# Health Technology Assessment Procedures for Monoclonal Antibodies for the Treatment and Prevention of COVID-19

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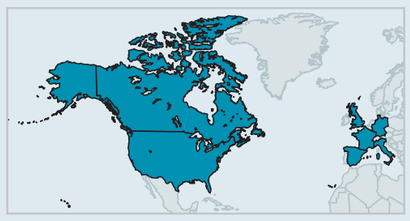
## BACKGROUND

- The SARS-CoV-2 virus that causes coronavirus disease 2019 (COVID-19) is thought to have emerged from China in December 2019 and was declared a pandemic by the World Health Organization in March 2020.[1]
- The pandemic created an unprecedented need for health technologies to be developed and made available with extreme urgency. In most cases, this meant that standard health technology assessment (HTA) procedures were bypassed.
- Monoclonal antibodies (mAbs) were among the first therapies approved for use against SARS-CoV-2 because they can be designed to target the virus with high specificity and reliability, making them likely to be effective for both the prevention and treatment of COVID-19.[2]
- As the extreme urgency of the response to the pandemic lessens over time, it is expected that agencies using HTA procedures will begin to use standard procedures for assessing COVID-19 technologies.

## METHODS

- MAb technologies that were available for use against SARS-CoV-2 in North America or Europe by the end of May 2022 were identified. Publicly available information relating to each country's HTA procedures and outcomes (if available) were identified from each agency's website in May 2022 and updated at the end of September 2022. Relevant information was extracted and qualitatively assessed.



## OBJECTIVE

- To research the procedures that have been used to assess COVID-19 technologies in the United States (US), Canada, and Europe's 5 largest pharmaceutical markets (France, Germany, Italy, Spain, and the United Kingdom [UK]); to assess whether the procedures for assessing COVID-19 technologies differ from established procedures for agencies using HTA procedures; and to assess which mAbs for the treatment and prevention of COVID-19 have been assessed to date.

## RESULTS

### Country Approaches to COVID-19 HTA

- Of the 7 chosen countries, 2 (Italy, Spain) were excluded from analysis because they use decentralised HTA procedures. The remaining 5 countries have centralised HTA procedures and were included in the analysis.
- For 3 of the 5 included countries (UK, Canada, US), standard HTA procedures were adapted to assess COVID-19 technologies as described in Table 1. In general, the adaptions were considered to accelerate rather than alter standard HTA procedures. The Institute for Clinical and Economic Review (ICER) also included additional steps into its procedures to assist decision-making, such as using both cost-recovery and cost-effectiveness analysis.
- For 2 of the 5 included countries (France, Germany), it was unclear whether standard or adapted procedures were being used to assess COVID-19 technologies.

**Table 1. Country Adaptions to HTA Procedures**

| Country (agency) | Adaptions to standard HTA procedures |
|---|---|
| UK (NICE) | Same process and steps as standard, but the steps are resequenced and with shorter timelines.[3] |
| Canada (CADTH) | A modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs. The contents of the modified approach are unclear.[4-6] |
| US (ICER) | Adaptions involve more flexible timelines, less opportunity for stakeholder input (because of the need for rapidity), assessments that will be subject to revisions, use of cost-recovery analysis in addition to cost-effectiveness analysis to inform pricing considerations in the context of a pandemic, use of a cost-effectiveness threshold of $50,000 in addition to more commonly cited thresholds, and use of a health system perspective in generating cost-effectiveness estimates.[7] |

CADTH = Canadian Agency for Drugs and Technologies in Health; NICE = National Institute for Health and Care Excellence.

### Monoclonal Antibody Technologies for COVID-19

- Overall, 8 mAb technologies were identified as being available for use against SARS-CoV-2 in the 5 countries assessed by end of May 2022.
- 4 mAbs are the subject of HTA. Casirivimab with imdevimab, and sotrovimab have been considered by 5 agencies. Tocilizumab has been considered by 2 agencies, and sarilumab has been considered by 1 agency. Information about the HTA for each mAb is presented in Table 2.
- No HTA information could be found for the remaining 4 COVID-19 mAbs (bebtelovimab, bamlanivimab with etesevimab, regdanvimab, tixagevimab with cilgavimab). It is unclear from each agency's publicly available information why these mAbs have not been subjected to HTA. In some cases, it may be because the mAb is not relevant. For example, bamlanivimab with etesevimab, and bebtelovimab are unlikely to be used in Europe because bamlanivimab with etesevimab has been withdrawn from the European Medicines Agency's regulatory process,[13] and bebtelovimab has not been made available in Europe.[14] It may also be that further evidence is required before HTA can begin. CADTH undertook relatively early assessments of several mAbs in 2021 and the lack of evidence prevented conclusions being made, therefore it may be considered pertinent to time HTA appropriately so that the conclusions made have the most value.
- No HTA information has been published on the use of mAbs for preventing SARS-CoV-2 infection or the development of COVID-19 disease.

**Table 2. Summary of Identified HTAs of Monoclonal Antibodies for Use Against SARS-CoV-2 and Outcomes as of September 2022**

| | Canada (CADTH) | France (HAS) | Germany (G-BA) | UK (NICE) | US (ICER) |
|---|---|---|---|---|---|
| **Casirivimab with imdevimab** | Unable to determine place in the COVID-19 treatment pathway based on 1 RCT that included patients with a confirmed SARS-CoV-2 infection[4] | Early access authorisation granted for the treatment of confirmed COVID-19 based on 1 RCT and data gathered from previous use in France[8] | In progress[9] | In progress[3] | Removed from scope because of reduced susceptibility to Omicron[10] |
| **Sarilumab** | Unable to determine place in the COVID-19 treatment pathway based on 2 RCTs of patients with suspected or confirmed SARS-CoV-2/COVID-19 disease[6] | — | — | — | — |
| **Sotrovimab** | No relevant evidence identified[5] | Opinion in favour of reimbursement for the treatment of COVID-19 based on 1 RCT[11] | In progress[12] | In progress[3] | Removed from scope because of reduced susceptibility to Omicron[10] |
| **Tocilizumab** | Unable to determine place in the COVID-19 treatment pathway because of variation in key aspects of 10 included trials such as inclusion criteria, standard of care, outcomes, definitions, and other factors[6] | — | — | In progress[3] | — |

G-BA = Gemeinsamer Bundesausschuss; HAS = Haute Autorité de Santé.

## DISCUSSION

- Relevant evidence was lacking for most HTAs. Where evidence was available, the HTA faced challenges because clinical trials used differing designs, definitions, outcomes, and standards of care.
- Further complexities include the impact of vaccine rollout and the emergence of SARS-CoV-2 variants and subvariants. The use of effective vaccines may initially reduce the need for mAbs, but as the SARS-CoV-2 virus evolves, vaccines and mAb treatments may become less effective against newer variants and subvariants. Therefore, the timing of clinical trials may affect clinical and cost-effectiveness estimates.
- Ongoing reviews and use of real-world evidence relevant to the country of interest (in terms of COVID-19 incidence, vaccination rate, variants of concern, etc.) is likely to form an important part of HTAs of COVID-19 technologies in the future.

## CONCLUSIONS

- Agencies are applying HTA procedures to COVID-19 technologies. Assessments, particularly for COVID-19 mAbs, will face challenges, and they may be reliant on real-world evidence.
- HTA decisions may lack longevity and will require frequent updates. Nonetheless, the heterogeneous nature of the pandemic and the rapidly changing landscape will continue to make HTA of COVID-19 therapeutics a challenge.

## REFERENCES

1. WHO. https://www.who.int/news/item/29-06-2020-covidtimeline.
2. Hwang Y-C, et al. J Biomed Sci. 2022;29(1):1.
3. NICE. 2022. https://www.nice.org.uk/guidance/indevelopment/gid-ta10936.
4. CADTH. 2021. https://www.cadth.ca/sites/default/files/covid-19/hc0015-ha0009-REGN-COV2-tecnology-review.pdf.
5. CADTH. 2021. https://www.cadth.ca/sites/default/files/covid-19/RC1384%20Sotrovimab%20for%20COVID%20Final.pdf.
6. CADTH. 2021. https://cadth.ca/sites/default/files/covid-19/hc0014-001-tocilizumab-and-sarilumab-update1-mar25.pdf.
7. ICER. 2020. https://icer.org/wp-content/uploads/2020/10/Adaptations-to-the-ICER-methods-for-evaluation-related-to-treatments-for-COVID_July18.pdf.
8. HAS. 2022. https://www.has-sante.fr/jcms/p_3318295/fr/ronapreve-casirivimab-imdevimab.
9. G-BA. 2022. https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/819/.
10. ICER. 2022. https://icer.org/wp-content/uploads/2021/08/ICER_COVID_19_Final_Evidence_Report_051022.pdf.
11. HAS. 2022. https://www.has-sante.fr/jcms/p_3344400/en/xevudy-sotrovimab-covid-19.
12. G-BA. 2022. https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/835/.
13. EMA. 2021. https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/bamlanivimab-etesevimab-covid-19#all-documents-section.
14. Medical Xpress. 2022. https://medicalxpress.com/news/2022-07-key-covid-drug.html.

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