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# Editorial: Post-Exposure Prophylactic Neutralizing Monoclonal Antibodies to SARS-CoV-2 for Individuals at High Risk for COVID-19

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**Abstract** Regulatory authorities, including the US Food and Drug Administration (FDA), have accelerated diagnostic and therapeutic approvals during the coronavirus disease 2019 (COVID-19) pandemic. Accelerated clinical development and approvals have resulted in vaccine programs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, some individuals remain at high risk for the progression of COVID-19. In the US, the FDA has given Emergency Use Authorization (EUA) for two neutralizing therapeutic monoclonal antibody 'cocktails,' casirivimab and imdevimab (REGEN-COV), bamlanivimab and etesevimab, and one monotherapy, bamlanivimab, for prophylactic post-exposure therapy in individuals at high risk of progressing to severe COVID-19. Preclinical and clinical studies showed consistent effectiveness of REGEN-COV against current variants of SARS-CoV-2. On 21st November 2020, the FDA approved an initial EUA for REGEN-COV to treat mild to moderate COVID-19 in adults and in children 12 years or older with exposure to SARS-CoV-2 at high risk for progression to severe COVID-19. On 30th July 2021, the FDA updated its EUA for REGEN-COV for emergency use as post-exposure prophylactic to prevent COVID-19 progression in adults and children aged 12 years or older. This Editorial aims to provide an update on accelerated regulatory authorization for post-exposure prophylactic neutralizing monoclonal antibodies to SARS-CoV-2 for individuals at high risk for COVID-19.

**Keywords:** **Editorial • Severe Acute Respiratory Syndrome Coronavirus 2 • COVID-19 • Antibodies, Bispecific • Post-Exposure Prophylaxis**

The US Food and Drug Administration (FDA) approves the compassionate use of as yet unapproved therapeutics awaiting clinical trials through the Expanded Access (EA) Program [1]. The FDA also allows Emergency Use Authorization (EUA) to experimental therapies or those having undergone preliminary safety and efficacy studies [1]. Both EA and EUA programs in the US, and similar accelerated authorization programs in other countries, have been increasingly implemented during the coronavirus disease 2019 (COVID-19) pandemic [1]. In the past year, vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been at the forefront of clinical development during the COVID-19 pandemic [1,2]. Also, antiviral agents, treatments to reduce the severity of COVID-19, and therapeutic monoclonal antibody therapies have undergone accelerated approvals worldwide [1,3]. The latest approach to controlling the severity of the clinical effects of SARS-CoV-2, which is now endemic among populations who may not be vaccinated or be clinically vulnerable, would be to neutralize the antibody in recently infected or exposed individuals [4].

In response to the COVID-19 pandemic, during the past 18 months, accelerated clinical development, clinical trials, and regulatory approvals have resulted in vaccination programs being implemented worldwide. Advances in genomic identification of variants of SARS-CoV-2 may result in refinements to vaccines to maintain their effectiveness. However, high-risk groups include individuals who are not fully vaccinated, have comorbidities, or are immunosuppressed [5,6]. Individuals who live in closed communities, large households, and institutions such as care homes are at increased risk of viral exposure and progression to severe COVID-19 [7,8].

Testing for SARS-CoV-2 has become widely available, as are mobile phone applications that alert or trace any contact with SARS-CoV-2-positive individuals [9]. The Centers for Disease Control and Prevention (CDC) in the US has defined the meaning of 'close contact' during the COVID-19 pandemic as the contact for 15 minutes or more during 24 hours within 6 feet (or 2 metres) of an infected individual who has laboratory-confirmed





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SARS-CoV-2 infection, or a clinically compatible illness [10]. Therefore, the time has come for an approach for post-exposure infection prophylaxis for high-risk individuals [4]. SARS-CoV-2 neutralizing antibody therapeutics is the logical next step [4].

Neutralizing monoclonal antibodies to SARS-CoV-2 to prevent COVID-19 or disease progression in hospitalized or ambulatory patients have recently undergone clinical trials and accelerated regulatory approvals. Currently, there are two therapeutic monoclonal antibody cocktails, casirivimab and imdevimab (REGEN-COV), bamlanivimab and etesevimab, and one monotherapy, bamlanivimab, which have received EUA by the FDA as prophylactic therapy in individuals at high risk of progressing to severe COVID-19 [4]. The European Medicines Agency (EMA) has also recommended the two monoclonal antibody 'cocktails' and one monotherapy to prevent disease progression in patients with COVID-19 not requiring supplemental oxygen but at high risk of progression to severe COVID-19 [4]. Neutralizing therapeutic monoclonal antibodies as a prophylactic approach to prevention or reduction of progression of COVID-19 is a welcome development. However, continued monitoring is required to determine whether all new vaccines and therapies protect against identified variants of concern (VOC) and variants of interest (VOI) of SARS-CoV-2 [11].

Studies are ongoing to determine whether mutations involving the SARS-CoV-2 spike protein may allow the virus to 'escape' the effects of neutralizing prophylactic antibodies [4]. Currently, preclinical and clinical studies have shown consistent effectiveness against current variants of SARS-CoV-2 for the casirivimab and imdevimab (REGEN-COV) monoclonal antibody 'cocktail' [12].

On 21st November 2020, the FDA approved an initial EUA for the therapeutic use of a monoclonal antibody 'cocktail,' REGEN-COV, which combines two monoclonal antibodies designed to attach to the spike protein of SARS-CoV-2 at two different sites, casirivimab and imdevimab [13]. The initial EUA was for the use of combined intravenous infusion of casirivimab and imdevimab to treat mild to moderate COVID-19 in adults and children 12 years of age or older with a positive direct test for SARS-CoV-2 at high risk for progression to severe COVID-19 [13]. Individuals at increased risk for COVID-19 progression include those 65 years of age or older, with chronic comorbidities, or who are immunosuppressed [13]. This initial therapeutic EUA for REGEN-COV was given following the findings from a double-blind, placebo-controlled, phase 1/3 trial that included 275 non-hospitalized patients with COVID-19 (NCT04425629) [14]. The interim analysis showed that the REGEN-COV antibody 'cocktail,' formerly known as REGN-COV2, reduced the viral load of SARS-CoV-2 in infected individuals [14]. REGEN-COV had a greater effect in patients who had yet to initiate a humoral response to SARS-CoV-2 infection or had a high viral load at baseline [14]. There were no differences in safety outcomes between the REGEN-COV dose group and the placebo group [14]. Combined intravenous administration of casirivimab and imdevimab (REGEN-COV) reduced visits to the emergency room and reduced hospitalization within 28 days following treatment compared with placebo [14].

The safety and effectiveness of the investigational therapy, REGEN-COV, continues to be evaluated. The combined therapeutic 'cocktail' of asirivimab and imdevimab is not authorized for hospitalized patients with COVID-19, or those on oxygen therapy, as there is currently no evidence from controlled clinical trials to support therapeutic use in this patient group [13]. However, since November 2020, further investigational clinical studies have resulted in a new approach to prophylactic monoclonal antibody therapy in high-risk patients.

On 30th July 2021, the FDA updated its EUA for the REGEN-COV monoclonal antibody 'cocktail,' with combined subcutaneous administration, for emergency use as post-exposure prophylactic to prevent COVID-19 in adults and children aged 12 years or older [15]. Individuals suitable for this preventive therapy include those at high risk for progression to severe COVID-19 (including hospitalization or death) in those not fully vaccinated or who may not develop an adequate immune response to current vaccines [15]. REGEN-COV is not authorized as pre-exposure prophylaxis but only after exposure to SARS-CoV-2 [15]. This re-issued EUA was supported by the findings from a phase 3 randomized, placebo-controlled clinical trial that studied the effects of a single dose of REGEN-COV to prevent COVID-19 (NCT04452318) [16]. The study participants in this trial were household contacts of individuals who tested positive for SARS-CoV-2 infection identified by real-time reverse transcription-polymerase chain reaction (RT-PCR) [16]. Subcutaneous administration of the REGEN-COV 'cocktail' resulted in an 81% reduction in confirmed symptomatic cases of COVID-19 compared with placebo cases at day 29 [16]. The most common reported side effect was an injection site reaction in 1% of cases [16].

The FDA has advised health care professionals that the authorized dose for REGEN-COV (casirivimab and imdevimab) for post-exposure prophylaxis, is 600 mg of casirivimab and 600 mg of imdevimab when administered together [17]. The FDA has also advised that REGEN-COV is indicated for post-exposure prophylaxis of COVID-19 in individuals who have a high risk for progression to severe COVID-19 [17]. This high-risk group includes individuals who are not fully vaccinated, or within two weeks of vaccination, or not expected to develop an adequate immune response due to conditions associated with immunosuppression [17]. The FDA has also drawn attention to the increased risk of vulnerable groups in institutions that include nursing homes and prisons [17]. Also, health





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care providers are advised that post-exposure neutralizing antibody therapy with REGEN-COV should not be regarded as a substitute for vaccination [17]. Clinical experience from health care providers on the practical use of this new post-exposure prophylactic neutralizing monoclonal antibody 'cocktail' will be of interest this year.

## Conclusions

The COVID-19 pandemic has driven accelerated clinical development and evaluation of clinical trial data, resulting in rapid regulatory evaluation and approvals. In parallel with vaccine development and therapeutic monoclonal antibodies, genomic analysis of emerging variants of SARS-CoV-2 has allowed the rapid development of effective post-exposure prophylactic neutralizing monoclonal antibodies. How these SARS-CoV-2 neutralizing antibodies may be used in clinical practice awaits the findings from real-world studies in high-risk populations.

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