problem. So, what's really important to realise is that since the start of May, we've been looking at the top symptoms in all the app users, and they're not the same as they were. So, the number one symptom is headache ... followed by sore throat, runny nose and fever."

- All of our contributors to the app are invited to request a PCR test via the NHS portal as soon as they report any new symptoms.
- The researchers modelled the early signs of COVID-19 infection and successfully detected 80% of cases when trained on the first three days of self-reported symptoms.

ARTICLES | ONLINE FIRST

Early detection of COVID-19 in the UK using self-reported symptoms: a large-scale, prospective, epidemiological surveillance study

Liane S Canas, PhD · Carole H Sudre, PhD · Joan Capdevila Pujol, PhD · Lorenzo Polidori, MSc · Benjamin Murray, MSc · Erika Molteni, PhD · et al. Show all authors · Show footnotes

Open Access · Published: July 29, 2021 · DOI: https://doi.org/10.1016/S2589-7500(21)00131-X ·

Check for updates

Summary
Introduction
Methods
Results
Discussion

Summary

Background

Self-reported symptoms during the COVID-19 pandemic have been used to train artificial intelligence models to identify possible infection foci. To date, these models have only considered the culmination or peak of symptoms, which is not suitable for the early detection of infection. We aimed to estimate the probability of an individual being infected with SARS-CoV-2 on the basis of early self-reported symptoms to enable timely self-isolation and urgent testing.

What is long COVID?

Long COVID symptoms include fatigue, breathlessness and ‘brain fog’. Image: Unsplash/ Bermix Studio

What is Long-COVID?

- Long COVID symptoms include fatigue, breathlessness and ‘brain fog’.
- A recent study suggests that more than two million adults in England - around 3.5% of the population - may have had long COVID.[1]
- Women, people who smoked, were overweight or obese, lived in deprived areas, or had been admitted to hospital, all had a higher risk of persistent symptoms, while Asian people had a lower risk.
- Increasing age was also linked with having persistent symptoms, with the risk rising by 3.5% with each decade of life.
- COVID vaccination might help reduce long-term symptoms.

Whitaker M et al. In press

» Treatment considerations

Therapeutic Management of Patients with COVID-19

- **Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the infection, the disease is primarily driven by replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Later in the course of infection, the disease is driven by an exaggerated immune/inflammatory response to the virus that leads to tissue damage.**
- **Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.**

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [30 July 2021].

Therapeutic management of non-hospitalized COVID-19 patients

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider in ED or an In-Person or Telehealth Visit	Anti-SARS-CoV-2 monoclonal antibody products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order):[a] • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab** in these patients due to an increase in the proportion of potentially resistant variants **(AIII)**.[a] See text for details. The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*[c]	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*[d]	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for adverse events **(BIII)**. There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for further discussion. The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

REGEN-COV™ (casirivimab with imdevimab) Reduced Risk of Hospitalization or Death by 70% in Non-hospitalized COVID-19 Patients

- A phase 3, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of REGEN-COV in 4,567 adults (mean age, 48.5 years; 49% men) with confirmed COVID-19 infection but who were not hospitalized. All patients had at least one risk factor for severe COVID-19, including chronic lung disease, asthma, obesity, cardiovascular disease and older age.

- The trial evaluated two REGEN-COV doses: 2,400 mg and 1,200 mg.
- Patients assigned REGEN-COV 2,400 mg had a 71% reduction in the risk for COVID-19-related hospitalization or all-cause death at day 29 compared with placebo ($P < .0001$) and those assigned the 1,200 mg dose had a 70% reduction in the primary endpoint compared with placebo ($P < .0024$).
- Both doses of REGEN-COV were associated with a shorter mean time to COVID-19 symptom resolution compared with placebo (10 days vs. 14 days).

- REGEN-COV at both doses reduced viral load by 0.71 log10 copies/mL and 0.86 log10 copies/mL at 7 days compared with placebo ($P < .0001$ for both).

High-Risk Criteria in the Emergency Use Authorizations for Anti-SARS-CoV-2 Monoclonal Antibodies

- The FDA EUAs for all available anti-SARS-CoV-2 monoclonal antibodies and combinations have the same criteria for use: nonhospitalized adults and children aged ≥12 years and weighing ≥40 kg who are at high risk for progressing to severe COVID-19 and/or hospitalization.
- High-risk individuals as specified in the EUA are those who meet at least one of the following criteria:
  - Body mass index (BMI) ≥35
  - Chronic kidney disease
  - Diabetes mellitus
  - Immunocompromising condition
  - Currently receiving immunosuppressive treatment
  - Aged ≥65 years
  - Aged ≥55 years and have:
    - Cardiovascular disease, *or*
    - Hypertension, *or*
    - Chronic obstructive pulmonary disease or another chronic respiratory disease.

The Medical Letter

Because the source matters.

The Medical Letter on Drugs and Therapeutics

FROM ISSUE 1627

June 28, 2021

An EUA for Sotrovimab for Treatment of COVID-19

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Revised 7/1/2021: The Availability paragraph has been revised.

Outline

Table

The investigational monoclonal antibody sotrovimab (VIR-7831; GSK/Vir Biotechnology) has been granted an FDA Emergency Use Authorization (EUA) for treatment of mild to moderate COVID-19 in patients ≥12 years old who weigh ≥40 kg and are at high risk of progressing to severe disease, including hospitalization and death.[1] Two other monoclonal antibody regimens are authorized for the same indication: casirivimab (REGN10933) and imdevimab (REGN10987) administered together,[2] and bamlanivimab (LY-CoV555) and etesevimab (LYCoV016) administered together.[3] The FDA revoked its EUA for bamlanivimab alone in April 2021 because an increasing percentage of COVID-19 cases in the US are being caused by SARS-CoV-2 variants that are resistant to monotherapy with the drug.[4]

MECHANISM OF ACTION — Sotrovimab binds to a preserved epitope on the spike protein of SARS-CoV-2. Its exact mechanism of action is unknown, but it appears to prevent membrane fusion after the virus binds to the human ACE2 receptor.

CLINICAL STUDIES — Issuance of the EUA was based on interim results from an unpublished double-blind trial (COMET-ICE; summarized in the FDA Fact Sheet) in 583 adult outpatients with mild to moderate COVID-19 who were ≥55 years old or had at least one comorbidity (diabetes, obesity, chronic kidney disease, heart failure, COPD, or moderate to severe asthma). Patients were randomized to receive a single IV infusion of sotrovimab 500 mg or placebo. The primary endpoint, progression of COVID-19 (hospitalization for >24 hours or death) by day 29, occurred in 1% of patients who received sotrovimab and in 7% of those who received placebo (HR 0.14 [95% CI 0.04-0.56]; NNT 16.2).[6]

Table 1. High-Risk Conditions for COVID-19 Outpatients[1]

- Age ≥65 years
- BMI ≥25 kg/m² (or, in patients 12-17 years old, BMI ≥85th percentile for age and gender[2])
- Pregnancy
- Chronic kidney disease
- Diabetes
- Cardiovascular disease
- Hypertension
- COPD, moderate to severe asthma, or other chronic respiratory disease
- Currently receiving immunosuppressive treatment
- Sickle cell disease
- Congenital or acquired heart disease
- Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity
- A medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])

BMI = body mass index; COPD = chronic obstructive pulmonary disease
1. Adult and pediatric patients (≥12 years old and weighing ≥40 kg) with ≥1 of the criteria listed are considered at high risk for progression to severe COVID-19 and/or hospitalization and are eligible for monoclonal antibody treatment (FDA. Fact sheet for health care providers. Emergency Use Authorization (EUA) of sotrovimab. Available at: https://www.fda.gov/media/149534/download. Accessed June 3, 2021).
2. Based on CDC growth charts (https://bit.ly/36U0twf).

No studies directly comparing sotrovimab with casirivimab and imdevimab or bamlanivimab and etesevimab are available.

VARIANTS — The World Health Organization has renamed COVID-19 variants using the Greek alphabet to avoid confusion and stigmatization. Sotrovimab appears to retain activity against the B.1.1.7 (Alpha; UK), B.1.351 (Beta; South Africa), P.1 (Gamma; Brazil), B.1.427/B.1.429 (Epsilon; California), B.1.526 (Iota; New York), and B.1.617 (Delta; India) variants of SARS-CoV-2. Casirivimab and imdevimab also appear to retain activity against prominent variants, but data on their effectiveness against the B.1.617 strain are lacking. Bamlanivimab and etesevimab are unlikely to have activity against the B.1.351 and P.1 variants; their distribution to states in which these variants cause >10% of COVID-19 cases has been paused.[7]

Treatment-emergent epitope variants were detected in 8 patients who received sotrovimab in COMET-ICE; some of these substitutions conferred reduced susceptibility to the drug.[6]

ADVERSE EFFECTS — The most common adverse effects of sotrovimab in COMET-ICE were rash (2%) and diarrhea (1%). Hypersensitivity reactions, including anaphylaxis, have occurred rarely with use of monoclonal antibodies, including sotrovimab, for treatment of COVID-19.

DOSAGE AND ADMINISTRATION — Sotrovimab is supplied in 500 mg/8 mL vials, which require refrigeration during storage. The authorized dosage is 500 mg administered as a 30-minute IV infusion

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FDA U.S. FOOD & DRUG ADMINISTRATION

FDA authorizes REGEN-COV monoclonal antibody therapy for post-exposure prophylaxis (prevention) for COVID-19

Prophylaxis with REGEN-COV is not a substitute for vaccination against COVID-19

Drug Safety and Availability

Information about Nitrosamine Impurities in Medications

Drug Alerts and Statements

Medication Guides

Drug Safety Communications

Drug Shortages

FDA Drug Safety Podcasts

The U.S. Food and Drug Administration today revised the emergency use authorization (EUA) for REGEN-COV (casirivimab and imdevimab, administered together) authorizing REGEN-COV for emergency use as post-exposure prophylaxis (prevention) for COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death. REGEN-COV is not authorized for pre-exposure prophylaxis to prevent COVID-19 before being exposed to the SARS-CoV-2 virus -- only after exposure to the virus.

REGEN-COV also remains authorized for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Prophylaxis with REGEN-COV is not a substitute for vaccination against COVID-19. FDA has authorized three vaccines to prevent COVID-19 and serious clinical outcomes caused by COVID-19, including hospitalization and death. FDA urges you to get vaccinated, if you are eligible. Learn more about FDA-authorized COVID-19 vaccines

Content current as of:
07/30/2021

Regulated Product(s)
Drugs

Therapeutic management of hospitalized adults with COVID-19 based on disease severity

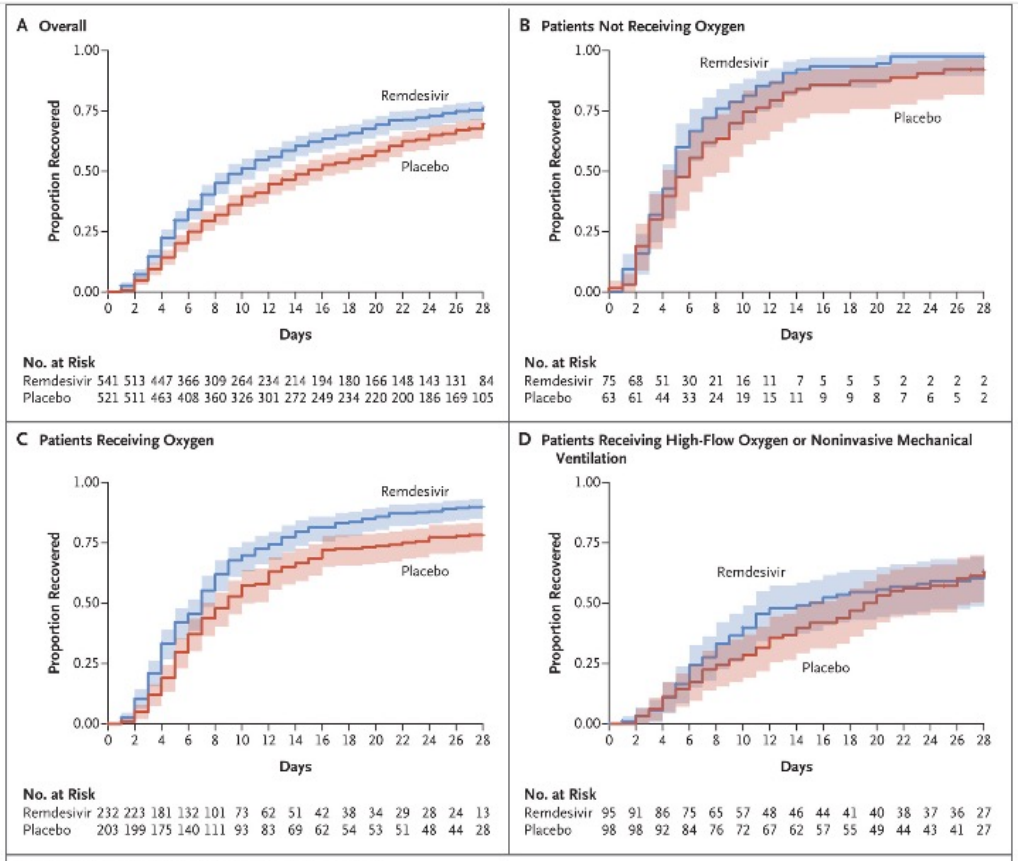
DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or other **corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone**[d] (when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)** For patients who were recently hospitalized[e] with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib**[f,g] **(BIIa)** or **tocilizumab**[f,h] **(BIIa)** to one of the two options above
Hospitalized and Requires IMV or ECMO	For most patients: • **Dexamethasone**[d,i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[d,i] **plus tocilizumab**[f,h] **(BIIa)**

Rating of recommendations: A – Strong; B – Moderate; C=Optional
Rating of Evidence: I=One or more randomized trials without major limitations; IIa=Other randomized trials or subgroup analyses of randomized trials, IIb=Nonrandomized trials or observational cohort studies, III=Expert opinion

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [30 July 2021].

Remdesivir

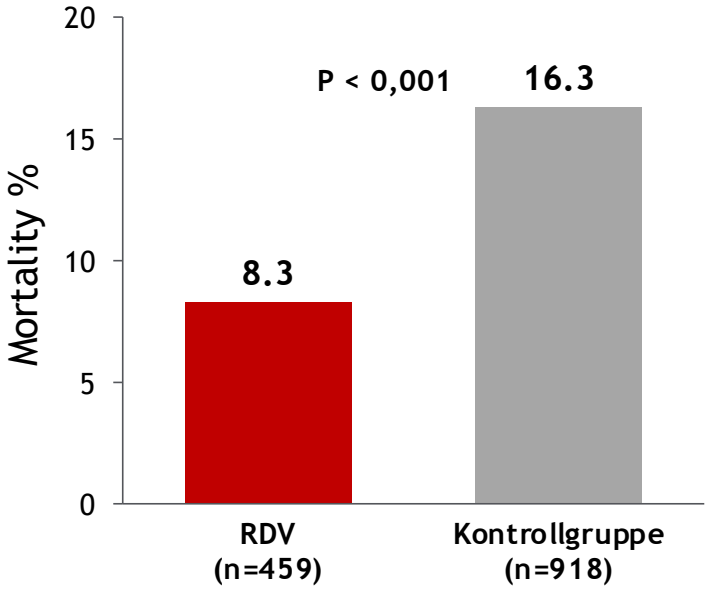
- **Remdesivir is currently the only drug that is approved by the FDA and EMEA for the treatment of COVID-19.**
- **It is recommended for use in hospitalized patients who require supplemental oxygen.**
- **However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease[1-4].**

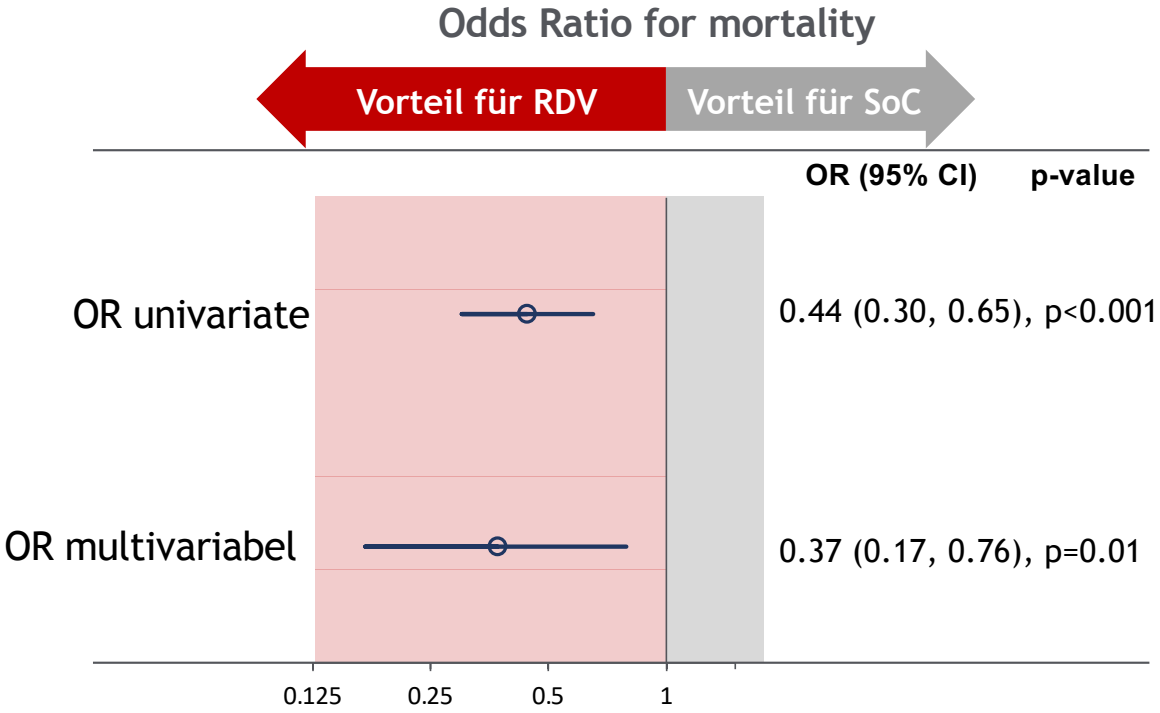


1.Beigel JH, et al. Remdesivir for the treatment of COVID-19 - final report. N Engl J Med. 2020. 2.Wang Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569-1578. 3.Spinner CD, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA. 2020;324(11):1048-1057. 4.Goldman JD, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. N Engl J Med. 2020.

LEOSS

Lower mortality under remdesivir treatment compared to control group in “complicated course” of disease





Appel K et al. 15. Kongress für Infektionskrankheiten und Tropenmedizin 2021. Poster a-359 (P-149).

Dexamethasone in Hospitalized Patients with Covid-19

- In this controlled, open-label trial patients who were hospitalized with Covid-19, were randomly assigned to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone.
- A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care.
- Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization.
- In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.

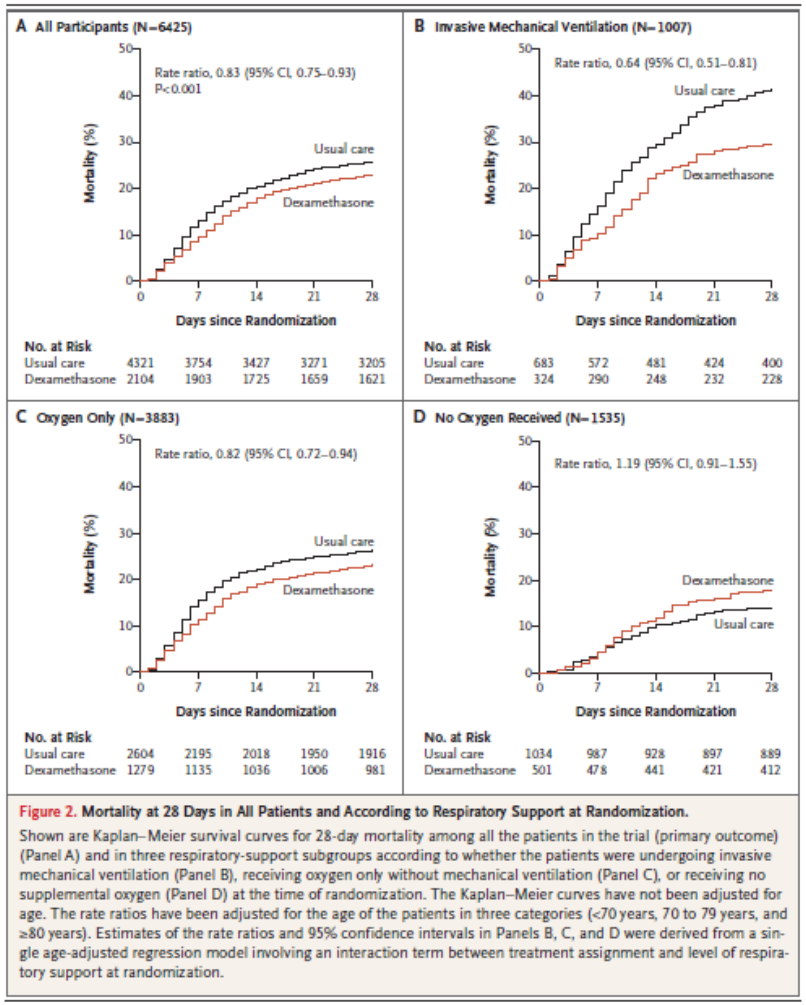


Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

Shown are Kaplan–Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory-support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen only without mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan–Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.

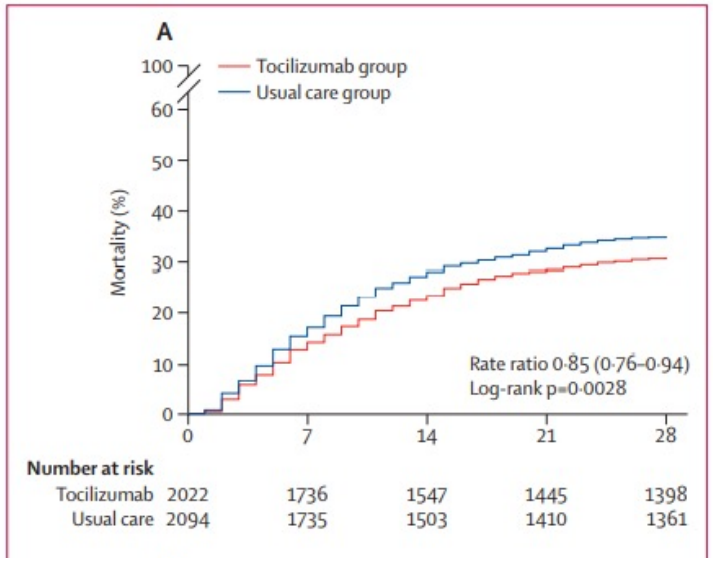
The RECOVERY Collaborative Group*N Engl J Med. 2020 Jul 17:NEJMoa2021436.

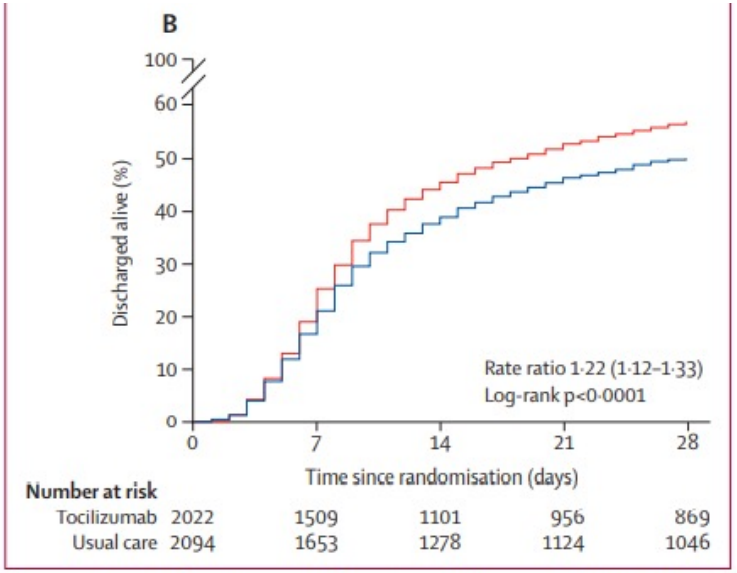
Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

Tocilizumab reduces deaths in patients hospitalised with COVID-19

11 February 2021

Effect of allocation to tocilizumab on 28-day mortality (A) and discharge from hospital within 28 days of randomisation (B)





RECOVERY Collaborative Group. Lancet 2021; 397: 1637–45

» Hot news about vaccines

Hot news about vaccines

- **Heterologous prime–boost vaccination**
- **Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant**
- **3rd booster vaccine in immune-suppressed patients**
- **Vaccine breakthroughs**

Current vaccines and their effectiveness

Primary PREVENTION

Vaccine/Company	Platform	Protection from hospitalisations or death[a]	Efficacy against milder disease[a]
BNT162b2 Pfizer-BioNTech[1]	mRNA in lipid nanoparticle	100%	95%
mRNA-1273 Moderna[1,2]	mRNA in lipid nanoparticle	100%	94.1%
ChAdOx1 nCoV-19 (AZD1222) AstraZeneca[1,3]	Non-replicating chimp adenovirus-DNA	100%	66.7% overall; 90% half-full dose 81.3% after longer prime-boost interval
Gam-COVID-Vac (Sputnik V) Gamaleya National Center[1,4]	Ad26 and Ad5 adenovirus/DNA	100%	91.4%
JNJ-78436725 Johnson & Johnson[1,2]	Non-replicating human adenovirus/DNA	100%	66% overall
NVX-CoV2373 Novavax[1,5,6]	Spike protein/RBD + Matrix M adjuvant	100%	89.3% UK 60% S. Africa
CoronaVac Sinovac[7]	Spike protein + Aluminium hydroxide-based adjuvant	85–100% hospitalisation; 80% death	50–84%[b]

No head to head trials have been conducted therefore direct comparisons cannot be made

[a] Due to COVID-19. [b] Data from 5 studies across Turkey, Chile, Indonesia and Brazil

mRNA: messenger RNA; RBD: receptor-binding domain

1. https://www.biospace.com/article/comparing-covid-19-vaccines-pfizer-biontech-moderna-astrazeneca-oxford-j-and-j-russia-s-sputnik-v/ (accessed May 2021).
2. http://www.healthdata.org/covid/covid-19-vaccine-efficacy-summary (accessed May 2021). 3. Voysey M, *et al. Lancet* 2021; 397:881–891. 4. Loguno D, *et al. Lancet* 2021; 397:671–681.
5. Callaway E & Mallapaty S. *Nature* 2021; 590:17. 6. https://www.pulsetoday.co.uk/news/clinical-areas/immunology-and-vaccines/novavax-to-seek-regulatory-approval-as-vaccine-found-100-effective-against-severe-covid/ (accessed May 2021). 7. World Health Organisation. Evidence Assessment: Sinovac/CoronaVac COVID-19 vaccine. Published Apr 2021.
Available at https://cdn.who.int/media/docs/default-source/immunization/sage/2021/april/5_sage29apr2021_critical-evidence_sinovac.pdf (accessed May 2021).

Conversations on COVID19
Practical perspectives for the clinic

Heterologous prime–boost vaccination with ChAdOx1 nCoV-19 and BNT162b2

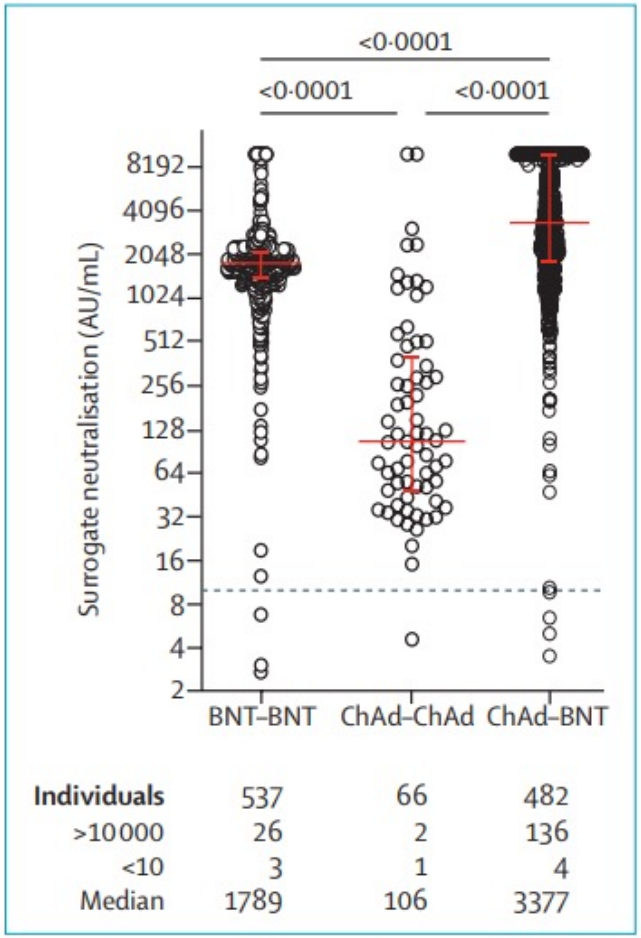


Figure: **Comparison of surrogate neutralisation activity induced by homologous and heterologous COVID-19 vaccine regimens**
Dots represent the results from individual vaccinees analysed by the two study laboratories (appendix pp 2–3). p values from a Dunn's test for multiple comparisons are shown above the graph. Median and interquartile ranges are indicated by red horizontal lines. Below the graph, the total numbers of individual participants, the numbers below the lower (<10) and above the upper (>10 000) cutoff of the surrogate neutralisation assay, and median values of each group are shown.

Tenbusch M et al. Lancet 2021, 29th July

HEALTH AND SCIENCE

Third Covid vaccine shot for people with weakened immune systems ‘very high priority,’ Fauci says

PUBLISHED THU, AUG 5 2021·12:47 PM EDT | UPDATED THU, AUG 5 2021·6:18 PM EDT

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KEY POINTS

- U.S. officials are working quickly to authorize a third Covid-19 vaccine shot for Americans with weakened immune systems, White House chief medical advisor Dr. Anthony Fauci said.
- It is clear now that immunosuppressed populations, in general, do not produce an adequate immune response after receiving two doses of a Covid vaccine, Fauci said.

Federal health officials are working “as quickly as possible” to authorize a third Covid-19 vaccine shot for Americans with weakened immune systems, White House chief medical advisor Dr. Anthony Fauci said Thursday.

It is clear now that such people – including cancer and HIV patients or those who have had organ transplants – in general do not produce an adequate immune response after receiving two doses of a Covid vaccine, Fauci said.

“Immunocompromised individuals are vulnerable,” Fauci said during a White House briefing. “It is extremely important for us to move to get those individuals their boosters, and we are now working on that and we will make

TRENDING NOW


1 Dr. Fauci: ‘Things are going to get worse’ — here’s what that could look like

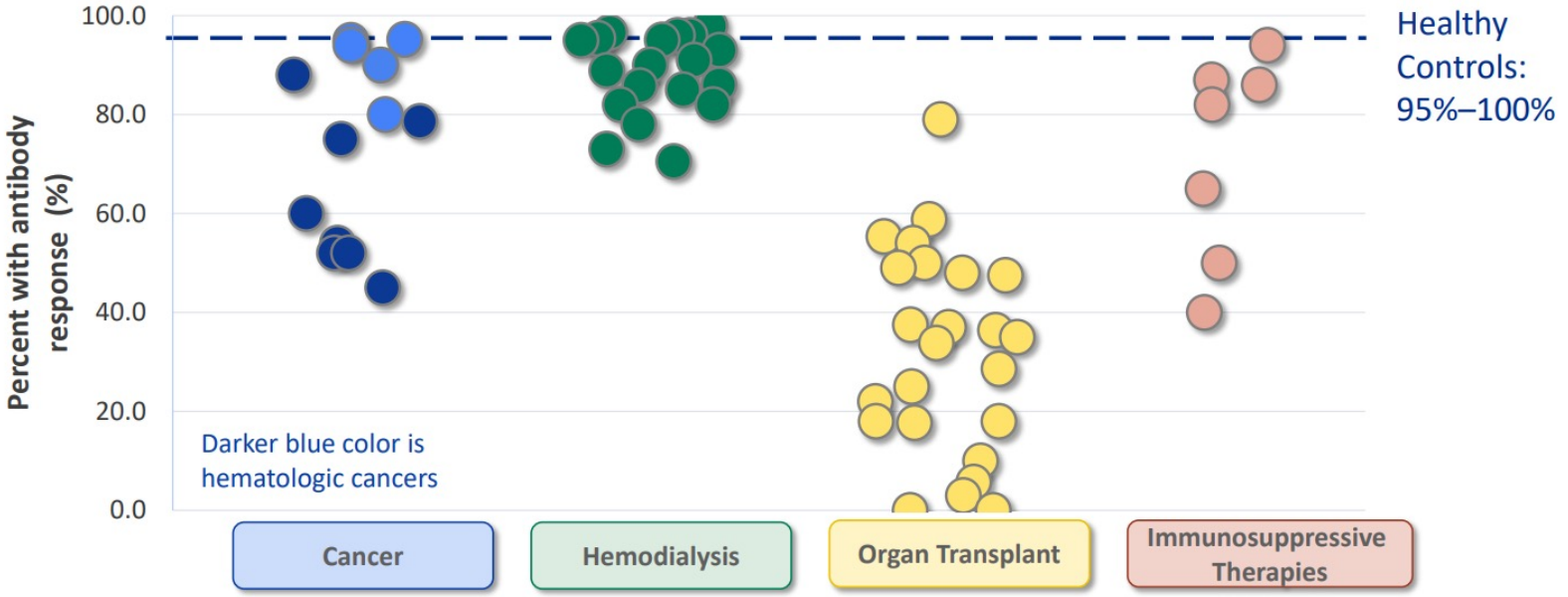

2 Target to pay 100% of college tuition and textbooks in bid to attract workers


3 ‘We couldn’t get in front of it.’ Spirit Airlines CEO explains the carrier’s meltdown this week


4 3 charts show how far Covid delta variant has spread around the world


5 China’s Xiaomi overtook Samsung and Apple in June smartphones sales

Percent of subjects with antibody response after two mRNA vaccine doses by immunocompromising condition and study (n=63)

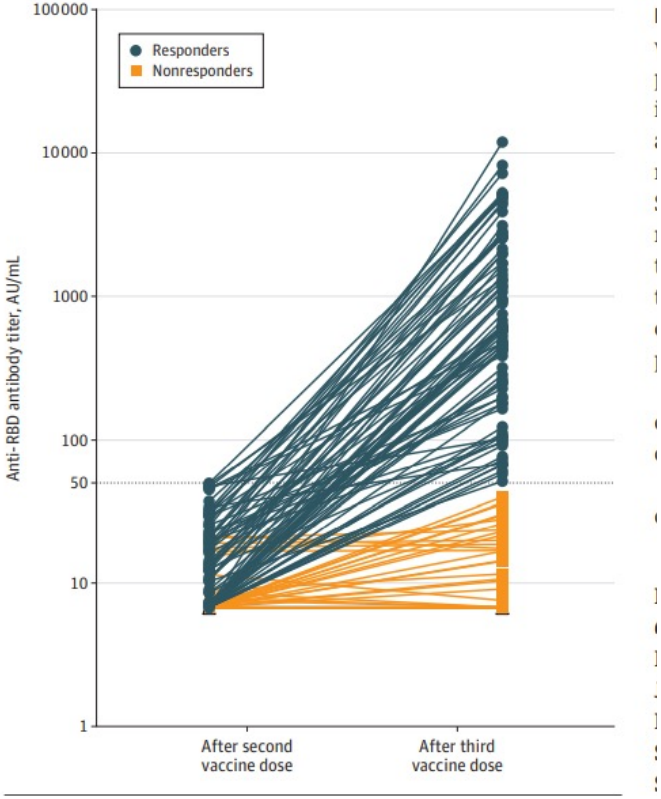


- Studies that compared response after 1st and 2nd dose demonstrated poor response to dose 1
- Antibody measurement and threshold levels vary by study protocol

See reference list at end

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/07-COVID-Oliver-508.pdf

Anti–Receptor-Binding Domain (RBG) IgG Antibody Titers Measured 28 Days After the Third Dose of mRNA-1273 SARS-CoV-2 Vaccine in 159 Kidney Transplant Recipients



Horizontal dotted line indicates the cutoff for positivity (50 arbitrary units [AU]/mL). Blue lines indicate the antibody titers of kidney transplant recipients who seroconverted after the third dose (titers 50 AU/mL); orange lines, the evolution of antibody titers among nonresponders (titers <50 AU/mL). mRNA indicates messenger RNA.

Benotmane I et al. JAMA 2021, published online July 23rd

Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant

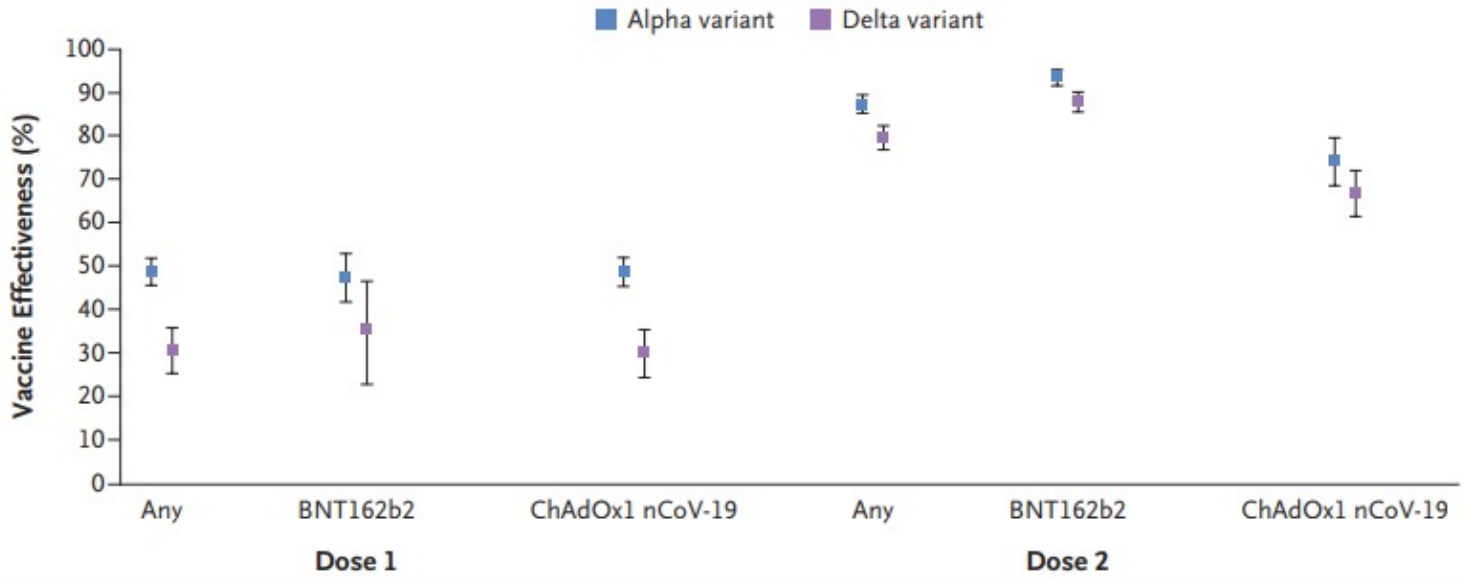


Figure 1. Vaccine Effectiveness against the Alpha and Delta Variants, According to Dose and Vaccine Type.

Shown is the effectiveness of one dose and two doses of the BNT162b2 and ChAdOx1 nCoV-19 vaccines, or either vaccine ("any"), against symptomatic disease with the B.1.1.7 (alpha) or B.1.617.2 (delta) variant of the severe acute respiratory syndrome coronavirus 2. I bars indicate 95% confidence intervals.

Bernal JL et al. N Engl J Medicine 2021, published July 21st

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Methods:

- A retrospective multicentre cohort study of 17 hospitals included patients fully vaccinated with Pfizer/BioNTech's BNT162b2 vaccine who developed COVID-19 more than 7 days after the second vaccine dose and required hospitalization.

Results:

- A total of 152 patients were included, accounting for half of hospitalized fully vaccinated patients in Israel. Poor outcome was noted in 38 patients and mortality rate reached 22% (34/152).
- Notably, the cohort was characterized by a high rate of co-morbidities predisposing to severe COVID-19, including hypertension (108; 71%), diabetes (73; 48%), congestive heart failure (41; 27%), chronic kidney and lung diseases (37; 24% each), dementia (29; 19%) and cancer (36; 24%), and only six (4%) had no comorbidities. Sixty (40%) of the patients were immunocompromised.
- Higher viral load was associated with a significant risk for poor outcome. Risk also appeared higher in patients receiving anti-CD20 treatment and in patients with low titres of anti-Spike IgG, but these differences did not reach statistical significance.

Other variants of concern….

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

New Results

SARS-CoV-2 Lambda variant exhibits higher infectivity and immune resistance

Izumi Kimura, Yusuke Kosugi, Jiaqi Wu, Daichi Yamasoba, Erika P Butlertanaka, Yuri L Tanaka, Yafei Liu, Kotaro Shirakawa, Yasuhiro Kazuma, Ryosuke Nomura, Yoshihito Horisawa, Kenzo Tokunaga, Akifumi Takaori-Kondo, Hisashi Arase, The Genotype to Phenotype Japan (G2P-Japan) Consortium, Akatsuki Saito, So Nakagawa, Kei Sato

doi: https://doi.org/10.1101/2021.07.28.454085

This article is a preprint and has not been certified by peer review [what does this mean?].

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Abstract | Full Text | Info/History | Metrics | Preview PDF

Summary

SARS-CoV-2 Lambda, a new variant of interest, is now spreading in some South American countries; however, its virological features and evolutionary trait remain unknown. Here we reveal that the spike protein of the Lambda variant is more infectious and it is attributed to the T76I and L452Q mutations. The RSYLTPGD246-253N mutation, a unique 7-amino-acid deletion mutation in the N-terminal domain of the Lambda spike protein, is responsible for evasion from neutralizing antibodies.

REUTERS

World | Business | Legal | Markets | Breakingviews | Technology | Investigations

August 6, 2021
6:17 PM CEST
Last Updated a day ago

Europe

Seven residents of Belgian nursing home die after outbreak of B.1.621 lineage of COVID-19

2 minute read

Reuters

A information sign is seen as members of the medical personnel take part in a meeting at the intensive care unit for patients suffering from the coronavirus disease in Antwerp, Belgium, March 31, 2021. REUTERS/Yves Herman

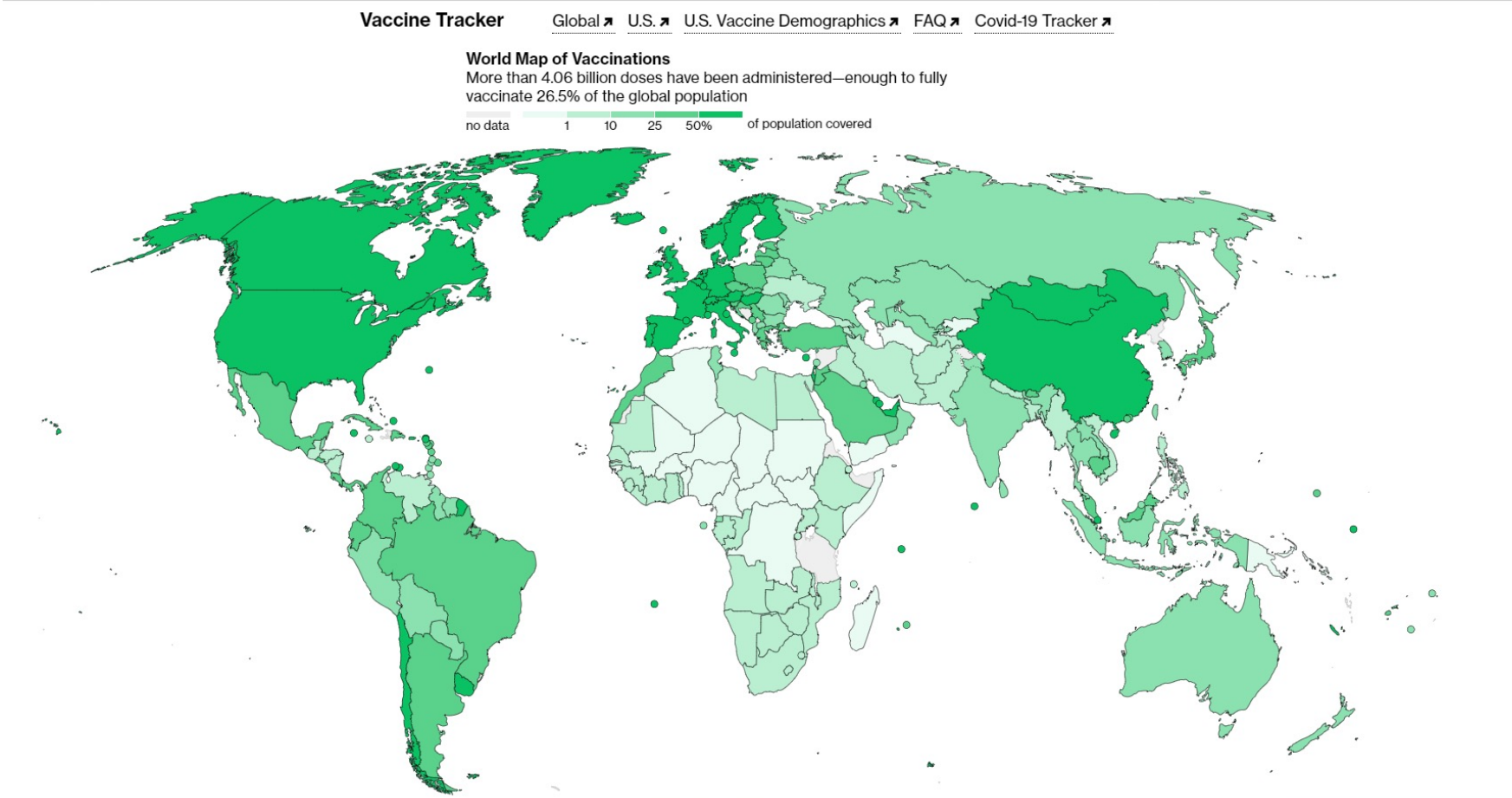
Aug 6 (Reuters) - Seven residents of a nursing home in Belgium have died after being infected with a lineage of the coronavirus first detected in Colombia despite being fully vaccinated, the virology team that conducted tests said on Friday.

The virology team said the residents had been infected with the B.1.621 lineage of COVID 19 that originated in Colombia and has been detected in recent weeks in the United States but cases in Europe have been rare.

The European Centre for Disease Prevention and Control has listed the B1.621 lineage as part of the Kappa variant of the coronavirus, but not as a variant itself.

The seven people who died at the nursing home in the Belgian town of Zaventem, near Brussels, were all in their 80s or 90s, and some of them were already in a poor physical condition, said Marc Van Ranst, a virologist at the University of Leuven which conducted tests on the virus found at the nursing home.

World map of vaccinations



https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution/

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting

- **All persons who were newly vaccinated during the period from December 20, 2020, to February 1, 2021, were matched to unvaccinated controls in a 1:1 ratio according to demographic and clinical characteristics. Study outcomes included documented infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), symptomatic Covid-19, Covid-19–related hospitalization, severe illness, and death**

Dagan N et al. N Engl J Med 28 Feb 2021

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Mary Addo
Christoph Boesecke
And
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Away
Amare Mundus: Latin for "World Love"


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