Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

# und

# Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

## Vorgang: 2022-B-164 Tixagevimab/Cilgavimab

Stand: September 2022

## I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

| **Tixagevimab/Cilgavimab<br>Präexpositionsprophylaxe von COVID-19**<br><br>**Kriterien gemäß 5. Kapitel § 6 VerfO** | |
|---|---|
| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“ |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | nicht angezeigt |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | Es liegen keine Beschlüsse vor. |
| Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören. | *Siehe systematische Literaturrecherche* |

## II. Zugelassene Arzneimittel im Anwendungsgebiet

| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet** |
|---|---|
| Zu bewertendes Arzneimittel: | |
| Tixagevimab/<br>Cilgavimab<br>N/N<br>EVUSHELD™ | Zugelassenes Anwendungsgebiet:<br>„EVUSHELD wird angewendet zur Präexpositionsprophylaxe einer Coronavirus-19-Erkrankung (coronavirus disease 2019, COVID-19) bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht (siehe Abschnitte 4.2, 5.1 und 5.2).“ |
| Casirivimab/<br>Imdevimab<br>N/N<br>Ronapreve® | - Behandlung einer Coronavirus-2019-Erkrankung (COVID-19) bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht, die keine zusätzliche Sauerstofftherapie benötigen und bei denen ein erhöhtes Risiko für einen schweren Verlauf von COVID-19 besteht.<br>- Prophylaxe von COVID-19 bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht. |

Gemeinsamer Bundesausschuss

## Abteilung Fachberatung Medizin

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

# Vorgang: 2022-B-164 (Tixagevimab/Cilgavimab)

| | |
|---|---|
| Auftrag von: | Abt. AM |
| Bearbeitet von: | Abt. FB Med |
| Datum: | 2. August 2022 |

# Inhaltsverzeichnis

# Abkürzungsverzeichnis

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|---|---|
| AE | adverse event |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| G-BA | Gemeinsamer Bundesausschuss |
| GIN | Guidelines International Network |
| GoR | Grade of Recommendations |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluation |
| HR | Hazard Ratio |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| KI | Konfidenzintervall |
| LoE | Level of Evidence |
| mAbs | monoclonal antibodies |
| NICE | National Institute for Health and Care Excellence |
| PrEP | pre-exposure prophylaxis |
| OR | Odds Ratio |
| RR | Relatives Risiko |
| SAE | serious adverse event |
| SIGN | Scottish Intercollegiate Guidelines Network |
| TRIP | Turn Research into Practice Database |
| WHO | World Health Organization |

# 1 Indikation

Präexpositionsprophylaxe einer Coronavirus-19-Erkrankung (coronavirus disease 2019, COVID-19) bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht

*Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.*

# 2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Prä- oder Post-Expositions-Prophylaxe einer COVID-19-Erkrankung* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 25.06.2021 durchgeführt, die folgende am 20.07.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 1993 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 4 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

# 3 Ergebnisse

## 3.1 Cochrane Reviews

**Hirsch C et al., 2022 [1].**

SARS-CoV-2-neutralising monoclonal antibodies to prevent COVID-19

**Fragestellung**

To assess the effects of SARS-CoV-2-neutralising mAbs, including mAb fragments, to prevent infection with SARS-CoV-2 causing COVID-19; and to maintain the currency of the evidence, using a living systematic review approach.

**Methodik**

Population:

- people of any age, gender, or ethnicity
- participants without defined exposure, or with potential exposure to SARS-CoV-2, but who did not have a confirmed diagnosis of COVID-19 (virus antigens or RNA detected). For PrEP, we included participants regardless of SARSCoV-2 antibody serostatus and for PEP, we included SARS-CoV-2 antibody seronegative participants.
- We did not exclude studies based on age, gender, ethnicity, or setting. We excluded studies that evaluated mAbs to prevent infection from other coronavirus diseases (e.g. SARS or MERS), or other viral diseases, such as influenza. If studies enrolled populations with mixed viral diseases, we only included these if trial authors provided subgroup data for participants with COVID-19.

Intervention:

We included the following interventions.

• SARS-CoV-2-neutralising mAbs, including mAb fragments.

• Combinations of SARS-CoV-2-neutralising mAbs.

Kontrolle:

• Any mAb prophylaxis compared with a control intervention, for example, vaccinations, drug prophylaxis (including but not limited to hydroxychloroquine, remdesivir), standard or hyperimmune immunoglobulin, convalescent plasma, other prevention strategies (e.g. protective clothing, face masks, social distancing), complementary medicine (e.g. quercetin, elderberry, zinc), or others.

• Any mAb prophylaxis compared with no prophylaxis or placebo.

Co-interventions were allowed, but these must have been comparable between intervention groups.

We included studies that compared several mAbs or mAb fragments with each other and another prophylaxis, placebo or no prophylaxis, as well as studies that compared several doses of one type of mAb or mAb fragments with another prophylaxis, placebo, or no prophylaxis.

Endpunkte:

confirmed COVID-19 infections;

development of COVID-19 symptoms;

death from any cause; – hospital admission; – quality of life; – unwanted effects, such as infections and cardiac disorders; – serious unwanted effects, such as life-threatening, hospitalisation, disability, or death.

Recherche/Suchzeitraum:

- Cochrane COVID-19 Study Register, MEDLINE, Embase, and three other databases on 27 April 2022

Qualitätsbewertung der Studien:

- RoB 2 tool; GRADE

**Ergebnisse**

Anzahl eingeschlossener Studien:

Pre-exposure prophylaxis (2 Studien): BLAZE-2; O'Brien 2021

BLAZE-2 (published data only)

Cohen MS, Nirula A, Mulligan M, Novak R, Marovich M, Stemer A, et al. Bamlanivimab prevents COVID-19 morbidity and mortality in nursing-home setting, 2021. www.croiconference.org/ abstract/bamlanivimab-prevents-covid-19-morbidity-andmortality-in-nursing-home-setting/ (accessed 1 June 2022).

* Cohen MS, Nirula A, Mulligan MJ, Novak RM, Marovich M, Yen C, et al. Effect of bamlanivimab vs placebo on incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities: a randomized clinical trial. JAMA 2021;326(1):46-55. [DOI: 10.1001/jama.2021.8828]

Knorr J, Tuttle JL, Sabo JA, East DH, Price KL, Shen L. Innovative clinical trial design and delivery: a phase 3 COVID-19 postexposure prophylaxis study in skilled nursing and assisted living facilities (BLAZE-2). Trials 2021;22:726. [DOI: 10.1186/ s13063-021-05699-3]

O'Brien 2021 (published data only)

Hassan H, Turner K, Davis J, Ganguly S, Irvin S, Partridge M, et al. P-071: pharmacokinetics and immunogenicity assessment of a single subcutaneous dose of casirivimab and imdevimab in household contacts of SARS-CoV-2 infected persons. American Society for Clinical Pharmacology and Therapeutics 111;-:S5-S80. [DOI: 10.1002/cpt.2521]

O'Brien M, Forleo-Neto E, Chen KC, Isa F, Heimann I, Sarkar N, et al. Casirivimab with imdevimab antibody cocktail for COVID-19 prevention: interim results, 2021. www.croiconference.org/ abstract/casirivimab-with-imdevimab-antibody-cocktailfor-covid-19-prevention-interim-results/ (accessed 1 June 2022):abstract no. 123.

O'Brien M, Forleo-Neto E, Musser B, Isa F, Chan KC, Sarkar N, et al. Subcutaneous REGEN-COV antibody combination for Covid-19 prevention. medRxiv [Preprint] 2021. [DOI: 10.1101/2021.06.14.21258567]

O'Brien M, Forleo-Neto E, Musser BJ, Isa F, Chan KC, Sarkar N, et al. COVID-19 prevention with subcutaneous administration of the monoclonal antibodies casirivimab and imdevimab: subgroup analysis in participants with cardiovascular disease and diabetes. American Heart Journal 2021;242:172-173, abstract no. 099. [DOI: 10.1016/j.ahj.2021.10.067]

O'Brien M, Forleo-Neto E, Sarkar N, Isa F, Hou P, Chan KC, et al. Subcutaneous REGEN-COV antibody combination in early SARS-CoV-2 infection. medRxiv [Preprint] 2021. [DOI: 10.1101/2021.06.14.21258569]

O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, Chan KC, et al. Effect of subcutaneous casirivimab and imdevimab antibody combination vs placebo on development of symptomatic COVID-19 in early asymptomatic SARS-CoV-2 infection: a randomized clinical trial. JAMA 2022;327(5):432-41. [DOI: 10.1001/jama.2021.24939]

* O'Brien M, Forleo-Neto E, Musser B, Isa F, Chan KC, Sarkar N, et al. Subcutaneous REGEN-COV antibody combination to prevent Covid-19. New England Journal of Medicine 2021;385:1184-95. [DOI: 10.1056/NEJMoa2109682]

Charakteristika der Population:

- One study (5197 people) compared tixagevimab/cilgavimab to placebo. Participants had been exposed to wild-type, Alpha, Beta, and Delta variants.

  Tixagevimab/cilgavimab: – reduces development of symptoms; – probably reduces number of people infected; – may reduce number of hospital admissions; – may have little or no effect on deaths from any cause, unwanted effects (any severity), and serious unwanted effect. We found no data for quality of life, or mild and severe unwanted effects.

- One study (969 people) compared casirivimab/imdevimab to placebo. Participants may have been exposed to wild-type, Alpha, and Delta variants. Casirivimab/imdevimab: – may reduce number of people infected and development of symptoms; – resulted in no deaths; – may increase unwanted effects (any severity) slightly; – we are uncertain whether casirivimab/imdevimab may have an effect on severe and serious unwanted effects.

  We found no data for number of people with COVID-19 within 30 days, development of symptoms within 30 days, hospital admissions within 30 days, quality of life, and mild unwanted effects.

Qualität der Studien:

- Siehe Summary of findings (Anhang)

Studienergebnisse:

- Pre-exposure prophylaxis Tixagevimab/cilgavimab versus placebo

  One study evaluated tixagevimab/cilgavimab versus placebo in participants exposed to SARS-CoV-2 wild-type, Alpha, Beta, and Delta variant. About 39.3% of participants were censored for efficacy due to unblinding and 13.8% due to vaccination. Within six months, tixagevimab/cilgavimab probably decreases infection with SARS-CoV-2 (risk ratio (RR) 0.45, 95% confidence interval (CI) 0.29 to 0.70; 4685 participants; moderate-certainty evidence), decreases development of clinical COVID-19 symptoms (RR 0.18, 95% CI 0.09 to 0.35; 5172 participants; high-certainty evidence), and may decrease admission to hospital (RR 0.03, 95% CI 0 to 0.59; 5197 participants; low-certainty evidence). Tixagevimab/cilgavimab may result in little to no difference on mortality within six months, all-grade AEs, and SAEs (lowcertainty evidence). Quality of life was not reported.

- Casirivimab/imdevimab versus placebo

  One study evaluated casirivimab/imdevimab versus placebo in participants who may have been exposed to SARS-CoV-2 wild-type, Alpha, and Delta variant. About 36.5% of participants opted for SARS-CoV-2 vaccination and had a mean of 66.1 days between last dose of intervention and vaccination. Within six months, casirivimab/imdevimab may decrease infection with SARS-CoV-2 (RR 0.01, 95% CI 0 to 0.14; 825 seronegative participants; low-certainty evidence) and may decrease development of clinical COVID-19 symptoms (RR 0.02, 95% CI 0 to 0.27; 969 participants; low-certainty evidence). We are uncertain whether casirivimab/imdevimab affects mortality regardless of the SARS-CoV-2 antibody serostatus. Casirivimab/imdevimab may increase all-grade AEs slightly (RR 1.14, 95% CI 0.98 to 1.31; 969 participants; low-certainty evidence). The evidence is very uncertain about the effects on grade 3 to 4 AEs and SAEs within six months. Admission to hospital and quality of life were not reported.

**Anmerkung/Fazit der Autoren**

For PrEP, there is a decrease in development of clinical COVID-19 symptoms (high certainty), infection with SARS-CoV-2 (moderate certainty), and admission to hospital (low certainty) with tixagevimab/cilgavimab. There is low certainty of a decrease in infection with SARS-CoV-2, and development of clinical COVID-19 symptoms; and a higher rate for all-grade AEs with casirivimab/imdevimab.

For PEP, there is moderate certainty of a decrease in infection with SARS-CoV-2 and low certainty for a higher rate for all-grade AEs with bamlanivimab. There is high certainty of a decrease in infection with SARS-CoV-2, development of clinical COVID-19 symptoms, and a higher rate for all-grade AEs with casirivimab/imdevimab.

Although there is high-to-moderate certainty evidence for some outcomes, it is insufficient to draw meaningful conclusions. These findings only apply to people unvaccinated against COVID-19. They are only applicable to the variants prevailing during the study and not other variants (e.g. Omicron). In vitro, tixagevimab/cilgavimab is effective against Omicron, but there are no clinical data. Bamlanivimab and casirivimab/imdevimab are ineffective against Omicron in vitro.

Further studies are needed and publication of four ongoing studies may resolve the uncertainties.

*Kommentare zum Review*

Es warden hier nur die Ergebniss zur PreP dargestellt.

## 3.2 Systematische Reviews

Es konnten keine relevanten Systematischen Reviews identifiziert werden.

## 3.3 Leitlinien

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**Lynch JB et al., 2020 [2].**

*Infectious Diseases Society of America (IDSA)*

Infectious Diseases Society of America Guidelines on Infection Prevention for Healthcare Personnel Caring for Patients With Suspected or Known Coronavirus Disease 2019

**Zielsetzung/Fragestellung**

Our objective was to develop evidence-based rapid guidelines intended to support healthcare personnel (HCP) in their decisions about infection prevention when caring for patients with suspected or known coronavirus disease 2019 (COVID-19).

**Methodik**

Grundlage der Leitlinie

**Anlage I** Repräsentatives Gremium: kein Patientenvertreter;

**Anlage II** Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;

**Anlage III** Systematische Suche, Auswahl und Bewertung der Evidenz;

**Anlage IV** Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;

**Anlage V** Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;

**Anlage VI** Regelmäßige Überprüfung der Aktualität gesichert: trifft zu.

Recherche/Suchzeitraum:

**Anlage VII** OVID Medline and Embase were searched to identify all relevant English language studies from inception to 14 April 2020 related to COVID-19 using the newly developed MeSH term. In certain circumstances, searches were also conducted to identify relevant literature including Google Scholar, World Health Organization (WHO), and Centers for Disease Control and Prevention (CDC) websites. Horizon scans were performed daily during the evidence assessment and recommendation process to locate additional gray literature and manuscript preprints from Medrxiv.

LoE/GoR

**Anlage VIII** Risk of bias was assessed using the Cochrane Risk of Bias Tool for RCTs

**Anlage IX** Grading of Recommendations Assessment, Development and Evaluation (GRADE)

**Anlage X** As per GRADE methodology, recommendations are labeled as “strong” or “weak/conditional”. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations.

Abbildung 1 provides the suggested interpretation of strong and weak/conditional recommendations for patients, clinicians, and healthcare policymakers. In some situations where the evidence was judged insufficient to provide a clear direction "for" or "against" a particular management strategy, the panel decided to make a "no recommendation."

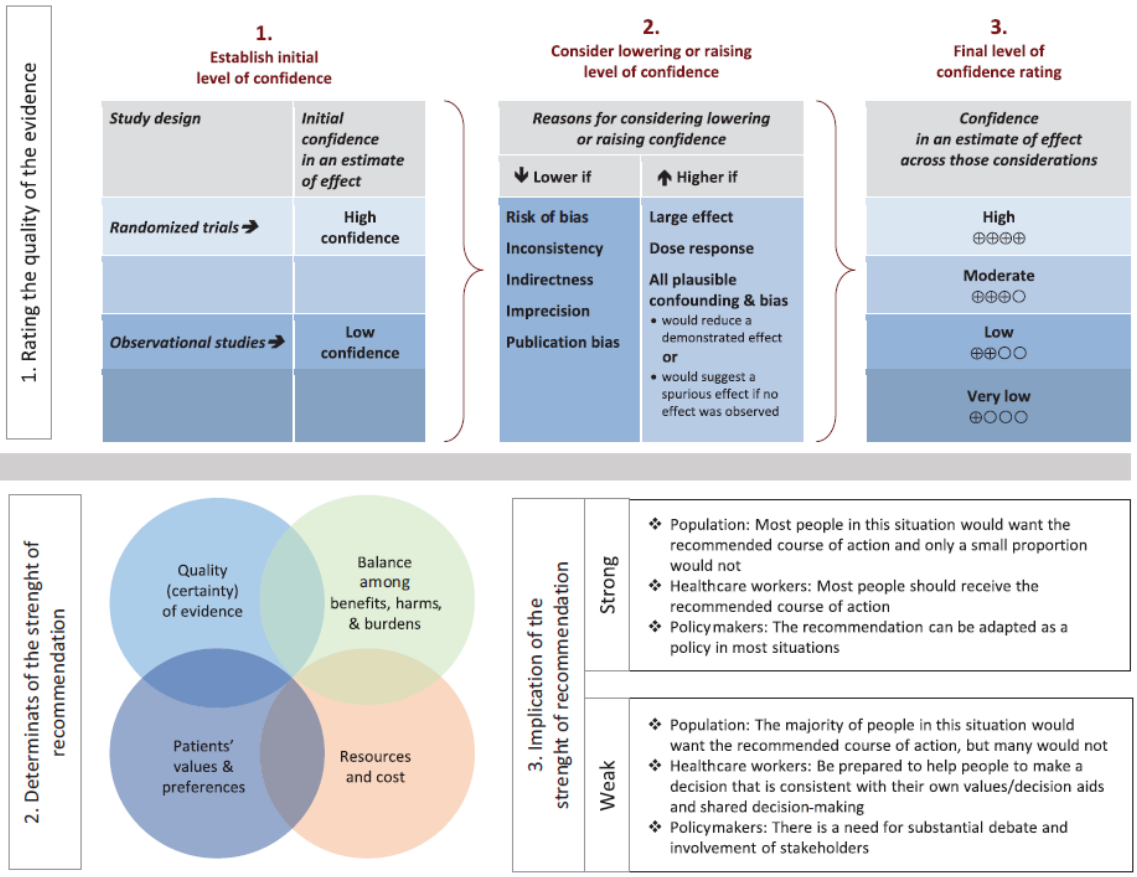


**Figure 2.** Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation methodology. Unrestricted use of the figure granted by the US GRADE Network.

<u>Sonstige methodische Hinweise</u>

**Anlage XI** In addition, given the need for an urgent response to a major public health crisis, the methodological approach was modified according to the Guidelines International Network/McMaster checklist for the development of rapid recommendations

**Anlage XII** Using a combination of direct and indirect evidence, the panel was able to provide recommendations for 8 specific questions on the use of personal protective equipment (PPE) for HCP who provide care for patients with suspected or known COVID-19. Where evidence was lacking, attempts were made to provide potential avenues for investigation. Significant gaps in the understanding of the transmission dynamics of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain, and PPE recommendations may need to be modified in response to new evidence.

**Definitions**

Surgical Masks: Masks with or without plastic shields are used as a physical barrier to protect the user from hazards, such as splashes of large droplets of blood or body fluids. Surgical masks also protect other people against infection from the person wearing the surgical mask. Such masks trap large particles of body fluids that may contain bacteria or viruses expelled by the wearer (14). Surgical masks and medical masks are used interchangeably in this document.

Respirator: Devices used to protect HCP from airborne particles that can lead to infection. This includes N95 filtering facepiece respirators and higher-level "mask-like" respirators (eg, N99, N100) and powered air-purifying respirators (PAPRs) and controlled air-purifying respirators.

Donning and Doffing Procedures: Donning refers to the practice of putting on PPE. Doffing refers to the practice of taking off PPE.

**Crisis Standards of Care**

Conventional capacity: Usual supplies available and used (1).

Contingency capacity: Conservation, adaptation, and substitution of supplies with occasional reuse of select supplies.

Crisis capacity: Critical supplies lacking. PPE extended use: The use of PPE for greater than a single patient encounter and without removing the PPE, with or without the use of additional devices (eg, a face shield over a surgical mask). Recommended for use only in contingency or crisis capacity settings (3).

PPE reuse: The use of PPE that is doffed after each patient encounter and redonned after a period of time and/or a processing step. Recommended for use only in contingency or crisis capacity settings (3).

**Recommendations**

For all recommendations listed below, the panel emphasizes the importance of "appropriate PPE," which includes gowns, gloves, and eye protection and adherence to standards for donning and doffing to minimize transmission.

**ROUTINE PATIENT CARE**

In Conventional Settings

**Recommendation 1:**
The IDSA guideline panel recommends that HCP caring for patients with suspected or known COVID- 19 use either a surgical mask or N95 (or N99 or powered airpurifying respirator) respirator as part of appropriate PPE.*

*Strong recommendation, moderate certainty of evidence.*

In Contingency or Crisis Capacity Settings

**Recommendation 2**:
While in contingency or crisis capacity settings (respirator shortages), the IDSA guideline panel recommends that HCP caring for patients with suspected or known COVID-19 use a surgical mask or reprocessed respirator instead of no mask as part of appropriate PPE.*

*Strong recommendation, moderate certainty of evidence.*

**Summary of the Evidence**

Direct evidence from the early stages of the COVID-19 pandemic provides information about the risk of infection among HCP and the effectiveness of N95 respirators and surgical masks. According to these studies, approximately 30% of unprotected HCP (wearing no masks) exposed to COVID-19 patients developed infection (15). In a retrospective cohort study that compared HCP wearing N95 respirators (N = 278) caring for high-risk COVID-19 patients with unmasked HCP (N = 213) caring for low-risk patients, 10/213 unmasked HCP became infected compared with 0/278 who wore N95 respirators (16). Overall, rates of infections in HCP were 3 times higher compared with the general population, likely due to inadequate PPE practices, although the most frequent failure mechanism (lack of proper masks, face shield, or contact precautions such as hand washing) remains unclear (17). Indirect evidence from the SARS epidemic was used to inform the question about the effectiveness of masks. Based on an existing systematic review of 5 observational studies in HCP, wearing any mask (surgical mask or N95 respirator) demonstrated a large reduction in the risk of developing infection (surgical masks: odds ratio [OR], 0.13; 95% confidence interval [CI], .03–.62 or N95 respirator: OR, 0.12; 95% CI, .06–.26) (18) (Table 1; *siehe Anhang)*. Studies that compared N95 respirators with surgical masks on rates of SARS infection failed to show or exclude a beneficial effect (OR, 0.86; 95% CI, .22–3.33) on rates of SARS infections. Four studies compared N95 respirators with surgical masks for prevention of viral respiratory infections (VRIs) also failed to show or exclude a beneficial effect (OR, 0.94; 95% CI, .80–1.11) (19) (see Table 2 and Supplementary Figure 2; *siehe Anhang*).

**Other Considerations**

Evidence to support the use of N95 respirators or surgical masks (compared with no masks) was based on observational studies that showed a very large reduction in the risk of infection during the SARS outbreak. The overall certainty of evidence was moderate. The quality of data on the use of N95 respirators compared with surgical masks for SARS or other VRIs was low or very low. If N95 respirators are used and the supply is in a contingency state, access may be mitigated by extending use (covering the respirator with a face shield or mask) over >1 patient encounter. The limitations of the evidence included small numbers of events, recall bias, and data on all viral infections (not limited to coronavirus).

<u>In Conventional, Contingency, or Crisis Capacity Settings</u>

**Recommendation 3:**

The IDSA guideline panel makes no recommendation for the use of double gloves vs single gloves for healthcare PPE.*

*Knowledge gap.*

**Recommendation 4:**

The IDSA guideline panel makes no recommendation for the use of shoe covers vs no shoe covers for HCP caring for patients with suspected or known COVID- 19 as part of appropriate PPE.*

*Knowledge gap.*

**AEROSOL-GENERATING PROCEDURES**

In Conventional Settings

**Recommendation 5:**
The IDSA guideline panel recommends that HCP involved with aerosol-generating procedures on suspected or known COVID-19 patients use an N95 (or N99 or powered air-purifying respirator) respirator instead of a surgical mask as part of appropriate PPE.*

*Strong recommendation, very low certainty of evidence*.

*Comment: Despite the very low-quality and indirect evidence supporting this recommendation, the IDSA guideline panel placed a high value on avoiding serious harms to exposed HCP.*

**Summary of the Evidence**

There was no direct evidence on AGPs and rates of COVID-19 infection among HCP. Indirect evidence from the SARS epidemic was used to inform this recommendation. Based on observational data, among infected HCP with SARS, exposure to an AGP such as tracheal intubation was associated with a higher risk of infection (33). Evidence from laboratory simulation data also provided indirect evidence on the viability of aerosolized SARS-CoV-2 (34). Additionally, data on environmental contamination was obtained by sampling various surfaces and air samples from confirmed COVID-19 patient rooms: 87% (13/15) of room sites (including air exhaust outlet fans) returned positive SARS-CoV-2 on reverse-transcription polymerase chain reaction (RT-PCR) results and 60% (3/5) of toilet sites (including toilet bowl, sink, and door handle) returned positive SARS-CoV-2 on RT-PCR results. Air samples were negative despite the extent of environmental contamination (35).

**Other Considerations**

Evidence to support the use of N95 or higher-level respirators instead of surgical masks for HCP involved in AGPs was based on observational studies and experimental laboratory data. The overall certainty of evidence was very low due to limitations in the retrospective observational data and recall bias. However, the IDSA guideline panel made a strong recommendation for N95 or higher-level respirators, placing a high value on preventing infection among HCP.

In Contingency or Crisis Capacity Settings

**Recommendation 6:**
While in contingency or crisis capacity settings (respirator shortages), the IDSA guideline panel suggests that HCP involved with aerosol-generating procedures on suspected or known COVID-19 patients use a reprocessed N95 respirator for reuse instead of surgical masks as part of appropriate PPE.*

*Conditional recommendation, very low certainty evidence*.

**Summary of the Evidence**

No direct evidence was found on infection rates among HCP using reprocessed and reused N95 respirators. Furthermore, indirect evidence from other pandemic outbreaks also did not reveal empiric data on infection rates. Indirect evidence on reprocessing strategies that use ultraviolet (UV) radiation, heat, 70% ethanol, or vaporized hydrogen peroxide (VHP) was used to inform this recommendation. These data were taken from experiments under laboratory conditions or anecdotal reports on reprocessing and reuse of N95 respirators with COVID-19 patients from different medical centers in the United States.

Three studies conducted in a laboratory setting using VHP showed effective decontamination of N95 respirators with no observable physical changes and no degradation to the filtration media after up to 30–50 cycles of exposure to VHP. However, after 20 cycles, the elastic straps became stiffer and there were concerns about respirator fit and comfort (40–42). UV germicidal irradiation (UVGI) to decontaminate and reuse N95

respirators showed similar results in up to 20 decontamination cycles with no effect on filtration efficacy in various laboratory studies (40, 43–45). However, there was discrepancy in fit testing after 10–20 cycles of UVGI, depending on the model of N95 respirator tested (44). Furthermore, anecdotal reports from hospitals that used UVGI for N95 decontamination showed that up to 50 cycles was acceptable before significant degradation in filtration efficiency was noted but that the average number of times masks were reused before fit testing failures was 3 (46).

Dry heat as a decontamination method was used in 4 studies reporting that heat administered at temperatures of 70°C–80°C had no effect on the filtration efficiency or degradation of the N95 respirator (45, 47, 48). In 1 study, N95 respirator fit was impaired; therefore, only 2 reuses after heat decontamination are recommended (49).

**Other Considerations**

No studies that evaluated the effectiveness of reprocessed masks on prevention of COVID-19 infection among HCP were found. The available evidence to inform this recommendation included anecdotal reports and experiments under laboratory conditions to assess mask integrity, filtration efficiency (filter aerosol penetration, airflow resistance), and fit performance of various reprocessing strategies. The overall certainty of evidence was very low due to the following limitations: no comparison of reprocessed N95 respirators with new or unprocessed N95 respirators and no direct evidence on infection rates using reprocessed masks.

**Recommendation 7**:

While in contingency or crisis settings (respirator shortages), the IDSA guideline panel recommends that HCP involved with aerosol-generating procedures on suspected or known COVID-19 patients add a face shield or surgical mask as a cover for the N95 respirator to allow for extended use as part of appropriate PPE.*

*Strong recommendation, very low certainty evidence.*

*Comment: This recommendation assumes correct doffing sequence and hand hygiene are performed before and after removing the face shield or surgical mask covering the respirator.*

**Recommendation 8:**

While in contingency or crisis settings (respirator shortages), the IDSA guideline panel suggests that HCP involved with aerosol-generating procedures on suspected or known COVID-19 patients add a face shield or surgical mask as a cover for the N95 respirator to allow for reuse as part of appropriate PPE.*

*Conditional recommendation, very low certainty evidence*.

*Comment: This recommendation assumes correct doffing sequence and hand hygiene are performed before and after removing the face shield or surgical mask covering the respirator.*

*Appropriate PPE includes, in addition to a mask or respirator, eye protection, gown, and gloves.

**Summary of the Evidence**

Extended use (50) is defined as wearing the same N95 respirator for multiple different and consecutive patient encounters without removal between encounters. The CDC recommends a maximum extended use period of 8–12 hours (50). Reuse is defined as wearing the same N95 respirator for multiple different patient encounters but doffing between encounters. Unless the manufacturer specifies otherwise, the CDC suggests limiting N95 respirator reuse to no more than 5 times per device (50). In contingency or crisis capacity settings (shortage of N95 respirators), no direct evidence on extended use or reuse of N95 respirator was identified. Additionally, no indirect comparative evidence on infection rates among HCP was identified.

**Other Considerations**

The available evidence to inform this recommendation included anecdotal reports, experimental laboratory data, and mathematical models. Strategies of using a face shield or surgical mask to cover an N95 respirator and extend the life of the respirator were used in other pandemics. Additionally, in vitro testing was performed on durability and fit endurance of N95 respirators. The overall certainty of the evidence was low due to concerns about the observational data and lack of evidence on infection rates in HCP using N95 respirators for extended periods or reusing respirators.

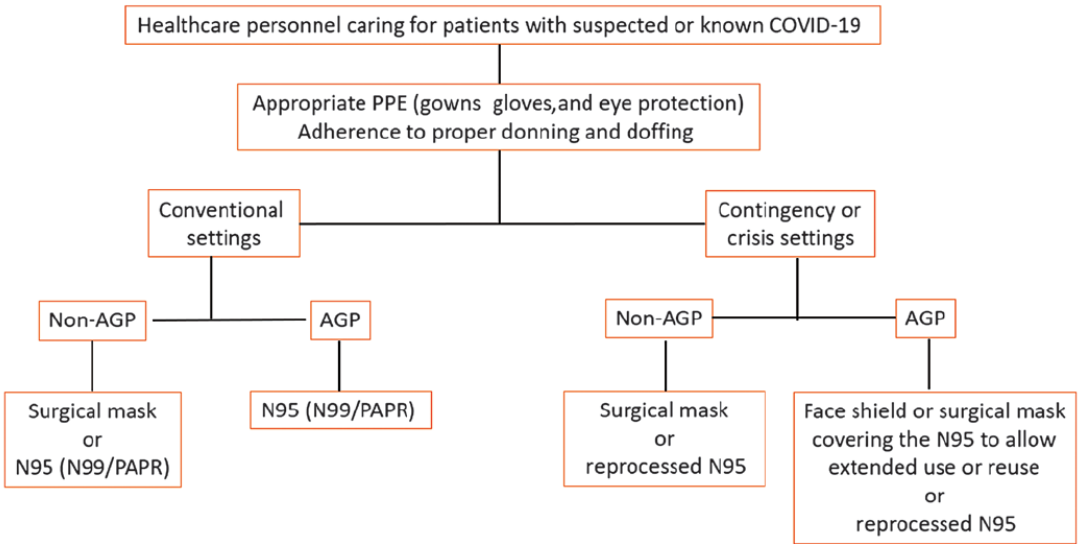


**Figure 1.** Infectious Diseases Society of America algorithm for appropriate PPE in conventional and contingency or crisis settings. Abbreviations: AGP, aerosol-generating procedures; COVID-19, coronavirus disease 2019; PAPR, powered air-purifying respirator; PPE, personal protective equipment.

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**World Health Organization (WHO), 2021 [4].**

WHO Living guideline: Drugs to prevent COVID-19; WHO-2019-nCoV-prophylaxes-2021.1

**Zielsetzung/Fragestellung**

What is the role of drugs for preventing COVID-19?

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- living systematic review, letzte Aktualisierung: 02. März 2021

LoE/GoR

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Sonstige methodische Hinweise

- This is a living guideline, so the recommendation included here will be updated, and new recommendations will be added on other prophylactic interventions for COVID-19.

**Recommendation**

7. Recommendations for prophylaxis

7.1 Hydroxychloroquine

Recommendation against

New

We recommend against administering hydroxychloroquine prophylaxis to individuals who do not have COVID-19 (strong recommendation, high certainty evidence).

*Remark: This recommendation applies to individuals with any baseline risk of developing COVID-19 and any hydroxychloroquine dosing regimen.*

Evidence to decision

**Benefits and harms**

Substantial net benefits of the recommended alternative

Used prophylactically, hydroxychloroquine has a small or no effect on death and hospital admission (high certainty), and probably has a small or no effect on laboratory-confirmed COVID-19 (moderate certainty). It probably increases the risk of adverse effects leading to discontinuation of the drug (moderate certainty).

There was no subgroup effect according to known exposure to a person with SARS-CoV-2 infection or hydroxychrloroquine dose regimen (extremely low event rates precluded investigation of subgroup effects for mortality). The panel therefore assumed similar relative effects across subgroups.

**Certainty of the Evidence**

High

For key outcomes of mortality and hospital admission, the panel had high certainty that hydroxychloroquine had no or a small effect. The certainty was moderate for the outcome of laboratory-confirmed COVID-19 due to serious risk of bias (lack of blinding in one trial), and also for adverse effects due to serious imprecision (in this case the panel assessed the certainty that the null effect could be excluded).

Hintergrundinformationen:

The latest evidence: The recommendation on hydroxychloroquine was informed by results from a systematic review and NMA that pooled data from six trials with 6059 participants who did not have COVID-19 and received hydroxychloroquine (3). Three trials enrolled participants who had a known exposure to infection.

The resulting GRADE evidence summary suggested that hydroxychloroquine has a small or no effect on mortality (odds ratio 0.70; 95 % CI 0.24–1.99; absolute effect estimate 1 fewer death per 1000, 95 % CI from 2 fewer – 3 more deaths per 1000 individuals; high certainty evidence) and on admission to hospital (odds ratio 0.87; 95 % CI 0.42–1.77; absolute effect estimate 1 fewer per 1000, 95 % CI 3 fewer – 4 more admissions to hospital per 1000 individuals; high certainty evidence). Hydroxychloroquine probably has a small or no effect on laboratory-confirmed SARS-CoV-2 infection (odds ratio 1.03; 95% CI 0.71–1.47; absolute effect estimate 2 more per 1000; 95 % CI 18 fewer – 28 more infections per 1000 individuals; moderate certainty evidence). In contrast, hydroxychloroquine probably increases adverse events leading to discontinuation (odds ratio 2.34; 95 % CI 0.93–6.08; absolute effect estimate 19 more per 1000, 95 % CI 1 fewer – 70 more adverse events per 1000 individuals; moderate certainty evidence).

There was no indication of a credible subgroup effect based on known exposure to a person with SARS-CoV-2 infection or hydroxychloroquine dosing regimen (extremely low event rates precluded investigation of subgroup effects for mortality).

Referenz:

3. Bartoszko JJ, Siemieniuk R, Kum E, et al. Prophylaxis against covid-19: living systematic review and network meta-analysis. medRxiv 2021.02.24.21250469 2021; Journal

*Kommentare zur Leitlinie:*

Hydrochloroquine ist in Deutschland in diesem AWG derzeit nicht zugelassen.

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**National COVID-19 Clinical Evidence Taskforce, 2022 [3].**

Australian guidelines for the clinical care of people with COVID-19: version 60.2

**Zielsetzung/Fragestellung**

This guideline aims to provide specific, patient-focused recommendations on management and care of people with suspected or confirmed COVID-19. With the exception of chemoprophylaxis for the prevention of infection in people exposed to COVID -19, the guideline does not include other interventions used in the prevention of COVID-19 infection or transmission. Within each recommendation, the patient population of interest is specified.

**Methodik**

Grundlage der Leitlinie

- Repräsentatives Gremium: multidisciplinary guideline panels;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: All panel members complete a declaration of potential conflicts of interest, and absent themselves from discussions related to these potential conflicts;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert

Recherche/Suchzeitraum:

- Ständige Aktualisierung – hier zuletzt am 22.07.2022

LoE/GoR

- For systematic reviews, the risk of bias or quality assessment of included studies presented in the review is used where available. For individual primary studies, each study is assessed for risk of bias. Randomised trials are assessed using the Cochrane Risk of Bias 2.0 assessment tool. Non-randomised studies are assessed using the ROBINS-I Risk of Bias assessment tool
- This guideline uses GRADE methodology, which is supported by the online guideline development and publication platform 'MAGICapp' (Making GRADE the Irresistible Choice)
- The following criteria are used in determining the strength of recommendations:
  - Strong for: moderate to high certainty evidence suggests that benefits in critical outcomes clearly outweigh the reported harms; a strong recommendation can be made in the absence of high-certainty evidence if patients are expected to highly desire such practice and there are no potential harms in providing it.
  - Strong against: moderate to high certainty evidence suggests harms outweigh benefits; high certainty evidence suggests lack of benefits.
  - Conditional for: moderate to high certainty evidence suggests equivalent benefits and harms, patients would mostly want to receive the practice, and there is no significant resources implication in doing so; low certainty evidence suggests benefits outweigh harms and there are no significant implications in patients' preferences or resources implications.

- Conditional against: moderate to high certainty evidence suggests equivalent benefits and harms, but there is expected large variation in patients' preference to receive this practice or important resource implications; low certainty evidence suggests harms outweigh benefits and there are no significant implications in patients' preferences or resource implications.
- Consensus statement: evidence is absent or of insufficient certainty; unclear balance between benefits and harms, and there is expected large variation in patients' preferences. No formal method of reaching consensus was used but this was addressed in internal reviews.

**Empfehlungen**

6.1 Recommended drug treatments

6.1.1 Casirivimab plus imdevimab (Ronapreve)

6.1.1.1 Casirivimab plus imdevimab (Ronapreve) for adults

Conditional recommendation

Consider using casirivimab plus imdevimab within 7 days of symptom onset in adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Where Omicron is likely to be the dominant circulating variant, use of casirivimab plus imdevimab should only be considered where other treatments are not suitable or available.

*While the clinical evidence supports use of casirivimab plus imdevimab to treat mild COVID-19, there is no clinical evidence to evaluate its effectiveness against the Omicron variant or BA.1 or BA.2 sub-variants. The Taskforce is aware of in vitro data that suggest potentially reduced efficacy against these variants and while the clinical implications of this are not certain, given the availability of other treatments, where infection with Omicron BA.2 is confirmed or considered likely, use of casirivimab plus imdevimab should not be considered unless other treatments are unsuitable or unavailable.*

*In adult outpatients with mild COVID-19, casirivimab plus imdevimab (Ronapreve) probably reduces hospitalisation and incidence of adverse events. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.*

*Included data comes from the three-phase REGEN-COV trial [504][570] in which adults with one or more risk factors for disease progression received either 1200 mg, 2400 mg or 8000 mg casirivimab plus imdevimab. Based on inclusion criteria of the trial, risk factors for disease progression include:*

- *Age ≥ 50 years*
- *Obesity (BMI ≥ 30 kg/m2)*
- *Cardiovascular disease (including hypertension)*
- *Chronic lung disease (including asthma)*
- *Type 1 or 2 diabetes*
- *Chronic kidney disease, including those on dialysis*
- *Chronic liver disease*
- *Immunocompromise (including in individuals with rheumatoid arthritis, HIV/AIDS and systemic lupus erythematosus receiving immunosuppressive treatment)*

*As there is insufficient data supporting one dose over another, the Taskforce recommends that the most frequently used dose across the studies (1200 mg) should be administered within 7 days of onset of symptoms.*

*The efficacy of casirivimab plus imdevimab in vaccinated adults or immunocompromised patients with mild or asymptomatic COVID-19 is not known.*

*As of 7 March 2022, the Taskforce has made conditional recommendations supporting the use of sotrovimab, casirivimab plus imdevimab, nirmatrelvir plus ritonavir, remdesivir and molnupiravir in adult outpatients with mild COVID-19. The relative effectiveness of these agents, or the effectiveness of these agents when used in combination, is unclear.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

Conditional recommendation

Consider using casirivimab plus imdevimab in **seronegative** adults hospitalised with moderate-to-critical COVID-19.

Where Omicron is likely to be the dominant circulating variant, use of casirivimab plus imdevimab should only be considered where other treatments are not suitable or available.

*While the clinical evidence supports use of casirivimab plus imdevimab to treat hospitalised patients with COVID-19, there is no clinical evidence to evaluate its effectiveness against the Omicron variant or BA.1 or BA.2 sub-variants. The Taskforce is aware of in vitro data that suggest potentially reduced efficacy against these variants and while the clinical implications of this are not certain, given the availability of other treatments, where infection with Omicron is confirmed or considered likely, use of casirivimab plus imdevimab should not be considered unless other treatments are unsuitable or unavailable.*

*In patients hospitalised with moderate-to-critical COVID-19 who are seronegative (no detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab (Ronapreve) probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.*

*The Taskforce notes that the RECOVERY trial administered a single intravenous 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab in 250 ml 0.9% saline) and assessed baseline serostatus using the Oxford (anti-spike IgG) immunoassay, the use of which has been supported by the UK National SARS-CoV-2-Serology Assay Evaluation Group [512].*

*It should be noted that the study by Somersan-Karakaya [622] initially included patients requiring ventilation but ceased their recruitment due to safety concerns, however no safety data were provided for these patients.*

*The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.*

*The sponsor has not submitted an application to the Therapeutics Goods Administration for use of casirivimab plus imdevimab in hospitalised patients and it is presently not approved for this indication.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

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Not recommended

Do not use casirivimab plus imdevimab in **seropositive** adults hospitalised with moderate-to-critical COVID-19.

*In patients hospitalised with moderate-to-critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab (Ronapreve) probably has little impact on risk of death, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

### 6.1.1.3 Casirivimab plus imdevimab (Ronapreve) for children and adolescents

Consensus recommendation

Consider using, in exceptional circumstances, casirivimab plus imdevimab within 7 days of symptom onset in **children and adolescents with COVID-19 aged 12 years and over and weighing at least 40 kg who do not require oxygen** and who are at high risk of deterioration.

*In adult outpatients with mild COVID-19, casirivimab plus imdevimab (Ronapreve) probably reduces hospitalisation and incidence of adverse events. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.*

*Decisions to provide casirivimab plus imdevimab to a child or adolescent should be based on the individual's combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.*

*Included data comes from the three-phase REGEN-COV trial [504][570] in which adults with one or more risk factors for disease progression received either 1200 mg, 2400 mg or 8000 mg casirivimab plus imdevimab. Available research does not currently provide enough evidence to determine the benefits of casirivimab plus imdevimab in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from casirivimab plus imdevimab. Based on international cohorts [574] potential factors to consider in patients with mild COVID-19 at high risk of progression may include:*

- *Paediatric Complex Chronic Conditions: congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions*
- *Severe asthma*
- *Obesity (above the 95th percentile on BMI for age growth chart)*

*As there is insufficient data supporting one dose over another, the Taskforce recommends that the most frequently used dose across the studies (1200 mg) should be administered within 7 days of onset of symptoms.*

*The efficacy of casirivimab plus imdevimab in vaccinated or immunocompromised children and adolescents with mild or asymptomatic COVID-19 is not known.*

*The Taskforce is aware of concerns about the potential for decreased effectiveness of casirivimab plus imdevimab against the Omicron variant, based on in vitro data. We will update this recommendation as definitive evidence becomes available.*

*As of 29 October 2021, the Taskforce has made conditional recommendations supporting the use of both sotrovimab and casirivimab plus imdevimab in adult outpatients with mild COVID-19. As there is no evidence directly comparing sotrovimab to casirivimab plus imdevimab, it is unclear if one treatment is more effective than the other.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

Not recommended

Do not use casirivimab plus imdevimab in **seropositive** children and adolescents hospitalised with moderate-to-critical COVID-19.

*In patients hospitalised with moderate-to-critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab (Ronapreve) probably has little impact on risk of death, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

### 6.1.7 Remdesivir (Veklury)

#### 6.1.7.1 Remdesivir (Veklury) for adults

Conditional recommendation

Consider using remdesivir in adults with COVID-19 who require oxygen but do not require non-invasive or invasive ventilation.

*In patients hospitalised with COVID-19 who do not require ventilation (invasive or non-invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) remdesivir (Veklury) probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir use both within and outside the context of a randomised trial.*

*It is unclear whether older people or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.*

*We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [50]. For a full description of the rationale underpinning this decision please see here.*

*It is unclear which regimen of remdesivir (5-day or 10-day) provides the optimal duration of treatment. In Australia, criteria for accessing remdesivir from the National Medical Stockpile limits the treatment course to 5 days for eligible patients.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

#### 6.1.7.3 Remdesivir (Veklury) for children and adolescents

Consensus recommendation

Updated

Consider using, in exceptional circumstances, remdesivir for the treatment of COVID-19 within 7 days of symptom onset in **children and adolescents aged 28 days and over and weighing at least 3 kg** who do not require oxygen and are at high risk of deterioration, where other treatments are not available / appropriate.

Consider using remdesivir only in children and adolescents who are not up-to-date with vaccination, or those who are immunocompromised regardless of vaccination status. Do not routinely use remdesivir in children and adolescents who are up-to-date with vaccination unless immunocompromised.

Decisions about the appropriateness of treatment with remdesivir should be based on the patient's individual risk of severe disease, including their age, presence of multiple risk factors, and COVID-19 vaccination status.

*Please note:*

*1. Remdesivir (Veklury) is not TGA approved for mild disease in children < 40 kg*

*2. There are potential concerns with the use of cyclodextrin in infants, so the benefits and risks should be carefully assessed*

*Decisions to provide remdesivir to a child or adolescent should be based on the individual's combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.*

*Available research does not currently provide enough evidence to determine the potential benefits and risks of remdesivir in specific subgroups of children and adolescents. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit from remdesivir. Based on international cohorts [574] potential factors to consider in patients at high risk of progression may include:*

- *Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions*
- *Severe asthma*
- *Obesity*

*There is no evidence evaluating the effectiveness of remdesivir in fully vaccinated patients, a low likelihood of development of severe disease, and a small risk of adverse events. Given this and the lower risk of deterioration in these patients, it is unlikely that remdesivir will be particularly valuable in fully vaccinated patients, unless the patient is immunocompromised.*

*There is no evidence on the effectiveness of remdesivir in immunocompromised children and adolescents. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that remdesivir will be beneficial for immunocompromised patients.*

*In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

## 7.4 Tixagevimab plus cilgavimab (Evusheld) for pre-exposure prophylaxis

Consensus recommendation

Do not routinely use tixagevimab plus cilgavimab as pre-exposure prophylaxis, however use may be considered in exceptional circumstances, in individuals who are severely immunocompromised.

Given the limited evidence of benefit or safety, small effect sizes and absence of evidence evaluating the effectiveness of tixagevimab plus cilgavimab for prevention of infection by SARS-CoV-2 variants of concern, rigorous data collection should be undertaken on indications and key outcomes for adults who receive pre-exposure prophylaxis with tixagevimab plus cilgavimab.

*Evidence regarding the potential effectiveness of tixagevimab plus cilgavimab in preventing SARS-CoV-2 infection is very limited, with small sample sizes and low event rates. Given the limited evidence, the panel was not able to reach consensus on whether use of tixagevimab plus cilgavimab should be recommended for pre-exposure prophylaxis. However some members of the panel felt that use could be considered in exceptional circumstances for people who are at high risk of progression, specifically those who are severely immunocompromised.*

*Results are based on the PROVENT trial [693], in which 5197 unvaccinated adults were administered a single 300 mg dose of Evusheld consisting of two intramuscular injections (150 mg tixagevimab and 150 mg cilgavimab). Included participants required an increased risk for inadequate response to vaccination, defined within the trial as:*

- *≥ 60 years old*
- *BMI ≥ 30 kg/m2*
- *Congestive heart failure*
- *Chronic obstructive pulmonary disease*
- *Chronic kidney disease (eGFR < 30 mL/min)*
- *Chronic liver disease*
- *Immunocompromised state from solid organ transplant, blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids or other immunosuppressive medicines*
- *Intolerant of vaccine*

*OR be at increased risk for SARS-CoV-2 infection based on location or circumstance, defined within the trial as:*

- *Healthcare workers*
- *Workers in industrial settings shown to have been at high-risk for SARS-CoV-2 transmission (e.g. meatpacking plants)*
- *Military personnel residing or working in high-density settings*
- *Students living in dormitory settings*
- *Others living in similar settings of similar close or high-density proximity*

*Pregnant and breastfeeding women and children and adolescents were not included in the trial.*

*A total of 18.4% of participants had received COVID-19 vaccination between time of tixagevimab plus cilgavimab administration and data cut-off (12.2% tixagevimab plus cilgavimab, 30.7% placebo). Results were not reported separately for this subgroup.*

*In vitro data varies around whether tixagevimab plus cilgavimab maintains efficacy against the Omicron variant; however the study was conducted before the Omicron variant was prevalent and there are no clinical data regarding the effectiveness of tixagevimab plus cilgavimab specific to the Omicron variant.*

*The Taskforce is aware of concerns about the suggestion of increased rates of cardiac events in intervention arms of the TACKLE and STORMCHASER trials, and will continue to monitor for further evidence as it emerges.*

*In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

# 4 Detaillierte Darstellung der Recherchestrategie

**Cochrane Library - Cochrane Database of Systematic Reviews (Issue 7 of 12, July 2022) am 20.07.2022**

| # | Suchfrage |
|---|---|
| 1 | [mh "Covid-19"] |
| 2 | [mh "SARS-CoV-2"] |
| 3 | (Covid* OR 2019ncov OR cov2 OR ncov19 OR sarscov* OR (ncov NEAR/3 2019) OR (ncov NEAR/3 19)):ti,ab,kw |
| 4 | (coronavir* OR (corona NEXT vir*) OR betacoronavir* OR (beta NEXT coronavir*) OR SARS*):ti,ab,kw |
| 5 | ((cov*) NEAR/3 (novel OR new OR 2019 OR 19 OR infection* OR disease* OR wuhan OR pneumonia* OR pneumonitis)):ti,ab,kw |
| 6 | (wuhan AND (virus* OR viral OR viridae OR pneumonia* OR pneumonitis)):ti,ab,kw |
| 7 | ("Severe Acute Respiratory Syndrome" OR "Severe Acute Respiratory Syndromes" OR "sudden acute respiratory syndrome" OR "severe acute respiratory infection" OR "severe acute respiratory infections" OR SARI):ti,ab,kw |
| 8 | {OR #1-#7} |
| 9 | #8 with Cochrane Library publication date Between Jul 2017 and Jul 2022 |

**Systematic Reviews in PubMed am 20.07.2022**

verwendete Suchfilter:
*Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.*

| # | Suchfrage |
|---|---|
| 1 | "COVID-19/prevention and control"[MeSH Major Topic] |
| 2 | COVID-19[MeSH Terms] OR SARS-CoV-2[MeSH Terms] |
| 3 | Covid*[ti] OR 2019ncov[ti] OR cov2[ti] OR ncov19[ti] OR sarscov*[ti] OR (ncov[ti] AND 2019[ti]) OR (ncov[ti] AND 19[ti]) |
| 4 | Coronavir*[ti] OR corona vir*[ti] OR betacoronavir*[ti] OR beta coronavir*[ti] OR SARS*[ti] |
| 5 | (cov[ti]) AND (novel[ti] OR new[ti] OR 2019[ti] OR 19[ti] OR infection*[ti] OR disease*[ti] OR wuhan[ti] OR pneumonia*[ti] OR pneumonitis[ti]) |
| 6 | (wuhan[tiab]) AND (virus*[ti] OR viral[ti] OR viridae[ti] OR pneumonia*[ti] OR pneumonitis[ti]) |
| 7 | (("Severe Acute Respiratory Syndrome"[ti] OR "Severe Acute Respiratory Syndromes"[ti] OR "sudden acute respiratory syndrome"[ti]) AND "2"[ti]) OR "severe acute respiratory infection"[ti] OR "severe acute respiratory infections"[ti] OR SARI[ti] |
| 8 | #2 OR #3 OR #4 OR #5 OR #6 OR #7 |

| # | Suchfrage |
|---|---|
| 9 | (prevent*[ti] OR control*[ti] OR precaution*[ti] OR prophylax*[tiab] OR prophylactic[tiab] OR Pre-Exposure[tiab] OR Preexposure[tiab] OR postexposure[tiab] OR post-exposure[tiab] OR exposed[ti] OR Chemoprevent*[tiab] OR Chemoprophylax*[tiab] OR Chemo-prevent*[tiab] OR Chemo-prophylax*[tiab] OR asymptomatic infection*[tiab] OR Inapparent Infection*[tiab] OR subclinical Infection*[tiab] OR presymptomatic infection*[tiab] OR pre-symptomatic infection*[tiab] OR asymptomatic[ti] OR presymptomatic[ti] OR pre-symptomatic[ti] OR Post-Exposure Prophylaxis[mh] OR Pre-Exposure Prophylaxis[mh] OR Chemoprevention[mh] OR infection control[majr] OR Universal Precautions[majr] OR Asymptomatic Infections[mh]) |
| 10 | ((therap*[ti]) AND (globulin*[ti] OR serum*[ti] OR sero*[ti] OR immunoglobulin*[ti])) OR (Antibod*[tiab] AND transfer*[tiab]) OR serotherap*[ti] OR immunotherap*[ti] OR immunization*[ti] OR passive immunization[majr] |
| 11 | #9 OR #10 |
| 12 | #8 AND #11 |
| 13 | #1 OR #12 |
| 14 | (#13) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab])))) |

| # | Suchfrage |
|---|---|
| | OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab])))))) |
| 15 | (#14) AND ("2017/07/01"[PDAT] : "3000"[PDAT]) |
| 16 | (#15) NOT "The Cochrane database of systematic reviews"[Journal] |
| 17 | (#16) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Leitlinien in PubMed am 20.07.2022**

verwendete Suchfilter:
*Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.*

| # | Suchfrage |
|---|---|
| 1 | "COVID-19/prevention and control"[MeSH Major Topic] |
| 2 | COVID-19[MeSH Terms] OR SARS-CoV-2[MeSH Terms] |
| 3 | Covid*[ti] OR 2019ncov[ti] OR cov2[ti] OR ncov19[ti] OR sarscov*[ti] OR (ncov[ti] AND 2019[ti]) OR (ncov[ti] AND 19[ti]) |
| 4 | Coronavir*[ti] OR corona vir*[ti] OR betacoronavir*[ti] OR beta coronavir*[ti] OR SARS*[ti] |
| 5 | (cov[ti]) AND (novel[ti] OR new[ti] OR 2019[ti] OR 19[ti] OR infection*[ti] OR disease*[ti] OR wuhan[ti] OR pneumonia*[ti] OR pneumonitis[ti]) |
| 6 | (wuhan[tiab]) AND (virus*[ti] OR viral[ti] OR viridae[ti] OR pneumonia*[ti] OR pneumonitis[ti]) |
| 7 | (("Severe Acute Respiratory Syndrome"[ti] OR "Severe Acute Respiratory Syndromes"[ti] OR "sudden acute respiratory syndrome"[ti]) AND "2"[ti]) OR "severe acute respiratory infection"[ti] OR "severe acute respiratory infections"[ti] OR SARI[ti] |
| 8 | #2 OR #3 OR #4 OR #5 OR #6 OR #7 |
| 9 | (prevent*[ti] OR control*[ti] OR precaution*[ti] OR prophylax*[tiab] OR prophylactic[tiab] OR Pre-Exposure[tiab] OR Preexposure[tiab] OR postexposure[tiab] OR post-exposure[tiab] OR exposed[ti] OR Chemoprevent*[tiab] OR Chemoprophylax*[tiab] OR Chemo-prevent*[tiab] OR Chemo-prophylax*[tiab] OR asymptomatic infection*[tiab] OR Inapparent Infection*[tiab] OR subclinical Infection*[tiab] OR presymptomatic infection*[tiab] OR pre-symptomatic infection*[tiab] OR asymptomatic[ti] OR presymptomatic[ti] OR pre-symptomatic[ti] OR Post-Exposure Prophylaxis[mh] OR Pre-Exposure Prophylaxis[mh] OR Chemoprevention[mh] OR infection control[majr] OR Universal Precautions[majr] OR Asymptomatic Infections[mh]) |

| # | Suchfrage |
|---|---|
| 10 | ((therap*[ti]) AND (globulin*[ti] OR serum*[ti] OR sero*[ti] OR immunoglobulin*[ti])) OR (Antibod*[tiab] AND transfer*[tiab]) OR serotherap*[ti] OR immunotherap*[ti] OR passive immunization[majr] |
| 11 | #9 OR #10 |
| 12 | #8 AND #11 |
| 13 | #1 OR #12 |
| 14 | (#13) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]*)* |
| *15* | (#14) AND ("2017/07/01"[PDAT] : "3000"[PDAT]) |
| 16 | (#15) NOT (retracted publication [pt] OR retraction of publication [pt]) |

**Iterative Handsuche nach grauer Literatur, abgeschlossen am 08.07.2022**

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

# Referenzen


1. **Hirsch C, Park YS, Piechotta V, Chai KL, Estcourt LJ, Monsef I, et al.** SARS-CoV-2-neutralising monoclonal antibodies to prevent COVID-19. Cochrane Database of Systematic Reviews [online]. 2022(6):Cd014945. URL: http://dx.doi.org/10.1002/14651858.CD014945.pub2.
2. **Lynch JB, Davitkov P, Anderson DJ, Bhimraj A, Cheng VC, Guzman-Cottrill J, et al.** Infectious Diseases Society of America Guidelines on infection prevention for health care personnel caring for patients with suspected or known COVID-19. Clin Infect Dis 2020 [Epub ahead of print].
3. **National COVID-19 Clinical Evidence Taskforce.** Australian guidelines for the clinical care of people with COVID-19: version 61.1 [online]. 02.08.2022. Melbourne (AUS): National COVID-19 Clinical Evidence Taskforce; 2022. [Zugriff: 02.08.2022]. URL: https://files.magicapp.org/guideline/446a3043-2c3d-4fe6-8099-34d23d013e9e/published_guideline_6557-61_1.pdf.
4. **World Health Organization (WHO).** WHO living guideline: drugs to prevent Covid-19; WHO-2019-nCoV-prophylaxes-2021.1 [online]. 02.03.2021. Genf (SUI): WHO; 2021. [Zugriff: 02.08.2022]. URL: https://apps.who.int/iris/rest/bitstreams/1334211/retrieve.

# Anhang

Lynch JB et al., 2020 [2].

**Table 1. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile: N95/Surgical Mask Compared With No Personal Protective Equipment (No Mask) or Infrequent PPE (Inconsistent Use of Mask)**

| Certainty Assessment | | | | | | | No. of Patients | | Effect | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of Studies | Study Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | N95 | No Personal Protective Equipment | Relative (95% CI) | Absolute (95% CI) | Certainty |
| Severe acute respiratory syndrome infection | | | | | | | | | | | |
| 5 [20–24] | Observational | Not serious | Not serious | Not serious [a] | Not serious | Strong association [b] | 9/163 (5.5%) | 86/234 (36.8%) | Odds ratio 0.12 (.06 –.26) | 302 fewer per 1000 (from 334 fewer to 236 fewer) | ⨁⨁⨁◯ Moderate |

Abbreviation: CI, confidence interval.

[a]Although the studies reported on the severe acute respiratory syndrome outbreak, given the similarities between severe acute respiratory syndrome coronavirus 1 and severe acute respiratory syndrome coronavirus 2, we did not rate down for indirectness.

**Table 2. Grading of Recommendations Assessment, Development and Evaluation Evidence Profile: N95 Respirator Compared With Surgical Mask**

| Certainty Assessment | | | | | | | No. of patients | | Effect | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of Studies | Study Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | N95 | Surgical Mask | Relative (95% CI) | Absolute (95% CI) | Certainty |
| Severe acute respiratory syndrome infection | | | | | | | | | | | |
| 3 [20, 22, 25] | Observational | Serious [a] | Not serious | Not serious [b] | Serious [c] | None | 4/141 (2.8%) | 24/452 (5.3%) | OR 0.86 (.22–3.33) | 7 fewer per 1000 (from 41 fewer to 104 more) | ⨁◯◯◯ Very low |
| Viral respiratory illness | | | | | | | | | | | |
| 4 [26–29] | Randomized | Not serious [d] | Not serious | Serious [e] | Serious [c] | None | 393/2464 (15.9%) | 416/1989 (20.9%) | OR 0.96 (.85–1.08) | 7 fewer per 1000 (from 26 fewer to 13 more) | ⨁⨁◯◯ Low |

Abbreviation: CI, confidence interval.

[a]There were concerns about recall bias.

[b]Although the studies reported on the severe acute respiratory syndrome outbreak, given the similarities between severe acute respiratory syndrome coronavirus 1 and severe acute respiratory syndrome coronavirus 2, we did not rate down for indirectness.

[c]There were concerns about imprecision with a low event rate and that the boundaries of the CI cross the clinical threshold.

[d]Although compliance to the assigned mask type was self-reported and it is not clear if there was a performance bias, study staff conducted regular checks on the study participants to control for performance bias, thus, we did not rate down for risk of bias.

[e]There were concerns about indirectness since upper respiratory infection viruses in addition to coronavirus were included in this outcome.

Hirsch C et al., 2022 [1].

**Summary of findings 1. Tixagevimab/cilgavimab compared to placebo for pre-exposure prophylaxis of COVID-19**

**Tixagevimab/cilgavimab compared to placebo in previously uninfected and unvaccinated people with increased risk of exposure to SARS-CoV-2 or increased risk for inadequate immune response to vaccination, or both**

**Patient or population:** SARS-CoV-2 uninfected people without defined exposure, or with potential exposure to SARS-CoV-2**Setting:** preventive measures

**Intervention:** tixagevimab/cilgavimab

**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | N° of participants (studies) | Certainty in the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with tixagevimab/ cilgavimab | | | | |
| **Infection with SARS-CoV-2** within 6 months | 27 per 1000 | **12 per 1000** (8 to 19) | **RR 0.45** (0.29 to 0.70) | 4685 (1 RCT) | ⊕⊕⊕⊖ **Moderate**[a] | Tixagevimab/cilgavimab probably decrease infection with SARS-CoV-2 within 6 months.<br>Participants were censored at unblinding or vaccination.<br>Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta.<br>Extended follow-up data cut-off was 29 August 2021. |
| **Development of clinical COVID-19 symptoms** within 6 months | 18 per 1000 | **3 per 1000** (2 to 6) | **RR 0.18** (0.09 to 0.35) | 5172 (1 RCT) | ⊕⊕⊕⊕ **High** | Tixagevimab/cilgavimab decrease development of clinical symptoms within 6 months.<br>Participants were censored at unblinding or vaccination.<br>Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta.<br>Extended follow-up data cut-off was 29 August 2021. |
| **All-cause mortality** within 6 months[b] | 4 per 1000 | **3 per 1000** (1 to 7) | **RR 0.64** (0.24 to 1.73) | 5197 (1 RCT) | ⊕⊕⊖⊖ **Low**[c,d] | Tixagevimab/cilgavimab may result in little to no difference on mortality within 6 months in participants regardless of RT-PCR SARS-CoV-2 status at baseline. |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta.<br><br>Extended follow-up data cut-off was 29 August 2021. |
| **Admission to hospital** within 6 months[b] | 4 per 1000 | **0 per 1000**<br><br>(0 to 2) | **RR 0.03**<br><br>(0.00 to 0.59) | 5197<br><br>(1 RCT/) | ⊕⊕⊖⊖<br><br>**Low**[e] | Tixagevimab/cilgavimab may decrease admission to hospital within 6 months in participants regardless of RT-PCR SARS-CoV-2 status at baseline.<br><br>Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta.<br><br>Extended follow-up data cut-off was 29 August 2021. |
| **Quality of life** at longest follow-up | — | — | — | — | — | We identified no studies reporting quality of life. |
| **Adverse events: grade 1 to 2** | — | — | — | — | — | We identified no studies reporting grade 1 to 2 adverse events. |
| **Adverse events: grade 3 to 4** within 6 months | — | — | — | — | — | We identified no studies reporting grade 3 to 4 adverse events. |
| **Adverse events: all grade** within 6 months[b] | 455 per 1000 | **455 per 1000**<br><br>(428 to 487) | **RR 1.00**<br><br>(0.94 to 1.07) | 5197<br><br>(1 RCT) | ⊕⊕⊖⊖<br><br>**Low**[f] | Tixagevimab/cilgavimab may result in little to no difference on the occurrence of all-grade adverse events within 6 months in participants regardless of RT-PCR SARS-CoV-2 status at baseline.<br><br>Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta.<br><br>Extended follow-up data cut-off was 29 August 2021. |
| **Serious adverse events** within 6 months[b] | 33 per 1000 | **37 per 1000**<br><br>(28 to 51) | **RR 1.12**<br><br>(0.83 to 1.52) | 5197<br><br>(1 RCT) | ⊕⊕⊖⊖<br><br>**Low**[g] | Tixagevimab/cilgavimab may result in little to no difference on the occurrence of serious adverse events within 6 months in participants regardless of RT-PCR SARS-CoV-2 status at baseline.<br><br>Participants had been exposed to SARS-CoV-2 wild-type and variants such as Alpha, Beta and Delta.<br><br>Extended follow-up data cut-off was 29 August 2021. |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

**CI:** confidence interval; **mAb:** monoclonal antibody; **RCT:** randomised controlled trial; **RR:** risk ratio; **RT-PCR:** reverse transcription polymerase chain reaction; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2.

**GRADE Working Group grades of evidence**

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for serious risk of bias (missing outcome data and potentially selection of the reported result).
[b]The safety population included participants with negative, positive and unknown RT-PCR SARS-CoV-2 status at baseline.
[c]Downgraded two levels for very serious imprecision, because of very low number of events and wide confidence intervals.
[d]We did not downgrade for serious risk of bias (measurement of the outcome) because for this outcome it is irrelevant whether participants were aware of the intervention received, and the number of people vaccinated was comparable in both arms.
[e]Downgraded two levels for very serious imprecision because of very low number of events.
[f]Downgraded one level for serious imprecision, because sample size did not meet optimal information size (6,435,640 participants) and one level for serious risk of bias (measurement of the outcome and potentially selection of the reported result).
[g]Downgraded one level for serious imprecision, because sample size did not meet optimal information size (55,674 participants) and one level for serious risk of bias (measurement of the outcome and potentially selection of the reported result).

**Summary of findings 2. Casirivimab/imdevimab compared to placebo for pre-exposure prophylaxis of COVID-19**

**Casirivimab/imdevimab compared to placebo in previously uninfected and unvaccinated people**

**Patient or population:** SARS-CoV-2 uninfected people without defined exposure, or with potential exposure to SARS-CoV-2

**Setting:** preventive measures

**Intervention:** casirivimab/imdevimab

**Comparison:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | N° of participants (studies) | Certainty in the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with casiriv- | | | | |

| | | imab/imde-vimab | | | | |
|---|---|---|---|---|---|---|
| **Infection with-SARS-CoV-2** within 6 months[a] | 96 per 1000 | **1 per 1000** (0 to 13) | **RR 0.01** (0.00 to 0.14) | 825 (1 RCT) | ⊕⊕⊖⊖ **Low**[b,c] | Casirivimab/imdevimab may decrease infection with SARS-CoV-2 within 6 months in participants SARS-CoV-2 antibody seronegative at baseline. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta. |
| **Development of clinical COV-ID-19 symptoms** within 6 months | 42 per 1000 | **1 per 1000** (0 to 11) | **RR 0.02** (0.00 to 0.27) | 969 (1 RCT) | ⊕⊕⊖⊖ **Low**[b,c] | Casirivimab/imdevimab may decrease development of clinical COVID-19 symptoms within 6 months. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta. |
| **All-cause mor-tality** within 6 months | 1 study reported mortality by week 24. There were no deaths. | | **Not estimable** | 969 (1 RCT) | ⊕⊖⊖⊖ **Very low**[b,d] | The evidence is very uncertain about the effect of casirivimab/imdevimab on mortality. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta. |
| **Admission to hospital** within 6 months | — | | — | — | — | We identified no studies reporting admission to hospi-tal. |
| **Quality of life** at longest follow-up | — | | — | — | — | We identified no studies reporting quality of life. |
| **Adverse events: grade 1 to 2** | — | | — | — | — | We identified no studies reporting grade 1 to 2 adverse events. |
| **Adverse events: grade 3 to 4** with-in 6 months | 13 per 1000 | **6 per 1000** (1 to 24) | **RR 0.44** (0.10 to 1.95) | 969 (1 RCT) | ⊕⊖⊖⊖ **Very low**[b,e] | The evidence is very uncertain about the effect of casirivimab/imdevimab on the occurrence of grade 3 to 4 adverse events within 6 months. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta. |
| **Adverse events: all grades** within 6 months | 483 per 1000 | **551 per 1000** (474 to 633) | **RR 1.14** (0.98 to 1.31) | 969 (1 RCT) | ⊕⊕⊖⊖ **Low**[b,f] | Casirivimab/imdevimab may increase the occurrence of all-grade adverse events within 6 months slightly. Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta. |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Serious adverse events** within 6 months | 8 per 1000 | **7 per 1000** (1 to 35) | **RR 0.82** (0.16 to 4.21) | 969 (1 RCT) | ⊕⊖⊖⊖ **Very low**[b,e] | The evidence is very uncertain about the effect of casirivimab/imdevimab on the occurrence of serious adverse events within 6 months.<br><br>Participants may have been exposed to SARS-CoV-2 wild-type and variants such as Alpha and Delta. |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk on the comparison group and the **relative effect** of the intervention (and its 95% confidence interval).

**CI:** confidence interval; **mAb:** monoclonal antibody; **RCT:** randomised controlled trial; **RR:** risk ratio; **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2.

**GRADE Working Group grades of evidence**

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The outcome was assessed in participants SARS-CoV-2 antibody seronegative at baseline.
[b]Downgraded one level for serious risk of bias (missing information regarding randomisation process and allocation concealment).
[c]Downgraded one level for serious imprecision, because of low number of events.
[d]Downgraded two levels for very serious imprecision, because there were no events, effect not estimable.
[e]Downgraded two levels for very serious imprecision, because of very low number of events and very wide confidence intervals.
[f]Downgraded one level for very serious imprecision, because of wide confidence intervals.

**Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6**

**2022-B-164**

**Kontaktdaten**

*Fachgesellschaften:*

***Deutsche Gesellschaft für Infektiologie (DGI)***

***Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN)***

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Indikation gemäß Beratungsantrag

Präexpositionsprophylaxe einer Coronavirus-19-Erkrankung (coronavirus disease 2019, COVID-19) bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht

**Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?**

Die Prophylaxe von nicht mit SARS-CoV-2-infizierten Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht erfolgt in Deutschland regelhaft nach Maßgabe der Ständigen Impfkommission des Robert-Koch Instituts (STIKO) mit zugelassenen Impfstoffen, welche nach intramuskulärer Verabreichung eine humorale und zelluläre Immunantwort induzieren können und im Verlauf eine Immunität gegenüber SARS-CoV-2 vermitteln (aktive Immunisierung). Für einige Risikogruppen mit angeborener oder erworbener Immundefizienz konnte nachgewiesen werden, dass entsprechende Impfungen zu keiner oder nur deutlich verminderter Immunantwort führen (1-5). Die STIKO hat Erkrankungen und immunsuppressive Therapien, bei denen eine relevante Einschränkung der Impfantwort zu erwarten ist in Ihren Empfehlungen übersichtlich dargestellt (Epidemiologisches Bulletin 21/2022). Als zusätzliches Kriterium können serologische Untersuchungen (i.d.R. anti-SARS-CoV-2 RBD/Spike IgG) nach erfolgten aktiven Immunisierungen i.S. einer Impferfolgskontrolle bei Patienten mit Immundefizienz herangezogen werden. Auch wenn keine klaren Grenzwerte existieren, welche als Korrelat für eine (fehlende) Immunität dienen, können *non-responder* und *low-responder* identifiziert werden und entsprechende Maßnahmen eingeleitet werden, um die Immunität zu verbessern. Hierzu zählen weitere Immunisierungsversuche mit Impfstoffen im Abstand von 4 Wochen und die SARS-CoV-2 Präexpositionsprophylaxe (PrEP), wobei durch Verabreichung von SARS-CoV-2 neutralisierenden monoklonalen Antikörpern (nMAK) eine passive Immunisierung erfolgt.

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In Deutschland sind aktuell mehrere nMAK-Präparate zur SARS-CoV-2 PrEP zugelassen. Als wirksam gegenüber aktuell zirkulierenden Virusvarianten (BA.2, BA.4 und BA.5) gilt auf Grundlage von in vitro Untersuchungen jedoch ausschließlich das seit März 2022 zugelassene Kombinationspräparat Tixagevimab/Cilgavimab (AZD7442, Evusheld), bzw. genauer der Bestandteil Cilgavimab dieses Präparats (6-8). In einer Phase III PROVENT-Studie (NCT04625725) mit Daten von 5172 Probanden konnte bei Probanden, die mit Tixagevimab/Imdevimab behandelt wurden eine relative Reduktion von SARS-CoV-2 Infektionen um 77% (bei median 6,5 Monaten Follow-Up) nachgewiesen werden [absolute Risikoreduktion 1% (17/1731) auf 0,2% (8/3441)]. Die relative Risikoreduktion für eine symptomatische COVID-19 Erkrankung lag entsprechend der Auswertung bei 83% (9, 10). Die Studiendaten aus PROVENT schließen im zeitlichen Kontext Infektionen mit Alpha-, Beta-, Gamma- und Delta-Varianten ein, nicht aber Infektionen mit Omikron-Varianten. In der aktuellen Konstellation mit BA.4/5-Dominanz wird europaweit die Notwendigkeit einer Erhöhung der der zugelassenen Evusheld-Dosis von 150/150 mg auf 300/300 mg diskutiert. Die U.S. amerikanischen Behörden haben während der dortigen Dominanz der Subvariante BA.1 auf Grundlage von eingereichten Daten und Modellen des pharmazeutischen Unternehmens bereits diese höhere Dosierung empfohlen (11). Eine Entscheidung der EMA wird im September erwartet.

Anwendung findet die SARS-CoV-2 PrEP insbesondere in großen Zentren mit hämato-onkologischem Schwerpunkt, in Transplantationszentren (insb. in der Nephrologie) und in Bereichen, in denen immunsuppressive Therapien verwendet werden, wie in der Rheumatologie und in der Neurologie (Behandlung der Multiplen Sklerose). Aufgrund der stetigen Generierung neuer Evidenz und der dynamischen Gesamtsituation hinsichtlich Zulassung, Kostenerstattung und Logistik für nMAK, sowie allgemein relativ niedrigem Bekanntheitsgrad in der Peripherie, wird die PrEP in Deutschland primär im stationären Umfeld, in spezialisierten Hochschulambulanzen und an Schwerpunktzentren angewendet. Daraus resultierend wird mit großer Wahrscheinlichkeit bisweilen nur ein Teil der Patienten mit einer Indikation eine SARS-CoV-2 PrEP, ggf. auch in Ergänzung zur aktiven Immunisierung, erhalten.

**Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der „Präexpositionsprophylaxe einer Coronavirus-19-Erkrankung (coronavirus disease 2019, COVID-19) bei Erwachsenen und Jugendlichen ab 12**

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**Jahren mit mindestens 40 kg Körpergewicht“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

In der AWMF S1- Leitlinie werden Schritte zur Indikationsstellung einer PrEP aufgezählt. Unter anderem muss eine relevante Grunderkrankung oder Therapie vorliegen, die mit einer relevanten Beeinträchtigung der Impfantwort der aktiven Immunisierung einhergeht und ein serologisches Impfversagen nach STIKO-konformer Impfung nachgewiesen werden. „Eine PrEP mittels passiver Immunisierung sollte Patienten angeboten werden, welche durch relevante Immundefizienz, z.B. in Rahmen einer hämato-onkologischen Grunderkrankung, einer Therapie mit Zytostatika oder Immunsuppressiva, einem angeborenen oder anderweitig erworbenen Immundefekt, ein deutlich erhöhtes Risiko für einen schweren Verlauf im Falle einer SARS-CoV-2 Infektion aufweisen und serologisch nachweislich nicht ausreichend auf eine erweiterte aktive Immunisierung mit einem der verfügbaren Impfstoffe angesprochen haben.“ (12). Es wird weiterhin explizit darauf hingewiesen, dass die PrEP kein Ersatz für (weitere) aktive Immunisierungsversuche sein soll. Personen, welche die in der Leitlinie genannten Kriterien erfüllen, können mit zwei intramuskulären Injektionen Tixagevimab/Cilgavimab behandelt werden. In Einzelfällen ist es medizinisch begründbar auf den Nachweis eines serologischen Impfversagens (erst) nach Vollendung der primären Impfserie zu verzichten. Dies gilt für spezielle Personengruppen, welche myeloablative oder spezielle immunsuppressive Therapien erhalten (12).

Eine Indikation zur SARS-CoV-2 PrEP mittels nMAK können zudem Personen haben, welche aus medizinischen Gründen nachweislich nicht mit einer aktiven Immunisierung geschützt werden können. Dies betrifft Personen mit (sehr seltenen) schwerwiegenden Impfkomplikationen, z.B. anaphylaktischer Schock, welche eine Kontraindikation für eine nochmalige aktive Immunisierungen gegen SARS-CoV-2 darstellen.

Es existieren aktuell keine vergleichbaren, als wirksam eingestuften medikamentösen Optionen zur Prophylaxe von COVID-19 mittels nMAK oder anderer antiviral wirkender Medikamente. Personen, welche zu den o.g. Risikogruppen gehören und nicht oder nicht in ausreichendem Maße auf eine aktive Immunisierung ansprechen, sollten die

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allgemeinen Infektionsschutzmaßnahmen beherzigen und sich bei Exposition oder Kontakt sehr frühzeitig auf SARS-CoV-2 testen lassen, damit eine antivirale Therapie eingeleitet werden kann (beobachtetes Abwarten).

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