INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

August 2021

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INA-RESPOND newsletter

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INA-RESPOND Secretariat

Badan Penelitian dan Pengembangan Kesehatan RI, Gedung 4, Lantai 5.
Jl. Percetakan Negara no.29,
Jakarta 10560
www.ina-respond.net

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FEATURES

INA-RESPOND Newsletter

TRIPOD, PROACTIVE, & ORCHID Study Updates

By: Eka Windari R., I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Nur Latifa Hanum, Retna Mustika Indah, Riza Danu Dewantara

STUDY UPDATES

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Per 06 May 2021, all the participants in the TRIPOD study have completed the study (from 490 enrolled participants). Two hundred and fifty-four participants have completed the study while 236 participants were terminated early (including death). From the uploaded CRFs, all participants from sites 520, 550, 560, 570, 580, 590, and 600 have completed the study.

The Source Document Worksheet has been completely uploaded by sites 520, 550, 560, 570, 580, 590, and 600.

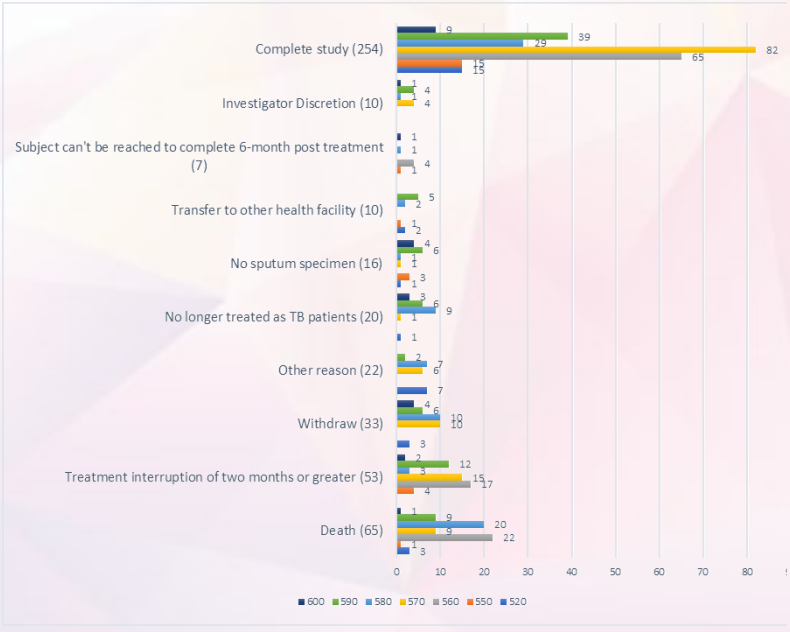
The database quality assurance (except for TB treatment pages) has been conducted for sites 520, 550, 560, 570, 590, and 600. The quality assurance of critical values for site 600 was conducted on 23 Jun and 01 Jul 2021, and the quality assurance for subject random was conducted on 2, 3, 7-9 Jul 2021.

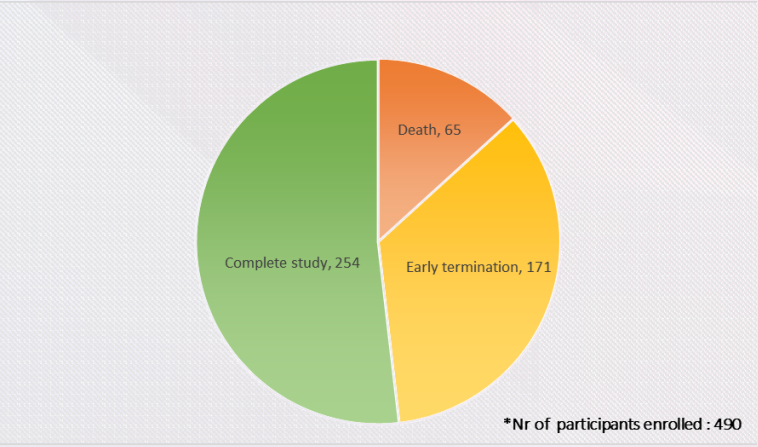
The Site Close-out Visits (SCVs) were conducted for site 520 on 30 November – 1 December 2020, site 570 on 15-16 December 2020, site 590 on 19-20 January 2021, site 560 on 20-21 April 2021, site 550 on 22-23 June 2021, and site 600 on 20-21 Jul 2021. All Site Close-out Visit (SCV) action items from sites 520, 570, 590, 560, and 550 are resolved. The upcoming SCV will be conducted at site 600 on 21-22 July 2021 and site 580 on 14-15 September 2021. All essential documents, CRF, SDW and laboratory test results are already available in the EDMS for all sites. The study documents from these sites will be archived in the IndoArsip for long term archival, at least 5 years after study closed.

The INA-RESPOND secretariat has announced an official letter and a final report on site closure to the hospital director and the local ethics commission. For sites 520, 570, 590, they were reported on 14-Apr 2021, and for site 560 they were reported on 18-May 2021. The procedure will also be done for site 550, 600 and 580 as soon as the SCV is completed at each of the site.

The TRIPOD isolate was sent to the Central Laboratory in Padjajaran University, Bandung on 12 April 2021 for subculture. Subculture will be prepared for several tests related to TB, including TB strain examinations which is one of the TRIPOD's secondary objectives.

Per protocol, there are 8 types of specimens collected in the TRIPOD study for future use. Status for Repository specimens is provided in figure 4.





Site	Site Closed Out Visit	Current Status/Awaiting Items
520 (n=32)	Done, 30 November – 1 December 2020	Study documents has been sent to Indo Arsip
550 (n=25)	Done, 22-23 June 2021	Final report has been finalized, the cover letter will need to be fully signed by Head of Centre Two, NIHRD. Study document is still being prepared by the local RA, then all of the study documentations will be sent to INA-RESPOND for inventory purpose.
560 (n=108)	Done, 20-21 April 2021	Study documents has been sent to Indo Arsip DST result for 1 subject
570 (n=128)	Done, 15-16 December 2020	Study documents has been sent to Indo Arsip
580 (n=83)	Planned, 14-15 September 2021	SCV preparation but not limited to QA Process by DM, File Review by CRSS and Specimen Management Review by CRA
590 (n=89)	Done, 19-20 January 2021	Study documents has been sent to Indo Arsip
600 (n=25)	Done, 21-22 July 2021	Final report has been finalized, the cover letter will need to be fully signed by Head of Centre Two, NIHRD. Study document still being prepared by the local RA, then all of the study documentations will be sent to INA-RESPOND for inventory purpose.

Site	Specimen Type	Whole blood (EDTA) - DNA	Whole blood (Heparin) - PBMCs	Whole blood (Heparin) – Plasma	Whole blood (PAXgene) - RNA	Urine	Saliva	Sputum	MTB Isolate
520 (n=32)	**BL (32)**	90	22	91	27	125	62	19	36
	M1 (24)	NA	18	64	21	99	NA	16	12
	M2 (24)	NA	22	68	24	93	NA	11	0
	EOT (15)	NA	28	45	15	60	30	2	0
560 (n=108)	**BL (108)**	382	204	328	102	440	216	131	272
	M1 (95)	NA	188	285	94	381	NA	107	60
	M2 (87)	NA	172	261	86	348	NA	91	20
	EOT (73)	NA	142	219	73	292	146	75	19
570 (n=128)	**BL (128)**	438	177	380	121	519	254	119	192
	M1 (104)	NA	162	311	103	416	NA	43	92
	M2 (97)	NA	162	294	98	392	NA	22	38
	EOT (80)	NA	162	243	81	320	160	4	12
580 (n=83)	**BL (83)**	235	130	210	67	308	147	26	42
	M1 (44)	NA	70	102	38	156	NA	18	6
	M2 (38)	NA	54	81	36	148	NA	16	0
	EOT (29)	NA	50	71	27	124	61	8	0
590 (n=89)	**BL (89)**	340	170	255	84	344	147	78	55
	M1 (59)	NA	98	147	49	196	NA	17	8
	M2 (56)	NA	80	120	41	164	NA	8	0
	EOT (40)	NA	46	72	24	96	46	9	0
600 (n=25)	**BL (25)**	100	50	75	25	100	50	50	30
	M1 (13)	NA	26	39	13	52	NA	26	4
	M2 (11)	NA	22	33	11	44	NA	22	4
	EOT (9)	NA	20	30	10	40	20	20	0
550 (n=25)	**BL (25)**	95	48	72	24	100	51	10	27
	M1 (20)	NA	36	54	19	68	NA	7	7
	M2 (20)	NA	36	54	17	72	NA	6	4
	EOT (15)	NA	26	39	13	52	25	0	2

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According to the data on 16 August 2021, from 4,336 subjects enrolled, 487 subjects are End of Study due to some reasons: 245 subjects completed the study, 179 subjects died, 26 subjects moved away to the city where a PROACTIVE site is not available, 26 subjects withdrew, six subjects were lost-to-follow-up, and five subjects had a negative HIV test result. As of 16 August 2021, there are 3,849 active subjects in this study. Below is the Chart of Enrolled and Active Participants by Sites. Meanwhile, Onsite SMV (Site Monitoring Visit) was conducted to Site 680 (Dr. Soedarso Hospital) on 22-24 June 2021 and Site 690 (Abepura Hospital) on 08 - 10 June 2021.

No	Site# / Name	1st Enrollment	Enrollment stop	# Enrolled			Active Participants	
				Ped	Adult	Total		
1	510 – Hasan Sadikin	7-Feb-19	31-Dec-19	10	198	208	203	97.60 %
2	520 – Sanglah	7-Nov-19	30-Jun-20	5	138	143	142	99.30 %
3	530 – Cipto M.	3-May-18	31-Aug-19	36	274	310	276	89.03 %
4	540 – Sulianti Saroso	25-Feb-19	31-Dec-19	20	162	182	176	96.70 %
5	550 – Wahidin	14-Mar-18	31-Aug-19	10	327	337	261	77.45 %
6	560 – Kariadi	14-Aug-18	31-Aug-19	12	218	230	212	92.17 %
7	570 – Soetomo	26-Apr-18	31-Aug-19	6	307	313	237	75.72 %
8	580 – Sardjito	14-Sep-18	30-Sep-19	4	216	220	216	98.18 %
9	590 – Persahabatan	19-Jul-18	31-Aug-19	10	239	249	218	87.55 %
10	600 – Adam Malik	12-Mar-18	31-Aug-19	2	336	338	267	78.99 %
11	610 – Tangerang	10-Jan-18	31-Aug-19	17	310	327	235	71.87 %
12	630 – Ansari Saleh	17-Jul-18	31-Aug-19	9	236	245	235	95.92 %
13	640 – St. Carolus	13-Aug-18	30-Sep-19	0	225	225	225	100.00%
14	650 – Budi Kemuliaan	2-Aug-18	31-Aug-19	4	225	229	205	89.52 %
15	660 – AW Sjahranie	3-Oct-18	30-Sep-19	17	205	222	219	98.65 %
16	670 – Zainoel Abidin	9-Apr-19	31-Dec-19	5	121	126	115	91.27 %
17	680 – Soedarso	4-Jul-19	31-Dec-19	8	107	115	107	93.04 %
18	690 – Abepura	2-Jul-19	30-Jun-20	4	133	137	129	94.16 %
19	700 – TC Hilers	8-Jul-19	30-Jun-20	10	170	180	171	95.00 %
			Total	189	4147	4336	3849	88.77 %

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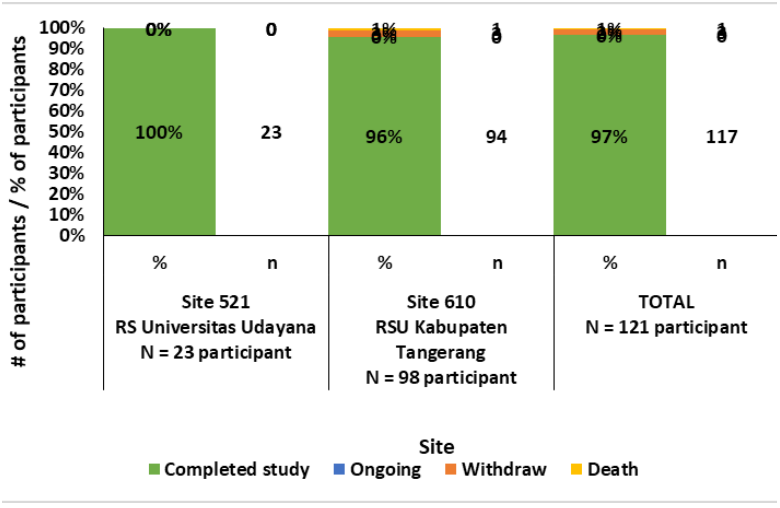
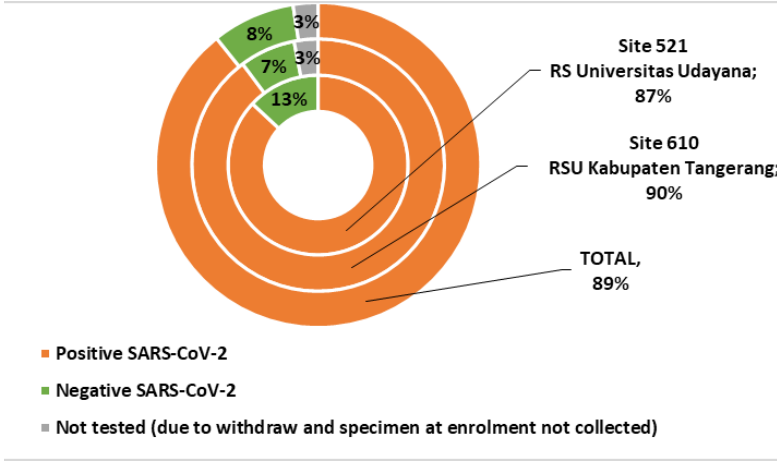
PARTICIPANT STATUS

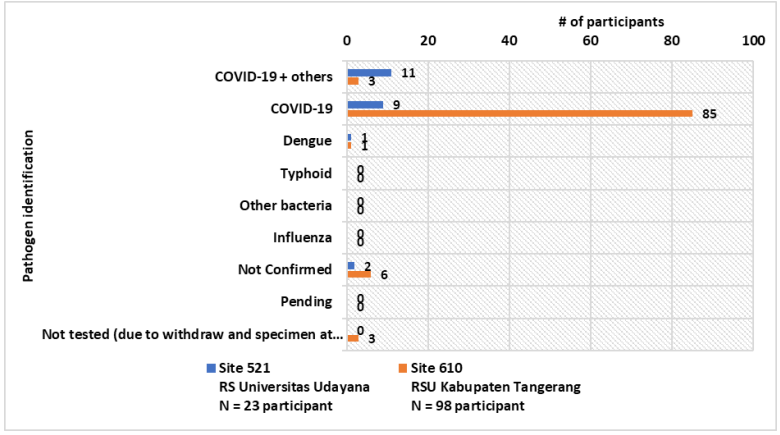
Based on the uploaded CRFs on 23 August 2021, a total of 121 participants were enrolled in ORCHID study, which consisted of 98 participants from site 610 (RSU Kabupaten Tangerang, Tangerang) and 23 participants from site 521 (RS Universitas Udayana, Denpasar). There were 117 participants (97%) who already completed this study, 1 participant passed away during the study, and 3 participants withdrew (figure 1).



Up to 23 August 2021, 108 participants (89%) were identified as positive for SARS-CoV-2, and only 10 participants (8%) were identified as negative for SARS-CoV-2. There were 3 participants not tested due to withdrawal. At site 610, the number of participants identified as positive for SARS-CoV-2 was 88 participants (90%), 7 participants were identified as SARS-CoV-2 negative, and 3 participants were not tested due to withdrawal. While at site 521 there were 20 participants (87%) identified as positive for SARS-CoV-2 and 3 participants (13%) identified as negative SARS-CoV-2 (figure 2).



Based on pathogen identification data, at site 521, 11 participants (48%) were identified as COVID-19 with others, and 9 participants (39%) were identified as COVID-19 only. While at site 610, 85 participants (87%) were identified as COVID-19 only, following 3 participants (3%) identified as COVID-19 with others. 8 participants were not confirmed for any pathogen, consisting of 2 participants at Site 521 and 6 participants at site 610. Only one participant was identified a single infection of Dengue at both sites. An examination cannot be performed for 3 withdrawn participants (figure 3).



The budget re-allocation to the next financial year is expected to cover 200 subjects at the end of the Orchid COVID-19 study with a focused laboratory evaluation; the type of the tests will be determined later based on the available test at the reference laboratory in conjunction with the specific budget.

Ethical approval from NIHRD IRB was granted on August 12, and Site Udayana can now enroll participants. INA-RESPOND Secretariat conducted a refresher training on the study procedures for Site Udayana on 20 August 2021. In addition, training on buffy coat sampling technique was also provided to Site Udayana on 23 August 2021. The site team at Udayana Hospital planned to enroll new patients this week. Meanwhile, the approval document from NIHRD IRB will be notified to the local Tangerang IRB.

INA-RESPOND Newsletter

FROM OUR PARTNER

THE INVITE STUDY: A MULTINATIONAL EFFORT TO UNDERSTAND COVID-19 VACCINE IMMUNOGENICITY

By: Renee Ridzon

Vaccines are one of the greatest triumphs of medicine and are used to prevent and control numerous bacterial and viral infections. While some vaccines have been only recently developed, others have been used for over 100 years, and each year globally, vaccines prevent millions of cases of disease and deaths. Understanding that the most effective intervention to control the global COVID-19 pandemic would be effective vaccines, researchers all over the world have used both established and novel vaccine platforms to develop and test COVID-19 vaccines. These efforts have been fruitful, and at this time there are numerous COVID-19 vaccines that have been proven efficacious in clinical trials and subsequently have been deployed across the globe.

In all cases, COVID-19 vaccines work by inducing antibodies to the receptor binding domain of the virus spike protein. As this is the portion of the virus that binds to human cells and allows entry of the virus, blocking this part of the virus can prevent infection. Vaccines that are currently being administered in many settings include inactivated virus vaccines Sinovac and Sinopharm from China; adenovirus-vectored vaccines CanSino from China, Vaxzevria from AstraZeneca in the UK, and Sputnik V from Russia; and mRNA vaccines Pfizer and Moderna. The Moderna vaccine was co-developed by NIAID.

Knowing vaccine immunogenicity and efficacy in controlled clinical trials is essential. However, understanding immunogenicity in the setting of a national vaccination implementation program is also equally important because populations and conditions of the "real world" do not completely mirror those of clinical trials. Examination of vaccine effectiveness in the context of vaccine roll-out will provide data that can help fill knowledge gaps and better inform best practices for vaccine programs. Important questions include the immunogenicity of vaccines in persons with chronic diseases, other underlying health problems, and pregnancy, as well as the duration of vaccine-induced antibody responses.

The International Study on COVID-19 Vaccine to Assess Immunogenicity, Reactogenicity and Efficacy (InVITE) is a multinational study created by NIAID that will take place in six countries: Democratic Republic of Congo, Guinea, Indonesia, Liberia, Mali, and Mexico. In this study that plans to enroll 3,000 participants total (500 per country), participants who receive a COVID-19 vaccine from the national immunization program will have a blood sample collected at the time of vaccination and several more times over the next year so that the immune response to the vaccine can be measured. Several different vaccines are available in the six countries participating in the study, (see table) and because of this, the researchers will be able to compare immune responses in different settings and to different vaccines. The study will also look for SARS-CoV-2 infections in study participants, allowing for a better understanding of the role of viral variants in causing breakthrough infections after vaccination.

Indonesia has experienced a recent surge in its number of COVID-19 cases, largely due to the import and spread of the delta variant of SARS-CoV-2. This increase in case

Country	Vaccine Name	Vaccine Type
DRC	Oxford/AstraZeneca	adenovirus
Guinea	Sputnik V	adenovirus
Indonesia	Moderna	mRNA
	Oxford/AstraZeneca	adenovirus
	Sinopharm/Beijing	inactivated virus
	Sinovac	inactivated virus
Liberia	Oxford/AstraZeneca	adenovirus
Mali	Oxford/AstraZeneca	adenovirus
Mexico	CanSino	inactivated virus
	Johnson&Johnson	adenovirus
	Oxford/AstraZeneca	adenovirus
	Pfizer/BioNTech	mRNA
	Sinovac	inactivated virus
	Sputnik V	adenovirus

Adapted from: Source information country by country
https://ourworldindata.org/covid-vaccinations

numbers has been accompanied by breakthrough infections in persons who have been previously vaccinated against COVID-19 with two doses of vaccine, generally Sinovac. This observation has raised concerns about the protection afforded against the delta variant by the vaccines currently available in the country. In response to this, the Indonesian Ministry of Health has started administering a booster dose of an mRNA vaccine to persons previously vaccinated, particularly health care workers.

There are scarce data on long-term protection against the delta variant and antibody response of a booster dose of an mRNA vaccine after inactivated virus vaccines. Data on the immunogenicity of combinations of vaccines are much needed and exceedingly important. Because of this, persons receiving these booster doses of vaccine will be included in the Indonesia InVITE study in addition to study participants receiving their first doses of vaccine. This unique data from InVITE will be useful in further informing global policies on the immunogenicity of boosters as well as combinations of different vaccines.

In Indonesia, the study will be led nationally by dr. Karyana, INA-RESPOND Network Director, at Tangerang Hospital by dr. Dewi Lokida, and at TC Hillers Hospital by dr. Asep Purnama. Participants will be recruited from Tangerang Hospital, TC Hillers Hospital, and local puskesmases and mass vaccination centers near these two hospitals. Excitingly, both sites activated on August 17, 2021, to begin enrollment on August 18, making Indonesia the first country to begin screening patients for InVITE.

Vaccination is the most important and effective strategy for combatting the global COVID-19 pandemic. With rising COVID-19 case numbers globally and Indonesia becoming an epicenter for COVID-19 cases in Asia, along with the threat of the highly transmissible delta variant, data on the immune response to COVID-19 vaccination in Indonesia will help the national immunization program best protect its citizens from this global health threat. Any approved vaccine is better than no vaccine, but finding the most effective vaccines and combinations of vaccines will be an important lifesaving tool.

INA-RESPOND
Newsletter

SCIENCE CORNER

NEUTRALIZING MONOCLONAL ANTIBODIES – SOLUTION FOR THE BOTTLENECK OF INEFFECTIVE REPURPOSED ANTIVIRAL DRUGS FOR COVID-19 TREATMENT?

By: Yan Mardian

In the midst of the current COVID-19 pandemic, major efforts have been made to search for effective treatments since the outbreak of the COVID-19 infection in December 2019. Despite the ongoing enrolment of protective vaccines, current supplies are too low to cover worldwide demand in the coming months. This situation has inspired multiple drug repurposing screens to find antiviral therapeutics that can be rapidly used for that purpose. Despite successful benefit shown on re-purposed anti-inflammatory drugs for treatment on the late course of the disease, but no repurposed drugs specifically aimed to inhibit SARS-CoV-2 replication has been found to be effective to date. Therefore, researchers are urgently looking for interventions to prevent new infections, or prevent disease progression, and lessen disease severity for those already infected (**Figure 1**). While vaccines remain the best strategy to prevent COVID-19, neutralizing monoclonal antibodies (mAbs) could potentially benefit certain vulnerable populations before or after exposure to SARS-CoV-2, such as the unvaccinated or recently vaccinated high-risk patients. mAbs can be considered a novel class of antiviral intervention and may be tailored as a new treatment for outpatients with COVID-19 who are at risk of progression to severe disease. Preliminary data also suggest that mAbs may play a role in preventing SARS-CoV-2 infection in household contacts of infected patients and during skilled nursing and assisted living facility outbreaks. Therefore, this writing will focus on mAbs as a potential therapy for COVID-19, with their associated benefit-to-risk ratio, and explain current evidence and recommendations of using anti-SARS-CoV-2 mAbs.

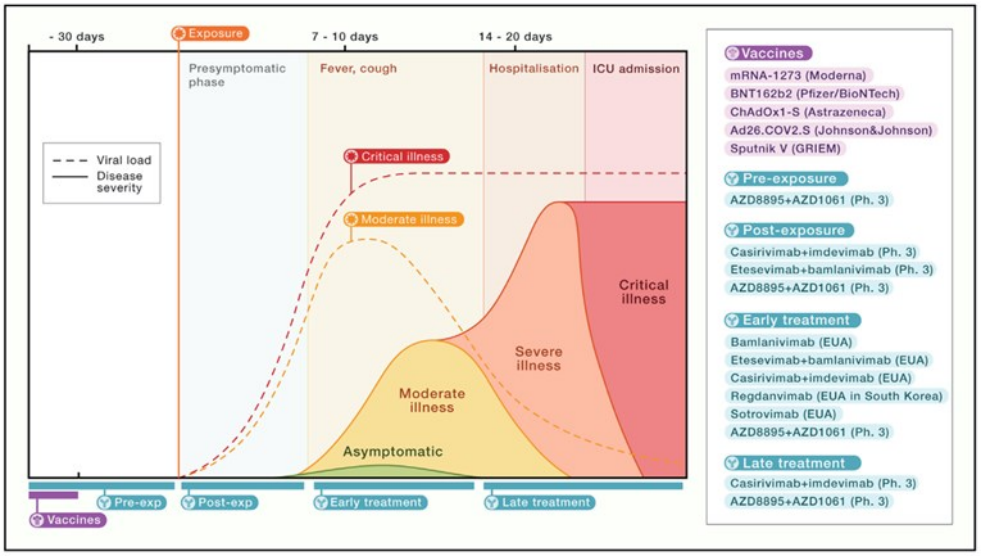


Figure 1. Prophylactic and therapeutic approaches to COVID-19

mAbs as Passive Immunotherapy

One of the strategies considered to block and/or neutralize SARS-CoV-2 is passive immunotherapy. The passive immunization strategies involve infusion antigen-specific mAbs or polyclonal antibodies derived from non-human or human blood products. There are two ways to guarantee passive immunization: (i) via natural antibodies using convalescent plasma therapy (CPT) in which plasma is extracted from a hyperimmune patient and transfused into a COVID-19 patient; or (ii) via antibodies that are biotechnologically designed, i.e., therapeutic mAbs or a cocktail of polyclonal antibodies (pAbs) (**Figure 2**). With careful screening (e.g., to assess for the presence of infectious agents and to establish antibody titer and neutralizing capacity), CPT can be effective with minimal safety risks and can be convenient and adaptable in resource-poor settings. However, the infusion of convalescent plasma in the late stages of the illness has proved unsuccessful at improving patient condition and recent reports CPT appears most efficacious when used early after the onset of symptoms rather than during severe or prolonged infection. Nowadays, there is an increasing focus on replacing CPT with neutralizing mAbs, where dosing to ensure

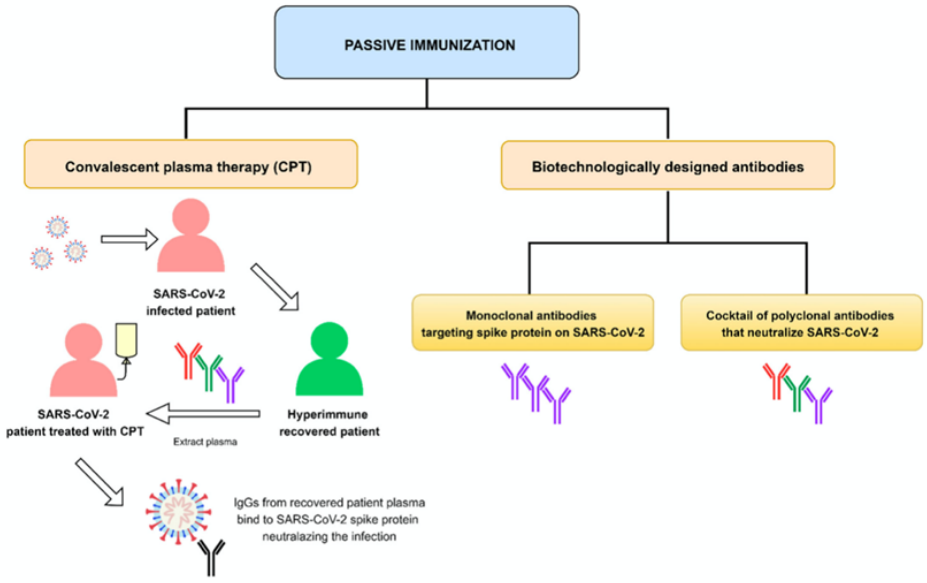


Figure 2. Different strategies to guarantee passive immunization using antibodies.

the appropriate neutralizing capacity of the antibodies can be more precise. In addition, neutralizing mAbs overcome limitations intrinsic to CPT (for example, the risk of blood-borne diseases, time to development of detectable high-affinity antibodies, and risk of low antibody titers, as well as variable epitope specificity). Furthermore, a high titer of neutralizing antibodies — which current evidence indicates is necessary for the efficacy of CPT — is inherent in neutralizing mAbs.

The SARS-CoV-2 genome encodes four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N), as well as nonstructural and accessory proteins. The S protein, composed of 1273 amino acids (aa) and located on the virus surface, is a key component in infection. This protein is composed of two subunits; the S1 subunit (14–685 aa) contains a receptor-binding domain (RBD) that engages with the host cell receptor angiotensin-converting enzyme 2 (ACE-2) and the S2 subunit (686–1273 aa) mediates fusion between the viral and host cell membranes. Through its RBD, S1 attaches to ACE2 on the host cell; this initiates a conformational change in S2 that results in virus-host cell membrane fusion and the consequent release of the viral genome into the host cell. The RBD region is considered a critical target for neutralizing antibodies (nAbs) since it binds the S protein to the cell receptor ACE2. mAbs act by binding to the receptor-binding domain (RBD), therefore inhibiting the union between the virus and the human-ACE2 receptor (**Figure 3**).

Neutralizing mAbs are recombinant proteins derived from the B cells of convalescent patients or humanized mice. High-throughput screening of these B cells permits the identification of antibodies with the necessary specificity and affinity to bind to a virus and block entry of the virus, therefore abrogating pathology associated with productive infection. These mAbs are termed 'neutralizing' and can ultimately be used as passive immunotherapy to minimize virulence (**Figure 4a**). mAbs can directly interfere with viral pathogenesis in multiple ways. First, binding a neutralizing antibody to the virion can prevent target cell binding and/or fusion. Furthermore, antibody binding opsonizes the virions or infected cells for phagocytic uptake. Finally, if viral proteins are intercalated into target cell membranes during viral egress, mAbs can facilitate target cell death via complement fixation and mem-

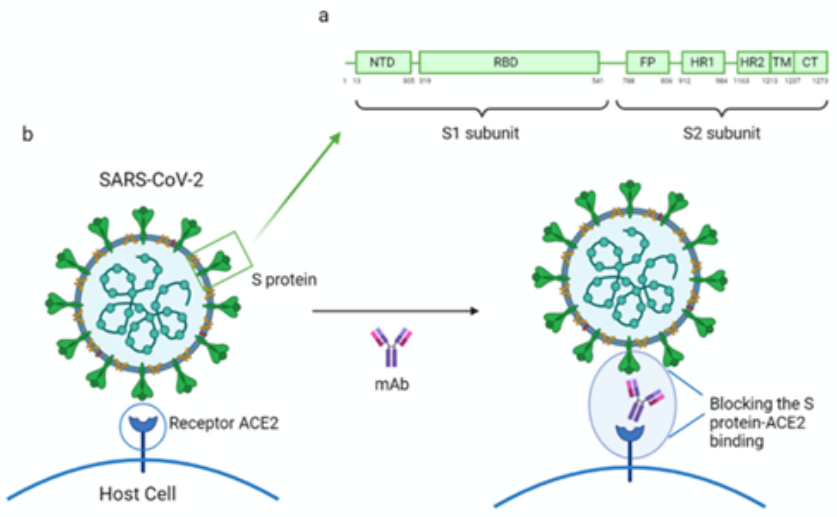


Figure 3. (a) Mechanism of action of a mAbs by blocking the SARS-CoV-2 S protein and human ACE2 receptor binding; (b) structure of the SARS-CoV-2 S protein.

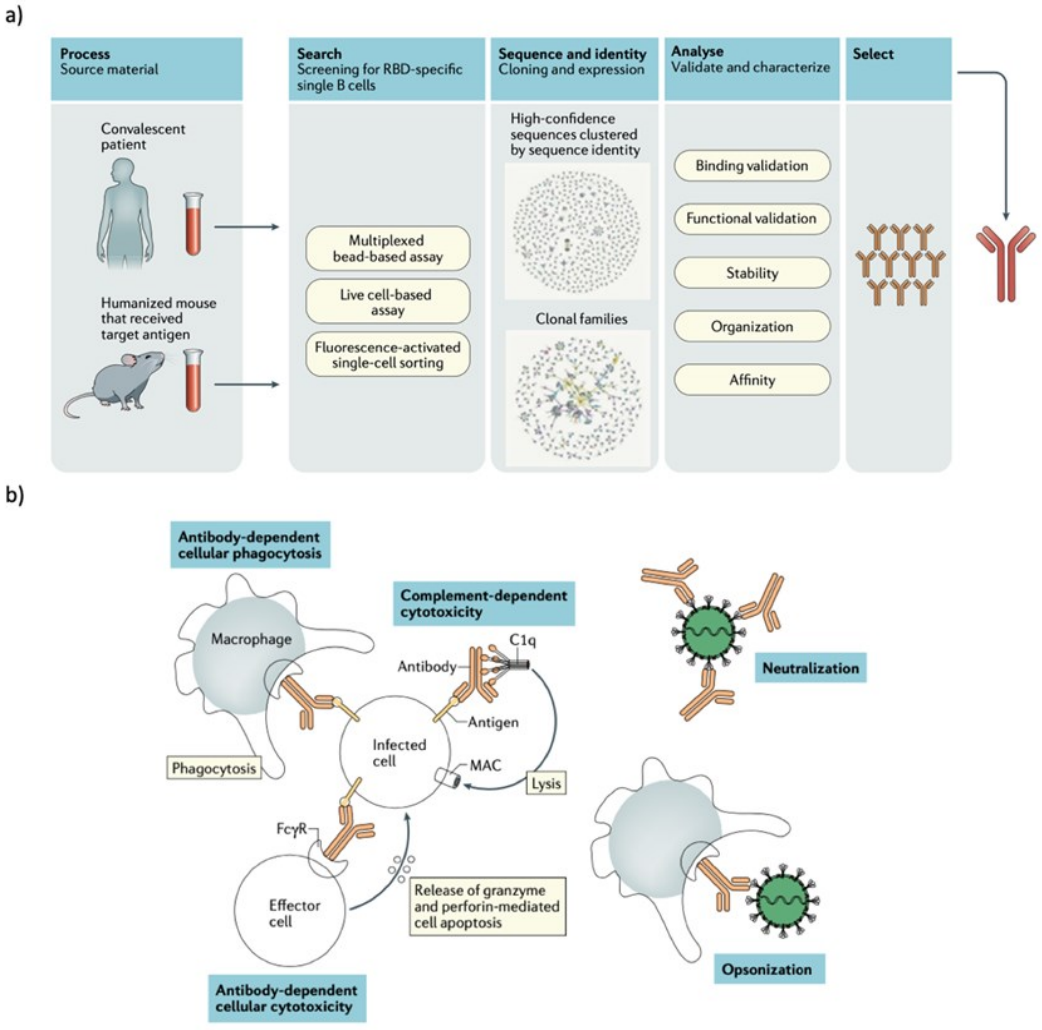


Figure 4. (a) Neutralizing monoclonal antibodies: identification, selection, and production; (b) mechanism of action of mAbs for viral infection

brane attack complex (MAC) activation or antibody-dependent cytotoxicity. These mechanisms may result in apoptosis or necrosis of the infected cell (**Figure 4b**).

Monoclonal Antibody Treatment for COVID-19

The recognition of the urgent need for therapies available on a global scale has prompted the rapid development of a large number of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-neutralizing mAbs. In only 16 months, six mAbs have been developed and received an Emergency Use Authorization (EUA) by the United States or South Korea regulatory agencies (FDA), and several additional ones are being evaluated in phase 3 clinical trials or currently seeking an EUA. An EUA is different from FDA approval and is based on all the available scientific evidence. The potential benefits of the drugs that have received an EUA outweigh the potential risks when used to treat COVID-19 in the authorized population. In randomized, placebo-controlled trials of nonhospitalized patients who had mild to moderate COVID-19 symptoms and certain risk factors for disease progression, the use of anti-SARS-CoV-2 mAbs products reduced the risk of hospitalization and death. In addition, in recently published data, subcutaneous mAbs prevented symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection in previously uninfected household contacts of infected persons. It is worth noting that these studies were conducted before the widespread circulation of Variant of Concern (VoC). The potential impact of these variants on susceptibility to different anti-SARS-CoV-2 monoclonal antibodies will be discussed later.

In addition, mAbs in development display a variety of mutations in the constant Fc region aimed to enhance or eliminate effector functions or improve mAb half-life and are being utilized as monotherapies or cocktails (**Figure 5**). The successes and failures of these trials will be key for the development of additional anti-infective mAbs, at least for respiratory viral pathogens. Although sterilizing immunity may be required for viruses establishing chronic infection, for acute viral infections such as COVID-19, it might be sufficient to blunt viral replication such that the passively administered mAb can act in concert with the host immune response to avoid the development of severe complications and limit onward transmission.

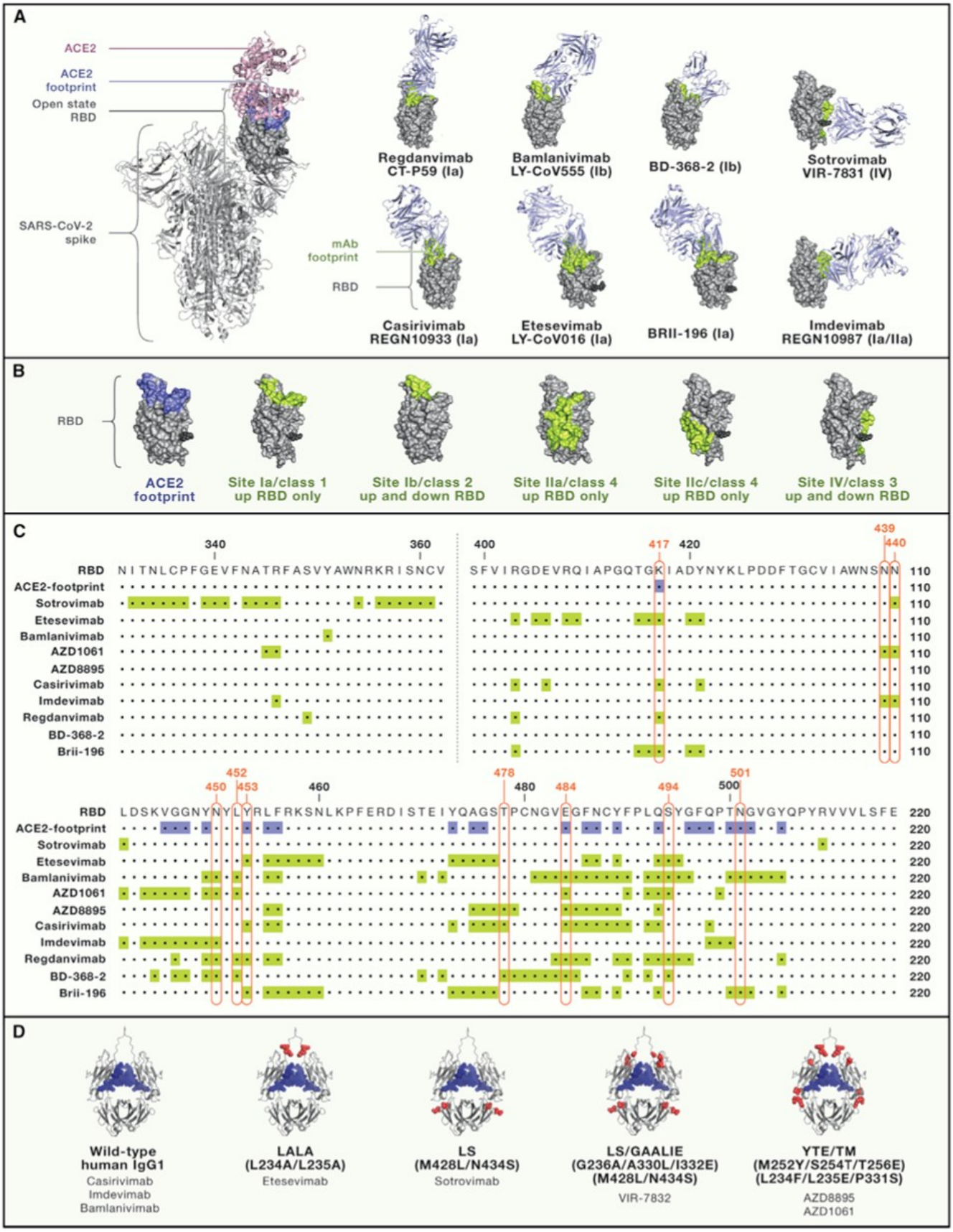


Figure 5. Fab-RBD complexes, epitopes, and Fc mutations of clinically relevant mAbs

Bamlanivimab Plus Etesevimab

The first mAb under clinical trial to receive an EUA (November 09, 2020) from the FDA was bamlanivimab (LY-CoV555), specifically designed to prevent the SARS-CoV-2 S protein from binding to and entering the host cells. Bamlanivimab is a potent neutralizing mAb (IgG1 with an unmodified Fc region) to the S protein derived from the convalescent plasma of a patient who had COVID-19. Bamlanivimab binds the S protein's RBD, engaging its cognate epitope in both up and down conformations, making this antibody potentially useful as a monotherapy. The bamlanivimab EUA is supported by an ongoing, randomized, double-blind, placebo-controlled, single-dose phase 2 clinical trial (NCT04427501) conducted amongst 452 non-hospitalized patients diagnosed with mild or moderate COVID-19. These patients were divided into four groups according to the dose of bamlanivimab or placebo they received via intravenous infusion: (1) 101 patients were assigned to 700 mg of LY-CoV555 monotherapy; (2) 107 patients were assigned to 2800 mg of LY-CoV555 monotherapy; (3) 101 patients were assigned to 7000 mg of LY-CoV555 monotherapy, and (4) 143 patients were assigned to the placebo group. The quantitative virologic endpoints and clinical outcomes were evaluated. The interim analysis (at day 11) showed that the second treatment (group 2) was the only one that appeared to accelerate the natural decline in viral load over time. Moreover, the patients who received LY-CoV555 showed slightly less severe symptoms over the period from day 2 to 6 than those in the placebo group. The percentage of COVID-19 patients who were hospitalized or had to visit an emergency department was lower (1.6%) in the LY-CoV555 patients than in the placebo group (6.3%).

The FDA later issued an EUA (February 09, 2021) for the combined administration of bamlanivimab (LY-CoV555) and etesevimab (LY-CoV016). In a similar way to bamlanivimab, etesevimab is specifically directed against the SARS-CoV-2 S protein and blocks the entry of the virus into the host cells. However, these mAbs bind to different, but overlapping, epitopes within the RBD of the SARS-CoV-2 S protein (**Figure 6**). This EUA relies on an ongoing, phase 2/3, randomized, double-blind, placebo-controlled clinical trial (NCT04427501) in which 577 non-hospitalized patients with mild to moderate COVID-19 symptoms were randomized receive a single infusion of bamlanivimab, the combination treatment, or a placebo. The results drawn from this study conclude that the viral load reduction was statistically significant at day 11 in the combination therapy, compared with the placebo group. Nevertheless, bamlanivimab monotherapy showed no significant improvements in terms of viral load reduction.

On April 16, 2021, the **FDA revoked the EUA** for bamlanivimab monotherapy since there had been an increase across the U.S. in the number of SARS-CoV-2 variants (Gamma (P.1) and Beta (B.1.351) VoC) resistant to this treatment. Therefore, the FDA concluded that the known and potential benefits of bamlanivimab as a monotherapy no longer outweighed its known and potential risks. However, the newest version of the US-NIH (August 4, 2021) guideline recommends against the use of bamlanivimab plus etesevimab to treat COVID-19 and distribute this agent has consequently been paused.

Casirivimab Plus Imdevimab

REGN-COV2 is a combination cocktail of two potent neutralizing mAbs — namely, casirivimab (REGN10933) and imdevimab (REGN10987), which are IgG1 mAbs with unmodified Fc regions. These two mAbs were chosen from a pool of more than 200 neutralizing mAbs present in the initial isolation of thousands of antibodies and were derived from parallel efforts using humanized mice and the sera of patients recovering from COVID-19. The antibodies bind two distinct and non-overlapping sites on the RBD (**Figure 7**). The main reason for employing a cocktail of mAbs was to reduce the risk of treatment-resistant mutant virus emergence. In extensive in vitro testing, this combination re-

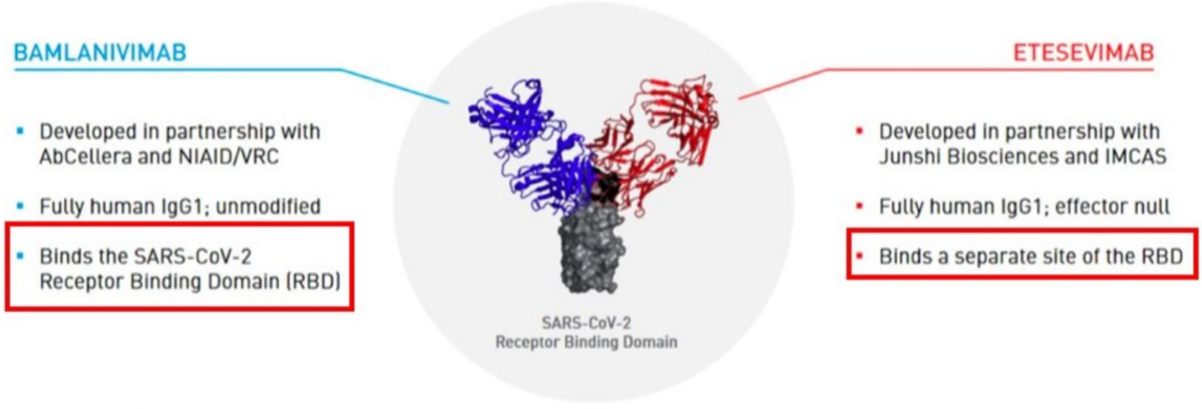


Figure 6. Inhibition of SARS-CoV-2 target cell engagement by Bamlanivimab Plus Etesevimab

tained its ability to neutralize all known S protein mutations. Further, casirivimab and imdevimab combination therapy initiated antibody-mediated cytotoxicity and cellular phagocytosis in virally infected cells in vitro. This product was tested in rhesus macaques and golden hamsters infected with SARS-CoV-2, which serve as models for mild and severe disease, respectively. In both models, prophylactic and therapeutic treatment with combination not only resulted in a reduction in viral load but also diminished the incidence and severity of lung disease relative to placebo.

Given the significant efficacy of REGN-COV2 shown in preclinical studies, a clinical trial (NCT04425629) was carried out in order to evaluate the decrease in viral load in symptomatic non-hospitalized COVID-19 patients and also to assess the safety and efficacy of this therapy. The first 275 patients included in this ongoing, multicenter, randomized, double-blind, phase 1–3 clinical trial were selected to describe the results of the initial analysis. All patients were randomly assigned: (1) 92 patients received 2.4 g of REGN-COV2; (2) 90 patients received 8.0 g of REGN-COV2; and 93 patients received a placebo. Results of the study revealed a reduction in the viral load when using this mAbs cocktail, on the basis of which the FDA decided to issue the EUA for REGN-COV2 on November 21, 2020.

On June 3, 2021, the FDA updated the EUA for casirivimab plus imdevimab. The authorized dosages were reduced from a single IV infusion of casirivimab 1,200 mg plus imdevimab 1,200 mg to casirivimab 600 mg plus imdevimab 600 mg. In addition, these lower doses of casirivimab and imdevimab may now be administered by SQ injection if IV infusions are not feasible or may delay treatment. It should be noted that SQ administration requires four injections (2.5 mL per injection) at four different sites (see the FDA EUA for details). The recommendation for using the lower dose of casirivimab 600 mg plus imdevimab 600 mg IV is based on the Phase 3 results from the R10933-10987-COV-2067 study (ClinicalTrials.gov Identifier NCT04425629). This study is a double-blind, placebo-controlled randomized trial in outpatients with mild to moderate COVID-19. The modified full analysis set included participants aged ≥18 years who had a positive SARS-CoV-2 polymerase chain reaction result at randomization and who had one or more risk factors for progression to severe COVID-19. The primary outcome of COVID-19-related hospitalization or death from any cause was reported in 7 of 736 participants (1.0%) in the casirivimab 600 mg plus imdevimab 600 mg IV arm and in 24 of 748 participants (3.2%) in the placebo arm (P = 0.0024), demonstrating a 2.2% absolute reduction and a 70% relative reduction in hospitalization or death among the casirivimab plus imdevimab recipients compared to the placebo recipients. These results are comparable to the results observed for IV infusions of casirivimab 1,200 mg plus imdevimab 1,200 mg. The primary outcome of COVID-19-related hospitalization or death from any cause was reported in 18 of 1,355 patients (1.3%) who received casirivimab 1,200 mg plus imdevimab 1,200 mg IV, compared with 62 of 1,341 patients (4.6%) who received placebo (P < 0.0001). These findings represent a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death among patients who received this dose of casirivimab plus imdevimab.

Sotrovimab

Sotrovimab is a recombinant engineered human IgG1 monoclonal antibody that binds to a highly conserved epitope on the spike (S) protein receptor binding domain (RBD) of SARS-CoV-2 with high affinity (dissociation constant Kd = 0.21 nM), but does not compete with human ACE-2 receptor binding (**Figure 8**). The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that extends antibody half-life, but does not impact wild-type Fc mediated effector functions in cell culture. There is a potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab. An E340A substitution emerged in cell culture selection of resistant virus and had a >100-fold reduction in activity in a pseudotyped virus-like particle (VLP) assay.

The data that support the EUA for sotrovimab come from the Phase 3 COMET-ICE trial (ClinicalTrials. gov Identifier NCT04545060). The

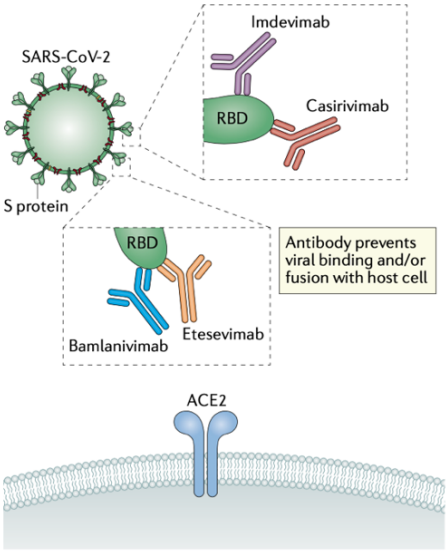


Figure 7. Inhibition of SARS-CoV-2 target cell engagement by neutralizing monoclonal antibodies. Neutralizing monoclonal antibodies (mAbs) being developed to combat COVID-19 are generated against the RBD of the spike S protein of SARS-CoV-2. The anti-RBD mAbs prevent binding of the S protein to its cognate receptor, ACE2 on target host cells. (1) Casirivimab and imdevimab bind distinct epitopes on the RBD with dissociation constants KD of 46 and 47 pM, respectively. Imdevimab binds the S protein RBD from the front or lower-left side, while casirivimab targets the spike-like loop from the top direction (overlapping with the ACE2-binding site. (2) Bamlanivimab and etesevimab bind to distinct, but overlapping, epitopes within the RBD of the S protein of SARS-CoV-2. Bamlanivimab binds an epitope on the RBD in both its open conformation and its closed confirmation with a dissociation constant KD=71pM, covering 7 of the approximately 25 side chains observed to form contact with ACE2. Etesevimab binds the up/active conformation of the RBD with a dissociation constant KD=6.45 nM; it contains the LALA mutation in the Fc region, resulting in null effector function.

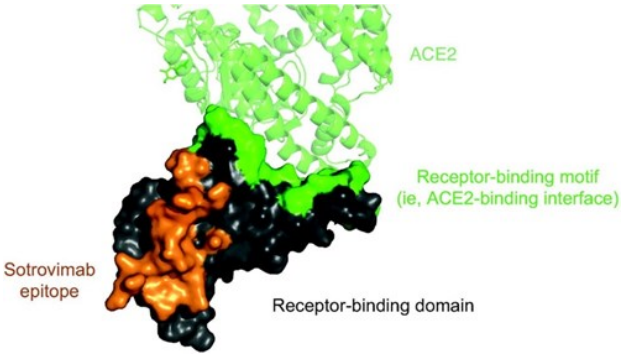


Figure 8. The conserved, pan-sarbecovirus binding site of sotrovimab on the spike protein of SARS-CoV-2.

COMET-ICE trial included outpatients with mild to moderate COVID-19 who were at high risk for progression to severe disease and/or hospitalization. A total of 583 participants were randomized to receive sotrovimab 500 mg IV (n = 291) or placebo (n = 292). The primary endpoint was the proportion of participants who were hospitalized (for ≥24 hours) or who died from any cause by Day 29. Endpoint events occurred in 3 of 291 participants (1%) in the sotrovimab arm and 21 of 292 participants (7%) in the placebo arm (P = 0.002), resulting in a 6% absolute reduction and an 85% relative reduction in hospitalizations or death among the sotrovimab recipients compared to the placebo recipients. An overview of the performed and ongoing clinical trials for all mAbs described is provided **in Table 1** below.

Monoclonal Antibodies for SARS-CoV-2 Variants

RNA viruses, such as SARS-CoV-2, are evolving biological entities. During the first few months of the COVID-19 pandemic, a modest rate of sequence divergence was observed, likely due to the coronavirus exonuclease ''proofreading'' activity enhancing replication fidelity. It is possible that the colossal number of infected patients, with very large estimated local seroprevalence at some locations, has imposed an immune pressure on the virus. In the early phase of the pandemic, the only mutation in S that became prevalent was D614G

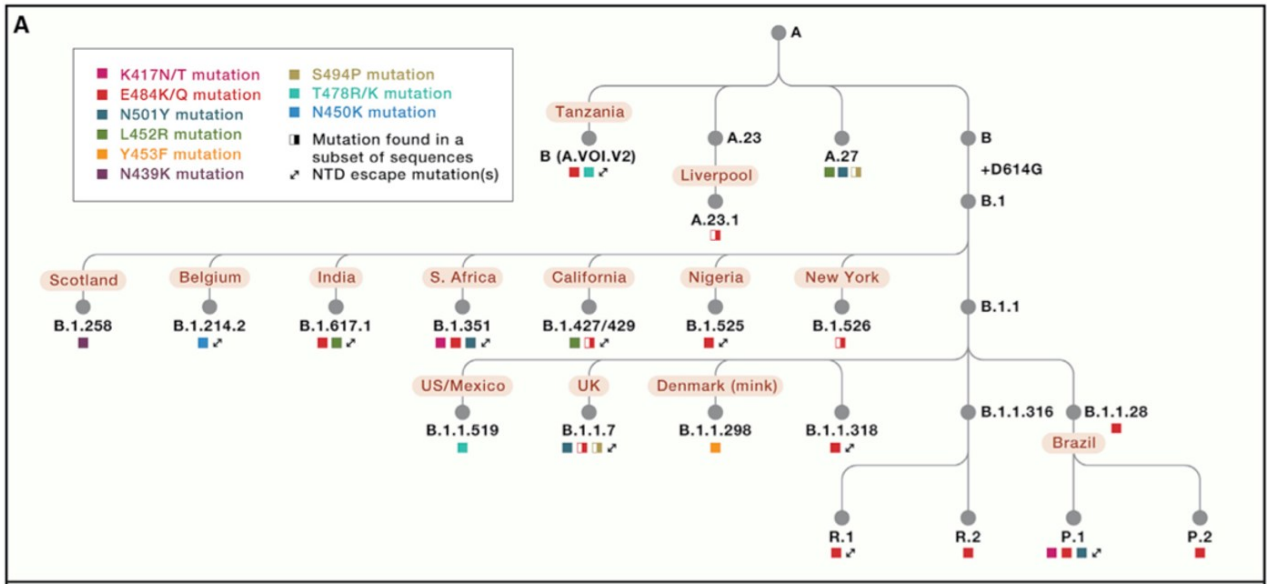
Name	Alternate name(s)	Company	Phase	Clinical trial identifier (disease indication)	Target population	Route	Dose (g)	Study name	Fc	PDB ID	Source and VH germline (% identity)	RBD site	Reference
VIR-7831 VIR-7832	S309 GSK4182136 sotrovimab	Vir Biotechnology GSK	2/3 EUA	NCT04545060 (early treatment)	at-risk adults	IV	0.5	COMET-ICE	LS	7JX3	SARS-CoV-immune donor VH3–23 (96.5%)	IV/class 3	Cathcart et al., 2021; Gupta et al., 2021; Lempp et al., 2021; Pinto et al., 2020; Tortorici et al., 2021
			2	NCT04634409, VIR-7831+ bamlanivimab (early treatment)	adults	IV	0.5 + 0.7	BLAZE-4	LS				
			3	NCT04501978 (late treatment)	hospitalized	IV	0.5	ACTIV-3	LS				
			1b/2a	(UK) (1b–2a) (early treatment) (VIR-7831 versus VIR-7832)	at-risk adults	IV	0.5	AGILE	LS-GAALIE versus LS				
			2	NCT04779879 (safety and pharmacokinetics)	adults	IV/IM	0.5	COMET-PEAK	LS				
REGN-COV2 (REGN10933, REGN10987 not co-formulated)	casirivimab imdevimab	Regeneron	1/2/3	NCT04426695 (late treatment)	hospitalized	IV	2.4 8	Study 2066	WT	6XDG	SARS-CoV-2-immunized hulg mice (REGN10987) and SARS-CoV-2 donor (REGN10987) VH3–11 (98.6%) VH3–30 (98.6%)	Ia/class 1	Baum et al., 2020a, 2020b; Copin et al., 2021; Hansen et al., 2020; Weinreich et al., 2021
			3	NCT04452318 (household contact prevention)	adults/ pediatrics	SC/IM	1.2	Study 2069					
			3	NCT04381936 (late treatment)	12 years and older (hospitalized)	IV	8	RECOVERY					
			1/2/3 EUA	NCT04425629 (early treatment)	adult/pediatrics and pregnant	IV	2.4 8	Study 2067					
			2	NCT04666441 (early treatment dose ranging study)	adults	IV/SC							
			1	NCT04519437 (safety repeat dosing)	adults	SC		Study 2093					
LY-CoV016	CB6, JS016, LY3832479, etesevimab	AbCellera Eli Lilly	N/A	N/A	N/A	N/A	N/A	N/A	LALA	7C01	SARS-CoV-2-immune donor VH3–66 (99.7%)	Ia/class 1	Shi et al., 2020
LY-CoV555	Ab169 LY3819253 bamlanivimab		1	NCT04411628 (healthy volunteer)	adults	IV		BLAZE-5	WT	7KMG	SARS-CoV-2-immune donor VH1–69 (99.7%)	Ib/class 2	Chen et al., 2021a; Gottlieb et al., 2021; ACTIV-3/TICO LY-CoV555 Study Group et al., 2021; Jones et al., 2021
			2	NCT04701658 (early treatment)	12 years and older	IV		BLAZE-5					
			2/3	NCT04518410 (early treatment)	adults	IV		ACTIV-2					
			4	NCT04656691 (early treatment, at-home infusion)	older adults	IV		UNITED					
				NCT04603651 (expanded access)	12 years and older	IV		ACTIV-2					
LY-CoV555 and LY-CoV016	CB6, JS016, LY3832479, etesevimab and Ab169 LY3819253 bamlanivimab		3	NCT04497987 prevention in nursing home residents and staff (post-exposure prophylaxis?)	adults	IV		BLAZE-2					
			EUA	NCT04427501 (early treatment)	12 years and older	IV		BLAZE-1					

AZD7442 (cocktail of AZD8895 and AZD1061)	COV2-2196	AstraZeneca	3	NCT04625725 (pre-exposure prophylaxis)	adults	IM	0.15+0.15	PROVENT	TM/YTE	N/A	SARS-CoV-2-immune donor VH1–58, VH3–15	Ia/class 1 Ib/class 2	Dong et al., 2021; Suryadevara et al., 2021; Zost et al., 2020
	COV2-2130		3	NCT04625972 (post-exposure prophylaxis)	adults	IM	0.15+0.15	STORM CHASER					
			3	NCT04723394 (early treatment)	adults	IM	0.6	TACKLE					
			3	NCT04501978 (late treatment)	hospitalized	IM		ACTIV-3					
BRII-196	1F11	Brii Biosciences	1	NCT04479631 (safety)	healthy volunteers	IV	1		?	7CDI	SARS-CoV-2-immune donor VH3–53 (?)	Ia/class 1	Ju et al., 2020
BRII-198			1	NCT04479644 (safety)	healthy volunteers	IV	1		?	N/A	?		
BRII-196 and BRII-198 combination			2	NCT04770467 (early treatment)	adults	IV							
			3	NCT04501978 (late treatment)	hospitalized	IV	1+1	ACTIV-3					
CT-P59	regdanvimab	Celltrion	2/3 EUA in South Korea	NCT04602000 (early treatment)	at-risk adults	IV	40 mg/kg		?	7CM4	SARS-CoV-2-immune donor VH-70 (?)	Ia/class 1	Du et al., 2020; Kim et al., 2021; Ryu et al., 2021
ADG20	ADG-2 parent ADI-55688	Adagio	1/2/3	NCT04805671 (early treatment)	adults	IM/IV	1 dose		WT/half-life ext. (?)	N/A	SARS-CoV-immune donor VH1–69?	Ia/class 1 IIa/class 4	Dejnirattisai et al., 2021; Rappazzo et al., 2021; Wec et al., 2020
BGB-DXP593	BD-368-2	BeiGene Singlomics	2	NCT04551898 (early treatment)	adults	IV	3 doses		?	7CHH	SARS-CoV-2-immune donor VH3–23 (?)	Ib/class 2	Cao et al., 2020
ABBV-47D11	47D11	AbbVie	1	NCT04644120 (safety and late treatment)	hospitalized	IV	3 doses		?	N/A	SARS-CoV-immunized hulg mice, N/A	?	Wang et al., 2020
ABBV-2B04	2B04								?	N/A	RBD-immunized mice (B6), humanized?	Ia/class 1	Alsoussi et al., 2020; Chen et al., 2021b; Liu et al., 2021b

hulg, humanized immunoglobulin; IV, intravenous; IM, intramuscular; N/A, not available; SC, subcutaneous; WT, wild type.

and was associated with higher viral loads and younger patient age. Since November 2020, SARS-CoV-2 has started to mutate more drastically, with the accumulation of several mutations and deletions in the RBD, NTD, and S2 subunit. This rapid evolution led to the simultaneous appearance of a plethora of SARS- CoV-2 VOCs or variants of interest (VOIs), such as B.1.1.7 (United Kingdom), B.1.351 (South Africa), B.1.525 (Nigeria), B.1.526 (New York), P.1 (Brazil), B.1.427/B.1.429 (California), B.1.258 (Scotland), and A.23.1 (Liverpool). Several mutations found in these VOCs/VOIs are found to reduce or abolish the neutralizing activity of several mAbs, including those already approved or in late stages of development (**Figure 9**)

As shown in figure 9, in laboratory studies, some CDC SARS-CoV-2 VoC or variants of interest (VoI) that harbor certain mutations have markedly reduced susceptibility to various FDA EUA monoclonal antibody therapies. However, the impact of these mutations on the patient's clinical response to anti-SARS- CoV-2 monoclonal antibody combinations varies, as do the proportions of these variants in different geographic regions. The new version of the US-NIH guideline (August, 4th, 2021) has summarize the impact of widely circulated VoCs and VoIs, including delta variant, to mAbs treatment susceptibility (Table 2). Some of the key variants that have been identified are:



B

	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

Figure 9. Mutations on the SARS-CoV-2 S in VOCs and resistance profile of clinical mAbs

- Alpha (B.1.1.7) variant: This VoC retains in vitro susceptibility to all the anti-SARS-CoV-2 monoclonal antibodies currently available through EUAs.
- Beta (B.1.351) variant: This VoC includes the E484K and K417N mutations, which results in a marked reduction in in-vitro susceptibility to bamlanivimab and etesevimab. In vitro studies also suggest that this variant has markedly reduced susceptibility to casirivimab, although the combination of casirivimab and imdevimab appears to retain activity; sotrovimab appears to retain activity as well.
- Gamma (P.1) variant: This VoC includes the E484K and K417T mutations, which results in a marked reduction in-in vitro susceptibility to bamlanivimab and etesevimab.This variant also has reduced susceptibility to casirivimab, although the combination of casirivimab and imdevimab appears to retain activity; sotrovimab appears to retain activity as well.
- Delta (B.1.617.2) variant: This is the predominant VoC now worldwide. The Delta variant contains the L452R mutation, which results in a modest decrease in in-vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not fully known. Sotrovimab and casirivimab plus imdevimab appear to retain activity.
- Epsilon (B.1.429/B.1.427) variant: This VoI (also called 20C/CAL.20C) includes the L452R mutation. There appears to be a modest decrease in in-vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not fully known.5 Sotrovimab and casirivimab plus imdevimab appear to retain activity.
- Iota (B.1.526) variant: This VoI includes the E484K mutation and is associated with a reduced in-vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not fully known. In vitro studies suggest that the E484K mutation may reduce susceptibility to casirivimab,

Table 2. SARS-CoV-2 VoC and VoI and Susceptibility to Anti-SARS-CoV-2 mAbs

WHO Label	Pango Lineage	CDC Variant Class	Notable Mutations	Bamlanivimab Plus Etesevimab		Casirivimab Plus Imdevimab		Sotrovimab	
				In Vitro Susceptibility[a]	Activity[b]	In Vitro Susceptibility[a]	Activity[b]	In Vitro Susceptibility[a]	Activity[b]
Alpha	B.1.1.7	VoC	N501Y	No change	Active	No change	Active	No change	Active
Beta	B.1.351	VoC	K417N, E484K, N501Y	Marked change	Unlikely to be active	No change[c]	Active	No change	Active
Gamma	P.1	VoC	K417T, E484K, N501Y	Marked change	Unlikely to be active	No change[c]	Active	No change	Active
Delta	B.1.617.2	VoC	L452R	Modest change[d]	Likely to be active	No change	Active	No change	Active
Epsilon	B.1.429 / B.1.427	VoI	L452R	Modest change[d]	Likely to be active	No change	Active	No change	Active
Iota	B.1.526	VoI	E484K	Modest change[d]	Likely to be active	No change[c]	Active	No change	Active

[a] Based on the fold reduction in susceptibility reported in the FDA EUAs.[5-7]

[b] Anticipated clinical activity against the variant, based on in vitro studies.

[c] Marked change for casirivimab and no change for imdevimab. The combination of casirivimab plus imdevimab appears to retain activity.

[d] Modest change for the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not fully known.

Key: CDC = Centers for Disease Control and Prevention; VoC = variant of concern; VoI = variant of interest; WHO = World Health Organization

although the combination of casirivimab and imdevimab appears to retain activity; sotrovimab appears to retain activity as well.

Potential Risks of Monoclonal Antibodies

Some patients could experience either an allergic or nonallergic infusion-related reaction. Both reactions are due to activation of the immune system in response to the antibody but occur in different ways. Infusion-related reactions seem to be rare but can cause flushing, itching, shortness of breath, or low blood pressure. There are also potential side effects of receiving any IV medication, including pain, soreness, or bruising around the IV site.

Who Should Have Monoclonal Antibody Treatment?

Although researchers are still learning which patients with COVID-19 are most likely to benefit from monoclonal antibody therapy, early data suggest greater benefit in high-risk patients, including those older than 65 years, with a suppressed immune system, or with certain medical conditions, including obesity. Monoclonal antibodies are intended for patients recently diagnosed with COVID-19 who are not sick enough to be in the hospital but have some risk factors for severe infection. Giving the infusion as early as possible in the course of infection is important, so patients should seek medical care and testing as soon as they develop symptoms. It remains a tenet that antivirals, whether small molecules or neutralizing mAbs, work best when deployed early. By extrapolation from early viral load data, ideally, patients would receive treatment as soon as possible (that is, within hours to days following a positive test or symptom onset). In the trial setting, by day 7 to day 11, most patients either are progressing towards clearance of the virus24 or have experienced clinical decline and hospitalization, further emphasizing the need for early intervention. As the clinical trial timelines typically represent an offset of several days from initial diagnosis, corresponding to day 10 –14 of clinical illness, the actionable message remains unchanged — treat patients as early as possible to maximize the chance of altering the disease trajectory and promote recovery.

The strength of the evidence for using anti-SARS-CoV-2 monoclonal antibodies varies depending on the factors that place patients at high risk for progression to severe COVID-19 and/or hospitalization. The recommendations for treatment are based on the following criteria from the FDA EUAs:

Medical Conditions or Other Factors That Were Represented in Clinical Trials That Evaluated Anti-SARS-CoV-2 Monoclonal Antibodies

* Aged ≥65 years (AIIa)
* Obesity (BMI >30) (AIIa)
* Diabetes (AIIa)
* Cardiovascular disease (including congenital heart disease) or hypertension (AIIa)
* Chronic lung diseases (e.g., chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension) (AIIa)

Other Conditions or Factors That Had Limited Representation in Clinical Trials but Are Considered Risk Factors for Progression to Severe COVID-19 by the Centers for Disease Control and Prevention

* An immunocompromising condition or immunosuppressive treatment (AIII). Many experts strongly recommend therapy for patients with these conditions, despite their limited representation in clinical trials.
* Being overweight (BMI 25–30) as the sole risk factor (BIII)
* Chronic kidney disease (BIII)
* Pregnancy (BIII)
* Sickle cell disease (BIII)
* Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies) (BIII)
* Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation that is not related to COVID-19) (BIII)

It is important to note that the likelihood of developing severe COVID-19 increases when a person has multiple high-risk conditions or comorbidities. Other factors (e.g., race or ethnicity) or medical conditions may also place individual patients at high risk for progression to severe COVID-19. The current EUAs state that the use of anti-SARS-CoV-2 monoclonal antibodies may be considered for many of these other patients.

Conclusion:

Although mAb production is time-consuming and expensive, especially for use against new pathogens, they have been regarded as a good option for the treatment of COVID-19. However, the outcomes of clinical trials for non-SARS- CoV-2 specific mAbs are proving controversial, as their efficacy has yet to be definitively demonstrated, whilst SARS-CoV-2 specific mAbs have demonstrated significant levels of efficacy. Neutralizing mAbs, particularly in combination with other medications, are an attractive approach with potential utility in both prophylactic and treatment settings. Encouraging early clinical trial data support further investigation of neutralizing mAbs to determine the optimal dosing regimen. Unanswered questions regarding this novel therapeutic approach set a pressing research agenda; we need to establish which at-risk individuals would benefit most from prophylactic neutralizing mAbs, the duration of protection offered by these mAbs, and any potential impact of mAb therapy on subsequent vaccination. It will also be important to determine the optimum timing for the administration of neutralizing mAbs on the basis of viral load, serology, and other potential clinical factors.

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INA-RESPOND Newsletter

KEEPING CHILDREN ACTIVE DURING THE COVID-19 PANDEMIC

By: Monica Surjanto

Introduction

Due to the COVID-19 pandemic, children and adolescents might engage in less physical activity and accumulate more sedentary behavior, including recreational screen-time.1 Children no longer had access to school based physical activities such as physical education, and walking to/from school. They spend almost all day just stay at home. Insufficient physical activity and excessive sedentary behavior among children represents a significant problem because health behavior patterns in childhood are likely to persist into adulthood and can lead to increased risk for a number of serious health conditions (e.g., overweight/obesity, type II diabetes, and metabolic syndrome) in later childhood and adulthood.2

Among children and young people, there are evidence suggesting that physical activity is important for health and well-being. Physical activity might improve not only cardiorespiratory and muscular fitness, cardio-metabolic health, bone health, weight status, and cognition, but also reduce the risk of depression.1

Therefore, it is important for children to do physical activity daily even in the Pandemic situation.

Recommendation physical activity for children and adolescents (aged 5-17 years)

Based on World Health Organization (WHO), it is recommended that children and adolescents should do at least an average of 60 minutes per day of moderate to vigorous-intensity, mostly aerobic, physical activity, across the week, and at least 3 days a week for muscle and bone strengthening exercise.

It's also stated that:

Doing some physical activity is better than doing none.

If children and adolescents are not meeting the recommendations, doing some physical activity will benefit their health.

Children and adolescents should start by doing small amounts of physical activity, and gradually increase the frequency, intensity, and duration over time.

It is important to provide all children and adolescents with safe and equitable opportunities, and encouragement, to participate in physical activities that are enjoyable, offer variety, and are appropriate for their age and ability.

Children and adolescents should limit the amount of time spent being sedentary, particularly the amount of recreational screen time.

The Challenges in Pandemic Era

Strategies to promote adequate physical activity of children during the pandemic need to be determined. Several studies have recognized the importance of home-based physical activity during the COVID-19 pandemic. Hammami et al suggested that those who safely and easily can access outdoor environments, such as parks and fields or similar, are recommended to use these to engage in physical activity. It has also been recognized that parents can be physically active with children, through play and exercise, and that many activities can be performed with family members.1

Schools should continue to maintain a physical

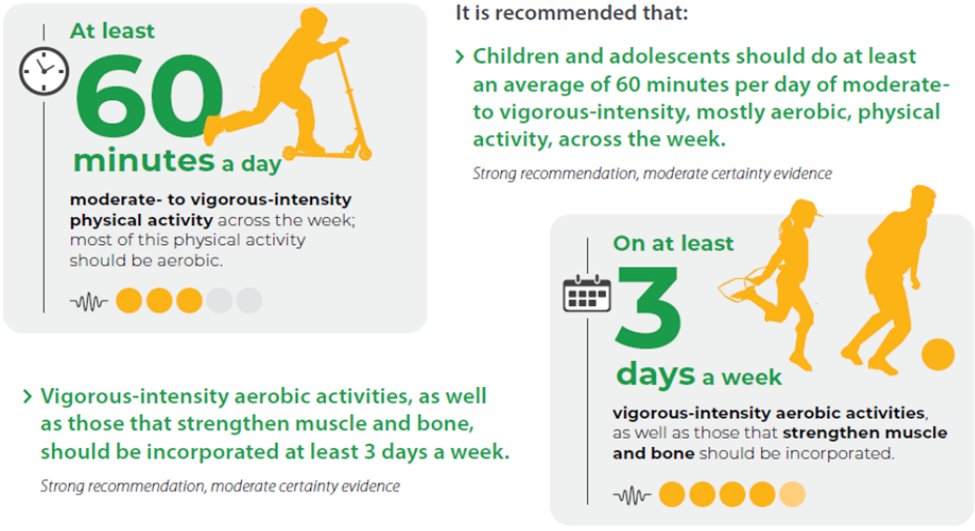

Fig1. Recommendation physical activity for children and adolescents3

exercise requirement as a critical educational component during the pandemic. For those schooling remotely, it is critical to prioritize online learning options in the school curriculum and provide access to physical activity promoting materials.4

Suggestions and recommendations of physical activities

Recommended activities that can be done by children and families, such as: walking (outdoor or at home), jogging, running (outdoor or on the spot at home), bicycling, stair climbing, lifting, and doing household tasks. Some household objects can be used as exercise equipment: broomstick, ropes, towels, water-filled bottles, backpacks, books, and furniture. Several papers suggested that health technologies could be used to facilitate physical activity, including videos or smartphone application-guided exercise programs, wearable sensors (e.g., pedometers), and online communication. It has also been acknowledged that active video games might be an appropriate approach to engage in physical activity.1

American Heart Association gives some examples for activities that can be done at home with family members. (Fig 2)

Fig 2. 25 ways to get moving at home5

Safety measures and precautions while being physically active

In terms of safety measures and precautions, it is recommended to pursue safe environments, maintain social distance, and avoid crowded environments. Others recommended to frequently sanitize exercise equipment (e.g., elastic bands, dumbbells and barbells, foam rollers, yoga blocks, and mats), and avoiding sharing bottles, using cellphones during exercise in shared indoor environments, as well as not allow children to climb on park equipment, slides, and outdoor fitness equipment, since they might provide a surface for coronavirus transmission. Parents were encouraged to practice hygiene with children, such as covering the mouth and nose when coughing and sneezing, avoid touching their eyes, nose, and mouth with unwashed hands. Also, to frequently wash hands, discourage handshakes with peers, and frequently sanitize sport or exercise equipment at home.1

Conclusion

All children are encouraged to be active during the pandemic. This is a big challenge for schools and especially parents to keep children active and reduce the sedentary behaviors. Parents should be a positive role model for children so the children will follow them. However, caution is required, and it is important to undertake safety measures and precautions, such as pursue safe environments, maintain social distance, and avoid crowded environments. In addition, it is important to facilitate hygiene, and interrupt exercise programs in the event of fever or signs of COVID-19.

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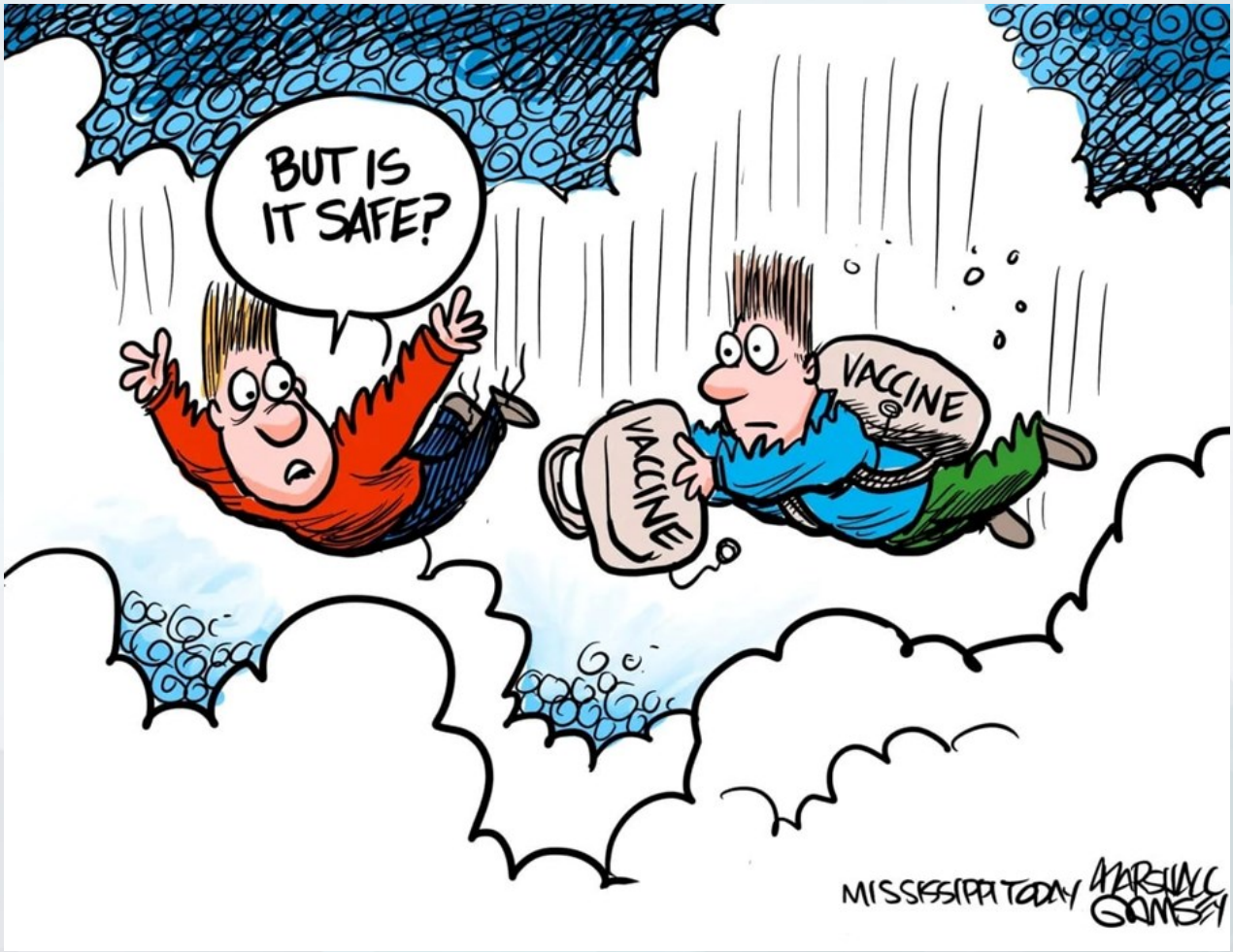
INA-RESPOND Newsletter

COVID-19 VACCINE ACCEPTANCE: IS COMMON SENSE STILL COMMON?

By: Aly Diana

COMIC CORNER



Addressing the drivers of vaccine hesitancy and the barriers to vaccine acceptance is a complex but important task. While the percentage of hesitant does vary from country to country and in time few, if any, countries are ever free from this problem. Overcoming hesitancy requires detection, diagnosis, and tailored intervention as there is no simple strategy that can address all the barriers to vaccine acceptance. Immunization program managers and health care workers need to become adept at recognizing and tackling hesitancy in all its incarnations if high levels of vaccine acceptance are to be achieved but must also actively support immunization acceptors to build and support vaccine acceptance resiliency.

Factors that affect the attitude towards acceptance of vaccination include complacency, convenience, and confidence. Complacency denotes the low perception of the disease risk; hence, vaccination was deemed unnecessary. Confidence refers to the trust in vaccination safety, effectiveness, besides the competence of the healthcare systems. Convenience entails the availability, affordability, and delivery of vaccines in a comfortable context. The complex

nature of motives behind vaccine hesitancy can be analysed using the epidemiologic triad of environmental, agent and host factors. Environmental factors include public health policies, social factors and the messages spread by the media. The agent (vaccine and disease) factors involve the perception of vaccine safety and effectiveness, besides the perceived susceptibility to the disease. Host factors are dependent on knowledge, previous experience, educational and income levels.

Studies on COVID-19 vaccine acceptance rates were collected from 33 different countries. Dates of survey distribution ranged from February 2020 until December 2020. Among adults representing the general public, the highest COVID-19 vaccine acceptance rates were found in Ecuador (97.0%), Malaysia (94.3%), Indonesia (93.3%) and China (91.3%).

The lowest COVID-19 vaccine acceptance rates were found in Kuwait (23.6%), Jordan (28.4%), Italy (53.7), Russia (54.9%), Poland (56.3%), and France (58.9%). For the vaccine acceptance rates in the US, it was 56.9% in April, and ranged from 67.0% to 75.0% in May, and reached 75.4% in June 2020.

However, the acceptance rate most likely related to the effectiveness of the vaccine. In Indonesia, 93.3% would like to be vaccinated for a 95% effective vaccine, but this acceptance decreased to 67.0% for a vaccine with 50% effectiveness. It should be noted that the acceptance rate was measured under the presumption that the vaccine was provided freely by the government. Therefore, in the case that the vaccine needs to be purchased, or if it is not fully subsided by government, analyses assessing the acceptance at certain vaccine prices (i.e., willingness to pay) will need to be conducted.

A more recent survey conducted in December 2020 to 9 February 2021 in 9 low- and middle-income countries, 76.4% were willing to be vaccinated if the vaccine was at least 90% effective, and 88.8% if the vaccine was at least 95% effective. Increased levels of fear/worry about being infected with COVID-19 consistently predicted higher odds of willingness to take the vaccine. Vaccine acceptance was also positively associated with COVID-19 knowledge, worry/fear regarding COVID-19, higher income, younger age, and testing negative for COVID-19. The main reasons underpinning vaccine refusal were fear of side effects (41.2%) and lack of confidence in vaccine effectiveness (15.1%).

Unfortunately, most surveys were conducted using hypothetical vaccine and before the delta variant hit the world. Data were mainly collected online and not representative of countries. Hopefully, the actual acceptance rates are higher than reported here. One thing though, in the US (where COVID-19 vaccines are widely available for free), in mid-August 2021, only 50.7% of total population was fully vaccinated. Again, I am still hopeful. The distribution of strategically placed public health information regarding COVID-19 vaccination, delivered in locally customized and culturally appropriate language, may be instrumental in increasing the general public's willingness to take the COVID-19 vaccine.

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