NICE National Institute for Health and Care Excellence

COVID-19 technology appraisal recommendations: surveillance and rapid update process statement

April 2023

1 Introduction

1.1 What this process statement is for

1.1.1 This process statement explains how NICE maintains and updates technology appraisal recommendations on medicines for preventing and treating COVID-19.

1.1.2 It gives an overview of the methods and process used for surveillance and for updates to recommendations.

1.1.3 It only covers medicines on which final technology appraisal guidance has been published.

1.2 Background

1.2.1 A process is needed to rapidly update technology appraisal recommendations on medicines for COVID-19. This may be in response to several triggers:

- new clinical evidence
- a change in the disease that significantly changes the hospitalisation or mortality rate
- emergence of a new variant of SARS-CoV-2 that affects the effectiveness of a medicine.

1.2.2 Updates are done based on triggers indicating that current recommendations are out of date, rather than on including evidence on an ongoing basis.

2 Methods

2.1 Overview

2.1.1 The process involves continuous surveillance and assessing triggers for updates. The surveillance approach considers data from the UK Health Security Agency (UKHSA), real-world evidence, information submitted by companies (including in vitro data) and published trial evidence.

2.1.2 For in vitro data, only data that follows the principles outlined in the Medicines and Healthcare products Regulatory Agency guidance on responding to emerging COVID-19 variants of concern is considered.

2.1.3 Updates are routed through a rapid technology appraisal update process, so that the legal funding requirement associated with

positive technology appraisal recommendations is maintained. The process is outlined in figure 1.

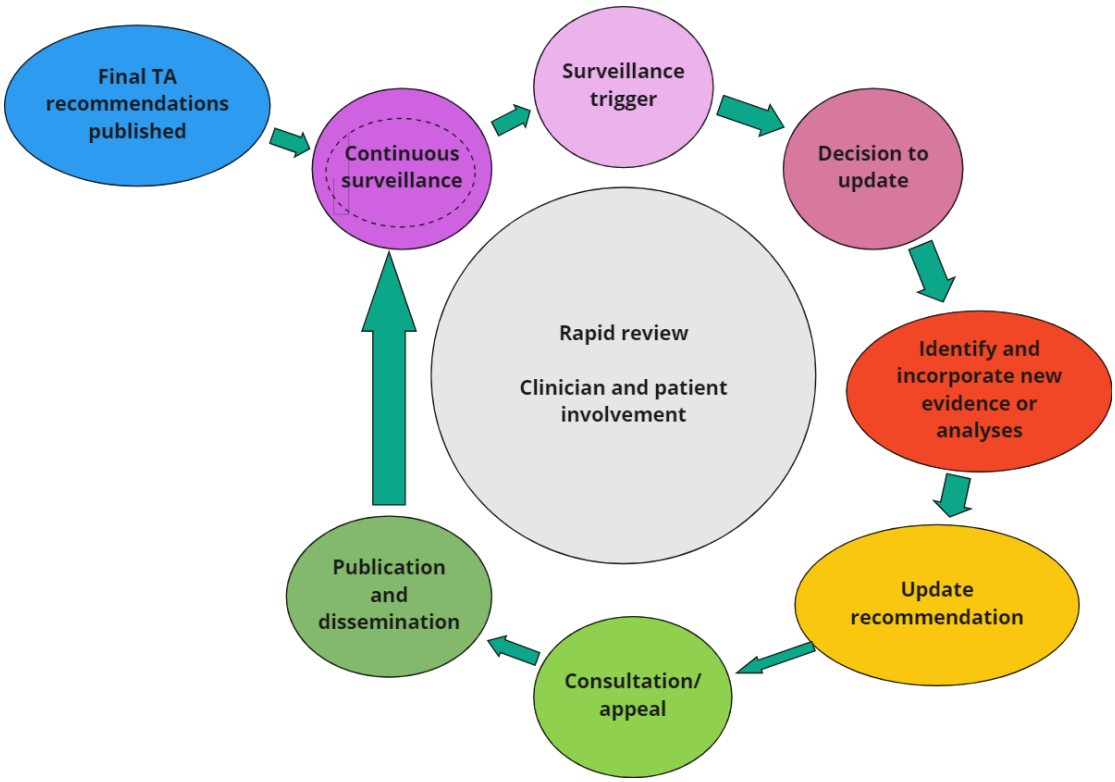


Figure 1 Rapid review cycle

2.2 Continuous surveillance

2.2.1 The aim of surveillance is to check that recommendations are up to date. The maintenance of technology appraisal recommendations on medicines for COVID-19 is supported by continuous surveillance to identify triggers for update.

2.2.2 A multifaceted surveillance approach is needed to identify triggers for update because different triggers could affect recommendations. This approach includes 3 key surveillance

streams: evidence, system intelligence and stakeholder submission.

Evidence surveillance stream

2.2.3 New evidence may indicate that, for a particular subgroup or the whole population, a not recommended technology could be clinically or cost effective or a recommended technology is no longer clinically or cost effective.

2.2.4 NICE regularly searches for new published trial evidence on COVID-19. Routinely, this is on a weekly basis. But the frequency will be reviewed over time, depending on the amount of new evidence being published. Currently, a broad COVID-19 search is done, and relevant studies are triaged to topic areas to consider their impact in detail.

2.2.5 A weekly search is also done for in vitro evidence. It involves considering the impact of studies on the in vitro neutralisation activity of the monoclonal antibodies (MABs) with technology appraisal recommendations against variants that have emerged since those recommendations were developed.

2.2.6 Key ongoing research is also monitored to supplement evidence searches. Relevant research studies are identified throughout recommendation development, updates and surveillance. Ongoing studies are continually monitored. The impact of information on recommendations is considered as soon as it becomes available, and may inform the decision about whether to update.

System intelligence surveillance stream

SARS-CoV-2 variants

2.2.7 The UKHSA's technical briefing documents on novel SARS-CoV-2 variants, produced and published on a monthly basis, are used as a source of intelligence on new SARS-CoV-2 variants under

investigation in the UK. The technical briefings are used as a resource to understand:

- growth rates of new SARS-CoV-2 variants or sublineages that have emerged since the recommendations were developed
- any new mutations identified in circulating variants, and the potential effect this may have on the neutralisation activity of MABs.

2.2.8 The interim methods framework outlined in appendix 1 is used to determine whether changes in circulating SARS-CoV-2 variants since recommendations were developed have been sufficient to trigger an update.

Real-world evidence

2.2.9 NICE assesses the effect of real-world evidence on recommendations. This includes data on:

- changes in baseline hospitalisation rates associated with SARS-CoV-2 infection because a large change in hospitalisation rates since recommendations were developed could affect the cost effectiveness of the medicines.
- the relative effects of Paxlovid compared with sotrovimab to support conclusions about the ongoing efficacy of sotrovimab because the effect of Paxlovid is not expected to vary depending on SARS-CoV-2 variants.

2.2.10 Data is reviewed at regular intervals, for example, to supplement and inform an ongoing surveillance review and help in any decision to update.

Intelligence gathering

2.2.11 A pragmatic targeted intelligence gathering approach, based on the evolving system and policy context, is used to gather feedback

from the broader health and care system and NICE stakeholders. This might include:

- external queries and comments received since publishing recommendations.
- information about implementing recommendations.
- changes in the licensing status of medicines
- updates or new national policy.

Stakeholder submission surveillance stream

Stakeholder and company data

2.2.12 Stakeholders (including companies) may have unpublished evidence that they would like to submit for consideration of how it might affect recommendations. This can be done by emailing covidsurveillance@nice.org.uk.

2.2.13 Company submissions of in vitro data will only be considered if it follows the principles outlined in the Medicines and Healthcare products Regulatory Agency guidance on responding to emerging COVID-19 variants of concern.

Changes in costs

2.2.14 A change in the price of a medicine may have an effect on recommendations. It is expected that the company marketing the medicine would inform NICE of such a change. This can be done by emailing covidsurveillance@nice.org.uk.

Decision making

2.2.15 If a potential trigger for update is identified through evidence, system intelligence or stakeholder submission surveillance, the impact on recommendations will be considered. The process of

considering triggers for impact is known as a surveillance review and the outcome is a surveillance decision.

2.2.16 Stakeholder consultations on surveillance decisions are not held routinely and are not published on the NICE website.

2.2.17 All surveillance decisions go through a validation and approval process at NICE.

2.3 Types of surveillance decisions and outcomes.

No update.

2.3.1 A 'no update' decision is reached when newly identified evidence or intelligence (including from topic experts, implementation, related guidance and policy) does not suggest that a change to recommendations would be likely. Alternatively, new evidence or intelligence may increase certainty in the current advice (supporting evidence). This assessment is done by the NICE team and no information is published if the decision not to update is reached.

Withdraw a recommendation.

2.3.2 If the marketing authorisation for a technology is removed or substantially altered, withdrawal of a recommendation is considered.

Refreshing recommendations.

2.3.3 When simple changes to recommendations or sections are needed that do not need further validation, the recommendations are refreshed with the editorial team. Examples include:

- changing existing hyperlinks
- adding new hyperlinks
- adding new guidance or a cross-reference
- changing terminology
- changes to ensure consistency across the suite of guidance

- amending text for clarity and to help implementation.

Rapid update of recommendations.

2.3.4 Guidance is updated if there are changes to the evidence base, clinical pathway or economic case that are likely to have a material effect on the recommendations. Guidance on MABs may be updated if there is a signal from in vitro data suggesting that:

- a MAB previously thought not to work against a SARS-CoV-2 variant may have neutralising activity against a new circulating dominant variant
- a MAB previously thought to work against a SARS-CoV-2 variant may no longer retain neutralising activity against a new circulating dominant variant.

2.4 Rapid updates process

Starting the rapid update process.

2.4.1 When the rapid update process is triggered by a change in evidence, the decision to proceed may be automatic, or depend on the manufacturer agreeing to pay a cost-recovery charge. At this stage, stakeholders will be alerted that evidence surveillance has triggered the rapid update process and outline next steps, including

whether proceeding is dependent on the company. Table 1 outlines the various recommendation scenarios.

Table 1 Recommendation scenarios

Current recommendation	Nature of change in evidence	Decision to proceed with update
Recommended	Evidence indicates technology may no longer be clinically or cost effective for a particular subgroup or whole population	Automatic
Recommended, but only for a subgroup in the marketing authorisation	Evidence indicates technology may be clinically or cost effective for a broader population within the marketing authorisation	Company agrees to pay the cost-recovery charge
Not recommended	Evidence indicates technology may be clinically or cost effective for a particular subgroup or whole population	Company agrees to pay the cost-recovery charge

Cost recovery.

2.4.2 NICE must recover costs for technology appraisal assessments. The cost-recovery charge associated with the rapid update process is £125,196 for 23/24. This is a new charge for the rapid COVID-19 review process and includes building a new surveillance function for the TA programme.

2.4.3 Because of the speed of potential reviews, it may not be possible to issue the charging invoice and receive payment before starting the rapid update. However, as part of the charging process the company will still need to provide NICE with a Unique Reference Number (URN) as their commitment to pay for the update. NICE

reserves the right to not publish final guidance until payment in full has been received.

Decision making committee.

2.4.4 To rapidly provide recommendations in the light of new evidence, a decision-making committee is set up. This includes a small subset of technology appraisal committee members and is likely to be the chair and vice-chair of a technology appraisal committee, a lay member, a clinical member and a cost-effectiveness specialist.

2.4.5 Additional optional attendees could include 2 members of the NICE COVID-19 NG191 guideline panel representing primary and secondary care. If NICE and Healthcare Improvement Scotland/Scottish Medicines Consortium continue to collaborate on COVID-19 guidance, it would also include a member of the Scottish Medicines Consortium committee.

2.4.6 A clinical expert and patient expert are recruited as advisory (non-decision making) members of the committee to provide written evidence, clarify issues about the evidence base and participate in committee meetings. They need to commit to standing, as required, for 12 months. These experts are identified by the NICE team from the pool of clinical and patient experts who have previously been involved in developing NICE guidance on COVID-19.

2.4.7 This committee's consideration of the evidence is based on the methods of economic evaluation outlined in section 4 of the health technology evaluation manual. Also, the committee may draw on

the advice in the In Vitro Advisory Group methods framework outlined in appendix 1.

2.4.8 The committee's decision making and recommendations follow section 6 of the health technology evaluation manual.

Stakeholder involvement

2.4.9 Because the rapid update process occurs as soon as possible after a surveillance trigger, no submissions are invited from stakeholders, including the company. But NICE may request data or clarification from stakeholders for use in the assessment.

2.4.10 Given the need to rapidly assemble the committee, it is not possible for its meetings to be held in public. Two company representatives are invited to answer any questions of clarification from the committee.

2.4.11 Stakeholders are informed if a rapid update is triggered and are able to participate in consultations and appeal against the recommendations (consultees only).

2.4.12 All non-company stakeholders that have completed a NICE confidentiality and undertaking form for COVID-19 appraisals continue to be stakeholders. New stakeholders may request to participate and may do so if they complete the NICE confidentiality and undertaking form.

Data analysis

2.4.13 For some updates, the data analysis is done by the NICE team and presented to the committee, for example, if the trigger for update is based on in vitro data.

2.4.14 Depending on the nature of the new evidence (such as new trial data that would need to be incorporated into the model), additional work may be requested from an external assessment group.

Representatives from the external assessment group may then be invited to attend a committee meeting.

Consultation and appeals

2.4.15 The approach to consultation and appeals depends on the nature of the update to the recommendation (see table 2). The appeal process will follow NICE's technology appraisal appeals process guide.

Table 2 Nature of recommendation update

Nature of change in recommendation	Stakeholder input	Approach to appeal
No change to a recommendation	NICE will issue draft guidance for a short consultation with registered stakeholders for 7 calendar days	The committee will then meet again to consider the consultation responses. After this, final draft guidance will be issued for appeal.
A previously positive recommendation being withdrawn	NICE will issue draft guidance for a short consultation with registered stakeholders for 7 calendar days	The committee will then meet again to consider the consultation responses. After this, final draft guidance will be issued for appeal.
A previously negative recommendation becomes positive	No consultation	Final draft guidance will be issued for appeal

Publication

2.4.16 Following resolution of any appeals, NICE publishes the final guidance. At this point, the 90 -day funding implementation period applies for commissioners. Requests to vary the funding requirement to take account of net budget impact will be considered in line with section 5.9 of the health technology evaluation manual.

Timelines

2.4.17 The timelines depend on the surveillance trigger and whether further work from the external assessment group is needed, for example, if a new trial publishes. But there is likely to be less need

for speed in this scenario. The quickest timeline will be when in vitro data suggests effectiveness of a medicine against current SARSCoV2 variants. This timeline is outlined in table 3. If more time is needed for external assessment group review, this is added at the start of the process, before committee consideration of the

evidence. For example, if 4 weeks is needed, all subsequent timeline steps move by 4 weeks.

Table 3 Timeline for when in vitro data suggests effectiveness of a medicine against current variants

Week	Action
Week -4	Surveillance trigger identified
Week -3	Surveillance review done
Week -2	Surveillance decision to update
Week -1	Planning the update into the work programme
Week 0	Inform stakeholders of update
Week 1	Preparation of evidence for committee
Week 2	Committee consideration of evidence
Week 3	High-level outcome to stakeholders Preparation of guidance document
Week 4	Positive recommendation: guidance issued for appeal (3 weeks) Negative recommendation: guidance issued for 1 week consultation
Week 5	Negative recommendation: consultation period ends
Week 6	Negative recommendation: committee considers consultation responses
Week 7	Positive recommendation: appeal period ends Negative recommendation: high-level outcome to stakeholders Preparation of guidance document
Week 8	Positive recommendation: final guidance publishes if no appeals Negative recommendation: guidance issued for appeal (3 weeks)

3 Publication

3.1.1 The updated technology appraisal guidance is published on the NICE website and cross-referenced in NICE's COVID-19 rapid guideline: managing COVID-19.

4 Conflict of interests

4.1.1 NICE staff comply with NICE's declaration of interests' policy.

5 Equality and diversity

5.1.1 Updates to recommendations are developed in line with NICE's equality scheme and declaration of interests' policy.

6 Review date

6.1.1 This process statement will be reviewed in March 2024.

Appendix 1: In vitro data on neutralising monoclonal antibodies for COVID-19: interim methods framework

6.2 Background

6.2.1 NICE has published a suite of guidelines on COVID-19. It has also developed a multiple technology appraisal on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19, and a single technology appraisal on tixagevimab plus cilgavimab for preventing COVID-19 is in development.

6.2.2 The virus, SARS-CoV-2, that causes COVID-19 evolves over time, resulting in new variants and subvariants. Clinical-effectiveness evidence for neutralising monoclonal antibodies (nMABs) is from clinical trials done before the Omicron variant became the predominant variant. Also, because SARS-COV-2 is evolving rapidly, it is difficult to do clinical trials in real time. This means that clinical trials on new variants will not be completed in time to help understanding about how effective nMABs are against those variants before the virus evolves again. It is also unlikely that findings from observational studies will be reported in the timeframe needed to inform decision making. So, NICE needs to develop methodology to help understanding about whether nMABs developed for a previous variant can be used for people infected, or at risk of infection, with a newer variant.

6.2.3 With little clinical trial and observational data on the efficacy of nMABs against newer variants, policy makers are using in vitro data. This data is generated from laboratory studies outside of a living body and usually involves cell culture. For these reasons, in vitro studies are not thought to fully replicate the conditions seen in humans, and the evidence type and quality differs from clinical trial evidence. In vitro data on nMABs is from laboratory studies

investigating their neutralisation effect on cells infected with the SARS-CoV-2 variant of interest.

6.2.4 In general, some in vitro data suggests that some nMABs may have reduced neutralisation against some of the more recent variants in circulation, such as the Omicron variant and subvariants. Timely decisions need making on whether these nMABs should be recommended for pre-exposure prophylaxis and treatment of COVID-19. But the clinical-effectiveness and in vitro data covers different situations because clinical-effectiveness data was obtained when previous SARS-CoV-2 variants were dominant and in vitro data has been generated from newer circulating variants. The fundamental challenge for decision making is around how in vitro data translates into clinical and health economic outcomes in the absence of clinical studies in people infected, or at risk of infection, with new SARS-CoV-2 variants.

6.2.5 This document outlines a framework to assist technology appraisal and guideline committees in making these decisions. See below for a framework overview.

6.3 Scope of this framework

6.3.1 This framework applies to in vitro data on nMABs for pre-exposure prophylaxis or treatment of COVID-19 only. Although there has been some suggestion that antivirals (for example, Paxlovid) could work differently against different variants, this has not transpired to date, so the principles outlined here do not cover those treatments.

6.4 How this framework was developed

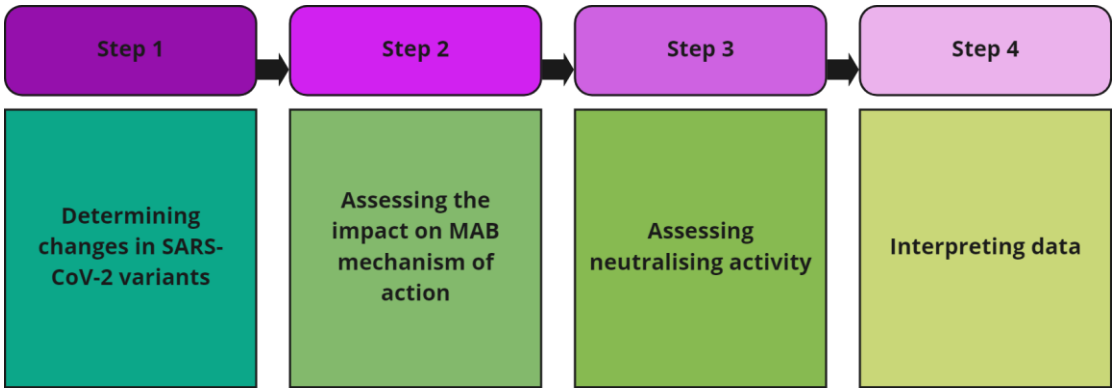
6.4.1 In December 2022, NICE established an in vitro data expert advisory group (In Vitro Advisory Group [IVAG], see appendix 2). This included people with expertise in using and understanding COVID-19 in vitro data, or making clinical and health economic decisions in the setting of uncertainty. The main aims of this group were to advise on translating in vitro evidence on the neutralising

activity of nMABs into clinical and health economic outcomes to help decision making for NICE guidance. This was to determine when nMABs were likely to be less effective or ineffective in the event of a new variant emerging, and to describe the uncertainty around those decisions. The group also advised on the type of data needed to inform decision rules and how to use the data. The group met times during December 2022, and the discussions were used to generate this interim framework and decision rules.

6.4.2 This is a living framework and will be updated as new information emerges.

6.5 Framework overview

Summary of key considerations for using in vitro data on the effectiveness of nMABs against new variants



Step 1: Determining changes in SARS-CoV-2variants

Anticipated future trajectory of circulating variants

6.5.1 The IVAG acknowledged the uncertainty around predicting the incidence of future variants, with reduced COVID-19 testing in the UK adding to this uncertainty. But, reflecting on the patterns and emergence of previous variants, the IVAG anticipated that these principles will apply:

- It is certain that new SARS-CoV-2 variants will emerge with significantly different antigenic properties. It is also possible but

less likely that new variants will have different properties in terms of transmissibility, cell tropism and disease severity. It is expected that there will continue to be 2 types of evolution of the virus:

  - frequent incremental changes leading to small changes in antigenicity
  - infrequent antigenic shifts leading to selective sweep of a new fit variant.

- There is a certain level of standing genetic diversity that can fluctuate over time and 'changes' to viral genotype are a continuous process. Historically, there has been a major sweep approximately every 6 months. What constitutes a major sweep of a new lineage is somewhat subjective. Less dramatic changes are a continuous process. At any given time, some lineages will be growing and slowly replacing other lineages. Antigenically similar previous variants are unlikely to re-emerge because of population immunity but cannot be ruled out. It is possible that a new lineage could emerge that is partially or completely ancestral to a previous lineage like Delta, but this would likely be antigenically distinct.
- A future variant could be neutralised by a given nMAB when this has not been seen for previous variants.

6.5.2 Based on the above assumptions, the IVAG supports steps for regular monitoring of the emergence of variants and determining whether further action is needed.

Surveillance and identification of new emergent variants

6.5.3 The UK Health Security Agency (UKHSA) has a surveillance system in place for monitoring the emergence of changes to SARS-CoV-2 variants. This intelligence will be shared with NICE.

6.5.4 Also, the World Health Organization (WHO) defines variants of concern as those meeting the following criteria:

- increase in transmissibility or detrimental change in COVID-19 epidemiology, or
- increase in virulence or change in clinical disease presentation, or
- decrease in effectiveness of public health and social measures or available diagnostics, vaccines and therapeutics.

6.5.5 The WHO also has a list of variants that it monitors. NICE will also use this information as a source of intelligence. But it is recognised that the WHO's information is not always relevant to the UK because there have been previous variants of concern recognised by WHO (for example, Beta) that have been important globally but have never become dominant in the UK.

Monitoring increasing prevalence of a variant (or subvariant)

6.5.6 Variants of interest are typically antigenically different from previous variants and generally exhibit 'immune escape', that is, the person's immune system is no longer able to recognise and eliminate the virus. For this reason, the variants tend to quickly

increase in prevalence across a population over a period of weeks to months.

Threshold for determining a new 'dominant' variant (or subvariant)

6.5.7 Predicting when a variant will become dominant is a complex task and depends on expert interpretation of evidence about the relative growth rates of cocirculating variants and interpretation of functional mutations in novel variants. There is also a distinction between genetic difference (such as a genetic shift away from a predominant variant) and immune escape, which links to the ability of a subvariant to increase in prevalence and replace other variants. The IVAG indicated that it is usually clear if a variant will replace others once it has reached about 10% sample frequency and has a logistic growth rate of over 25% per week. Intelligence from the UKHSA and the WHO should indicate which variants are emerging and increasing in prevalence, and should be used as a trigger to move to the next step in this framework.

6.5.8 Actions in this step of the framework:

- UKHSA shares surveillance intelligence on emerging variants that it anticipates will increase in prevalence or become dominant in the UK.
- NICE considers the UKHSA data in addition to the WHO's information on variants of concern.
- NICE, with input from the UKHSA, will decide whether there has been a step-change in variants from those that informed the decisions when the guideline recommendations were developed.

Decision point: If a new variant is becoming dominant, NICE will move to the next step on assessing impact on nMAB mechanism of action.

Step 2: Assessing impact on MAB mechanism of action

MAB and mechanism of action

6.5.9 MABs have different mechanisms of action in terms of which proteins they bind to, meaning they can neutralise the SARS-CoV-2 virus in different ways. This is important when considering the MAB of interest. Some treatments include a combination of 2 antibodies and it is possible that one but not the other may retain activity against a variant. NICE is evaluating the clinical and cost effectiveness of 3 nMABs; these have the following reported mechanism of action against the SARS-CoV-2 virus:

- **Casirivimab plus imdevimab (Ronapreve)** is a combination of 2 non-competing recombinant human IgG1 MABs. This combination targets 2 distinct epitopes (the part of the virus to which the nMABs attach) binding simultaneously to the S protein receptor-binding domain. Casirivimab plus imdevimab block the virus's interaction with the angiotensin-converting enzyme 2 (ACE2) receptor that is used by the virus to enter host cells.
- **Sotrovimab (VIR-7831)** is a dual-action, engineered human IgG1 MAB that binds to a conserved epitope on the spike protein receptor-binding domain of SARS-CoV-2. Amino acid substitutions in the Fc region result in a median half-life of 49 days while retaining the ability of the antibody to recruit effector functions.
- **Tixagevimab and cilgavimab (Evusheld)** is a combination of 2 recombinant human IgG1 MABs, with amino acid substitutions in the Fc regions that extend antibody half-life. Tixagevimab plus cilgavimab have longer half-lives of 87.9 and 82.9 days respectively. Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the spike protein receptor-binding domain of SARS-CoV-2.

6.5.10 The IVAG noted that the nMABs exhibit dose-linear and proportional pharmacokinetics across the range of doses at which they have been studied. What this generally means in practice is that, if the dose is doubled, the concentrations in serum are doubled and, if the dose is halved, the concentration in serum is halved.

6.5.11 Most available nMABs were developed in the context of early SARS-CoV-2 variants. Some in vitro data has shown that many of them may be less effective at neutralising newer variants, resulting in a perception that they may work less well in people infected with or exposed to new variants.

6.5.12 Considering the mechanism of action of nMABs in relation to new variants, NICE sought advice from the IVAG to determine whether it is likely that nMABs could retain neutralising activity. For example, if a specific nMAB target epitope is lost in a new variant, this could be a potential trigger for considering whether neutralisation activity is reduced or lost.

6.5.13 Based on its experience, the IVAG indicated that:

- Neutralisation activity of combination treatments may be more resilient to changes in variants because they tend to have a broader mechanism of action.
- Drug-selected resistance has been seen during use against susceptible variants (up to Omicron BA.1).
- Marked reductions in neutralisation have been reported since Omicron BA.2 and subsequent sublineages emerged.
- Neutralisation can also be compromised when mutations occur outside of the specific epitope because of the overall effect on protein structure.

6.5.14 Actions in this step of the framework:

- Determine whether the nMABs' mechanism of action is still effective against the new variant:
  - The main impact is expected when a variant has a mutation eliminating the target epitope of the nMAB or a mutation outside of the specific epitope that compromises neutralisation.
  - Assessment of impact will need a combination of evidence on mechanism of action and expert input.

Decision point: If there is a potential impact on the effectiveness of the nMAbs' mechanism of action move to next step of assessing neutralising activity.

Step 3: Assessing neutralising activity

Determining the evidence base

6.5.15 NICE needs in vitro data to inform discussions on whether the nMABs included in NICE guidance still have neutralising activity against the new dominant variants. NICE's search strategy for identifying published evidence is outlined in appendix 3. NICE may get additional data from the UKHSA, regulators and companies.

Relationship between in vitro neutralisation data and clinical effectiveness

6.5.16 Neutralisation assays are considered the gold standard for determining antibody efficacy against viruses. The results of these in vitro ELISA assays, usually reported as the 50% and 90% effective concentrations (EC50 and EC90), show the concentration of drug needed to neutralise 50% or 90% of the virus. The goal of neutralisation is not necessarily to neutralise the virus completely, but to reduce the growth rate of the virus to below a self-sustainable level. The IVAG indicated that different nMABs may remain effective despite having reduced neutralising activity against a different variant than that prevalent when the clinical trial

which led to marketing authorisation was done. This may occur if the concentration of the treatment used in clinical practice is, for example, 100-fold higher than that needed to reduce the viral level. In this example, the nMABs may have a similar effect on viral growth rate even if there is a 100-fold reduction in neutralising activity against a new viral variant compared with original studies against older variants. In an attempt to maximise a positive outcome in clinical trials, some companies have used the highest dose possible initially followed by lower doses. For example, a clinical trial on casirivimab plus imdevimab used doses of 8.0 g, 2.4 g and 1.2 g (O'Brien et al. 2021). This is important to note when considering the neutralising activity of the nMABs.

6.5.17 The gold standard for assessing the clinical effectiveness of medicines is blinded randomised controlled trials (RCTs). In the absence of RCTs on the effectiveness of nMABs against new SARS-CoV-2 variants, whether there could be a plausible link between in vitro neutralisation data and clinical and health economic outcomes needs to be established. While there is no consensus on the exact relationship between in vitro neutralisation data and clinical outcomes for COVID-19 (such as reducing hospitalisation rates or mortality), the IVAG concluded that it is plausible that an association exists. The main reason for this conclusion is because scientists have consistently used in vitro neutralisation data to select antibodies and doses for further testing in RCTs for several decades of antiviral pharmacological research. The IVAG noted, however, that a link between in vitro data showing a fold change in neutralisation activity against newer variants and clinical outcomes is difficult to establish because of how a new variant may affect disease severity.

6.5.18 One of the key methodological steps in the usual process of reviewing evidence of clinical effectiveness is to appraise the clinical trials to critically to assess quality and robustness, risk of

bias and generalisability. There is no validated tool for appraising in vitro neutralisation data. So, the IVAG discussed key components of quality for studies on in vitro neutralisation and identified important characteristics to consider when assessing studies. The IVAG was also aware of the ongoing work of the Department of Health and Social Care Antivirals and Therapeutics Taskforce, which aims to standardise aspects of in vitro neutralisation studies.

Key components of in vitro neutralisation studies

Virus and cell lines

6.5.19 In vitro neutralisation studies typically use either pseudovirus or live virus. Pseudoviruses do not replicate and have their surface envelope proteins replaced with those of SARS-CoV-2. The IVAG agreed that it preferred studies using live SARS-CoV-2 virus but acknowledged that both types of virus were associated with uncertainty. The IVAG agreed that in vitro data from pseudovirus generally agrees with in vitro data from live virus, and the advantage is that results from pseudovirus are generated quicker.

6.5.20 The IVAG noted it is also important that the cell line used for viral culture has been clonally selected and that the batch of virus has been sequenced, characterised and reported in the studies. This would enable NICE to assess the consistency across studies.

Reproducibility of assays

6.5.21 The IVAG agreed that in vitro neutralisation assays should be reproducible, so studies should clearly detail the methods used.

6.5.22 Different manufacturers of nMABs assume different degrees of tissue penetration, and some, but not all, companies also include a margin of error (up to 10-fold) in their assays. According to the IVAG, few companies use EC50 because inhibiting only 50% of replication is not a recognised basis for efficacy of medicines to

prevent or treat viral illnesses, and EC90 is at least 9-fold higher than EC50.

6.5.23 The IVAG concluded that EC50 values would be acceptable to initially assess whether an nMAB has lost efficacy against new variants relative to older variants. But, when detailed pharmacokinetic and pharmacodynamic (PK/PD) assessments are needed, EC90 should be used.

Repeatability of results

6.5.24 When new SARS-CoV-2 variants emerge, it is likely that numerous groups of scientists will generate and publish in vitro data. The IVAG considered it important that results are broadly consistent across studies. The IVAG noted, however, that fold-differences in neutralisation between different variants have generally been more reproducible than the absolute concentrations of nMAB needed for neutralisation.

Comparator

6.5.25 The IVAG discussed that in vitro neutralisation studies should report fold change in EC50 against the new variants relative to the ancestral or reference variants.

Measuring uncertainty in the results

6.5.26 The IVAG discussed that using 95% confidence intervals (95% CIs) when reporting EC50 and EC90 point estimates would be helpful for measuring uncertainty in the results. For example, comparing 2 absolute EC50 values without a 95% CI could be misleading.

However, the IVAG acknowledged that 95% CIs are not always reported in the literature.

6.5.27 Actions in this step of the framework:

- Search for in vitro data to determine if there are any studies that report neutralisation data for nMABs against new variants of interest.
- Determine the quality and reproducibility of the data using the appraisal approach outlined in appendix 4.

Decision point: If there is in vitro data available that is of sufficient quality and reproducible, move to next step of interpreting the data.

Step 4: Interpreting changes to in vitro neutralisation by monoclonal antibodies

In vitro data presentation

6.5.28 There are generally 2 presentation types for in vitro data used in the published literature:

- heat maps (for example, as shown in Wang et al. 2022)
- concentration dose–response curves (for example, as shown in Planas et al. 2022).

6.5.29 These present the concentration of nMABs needed to neutralise the variant in vitro to a stated degree (for example, EC50). Heat maps show the nMABs drugs in columns, and the variants in rows (see figure 2). A red colour represents a loss of neutralising activity while no colour reflects maintained neutralising activity. A dose–response curve plots drug concentration on the x axis as a function of percent viral inhibition on the y axis. With separate plots per treatment, each neutralisation curve reflects neutralisation activity of therapeutic monoclonal antibodies against variants of interest. Although the IVAG acknowledged that heat maps provide a good summary of a lot of data, the IVAG concluded that it preferred

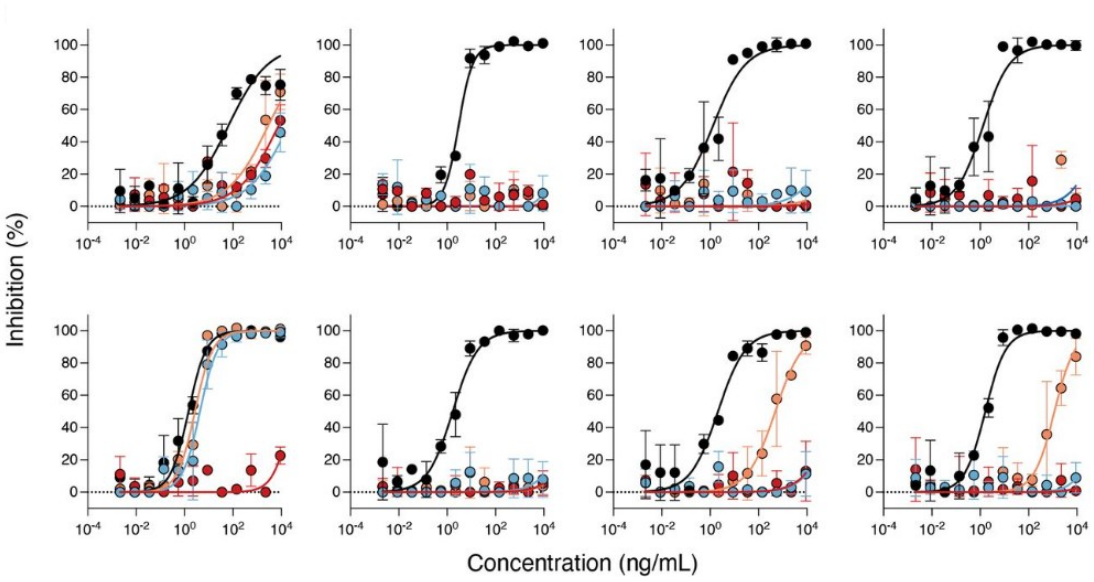
dose–response curves (see figure 3) because they provide more information. Specifically, they enable assessment of whether the slope of the concentration response curve changes between variants. If the slope changes (showing that higher concentrations of nMAbs are needed to retain neutralisation), the EC90 moves even further away from the EC50 and, in some cases, the nMAB cannot achieve EC90.

Figure 2 Example heatmap from Wang et al. 2022

IC$_{50}$ (μg/ml)	NTD	NTD-SD2	SD1	RBD Class 1				RBD Class 2				RBD Class 3											RBD Class 4	Evusheld
	C1520	C1717	S3H3	S2K146	Omi-3	Omi-18	BD-515	XGv051	XGv347	ZCB11	COV2-2196	LY-CoV1404	XGv289	XGv264	S309	P2G3	SP1-77	BD55-5840	XGv282	BD-804	35B5	COV2-2130	10-40	
D614G	0.002	0.125	0.022	0.004	0.004	0.012	0.010	0.001	0.002	0.002	0.002	0.002	0.002	0.001	0.023	0.001	0.003	0.002	0.001	0.011	0.014	0.007	0.049	0.003
BA.4/5	0.001	0.209	0.014	0.090	0.023	0.013	0.010	0.050	3.450	4.868	>10	0.001	0.038	0.002	0.514	0.002	0.005	0.009	0.001	0.019	>10	0.021	2.414	0.035
BQ.1	0.001	0.666	0.019	0.585	0.860	0.131	0.343	0.159	2.830	>10	>10	>10	0.425	0.494	0.600	1.608	>10	0.034	0.020	>10	>10	>10	>10	>10
BQ.1.1	0.003	1.117	0.025	0.527	0.804	0.170	0.377	0.191	3.311	>10	>10	>10	1.013	>10	2.140	>10	>10	>10	0.093	>10	>10	>10	>10	>10
BA.4/5-R346T	0.002	0.141	0.009	0.081	0.019	0.009	0.006	0.042	2.166	2.560	>10	0.001	0.045	0.003	1.726	0.041	>10	1.447	0.001	>10	>10	>10	5.069	>10
BA.4/5-K444T	0.002	0.116	0.009	0.104	0.016	0.010	0.006	0.040	4.766	3.731	>10	>10	0.161	0.273	0.552	1.245	4.007	0.038	0.006	>10	>10	>10	6.976	>10
BA.4/5-N460K	0.002	1.166	0.016	0.542	1.279	0.186	0.431	0.152	3.046	>10	>10	0.002	0.353	0.003	0.934	0.003	0.009	0.012	0.002	0.122	>10	0.030	>10	0.063
BA.2	0.002	0.561	0.016	0.028	0.015	0.005	0.012	0.001	0.003	0.012	1.924	0.001	0.067	0.003	0.833	0.002	0.006	0.014	0.001	0.036	0.827	0.009	8.770	0.019
XBB	>10	0.836	0.016	0.223	1.181	0.468	0.555	>10	>10	>10	>10	>10	>10	>10	0.343	>10	>10	>10	>10	>10	>10	>10	>10	>10
XBB.1	>10	0.693	0.019	0.190	1.705	0.605	0.803	>10	>10	>10	>10	>10	>10	>10	0.405	>10	>10	>10	>10	>10	>10	>10	>10	>10
BA.2-V83A	0.001	0.354	0.015	0.036	0.019	0.007	0.015	0.002	0.003	0.013	3.039	0.001	0.070	0.002	0.641	0.002	0.007	0.019	0.001	0.045	1.274	0.011	>10	0.025
BA.2-Del144	0.002	0.501	0.011	0.026	0.016	0.004	0.011	0.002	0.002	0.008	4.134	0.001	0.063	0.002	0.455	0.002	0.005	0.014	0.001	0.031	0.341	0.010	8.766	0.021
BA.2-H146Q	0.001	0.356	0.011	0.032	0.011	0.004	0.009	0.002	0.002	0.010	2.924	0.002	0.055	0.002	0.641	0.003	0.007	0.019	0.001	0.044	1.107	0.009	9.106	0.019
BA.2-Q183E	0.002	0.307	0.019	0.034	0.018	0.006	0.014	0.002	0.003	0.013	3.098	0.001	0.067	0.003	0.649	0.002	0.008	0.020	0.002	0.028	1.019	0.010	9.251	0.022
BA.2-V213E	0.002	0.406	0.013	0.030	0.014	0.004	0.010	0.002	0.002	0.006	2.177	0.001	0.047	0.003	0.720	0.002	0.006	0.014	0.001	0.026	1.247	0.009	8.198	0.018
BA.2-G252V	0.001	0.577	0.013	0.030	0.012	0.004	0.008	0.002	0.003	0.008	2.258	0.001	0.048	0.002	0.564	0.002	0.005	0.012	0.001	0.032	0.939	0.011	>10	0.026
BA.2-G339H	0.001	0.485	0.017	0.034	0.020	0.006	0.012	0.002	0.002	0.010	3.876	0.002	0.114	0.002	0.302	0.002	0.007	0.040	0.002	0.050	0.661	0.012	8.575	0.023
BA.2-R346T	0.003	0.372	0.012	0.017	0.010	0.003	0.007	0.001	0.002	0.007	2.109	0.002	0.048	0.004	1.433	0.007	>10	1.442	0.001	0.112	>10	>10	7.767	1.486
BA.2-L368I	0.003	0.453	0.019	0.027	0.010	0.004	0.010	0.002	0.001	0.006	2.603	0.001	0.030	0.002	0.605	0.002	0.005	0.021	0.001	0.026	0.324	0.008	3.202	0.018
BA.2-V445P	0.001	0.433	0.019	0.026	0.009	0.004	0.009	0.002	0.002	0.008	2.313	>10	>10	1.141	0.428	>10	0.007	0.144	>10	1.582	0.486	>10	6.311	3.135
BA.2-G446S	0.002	0.367	0.012	0.021	0.009	0.004	0.009	0.001	0.003	0.008	2.614	0.002	0.026	0.004	0.686	0.002	0.004	0.014	0.022	0.026	0.965	0.017	5.774	0.029
BA.2-N460K	0.002	1.323	0.012	0.132	0.764	0.013	0.358	0.007	0.004	0.073	1.756	0.001	0.355	0.003	0.878	0.002	0.011	0.017	0.001	0.058	1.957	0.013	>10	0.025
BA.2-F486S	0.002	0.677	0.008	>10	0.583	0.011	0.017	>10	>10	>10	>10	0.001	0.049	0.003	0.581	0.002	0.006	0.009	0.002	0.060	2.264	0.011	>10	0.023
BA.2-F490S	0.001	0.428	0.014	0.022	0.033	0.004	0.008	0.001	0.004	0.012	1.105	0.001	0.030	0.002	0.564	0.002	0.006	0.011	>10	0.048	>10	0.013	5.337	0.016
BA.2-R493Q	0.003	0.338	0.024	0.005	0.006	0.006	0.006	0.001	0.001	0.002	0.034	0.001	0.045	0.002	1.109	0.002	0.007	0.022	0.000	0.010	1.175	0.010	3.419	0.008

>10	1-10	0.1-1	0.01-0.1	<0.01

Figure 3 Example concentration dose–response curves from Planas et al. 2022



In vitro neutralisation activity interpretation

6.5.30 The IVAG discussed different scenarios (see table 1) of changes in neutralising activity against variants compared to the reference strains. It concluded that some scenarios had a clear interpretation that could inform recommendations made by technology appraisal or guidelines committees. These scenarios are when there can be no plausible argument for continuing efficacy for the antibodies against a new variant (see table 1). But there will also be scenarios in which the fold change in neutralising activity, particularly at higher concentrations of drugs, will be harder to interpret without further information. The IVAG indicated that, if the in vitro data shows a fold change but in vitro neutralisation is still achieved at concentrations that could be achieved in serum, then the nMAB may still be effective at a higher dose. But the IVAG considered that this may need higher dosages than licensed and acknowledged that NICE must make recommendations based on the licensed dose only.

Table 1 Scenarios for changes in the in vitro neutralising activity relative to the reference variant (either ancestral variant or predominant variant in pivotal RCT) - applicable to prophylaxis and treatment

Scenario	Agreed action	Rationale
No or minimal fold change in neutralising activity relative to the reference variant.	Use existing randomised controlled trial (RCT) evidence for decision making.	We are confident that the neutralising activity has been minimally impacted therefore the conclusions from the RCT hold.
No or minimal neutralising activity at very high concentrations.	Move to decision to not recommend a nMAB.	These concentrations could not be achieved in the body. Clear in vitro evidence that nMABs will not be clinically

		effective (or by extension cost effective).
Some neutralisation at higher concentration, but substantial fold change compared with the reference variant.	Insufficient information to make a decision.	If there is a substantial fold change, PK/PD data is needed to attempt linking of the data to clinical outcomes.

Visualising the scenarios

Figure 4 Example showing no or minimal neutralising activity at very high concentrations for the variants in blue and red compared with the black reference variant (Planas et al. 2022)

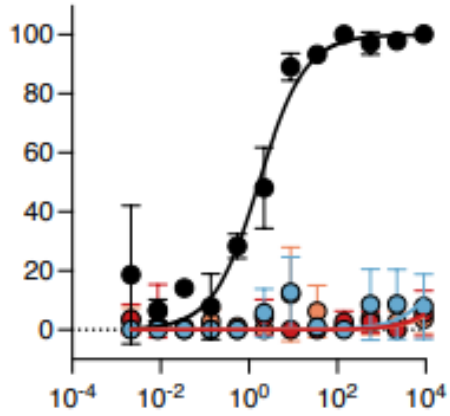
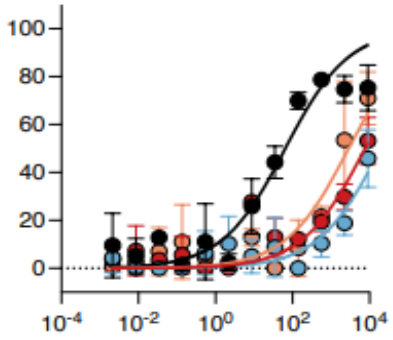


Figure 5 Example showing some neutralisation at higher concentrations (Planas et al. 2022)



Pharmacokinetic and pharmacodynamic (PK/PD) data

6.5.31 The IVAG stated that simply interpretating the fold-difference in the ability of an nMAB to neutralise a variant without considering the

compartmental pharmacokinetics, including how the drug interacts in different bodily compartments, does not give a complete picture.

6.5.32 In general terms, the plausibility of continued efficacy of a nMAB against new viral variants needs consideration of the plausibility of the antibody still achieving sufficient neutralisation activity in patients, and this needs an understanding of the pharmacokinetics. The nMABs exhibit dose-linear and proportional pharmacokinetics. What this means in practice is that if the dose is doubled, the concentrations in serum are doubled, and if the dose is halved then the concentration in serum is halved. The IVAG indicated that there is an important step in understanding the compartmental pharmacokinetics that correspond to the clinical-effectiveness measures achieved in RCTs. This includes the doses of nMABs needed to neutralise and how a double dose that doubles the concentration in serum, for example, might overcome an expected fold reduction of neutralisation in vitro.

6.5.33 The IVAG concluded PK/PD data is needed to try to link in vitro neutralisation data to clinical outcomes when there is a substantial fold change, but some neutralisation is retained in vitro. Without this data, it is not possible to determine how this fold change may be associated with clinical outcomes.

6.5.34 The IVAG considered it essential to know the minimum concentration needed to neutralise the ancestral (or reference) viral strain and whether this differs from the licensed dose of a nMAB treatment. If this dose was substantially above the minimum concentration, then there is potentially still a tolerance to accommodate a large fold reduction in neutralisation in vitro. If the neutralisation activity achieved by the dose was close to the minimum needed for effectiveness in the ancestral (or reference) viral strain, then there is a high possibility that even a small fold

change in neutralisation would render the nMAB clinically ineffective.

6.5.35 The IVAG agreed that clinical trials reporting failed doses provide important information. Although it did note that the more data points presented, the more confidence this adds to the dose–clinical response relationship. From this data, the concentration of drug or level of neutralisation of virus the investigators found to be clinically ineffective is known. Unfortunately, for most nMABs, IVAG acknowledged that this PK/PD data is not available. It suggested that the regulators and NICE should encourage companies to collect this data in registrational trials to allow rapid assessment based on in vitro data.

Differences between the monoclonal antibodies

6.5.36 The IVAG noted that there is some in vitro data showing that tixagevimab and cilgavimab for pre-exposure prophylaxis of COVID-19 does not neutralise newer dominant variants of the virus. According to the IVAG, sotrovimab shows some neutralisation if the concentration used in vitro is increased. But the higher concentrations of sotrovimab needed to inhibit some variants in vitro were much larger than the drug dosages used in published RCTs. Also, the IVAG indicated that the mechanism of sotrovimab differs from other nMAbs and that it may have additional beneficial effects beyond neutralisation through 'effector functions'. The IVAG acknowledged that this may be an additional benefit, but is hard to quantify. Overall, the IVAG concluded that evidence of in vitro neutralisation is a necessary requirement, and evidence of an effector function effect alone is insufficient to conclude clinical benefit.

6.5.37 Actions in this step of the framework:

- Use the appraised in vitro data to determine which scenarios from table 1 apply.

- Use the scenarios outlined in table 1 to determine the appropriate action.
- Seek expert advice on interpreting in vitro data and the proposed action.

Decision point: There are 3 outcomes in this step of the framework:

- No or minimal fold change in neutralising activity of a drug against a viral variant relative to the ancestral variant: no action is needed, continue to monitor.
- No or minimal neutralising activity at very high concentrations: determine whether there is a need to update recommendation.
- Some neutralisation at higher concentrations, but substantial fold change compared with ancestral variant: there is insufficient information to make a decision, seek expert input and ask companies for dose-failure data.

Appendix 2: IVAG members

Amanda Adler (Chair)

Director, Diabetes Trials Unit, University of Oxford

David Bauer

Group Leader and Head, RNA Virus Replication Laboratory. The Francis Crick Institute

Rupert Beale

Clinician Scientist Group Leader, Consultant Nephrologist, The Francis Crick Institute, UCL Division of Medicine

Sanjay Bhangani

Consultant Physician and Honorary Associate Professor, Royal Free Hospital and University College London

Neil Ferguson

Director, MRC Centre for Global Infectious Disease Analysis, Imperial College London

Neil Hawkins

Professor of Health Technology Assessment, University of Glasgow

Mark Jit

Professor of Vaccine Epidemiology, London School of Hygiene and Tropical Medicine

Saye Khoo

Professor in Pharmacology, Honorary Consultant Physician in Infectious Diseases, University of Liverpool

David Lalloo

Director, Liverpool Tropical School of Medicine

Siraj Misbah

Consultant Clinical Immunologist, Oxford University NHS Foundation Trust

Andrew Owen

Professor of Pharmacology, University of Liverpool

Derek Smith

Professor of Infectious Disease Informatics, Zoology Department at Cambridge University

David Stuart

MRC Professor of Structural Biology, University of Oxford

Mark Sutton

Scientific Leader at Healthcare Biotechnology, and Professor for Antimicrobial Therapy, UKHSA and King's College London

Laurie Tomlinson

NIHR Research Professor, Honorary Consultant Nephrologist, London School of Hygiene and Tropical Medicine

Erik Volz

Reader in Population Biology of Infectious Diseases, Faculty of Medicine, School of Public Health, Imperial College London

Appendix 3: Search strategy

The search is run once a week to identify journal articles, letters, editorials, preprints and grey literature.

The following databases are searched:

- Embase (via Ovid)
- Europe PMC (via https://europepmc.org)
- MEDLINE ALL (via Ovid)

The initial database strategies take the format:

(Variant of Concern) AND (MABs or Named drugs)

OR

(Variant of Concern) AND (In Vitro Studies)

OR

(Named Drugs AND In Vitro Studies)

The structure of the strategies may be reviewed as appropriate, according to the volume of results and the relevant papers that are identified.

The principal search strategy for MEDLINE (Ovid interface) is shown below. This will be adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage.

The Europe PMC search will be limited to preprints using the SRC:PPR command.

No other limits will be applied to the search strategy. Editorials, letters, comments, conference papers and animal studies will be retained in the search results. Non-English language papers will be retained. The appropriate limits may be reviewed in agreement with the technical team.

A date limit of 2020-current will be applied to the main search. The weekly searches will be limited to records added to the databases in the previous 10 days using the appropriate commands.

The Information Services team at NICE will quality assure the principal search strategy and peer review the strategies for the other sources.

The content of the Medicines Daily Alerts provided by the Specialist Pharmacy Service to NICE will be reviewed as appropriate. Items suggested by the technical team or other experts will be added to the search results as appropriate.

The search strategy should include the names of any relevant variant of concern and its Pango lineage, including the descendant lineage and sublineages. The search strategy should be reviewed regularly using any information provided by the technical team or other experts. Once a new variant of concern or new sublineage has been identified, terms will be added as appropriate to the search strategies using the tables available at:

- European Centre for Disease Prevention and Control SARS-CoV-2 variants of concern
- UKHSA SARS-CoV-2 variants of concern and variants under investigation in England technical briefings
- WHO tracking SARS-CoV-2 variants.

The search strategy will also contain terms to retrieve records on unidentified or unnamed variants of concern.

The database search results are downloaded to EPPI-Reviewer version 5 for deduplication and processing. Duplicates are removed in EPPI-R5 using a 2-step process. First, automated deduplication is done using a high-value algorithm. Then, manual deduplication is used to assess low-probability matches.

MEDLINE search strategy

#	Searches

1	omicron*.ti,ab,kf.
2	("B.1.1.529" or B11529 or "BA.5" or BA5 or "BF.7" or BF7 or "BF.14" or BF14 or "BQ.1" or BQ1 or "BQ.1.1" or "BQ1.1" or BQ11 or "BA.2.75" or "BA2.75" or BA275 or "BA.2" or BA2 or "BA.4.6" or "BA4.6" or "BA46" or "BA.4" or BA4 or XBB or "XBB.1.5" or "XBB1.5" or XBB15 or "BA.2.3.20" or "BA2.3.20" or "BA23.20" or BA2320 or "BA.2" or BA2 or "BA.4/5" or XBC or "BN.1" or BN1 or "CH.1.1" or CH11 or "CH.11").ti,kf.
3	("B.1.1.529" or B11529 or "BA.5" or BA5 or "BF.7" or "BF7" or "BF.14" or BF14 or "BQ.1" or BQ1 or "BQ.1.1" or "BQ1.1" or BQ11 or "BA.2.75" or "BA2.75" or BA275 or "BA.2" or BA2 or "BA.4.6" or "BA4.6" or "BA46" or "BA.4" or BA4 or XBB or "XBB.1.5" or "XBB1.5" or XBB15 or "BA.2.3.20" or "BA2.3.20" or "BA23.20" or BA2320 or "BA.2" or BA2 or "BA.4/5" or XBC or "BN.1" or BN1 or "CH.1.1" or CH11 or "CH.11").ab. and (variant* or variation* or VOC or VOCs or VOI or VOIs or VOCI or lineage* or strain* or sublineage* or subvariant* or subvariation* or CoV or coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kf.
4	("B.1.1.529" or B11529 or "BA.5" or BA5 or "BF.7" or "BF7" or "BF.14" or BF14 or "BQ.1" or BQ1 or "BQ.1.1" or "BQ1.1" or BQ11 or "BA.2.75" or "BA2.75" or BA275 or "BA.2" or BA2 or "BA.4.6" or "BA4.6" or "BA46" or "BA.4" or BA4 or XBB or "XBB.1.5" or "XBB1.5" or XBB15 or "BA.2.3.20" or "BA2.3.20" or "BA23.20" or BA2320 or "BA.2" or BA2 or "BA.4/5" or XBC or "BN.1" or BN1 or "CH.1.1" or CH11 or "CH.11").ab. and (SARS-CoV-2/ or COVID-19/)
5	(((new* or emerge or emerges or emerging* or emergent* or unidentif* or unique* or unname* or unlabel* or unspecif* or nameless* or unknown* or novel* or denovo or "de novo") adj3 (variant* or variation* or VOC or VOCs or VOI or VOIs or VOCI or lineage* or strain* or sublineage* or subvariant* or subvariation* or mutat*)) and (CoV or coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2)).ti,kf.
6	((new* or emerge or emerges or emerging* or emergent* or unidentif* or unique* or unname* or unlabel* or unspecif* or nameless* or unknown* or novel* or denovo or "de novo") adj3 (variant* or variation* or VOC or VOCs or VOI or VOIs or VOCI or lineage* or strain* or sublineage* or subvariant* or subvariation* or mutat*) adj1 (CoV or coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2)).ab.
7	or/1-6
8	limit 7 to yr="2020 -Current"
9	COVID-19 Drug Treatment/
10	Antibodies, Monoclonal/
11	Antibodies, Monoclonal, Humanized/
12	Antibodies, Monoclonal, Murine-Derived/
13	Antibodies, Neutralizing/
14	(MAB or MABS or NMAB or NMABS).ti,ab,kf.

15	((monoclonal* or neutrali* or humani*) adj2 antibod*).ti,ab,kf.
16	(Sotrovimab* or "GSK 4182136" or GSK4182136 or "VIR-7831" or VIR7831 or "VIR-7832" or VIR7832 or Xevudy*).ti,ab,kf.
17	(casirivimab* or imdevimab* or REGN10933 or REGN10987 or "REGN 10933" or "REGN 10987" or Ronapreve* or REGNCOV2 or "REGN-COV2").ti,ab,kf.
18	(tixagevimab* or cilgavimab* or Evusheld* or AZD7442 or "AZD-7442" or AZD8895 or AZD1061 or "AZD 8895" or "AZD 1061").ti,ab,kf.
19	Antiviral agents/
20	("anti viral*" or antiviral* or "anti microbial*" or antimicrobial*).ti,kf.
21	(("anti viral*" or antiviral* or "anti microbial*" or antimicrobial*) adj3 (drug* or agent* or therapy* or therapies* or medicine* or treatment*)).ab.
22	or/9-21
23	8 and 22
24	exp In Vitro Techniques/
25	("in vitro" or invitro or preclinical* or "pre clinical*").ti,kf.
26	(("in vitro" or invitro or preclinical* or "pre clinical*") adj3 (study* or studies* or analy* or observation* or design* or method* or research* or data* or review* or test* or technique* or assay* or procedure*)).ab.
27	(EC50 or EC90 or "effective concentration*").ti,ab,kf.
28	COVID-19 Serological Testing/
29	Biological Assay/ or exp Immunoassay/ or Serologic Tests/ or Immunologic Tests/ or Serotyping/
30	((serolog* or immunoglobulin* or biological* or Immunologic*) adj3 (test* or technique* or assay* or procedure*)).ti,ab,kf.
31	(Serotyping* or Immunoassay* or Bioassay* or immunodetect* or "immuno detect*").ti,ab,kf.
32	exp Cytological Techniques/
33	Cells, Cultured/
34	Cell Line/
35	((Cell* or Cytolog*) adj1 (line* or culture*)).ti,ab,kf.
36	Neutralization Tests/
37	(neutralisation* or neutralization* or immunoneutralisation* or immunoneutralization*).ti,kf.
38	((neutralisation* or neutralization* or immunoneutralisation* or immunoneutralization*) adj3 (test* or technique* or assay* or procedure*)).ab.
39	exp Drug Resistance/
40	((drug* or "anti viral*" or antiviral* or agent* or therapy* or therapies* or medicine* or multidrug*) adj3 (evad* or evasion* or escap* or resist* or efficacy*)).ti,ab,kf.
41	*Antibodies, Viral/
42	(antibod* adj3 (evad* or evasion* or escap* or resist* or efficacy* or sensitiv* or neutral* or response* or detect*)).ti,ab,kf.
43	Immunity, Humoral/

44	(humoral adj1 immun*).ti,ab,kf.
45	"Antigenic Drift and Shift"/
46	Antigenic Variation/
47	immune evasion/
48	((antigen* or viral* or virus* or virolog* or immun*) adj3 (shift* or drift* or mutat* or evad* or evasion* or escap* or switch* or variable* or variabilit* or variation* or neutralis* or neutraliz* or immunoneutralis* or immunoneutraliz* or detect*)).ti,ab,kf.
49	"breakthrough infections"/
50	((breakthrough* or "break through*" or rebound* or reemergent* or emergent*) adj1 infect*).ti,ab,kf.
51	or/24-50
52	8 and 51
53	23 or 52
54	16 or 17 or 18
55	51 and 54
56	limit 55 to yr="2020 -Current"
57	53 or 56
58	limit 57 to ed=YYYYMMDD-YYYYMMDD [Adjusted each week]
59	limit 57 to dt= YYYYMMDD-YYYYMMDD [Adjusted each week]
60	58 or 59

Appendix 4: Appraisal of the evidence

The risk of bias assessment is to be completed using the adapted toxicological data reliability assessment tool (TOXRTOOL). The 23 questions in table 1 are allocated a score of 0 or 1.

Table 1 Risk of bias assessment questions

Number	Criteria	Score
1	**Test substance identification (monoclonal antibody [MAB]):** 1. Was the monoclonal antibody named/described in the study? 2. Is information on the source or origin of the MAB given? Generally, only authentic product provided by the manufacturer should be accepted for interpretation of the findings. This should include manufacturer name. 3. Does the test substance accurately reflect MABs used in clinical practice?	**0**
2	**Test system characterisation (neutralisation assay):** 4. Is the test system described? At a fundamental level, comparison of in vitro data across laboratories is hampered by the use of different cell lines that may be infected by SARS-CoV-2 variants to different extents. Emerging evidence suggests that MABs binding outside the receptor-binding domain may be sensitive to angiotensin-converting enzyme 2 expression levels and this should be considered. 5. Was the neutralisation assay appropriate? It is expected that all neutralisation assays would be ELISA assays done in at least 2 independent experiments. 6. Is information given on the source or origin of the test system, and is there data available on the validity of that test system? This could include: • laboratory or scientist providing cell lines • commercial provider of test systems • a description of how the reactivity of the nMAB was validated • origin of tissues and primary cells. 7. Are necessary information on test system properties, and on conditions of cultivation and maintenance given? (Type of assay, type of virus, type of cell line, type of media)	**0**

	There is broad agreement that in vitro methodology should employ authentic SARS-CoV-2 isolates, and that routine sequencing of virus stocks is needed because cell culture adaptation and mutations can occur and can change replication of virus in cells. It is currently unclear whether variants isolated from different countries will behave the same in cell culture since a large study comparison has not been reported. There is evidence that some methods to propagate the virus have led to additional mutations. Pseudovirus assays present several advantages over live virus, which include the speed at which data can be generated after emergence of a new variant, and the lack of reliance upon BSL-3 facilities, and the controlled evaluation of the effect of specific mutations. But limitations are also evident because the pseudovirus may not contain the full suite of mutations or may not function like an authentic virus in every way. So, it is suggested that data from pseudovirus assays should be considered based on a clear understanding of the inherent benefits and limitations of the data. Widely available cell lines should be used such as VeroE6 and VeroE6-TMPRSS2, Calu-3 cells and A549 cells. 8. Has sufficient detail been reported on the methods to replicate the study? 9. Does the study confirm that an appropriate cell line has been used? Investigators may use cell lines which have been shown to be inappropriate for assaying certain classes of monoclonal antibodies.	
3	**Study design description** 10. Are doses administered or concentrations of test substances analysed given? 11. Are frequency and duration of exposure as well as time-points of observations explained? (duration of incubation with virus, duration of assay) Timing of assay readouts should be validated. 12. Have a range of antibody concentrations been tested that are relevant to those needed for neutralisation in serum? A limitation of many in vitro studies is the range of antibody concentrations tested, which are often lower than the average maximum serum concentrations. 13. Were negative controls included? 14. Were positive controls included? 15. Is the number of replicates (or complete repetitions of experiment) given?	**0**

	16. Is the study methodology likely to produce reliable comparison data? For example, have the study investigators utilised an assay calibrated with the WHO International Standard for anti-SARS-CoV-2 immunoglobulin and reporting of neutralisation titres in International Units – an assay useful for standardised comparisons of different monoclonal antibodies against various variants. Testing should be done on an ancestral strain of the virus or reference strain used in a randomised controlled trial in parallel to the variant under investigation.	
4	**Study results documentation** 17. Are the study endpoint(s) and their method(s) of determination clearly described? A 4-paramater, variable slope dose–response analysis has been proposed as the most effective way to determine EC50 and EC90 parameters. Luciferase endpoints for pseudovirus assays and nucleocapsid measurements (anti-N with high content imaging) for authentic live virus have been highlighted as providing reliable readouts. Cytopathic effect (for example, measured by cell titer glo) has been reported to be heterogeneous between different variants studied to date. qPCR readouts have an excellent signal to noise ratio but may not be applicable to pseudovirus assays. 18. Is the description of the study results for all endpoints investigated transparent and complete? 19. Are the outcomes appropriate, and clearly and transparently reported? EC50 and EC90 values should be generated as outcomes from the in vitro testing. 20. Were the study outcomes determined prior to analysis? 21. Are the statistical methods for data analysis given and applied in a transparent manner? 22. Are confidential intervals included? Confidence intervals are important in evaluating the uncertainty of any possible changes in neutralisation; particularly when considering IC90 values, which lie close to the plateau of the dose–response curve and are inherently noisy.	**0**
5	**Plausibility of study design and data** 23. Are the quantitative study results reliable?	**0**
-	Total score	**0**

Based on the total score, studies are allocated to category 1, 2 or 3, as indicated in table 2. Category 1 is assigned if the total score is 20 or more, category 2 is assigned for scores of 16 or more, and category 3 is assigned for scores of 15 or less.

Table 2 Study allocation based on score

Category	Definition
Reliable without restrictions	"Studies or data from the literature or reports which were carried out or generated according to generally valid and/or internationally accepted testing guidelines (preferably performed according to good laboratory practice (GLP)) or in which the test parameters documented are based on a specific (national) testing guideline (preferably performed according to GLP) or in which all parameters described are closely related/comparable to a guideline method."
Reliable with restrictions	"Studies or data from the literature, reports (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable."
Not reliable	"Studies or data from the literature/reports in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiological pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment."

NICE would like to acknowledge the National Australian COVID 19 Clinical Evidence Taskforce who shared an initially adapted version of the TOXRTOOL and devised the categorisation of studies.

Appendix 5: Glossary of terms used

Ancestral: the original strain of SARS-CoV-2 identified in Wuhan.

Cell line: a defined population of cells that can be maintained in culture for an extended period of time and can be used for in vitro experiments.

Conserved epitope: an epitope retained by multiple strains of virus as a key target of a broadly neutralising antibody.

EC50: concentration needed to neutralise 50% of the virus population leaving the remaining 50% of the virus to be able to replicate.

EC90: concentration needed to neutralise 90% of the virus population, with concentration at least 9-fold higher compared with EC50.

Effector functions: when antibodies induce innate and adaptive immune responses beyond neutralisation, including antibody-dependent cellular cytotoxicity.

Epitope: a structure on the surface of an antigen that is recognised by and can bind to a specific antibody.

Immune escape: when the immune system of a host is unable to respond to an infectious agent, such as a virus.

In vitro*:* tests and experiments that researchers perform outside of a living organism in a controlled environment, for example, a test tube or petri dish.

Neutralising monoclonal antibodies: monoclonal antibodies that bind to and neutralise SARS-CoV-2.

Neutralisation curves: graphs in which the y axis is percentage inhibition and the x axis is concentration of drug, with different curves for different variants including 'ancestral' line (for example, Delta) and different graphs for each drug.

PK/PD data: a pharmacokinetic and pharmacodynamic model that describes exposure response in vivo.

Receptor-binding domain: a part of the SARS-CoV-2 virus located on its 'spike' protein that allows it to dock to body receptors to gain entry into cells and cause infection.