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Diagnostics and Treatments of COVID-19: A Living Systematic Review of Economic Evaluations

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ABSTRACT

Objectives: As healthcare systems continue to respond to the COVID-19 pandemic, cost-effectiveness evidence will be needed to identify which tests and treatments for COVID-19 offer value for money. We sought to review economic evaluations of diagnostic tests and treatments for COVID-19, critically appraising the methodological approaches used and reporting cost-effectiveness estimates, using a “living” systematic review approach.

Methods: Key databases (including MEDLINE, EconLit, Embase) were last searched on July 12, 2021. Gray literature and model repositories were also searched. Only full economic evaluations published in English were included. Studies were quality assessed and data were extracted into standard tables. Results were narratively summarized. The review was completed by 2 reviewers independently, with disagreements resolved through discussion with a senior reviewer.

Results: Overall, 3540 records were identified, with 13 meeting the inclusion criteria. After quality assessment, 6 were excluded because of very severe limitations. Of the 7 studies included, 5 were cost-utility analyses and 2 were cost-effectiveness analyses. All were model-based analyses. A total of 5 evaluated treatments (dexamethasone, remdesivir, hypothetical) and 2 evaluated hypothetical testing strategies. Cost-effectiveness estimates were sensitive to the treatment effect on survival and hospitalization, testing speed and accuracy, disease severity, and price.

Conclusions: Presently, there are few economic evaluations for COVID-19 tests and treatments. They suggest treatments that confer a survival benefit and fast diagnostic tests may be cost effective. Nevertheless, studies are subject to major evidence gaps and take inconsistent analytical approaches. The evidence may improve for planned updates of this “living” review.

Keywords: cost-effectiveness, COVID-19, diagnostics, economic evaluation, health technology assessment, pharmacological treatments, SARS-CoV-2, systematic review.

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Introduction

The novel severe acute respiratory syndrome coronavirus 2 and its associated disease (COVID-19) pandemic have placed healthcare systems and wider economies under massive strain, with successive surges in infections since late 2019. With little scientific understanding of the disease and no treatments, governments prioritized identifying cases and reducing transmission through public health interventions while vaccines and treatments were developed. Speed of decision making was also prioritized, with interventions typically implemented without a full assessment of their expected value for money. Several diagnostic tests (polymerase chain reaction, rapid lateral flow) and repurposed pharmaceutical treatments (corticosteroids, interleukin-6 inhibitors, remdesivir) have entered clinical practice based on effectiveness data alone.

In healthcare systems with established health technology assessment (HTA) processes, a rigorous evidence review is usually required before a technology can enter clinical practice, often including an economic evaluation based on the principle of opportunity cost. During the early phase of the pandemic, with time to act and evidence in both short supply and the unprecedented burden of COVID-19, this may have been reasonable. Nevertheless, going forward, healthcare systems will need to pay closer attention to the cost effectiveness of interventions for COVID-19. Although some public health measures, such as screening and vaccination programs, have been the subject of economic evaluations, HTA agencies are typically most interested in the value of diagnostic and therapeutic interventions. Evidence from previous pandemics with similar characteristics suggests antiviral treatments may represent a cost-effective use of resources, but assessments specific to COVID-19 are needed.

Next Generation Health Technology Assessment is a Horizon 2020 project supported by the European Union, lasting for 5 years from January 2019. Its main aim is to create a framework for the next generation of HTA to support patient-centered, societally oriented, real-time decision making on access to and reimbursement for health technologies throughout Europe. In particular, it
seeks to improve decision making about personalized combinations and sequences of treatments, which pose a complex challenge for HTA agencies. Assessing the value of interventions for COVID-19 during a pandemic has emerged as another significant challenge for HTA. Agencies will need to consider the latest cost-effectiveness evidence for novel and repurposed technologies, to identify which interventions offer value for money and understand where important evidence gaps and uncertainties lie.

Therefore, as part of a Next Generation Health Technology Assessment workstream to develop best-practice guidance for assessing COVID-19 technologies,\textsuperscript{15} we conducted a systematic review of economic evaluations of tests and treatments for COVID-19, to identify (1) estimates of their cost effectiveness, such as incremental cost-effectiveness ratios (ICERs), and (2) economic evaluation approaches used, including key uncertainties and limitations. Because COVID-19 remains a novel and evolving disease and the evidence base is likely to develop rapidly, we plan to rerun the search every 6 months and update this “living” review with contemporary studies.

Methods

Selection of Literature Databases

We conducted a systematic literature review to identify full economic evaluations of technologies for the diagnosis (eg, tests) and treatment (eg, pharmaceuticals) of COVID-19. The following databases were searched (Ovid unless stated): MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead Of Print, EconLit, Embase, Cochrane Database of Systematic Reviews (Cochrane), and International HTA Database (International Network of Agencies for Health Technology Assessment). The search was last updated on July 12, 2021. Citation checking was also performed on included studies. Update searches are planned approximately every 6 months.

Search Strategy

To identify studies in the relevant population (COVID-19), an existing population search strategy developed for the National Institute for Health and Care Excellence (NICE) rapid COVID-19 guidelines\textsuperscript{16,17} was used as the starting point for this search. The strategy was adapted by the addition of known treatment terms (eg, corticosteroids, remdesivir) and the use of diagnosis, economic evaluation, quality of life (QOL), and cost-utility filters. The search strategies are provided in an Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.01.001. Results were limited to articles published in English from January 1, 2020. Supplemental desk searching of the following databases were searched (Ovid unless stated): MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead Of Print, EconLit, Embase, Cochrane Database of Systematic Reviews (Cochrane), and International HTA Database (International Network of Agencies for Health Technology Assessment). The search was last updated on July 12, 2021. Citation checking was also performed on included studies. Update searches are planned approximately every 6 months.

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Data Extraction

Data extraction tables were developed to collate the key characteristics, methods, and findings from included studies, adapted from the tables used in a recent cost-effectiveness review of antiviral treatments for respiratory illnesses.\textsuperscript{15} Study characteristics and methods extracted (Table 2\textsuperscript{24-30}) were country, setting, interventions and comparators, type of economic evaluation, analysis approach and perspective, time horizon, discount rate, costs included, currency and price year, health outcome measures, and sources of effectiveness and utility data. Study findings extracted (Table 2\textsuperscript{24-30}) were total and incremental cost and health outcomes, ICERs, the relevant cost-effectiveness threshold, key sensitivity analyses, and the authors’ conclusions and self-reported study limitations.

Results

Included Studies

The search results per database are provided in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.01.001, and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis diagram\textsuperscript{11} is provided in Figure 1. The searches returned 3540 unique titles and abstracts for initial screening. After screening, 3520 records were excluded, most commonly because they were not economic evaluations, so 20 studies proceeded to full-text review. An additional 3 studies were identified from citations of included studies, HTA reports, and theses, meaning 23 full texts were reviewed in total. The inclusion criteria were met by 13 studies, but 6 were subsequently excluded because of serious limitations (Table 3\textsuperscript{24-30,32-37}).\textsuperscript{24-30} Therefore, 7 studies were included.\textsuperscript{24-30} Most studies were in a hospital setting (5 of 7), although the specific population varied by level of respiratory support (2); department, including intensive care unit (ICU) with and without mechanical ventilation (1) and emergency department...
Presentations (1); and a general hospitalized population (1). A healthcare payer perspective was exclusively taken by 5 of 7 studies. One study, in a community setting, used a societal perspective and another reported results from both perspectives. Studies from the United States (3 of 7) and South Africa (1 of 7) reported costs in 2020 US dollars. The remaining 3 studies were from the United Kingdom. For this review, their costs were converted to 2020 US dollars.

Most studies (5 of 7) evaluated therapeutic interventions, including remdesivir (2) and dexamethasone (2). The remaining studies evaluated hypothetical treatments (2 of 7) or hypothetical diagnostic tests (2 of 7). In all cases, standard care without the intervention of interest was a comparator.

The type of economic evaluation was either a cost-utility analysis (5 of 7) or a cost-effectiveness analysis (2 of 7). One study (1 of 7) was a decision tree, combining a series of probabilities and outcomes to estimate cost-effectiveness results, and another conducted similar calculations based on projections from a national epidemiological model (1 of 7). Markov models were used in 3 of 7 studies; of those, 1 used a hybrid structure, with a decision tree for the short-term hospitalization period followed by a long-term Markov model. The studies evaluating hypothetical diagnostic tests used very similar individual patient stimulations (2 of 7), characterizing the experience of a hospital emergency department and a residential care home for older people. All studies that evaluated hypothetical interventions were exploratory analyses.

Cost Effectiveness

Due to the extensive heterogeneity between studies, including the use of country-specific inputs (eg, cost data) that are not transferable, a quantitative synthesis of cost-effectiveness estimates was not attempted. Results are compared narratively where possible.

For inpatients who need supplemental oxygen, dexamethasone had an ICER of $1300/life-year gained compared with standard care in the United Kingdom. When evaluated in an ICU setting in South Africa, its ICER was $231/death averted compared with standard care. In the same study, the dexamethasone ICER was $52 000/death averted compared with remdesivir for non-ventilated ICU patients. In this population, remdesivir, at a local price of $330 per course, had lower overall costs than standard care without dexamethasone and averted deaths by reducing length of stay and freeing up ICU capacity. A US study estimated that remdesivir would have higher costs than standard care including dexamethasone. The remdesivir ICER for patients on respiratory support (oxygen with or without ventilation, local course price $3990) was $298 000 (quality-adjusted life-year (QALY) gained), and for patients not on respiratory support (local course price $2750), it was $1.85 million/QALY gained.

The study evaluating a hypothetical hospital treatment in the United States, costing $2500 per course, effective at reducing inpatient mortality, length of stay, and need for mechanical ventilation relative to standard care, estimated ICERS of $19 000 to $23 000/QALY gained from a healthcare perspective and $8000 to $11 000/QALY gained from a societal perspective. The study evaluating a hypothetical community treatment for mild COVID-19 in the United States, costing $1000 and effective at reducing the probability of worsening disease and hospitalization, found that it dominated a “no treatment” strategy from a societal perspective. It saved $816 per person and gained 0.003 QALYs.

Stevenson et al reported the hypothetical diagnosis strategy that would be most cost effective at different thresholds used by NICE in the UK ($28 000, $42 000, and $69 000/QALY gained), for people presenting at an emergency department. At the lowest threshold, the cost-effective strategy was “no testing.” At the middle threshold, testing patients using a laboratory-based test giving results in 6 hours or less was optimal. That strategy, extended to include weekly testing of asymptomatic hospital staff, was optimal at the highest threshold. The same authors developed a similar simulation model evaluating hypothetical laboratory and point-of-care testing strategies in a residential care home. Based on test characteristics from real-world evidence, point-of-care tests appear to be preferable in settings with en suite rooms or where the infection is already circulating. If better point-of-care tests are developed, with “desirable” diagnostic accuracy as defined by the Medicines and Healthcare Products Regulatory Agency, it is likely they would be highly cost effective across all thresholds.

Sensitivity analyses among included studies report that the cost effectiveness of treatment is influenced by its effect on survival, length of hospital stay, ICU capacity, and its cost. The exploratory diagnostic study in an emergency department setting found that the time to wait for results, cost, and underlying disease severity (probability of requiring ICU) were important determinants of the cost effectiveness of testing strategies. In a residential care setting, diagnostic accuracy and test costs were important factors. Accurate tests may remain cost effective even when staff and residents are vaccinated.

Discussion

This systematic review included 7 full economic evaluations of diagnostic and therapeutic interventions for COVID-19. The studies were highly heterogeneous, meaning their cost-effectiveness results could not be synthesized. In general, they showed that if a treatment confers a survival benefit, it is likely to be cost effective compared with standard care, in both the hospital setting and for mild disease in the community.

At the time of writing, clinical evidence suggests that only corticosteroids (including dexamethasone) have a significant effect on COVID-19 mortality compared with standard care. Dexamethasone has a low acquisition cost, so it is unsurprising that the included studies conclude it may be cost effective in the hospital setting. Nevertheless, conclusions about the cost effectiveness of remdesivir are unclear because of heterogeneous prices across studies. At $330 per course for nonventilated ICU patients, Jo et al (2021) predicted that adding it to standard care with dexamethasone may have an ICER below $50 000/QALY in South Africa. The HTA by I.C.E.R. (2020) estimated the course price that would give an ICER of $50 000/QALY in the United States: $2470 for people requiring respiratory support (with or without ventilation) and $70 for people not having respiratory support. Although their ICERS lack comparability, these studies suggest remdesivir is more likely to be cost effective and could justify a higher value-based price, only in populations where mortality benefit is demonstrated. Sheinon et al (2021) concluded that a hypothetical hospital intervention costing $2500 per course in the United States would be cost effective if it reduced the mortality hazard by 11% to 33% in patients needing respiratory support. Padula et al (2020) reached a similar conclusion for a hypothetical treatment for mild disease in the community in the United States, with a price of $1000 per course and a survival benefit caused by reducing disease progression.

The 2 included studies evaluating diagnostic interventions for COVID-19 were also exploratory analyses, comparing hypothetical testing strategies. In a hospital emergency department, Stevenson et al found that not testing was
optimal at lower UK cost-effectiveness thresholds, whereas at normal or higher thresholds, 6-hour laboratory testing of patients and staff would be optimal. The appropriate cost-effectiveness threshold during a pandemic is unclear. Nevertheless, a “no testing” strategy may be politically and ethically unacceptable, and rapid laboratory tests for patients and staff may be unachievable in all hospitals. Notably, the authors estimated that a point-of-care test just satisfying the

| Study | Country | Currency (cost year) | Population/setting | Interventions and comparators | Evaluation type | Analysis approach | Perspective | Time horizon |
|-------|---------|----------------------|---------------------|-------------------------------|-----------------|-------------------|-------------|--------------|
| Águas et al (2021) | UK | GBP (2020) | Hospitalized patient who needs supplemental oxygen | Dexamethasone vs SoC | CEA | Decision tree algorithm | Provider (healthcare) | Lifetime |
| I.C.E.R. (2020) | US | USD (NR) | Hospitalized patient (moderate to severe – respiratory support; mild – no respiratory support) | Remdesivir + SoC (inc Dex) vs SoC | CUA | Markov model with 1-mo cycles (cycle 1 in hospital) | Payer (bundled insurance payments) | Lifetime |
| Jo et al (2021) | South Africa | USD (2020) | ICU, V and NV patients | Dex (V) and Rem (NV) | CEA | Cost-effectiveness analysis based on projections from National COVID-19 Epidemiology Model | Healthcare system | 6 months (August 2020 to January 2021) |
| Padula et al (2020) | US | USD (2020) | Mild disease, community setting (not hospitalized) | Hypothetical antiviral treatment vs “do nothing” strategy | CUA | Markov model (10 states) with 1-day cycles | Societal | 1 year |
| Sheinson et al (2021) | US | USD (2020) | Hospitalized patients (age 62.5, male 64%) | Hypothetical treatment vs SoC | CUA | Short-term decision tree (hospital) and long-term 3-state Markov cohort model with 1-year cycles | Three: payer (bundled insurance payments), societal, fee for service | Lifetime |
| Stevenson et al (2021) | UK | GBP (2020) | Patients attending ED | Hypothetical rapid point-of-care tests vs laboratory tests | CUA | Individual patient model, including transmission within and between patients and staff in the hospital | Healthcare system | ED simulated for 90 days; patient care up to 200 days; lifetime QALYs projected |
| Stevenson et al (2021) | UK | GBP (2020) | Residents in a care home for older people | Hypothetical rapid point-of-care tests vs laboratory tests. Lateral flow tests included in sensitivity analysis | CUA | Individual patient model, including transmission within and between residents and staff in the care home | Healthcare system | Care home simulated for 90 days, then lifetime QALYs projected |

ARDS indicates acute respiratory distress syndrome; BMJ, British Medical Journal; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; Dex, dexamethasone; ED, emergency department; GBP, British pound; ICU, intensive care unit; I.C.E.R., Institute for Clinical and Economic Review; LYG, life-years gained; MHRA, Medicines and Healthcare Products Regulatory Agency; NA, not applicable; NMA, network meta-analysis; NMB, net monetary benefit; NR, not reported; NV, nonventilated population; POC, point of care; QALY, quality-adjusted life-year; RCT, randomized controlled trial; Rem, remdesivir; SARS, severe acute respiratory syndrome; SoC, standard of care; US, United States; UK, United Kingdom; USD, US dollars; V, ventilated population; WHO, World Health Organization.
Medicines and Healthcare Products Regulatory Agency’s “acceptable” criteria is unlikely to be cost effective, for example, compared with a 24-hour laboratory test. Similarly, in a residential care facility, tests were much more likely to be cost effective if they had diagnostic accuracy superior to the “acceptable” criteria. Here, almost all testing strategies are likely to confer value compared with “no testing,” particularly if the care home already has an infected resident.

Table 1. Continued

| Costs included                                      | Discounting | Health outcomes | Source of efficacy data       | Source of utility data (if relevant) | Uncertainty analyses                      |
|-----------------------------------------------------|-------------|-----------------|-------------------------------|--------------------------------------|-------------------------------------------|
| Inpatient costs, intervention                       | NR          | LYG             | RCT: Recovery                 | NA                                   | Probabilistic and limited one-way (Dex efficacy) analyses |
| Inpatient costs, interventions (Rem course $3990 in moderate to severe, $2750 in mild) | 3%          | LYG, QALYs      | RCTs: ACTT1, NCT04292730, Recovery, WHO Solidarity. | Age-adjusted general population. Disutilities for symptoms 0.19, hospitalization 0.30, oxygen 0.50, ventilation 0.60 from literature | Scenario and price-threshold analyses |
| ICU cost per day (capital, staff, overheads); interventions (Dex course $31, Rem course $330) | 5% (to estimate cost annualized cost of capital expenditure) | Deaths averted | RCTs: ACTT1, Recovery, WHO Solidarity. | NA | Probabilistic, one-way and scenario analyses |
| Primary, secondary, emergency and critical care; medications; productivity loss; intervention ($1000) | 3%          | QALYs           | RCT: zanamivir for influenza   | Mild disease 0.614 (source unclear); moderate 0.5, severe 0.25, critical 0.05 (literature: lower bounds of values for SARS from 4 clinical experts) | Probabilistic, one-way and scenario analyses |
| Inpatient costs, unrelated long-term costs, hypothetical intervention ($2500), productivity loss | 3%          | LYG, QALYs      | RCTs: Covid-NMA, BMJ living NMA, ACTT1, Recovery, WHO Solidarity. | Age-adjusted general population. Disutilities for symptoms 0.27, hospitalization 0.11, oxygen 0.36, ventilation 0.56, and 5 years postdischarge (0.13-0.02, ARDS) from literature | Probabilistic, one-way and scenario analyses |
| ICU admission; tests (including staff time)         | 3.5%        | NMB             | Symptomatic patient: Laboratory tests: Sensitivity 95%-99% (MHRA target criteria) or 89% (meta-analysis), Specificity 100% (Foundation for Innovative New Diagnostics). Rapid POC test: Sensitivity 71-86% (MHRA target criteria) or 84.7% (real-world data). Specificity 95-99% (MHRA target criteria). Asymptomatic patient: Sensitivity 17.4% lower | Age- and sex-adjusted general population EQ-SD. 20% utility reduction following ICU (assumed) | Probabilistic simulation. Scenario analyses |
| Testing (unit costs equal in base case)             | 3.5%        | NMB             | As in Stevenson et al (2021) (emergency department), except MHRA target sensitivity for POC test increased to 80%-97%. | Age- and sex-adjusted general population EQ-SD. Isolation: 0.25 (assumed: worsening of anxiety/depression and 50-50 split between no/some problems at baseline). A total of 10% utility reduction following hospitalization (assumed) | Probabilistic simulation. Scenario analyses |
Perhaps more important than cost-effectiveness conclusions for specific treatments, this review has identified important gaps in the evidence needed to inform a robust economic evaluation and a lack of consistency in the approaches taken so far. First, the COVID-19 clinical evidence base remains relatively immature. This means long-term model inputs are at best uncertain or may limit evaluations to using oversimplified structures and modeling assumptions that do not characterize the disease sufficiently or capture all important outcomes. For example, a study published early in the pandemic used efficacy data for the antiviral treatment zanamivir for severe acute respiratory syndrome as a proxy for a hypothetical treatment for COVID-19.27 It also used a relatively short analysis time horizon, as did Jo et al (2021),26 which was 1 of 2 simple decision tree–type analyses.24 These typically require less data than state-transition and simulation models and are therefore more feasible with a weak evidence base. Furthermore, that 4 of 7 studies evaluated hypothetical treatments and the others only evaluated dexamethasone and remdesivir indicates an immature clinical evidence base for other technologies (e.g., interleukin-6 inhibitors) with which to inform an economic evaluation.

Second, the increasingly rapid advent of new clinical data and scientific understanding of COVID-19 mean any cost-effectiveness model risks becoming outdated even before it is published. For example, there is increasing evidence of lasting, long-term effects of COVID-19, with clusters of symptoms that can fluctuate and change over time and affect any system in the body.41 None of the included studies explicitly capture the effects of “long COVID.” In those that estimated lifetime outcomes, patients were assumed to recover to something like general population health, for example, by accruing average life expectancy or QALYs after recovery.24,25 This may be a reasonable approach until high-quality evidence about “long COVID” becomes available, because although omitting long-term effects from a model is a known limitation, the alternative of using low-quality evidence or assumptions may be even more incorrect. Only 3 of 7 studies attempted to include ongoing symptoms, by applying a utility reduction after ICU or hospitalization10 or including a phased return to pre-COVID QOL for severely affected patients.26 Nevertheless, people who have less severe COVID-19 symptoms may also experience long-term effects.42 The effect of appropriately capturing long-term symptoms on conclusions is unclear. Treatments may be less cost effective if patients are only able to recover to lower levels of health. Conversely, treatments that prevent symptoms from worsening may be more cost effective if this reduces the likelihood of long-term negative consequences.43

The evidence base is lacking in utility (and disutility) values derived from high-quality quality-of-life studies conducted in COVID-19 populations. Padula et al (2020)27 used a combination of a Chinese modeling study and a 2005 study of 4 clinicians in the context of a hypothetical severe acute respiratory syndrome outbreak, ranging from utility of 0.614 in people with mild symptoms to 0.050 in people receiving critical care. These would not typically be considered high-quality evidence sources, yet Sheinson et al (2021)28 cited the same data to derive utility values, demonstrating the lack of alternative sources: the I.C.E.R. model (2020)25 used a combination of a 2002 influenza study, a French *Clostridium difficile* infection study, and assumptions to inform disutility values, ranging from 0.19 (symptomatic) to 0.79 (mechanical ventilation). In the emergency department diagnostic study,26 long-term QOL was assumed to be 20% lower than normal after ICU. In the care home study,26 this reduction was lower (10%) for hospitalized patients, given that not all of them would require intensive care. The authors also included a 0.25 utility reduction for residents while in isolation after a positive test, assumed to reflect an increase in anxiety or depression among residents with a 50-50 split between having “no” or “moderate” baseline anxiety or depression.

Only 3 of 7 evaluations included models that attempted to characterize wider implications beyond the specific individuals being tested or treated for COVID-19. One modeled the setting of a capacity-constrained ICU, where a treatment that reduces length of stay might ease pressure on facilities and allow more patients to be treated.26 System dynamics like these are often not captured in cost-effectiveness models for HTA. The diagnostic evaluation models23,30 included transmission dynamics. They simulated the experience of patients and staff in an emergency department and in a residential care home, for example, including time spent waiting for test results, people posing an infection risk to other people, and residents having to isolate themselves. These effects are more commonly modeled when evaluating vaccination and public health interventions, but they are necessary to capture the value of tests and treatments that reduce transmission. Antiviral treatments for COVID-19 (such as remdesivir) may also create wider implications for healthcare systems through antimicrobial resistance. Nevertheless, none of the included studies that evaluated either remdesivir (2 of 7) or a hypothetical treatment with characteristics based on an existing antiviral (2 of 7) considered the impact of COVID-19 becoming resistant to such treatments.

Two evaluations reported analyses from a societal perspective.27,28 In both cases, this was limited to capturing costs associated with lost productivity. It led to lower ICERs than a healthcare perspective.28 Although this represents a narrow definition of a societal perspective, the emergency nature of the pandemic and its far-reaching social consequences warrant discussion about what analysis perspective is the most relevant to demonstrate the value of effective COVID-19 technologies.40 Nevertheless, broadening the scope of costs and benefits for an economic evaluation to capture wider societal outcomes would further increase the need for high-quality data.

This review has some limitations. First, it is likely that the volume of published economic evaluations for COVID-19 technologies will increase rapidly as the clinical evidence base matures and more technologies enter the decision space. At present, the findings reflect the very limited cost-effectiveness evidence base. As the focus shifts from public health measures and vaccination programs to diagnostic and therapeutic technologies, economic evaluations will be needed to determine whether they offer value for money. Therefore, at this time, our review represents an early snapshot of an immature evidence base, but, as a “living” review, planned updates approximately every 6 months will capture any new, relevant evaluations.

Second, we excluded 6 studies that met the inclusion criteria because of their very serious limitations (Table 3). This follows a process used to select evidence to inform NICE clinical guideline development,25 to prevent low-quality studies being conflated with more robust analyses. Nevertheless, we recognize that any quality assessment is subjective. We also excluded poster abstracts that lacked detail and studies that were not published in English and did not explicitly search for preprint articles. Because COVID-19 is a recent health issue, these exclusions may have omitted relevant economic evaluations that were disseminated quickly in response to the pandemic, before full publication or translation into English. Excluding articles not published in English may reduce the generalizability of this review to lower and middle-income settings. All included studies were from high- (6 of 7) or upper-middle-income (1 of 7) settings.
### Table 2. Results of included studies.

| Study                      | Cost and health outcomes results (USD, 2020) | ICER/net benefit of interventions vs comparators | Cost-effectiveness threshold (if relevant) | Sensitivity and scenario analyses | Authors’ conclusions regarding cost effectiveness | Authors’ reported limitations and challenges |
|----------------------------|---------------------------------------------|-----------------------------------------------|------------------------------------------|----------------------------------|-----------------------------------------------|-----------------------------------------------|
| Águas et al (2021)         | Dex vs SoC Incremental cost: $117m (90% CI $8.3-$455m). LYG: 102K (90% CI 37K-240K). Results assume 5-15% COVID-19 exposure. | $1300/LYG (90% CI $90/LYG-$2800/LYG) | $0 to $3000/LYG | PSA: 95% of ICERs < $2000/LYG. Scenarios exploring Dex efficacy in people who need but cannot access oxygen (base case = 100%): 25%, 50% and 75%. ICER remains $700-800/LYG. | Dex can be highly cost effective if given to hospitalized patients with COVID-19 requiring oxygen therapy. | Important uncertainty remains regarding relative clinical effects and complications of hospitalizations by COVID-19 severity; assimilation costs; long-term cost and health outcomes: evidence for other interventions. |
| I.C.E.R. (2020)            | Moderate to severe LYG: SoC = Rem = 15.164. QALYs: SoC 12.182; Rem 12.189 (+0.006). Costs: SoC $311 620; Rem $313 450 (+1830). Rem course: $3990. Mild LYG: SoC = Rem = 16.867. QALYs: SoC 13.703; Rem 13.704 (+0.001). Costs: SoC $315 630; Rem $318 380 (+2750). Rem course: $2750. | Moderate to severe: L298 160/QALY Mild: $1.85m/QALY | $50K/QALY: Rem price $2470 (moderate to severe), $70 (mild), $100K/QALY: Rem price $2770 (moderate to severe), $150 (mild). $150K/QALY: Rem price $3080 (moderate to severe), $220 (mild). | Scenario with Rem survival benefit (HR = 0.84): $50K/QALY: Rem course $3980-4140 (moderate to severe), $690-760 (mild). $100K/QALY: Rem course $8750-9080 (moderate to severe), $2620-2740 (mild). $150K/QALY: Rem course $13 520-$14 020 (moderate to severe), $4540-4720 (mild). No PSA reported. | The pricing estimate related to the threshold of $50K/QALY is the most policy-relevant consideration. This suggests a price of $2470 per Rem course for moderate to severe (vs actual $3990) and $70 for mild (vs actual $2750). | Important uncertainty remains regarding relative clinical effects and complications of hospitalizations by COVID-19 severity; assimilation costs; long-term cost and health outcomes: evidence for other interventions. |
| Jo et al (2021)            | SoC: $83 937. Dex (V) and Rem (NV): $69 3m; 408 deaths averted (vs SoC). Dex (N and NV): $84 1m; 689 DA (vs SoC). Rem (NV): $69 3m; 26 DA (vs SoC). Dex (V): $84 0m; 382 DA (vs SoC). | All vs SoC | $36K/death averted (from £38/DALY averted, assuming average discounted life expectancy = 17 years (12 DALYs per death)). | Dex (V) and Rem (NV) no longer cost saving if ICU capacity is breached for 6 months. Rem not cost saving if ICU always at full capacity. Otherwise, cost saving even if LoS reduction is 1 day. PSA, Dex (V and NV): ~100% ICERs < $1000/death averted. Rem strategies: ~75% ICERs dominant, if Rem mortality efficacy is 30% (instead of 0%), fully incremental analysis: Dex (V) and Rem (NV) ICER: $78/DA. | Dex (V) and Rem (NV) could avert 408 deaths and save $15 million vs SoC. Dex (V and NV) would maximize deaths averted (689) at an incremental cost of $159K. | Confounding factors not captured can influence ICU capacity breaches: epidemic conditions, system capacity, policy. Did not consider changes in disease progression or severity, eg, time since symptom onset, age, comorbidities, adverse events, other medications. Cost associated with adverse events were not included. Time horizon was limited to projections from the NCEM. |
| Padula et al (2020)        | Hypothetical antiviral treatment: $1 299, 877 QALYs. Do nothing: $2 115, 874 QALYs. | Dominant (lower cost, higher QALYs) | $50K/QALY | PSA: treatment almost certainly cost effective vs no treatment. Results most sensitive to treatment efficacy. | A treatment for COVID-19 presents excellent value to the US healthcare system and economy, if it is priced between $750 and $1250. | Probabilities are not time dependent, because of limited understanding of the disease. Risks and effects assumed equal for all groups and ages. Static population, no death from other causes. Utilities obtained from non-COVID-19 population (SARS). Not all cost items relevant to healthcare system are captured. | continued on next page |
| Study | Cost and health outcome results (USD, 2020) | ICER/net benefit of interventions vs comparators | Cost-effectiveness threshold (if relevant) | Sensitivity and scenario analyses | Authors’ conclusions regarding cost effectiveness | Authors’ reported limitations and challenges |
|-------|------------------------------------------|-----------------------------------------------|------------------------------------------|---------------------------------|-----------------------------------------------|-----------------------------------------------|
| Sheinson et al (2021) | LYs: SoC 12,423; tmt 12,961 (+0.538); QALYs: SoC 9,790; tmt 10,228 (+0.438). Costs: Payer: SoC $277,978; tmt $288,005 (+10.027). Payer and societal: SoC $301,259; tmt $306,284 (+5025). FFS: SoC $261,684; tmt $290,196 (+8512). FFS and societal: SoC $304,965; tmt $307,284 (+3510). | Payback: $22,933/QALY Payer and societal: $11,492/QALY FFS: $19,469/QALY FFS and societal: $100K/QALY | $100K/QALY → FFS VBP = $37,710 $150K/QALY → FFS VBP = $59,572 | All OWSA < £50K/QALY. Most sensitive parameter varies by perspective, eg, societal, age at death: 95 y → £18,632; 64 y → dominant. If no LoS benefit: FFS ICER (50K): £29,108. PSA (n = 5000), >99% ICERS < $100K/QALY, max 95% upper bound: payer → $30,937. Almost all results in NEQ. | Potential treatments reducing LoS, mortality, and mechanical ventilation use are likely to be cost effective, at a cost of $2500 per course. | The COVID-19 evidence base is immature, so the model may need to evolve in complexity as data emerge. Examines a hypothetical treatment with a proxy drug cost, rather than an actual potential treatment. Uncertainty exists for mechanical ventilation and long-term outcomes (used ARDS data instead). |
| Stevenson et al (2021) | (From 22,500 patients entering the model in 90 days) Laboratory test with 6-h results: $214K, 11.5 QALYs lost. Rapid test with desirable TPP: $275K, 10.5 QALYs lost. Rapid test with acceptable TPP: $272K, 14.2 QALYs lost. Laboratory test (6 h) with weekly testing of asymptomatic staff: $307K, 9.4 QALYs lost. | Highest NMB strategies: At $69K/QALY: laboratory test (6 h) with weekly testing of asymptomatic staff → $320K. At $42K/QALY: laboratory test (6 h) → $260K. At $28K/QALY: “no testing” strategy, → $80K (laboratory test (6 h) provides highest NMB among strategies with testing) | $69K/QALY, $42K/QALY, and $28K/QALY (used in NICE appraisals). | Results highly sensitive to test costs (if equal, rapid test with desirable TPP has highest NMB at $42K/QALY; including weekly testing of asymptomatic staff at $69K/QALY). Results sensitive to risk of a hospitalized patient needing ICU care (90% risk reduction → testing has much lower NMB). Various scenario analyses comparing “plausible” strategies (1 lab, 2 POC). In general, laboratory test (24 h) highest NMB at $42K/QALY, POCs (including weekly for asymptomatic staff) highest NMB at $69K/QALY. If laboratory test results take 6 h or less, POC tests unlikely to have ICER < $42K. If laboratory test results take ≥ 16 h and POC test results take 6 h or less, POC tests likely to have ICER < $42K. | Given the heterogeneity of hospitals, no blanket solution can be provided. A POC test with a desirable TPP would appear to have a relatively high NMB, but this may be lower than a laboratory test with 6-h results. A POC test with an acceptable TPP would appear to have a lower NMB than a laboratory test with 24 h results. Testing asymptomatic staff and removing them from duty appears to have higher NMBs at higher cost/QALY thresholds. | The model did not consider hospitalization via a different route than ED; implications for people with existing respiratory diseases; testing at discharge; cost of shutting clinics because of an outbreak. Simplifying assumptions for rapid tests (eg, no dedicated staffing). Considerable uncertainty in input parameters. Some sampling error. |
Table 2. Continued

| Study | Cost and health outcome results (USD, 2020) | ICER/net benefit of interventions vs comparators | Cost-effectiveness threshold (if relevant) | Sensitivity and scenario analyses | Authors’ conclusions regarding cost effectiveness | Authors’ reported limitations and challenges |
|-------|---------------------------------------------|---------------------------------------------|---------------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Stevenson et al (2021) | Residential care home | (From 16 residents and 9 staff, using observed, real-world accuracy data, assuming facility is penetrated by 1 SARS-CoV-2 infection) | En suite care facility | Rapid POC test: $7365, 2.37 QALYs lost. Laboratory test: $7786, 3.37 QALYs lost. | Shared care facility | Rapid POC test: $8090, 3.31 QALYs lost. Laboratory test: $7557, 2.97 QALYs lost. | (Note: these results are erroneously transposed in primary study.) | At all thresholds, POC test with desirable TPP characteristics provides highest NMB. All testing strategies cause a gain in NMB if the facility has been penetrated by an infection. All testing strategies cause a reduction in NMB if the facility has not been penetrated by an infection, because of unnecessary test costs and isolation | $69K/QALY, $42K/QALY and $28K/QALY (used in NICE appraisals). | Results highly sensitive to diagnostic accuracy values and cost differential between the 2 types of test. Tests with desirable and observed accuracy may still have positive NMB if vaccination reduces the risk of critical care by up to 90% or reduces immunity by up to 90%. Regular lateral flow testing, with accuracy data from Public Health England and assuming $14 cheaper, may be cost effective (but this is exploratory, eg, assumes perfect adherence). | It is only possible to draw broad conclusions from this analysis. POC tests have considerable potential for benefit for use in residential care facilities, providing they are sufficiently accurate. | Unclear whether the MHRA criteria for a “desirable” test can or will be met; may be unrealistic. Limitations include residents not stratified by risk for COVID-19; facilities only penetrated by 1 case initially; model progression time of 6 h may be too long to capture very small time effects; cost of hospitalization not included (this will favor less accurate tests); societal and wider capacity effects not captured. |

ARDS indicates acute respiratory distress syndrome; CI, confidence interval; DA, deaths averted; DALY, disability-adjusted life-year; Dex, dexamethasone; ED, emergency department; FFS, fee for service; ICER, incremental cost-effectiveness ratio; I.C.E.R., Institute for Clinical and Economic Review; ICU, intensive care unit; K, thousand; LoS, length of stay; LY, life-year; LYG, life-years gained; m, million; MHRA, Medicines and Healthcare Products Regulatory Agency; NEQ, north-east quadrant of the cost-effectiveness plane; NMB, net monetary benefit; NR, not reported; NV, nonventilated population; OWSA, one-way sensitivity analysis; POC, point of care; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; Rem, remdesivir; SARS, severe acute respiratory syndrome; SoC, standard of care; TPP, target product profile for a diagnostic test; US, United States; USD, US dollars; V, ventilated population.

Figure 1. PRISMA diagram showing study selection process.
### Table 3. Summary of quality assessment and subsequent inclusion or exclusion decisions.

| Study                        | Notable limitations identified                                                                                                                                                                                                 | Assessment                      | Decision |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|----------|
| Águas et al (2021)           | Estimates of relative treatment effect were derived from 1 randomized controlled trial. Some resource use inputs (hospital days) were derived from 1 early study in the Chinese setting. Tariff costs may not always reflect the true cost of providing healthcare in the UK. | Potentially serious limitations  | Include  |
| Bastos et al (2021)          | The study did not provide a robust estimate of cost effectiveness because it did not account for false-positive test results of the diagnostic under evaluation. In addition, no longer-term costs or outcomes were included. The time horizon was not reported, although it appears to be short term, meaning the impact of potential longer-term effects of COVID-19 and treatment effects could not be explored. | Very serious limitations         | Exclude  |
| I.C.E.R. (2020)              | The study did not capture the long-term effects of COVID-19 or treatment. Limited uncertainty analyses were reported; for example, probabilistic sensitivity analysis was not reported. | Potentially serious limitations  | Include  |
| Jiang et al (2020)           | Several intervention effects, costs, and resource use inputs relevant to the treatment under evaluation were either omitted, and therefore could not be examined, or the input data were not taken from the best available sources. | Very serious limitations         | Exclude  |
| Jiang et al (2021)           | The study did not provide a robust estimate of cost effectiveness. The published evidence used to inform the model does not show a survival benefit for the treatment under evaluation. Nevertheless, the model structure used generated substantial gains in life expectancy for the treatment because of an indirect survival benefit. This contradicts the underlying clinical evidence. | Very serious limitations         | Exclude  |
| Jo et al (2021)              | The time horizon was 6 months, meaning the impact of potential longer-term effects of COVID-19 and treatment effects could not be explored.                                                                                                                                                     | Potentially serious limitations  | Include  |
| Padula et al (2020)          | The time horizon was 1 year, meaning the impact of potential longer-term effects of COVID-19 and treatment effects could not be explored. Some data were from proxy (non-COVID) conditions, including relative effectiveness; nevertheless, the treatment under consideration was hypothetical. | Potentially serious limitations  | Include  |
| Ricks et al (2021)           | Baseline outcomes were based on assumptions, and relative effectiveness estimates were derived from separate nonrandomized studies with no adjustment for confounding factors. Critical illness, including intensive care and ventilation, and recovery from COVID-19 were omitted. The time horizon was not reported, although it appears to be short term, meaning the impact of potential longer-term effects of COVID-19 and treatment effects could not be explored. An appropriate incremental cost-effectiveness analysis could not be calculated from the results. | Very serious limitations         | Exclude  |
| Sheinson et al (2021)        | Some proxy data from related conditions were used. There is a potential conflict of interest because the study was sponsored by a manufacturer of a therapeutic for COVID-19 (tocilizumab); nevertheless, the treatment under consideration was hypothetical. | Potentially serious limitations  | Include  |
| Sinha and Linas (2021)       | The study did not provide a robust estimate of cost effectiveness because several important and relevant costs were omitted. For example, the cost of an inpatient hospital admission only includes the cost of the treatment under evaluation. In addition, the source of the quality-of-life values used in the analysis is unclear, and they have not been subjected to sensitivity analysis. | Very serious limitations         | Exclude  |
| Stevenson et al (2021)       | Long-term effects of COVID-19 were only included for critical illness, by an assumed reduction in quality of life. Cost of intensive care was omitted, but this was informed by the simulation identifying negligible difference in length of intensive care stay between the strategies under consideration. | Minor limitations               | Include  |

*continued on next page*
Table 3. Continued

| Study | Notable limitations identified | Assessment | Decision |
|-------|--------------------------------|------------|----------|
| Stevenson et al (2021) | Long-term effects of COVID-19 were only included for severe illness, by an assumed reduction in quality of life. Cost of hospitalization was omitted for simplicity, which will favor strategies that result in more infections. General population utility values may overstate the quality of life of elderly care home residents. | Potentially serious limitations | Include |
| Wu et al (2021) | The study did not provide a robust estimate of cost effectiveness. It used a 30-day time horizon for the model, which is insufficient to capture all relevant differences between the intervention and comparator groups. Longer-term outcomes would be expected to influence cost-efffectiveness results because the authors assume the treatment under evaluation confers a survival benefit. | Very serious limitations | Exclude |

UK indicates United Kingdom.

Finally, the findings of this review do not provide definitive conclusions about the cost effectiveness of specific COVID-19 technologies. We identified full economic evaluations of dexamethasone, remdesivir, the 2 in combination, and hypothetical interventions. Many other technologies are being investigated for use in COVID-19. The included studies are highly heterogeneous, in terms of target population (by disease severity and setting), data sources used, health outcome of interest, analytical approach, and the extent to which they consider wider outcomes (such as system capacity). In the case of remdesivir, even its price varied by an order of magnitude, invariably affecting conclusions about cost effectiveness.

In the context of an immature evidence base, studies exploring the conditions that would make a hypothetical test or treatment cost effective are perhaps the most insightful. Their findings could provide the starting point to assess the value of such interventions, such as a “living” cost-effectiveness model. This could attempt to link the diagnostic and treatment elements of COVID-19, which, so far, have been evaluated separately, in a unified disease model. It could also attempt to disentangle the various COVID-19 population subgroups, for example, by their need for ventilation, allowing decision makers to assess interventions at the appropriate point in the pathway and, potentially, different sequences of treatments. This would give a more accurate estimate of the cost effectiveness of treatments used early in the pathway (eg, for mild disease) and diagnostic tests, whose value is intrinsically linked to downstream outcomes and costs.

Conclusions

The findings of our review show that effective treatments for confirmed COVID-19 have the potential to offer value for money to healthcare systems in the investigated countries, particularly if they confer a survival benefit and reduce the need for hospitalization. Diagnostic tests are more likely to be cost effective if they can provide accurate results quickly, to limit further infections. The cost effectiveness of remdesivir is uncertain, because of its variable price in different countries and limited evidence of a survival benefit. Nevertheless, there is evidence that low-cost dexamethasone—already widely used for severe COVID-19—may provide value for money in hospitalized patients.

The clinical evidence base is presently limited and immature. A robust cost-effectiveness analysis relies on high-quality clinical evidence; therefore, the economic evidence base is similarly limited. Exploratory modeling analyses have begun to develop analytical approaches that may be suitable for identifying cost-effective interventions. As the COVID-19 evidence base grows, a common model for assessing the value for money of diagnostics and treatments; capturing linked decision points, applicable to different settings; and making use of all available evidence (including suitable real-world evidence) would be beneficial.

These conclusions will be updated and may change when relevant new economic evaluations are identified. Any such studies will be included in planned future updates of this living review.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.01.001.

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