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Cost of the COVID-19 pandemic versus the cost-effectiveness of mitigation strategies in EU/UK/OECD: a systematic review

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ABSTRACT

Objectives The economic burden of COVID-19 pandemic is substantial, with both direct and indirect costs playing a significant role.

Design A systematic literature review was conducted to estimate the cost of the COVID-19 pandemic and the cost-effectiveness of pharmaceutical or non-pharmaceutical interventions. All cost data were adjusted to the 2021 Euro, and interventions compared with null.

Data sources Ovid MEDLINE and EMBASE were searched from January 2020 through 22 April 2021.

Eligibility criteria Studies regarding COVID-19 outbreak or public health preparedness measures or interventions with outcome measures related to the direct and indirect costs for disease and preparedness and/or response in countries of the European Union (EU), the European Economic Area (EEA), the UK and the Organisation for Economic Co-operation and Development (OECD) of all relevant epidemiological designs which estimate cost within the selected time frame were considered eligible.

Data extraction and synthesis Studies were searched, screened and coded independently by two reviewers with high measure of inter-rater agreement. Data were extracted to a predefined data extraction sheet. The risk of bias was assessed using the Consensus on Health Economic Criteria checklist.

Results We included data from 41 economic studies. Ten studies evaluated the cost of the COVID-19 pandemic, while 31 assessed the cost-benefit of public health surveillance, preparedness and response measures. Overall, the economic burden of the COVID-19 pandemic was found to be substantial. Community screening, bed provision policies, investing in personal-protective-equipment and vaccination strategies were cost-effective. Physical distancing measures were associated with health benefits; however, their cost-effectiveness was dependent on the duration, compliance and the phase of the epidemic in which it was implemented.

Conclusions COVID-19 pandemic is associated with substantial short-term and long-term economic costs to healthcare systems, payers and societies, while interventions including testing and screening policies, vaccination and physical distancing policies were identified as those presenting cost-effective options to deal with the pandemic, dependent on population vaccination and the R_e at the stage of the pandemic.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The systematic review is adhering to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) framework.
⇒ The risk of bias was assessed using the Consensus on Health Economic Criteria (CHEC) checklist.
⇒ Studies were searched in two databases, Ovid MEDLINE and EMBASE.
⇒ The population of interest is restricted to the European Union (EU)/UK/European Economic Area (EEA)/Organisation for Economic Co-operation and Development (OECD).

INTRODUCTION

In the aftermath of significant outbreaks since the beginning of the 21st century, including among others those of Ebola, avian influenza (H5N1, H7N9), the 2009 H1N1 influenza virus pandemic, Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), it was acknowledged that large-scale infectious disease outbreaks represent a menace for loss of life, economic disturbance and social disruption.[1] The most recent pandemic caused by SARS-CoV-2 has undoubtedly hit hard on societies and healthcare systems.[2 3] According to the situation update conducted by European Centre for Disease Prevention and Control (ECDC), as of week 17 of 2022, 512 690 034 cases of COVID-19 have been reported, including 6 252 316 deaths.[4] To mitigate the pandemic and given the lack of preventative treatments until the rollout of vaccines in late 2020, governments worldwide implemented various non-pharmaceutical interventions (NPIs).[5] These measures included personal protective, environmental, and physical distancing strategies as well as travel restrictions[6] which have been loosened and reinforced depending on the variation of the epidemiological situation,[7] leading to an unprecedented decline in global economic activities and an economic burden both from direct costs of the NPIs and indirect costs. The closure of businesses led to significant disruptions to the global value chains in the first quarter of 2020 through increased unemployment rates, revenue loss and a sharp decrease in personal incomes while the earlier action of NPIs implementation contributed to reduced economic impact as was shown in a study assessing the short-term economic consequences of the first-wave of the COVID-19 pandemic.[8]

In the USA, the cost of the COVID-19 pandemic has been estimated at US$13 trillion for the first 20 weeks of the pandemic (90% of the country's annual Gross Domestic Product (GDP)) when drastic NPIs were predominately implemented, and approximately half of that figure corresponds to the projected 10-year decline in GDP attributable to the pandemic.[9] Additionally, the global cost of the COVID-19 crisis has been estimated at 14% of the 2019 GDP (around US$12 206 million), while for Europe, it is even higher: 16% for the Eurozone and 19% for the UK.[10] Considering the cost-effectiveness of NPIs, in a recent systematic review and meta-analysis conducted by Zhou *et al*,[11] the pooled incremental net benefit (INB) for NPIs was estimated at US$972.05, with subgroup analyses indicating that the highest pooled INBs were for screening (US$2390.89) and suppression (US$2156.00) interventions.[11]

Robust national preparedness and response strategies require recent data on the health impacts and the economic burden of respiratory infectious disease outbreaks in contrast to those associated with emergency response and preparedness actions. This evidence will ensure well-informed decisions regarding the proper allocation of resources,[12 13] information relevant not only for the COVID-19 pandemic but also for future pandemics.

This systematic review aims to (1) summarise the total direct and indirect costs of the COVID-19 pandemic across countries of the European Union (EU), the European Economic Area (EEA), the UK and the Organisation for Economic Co-operation and Development (OECD), and (2) to identify the costs and the cost-benefit of public health surveillance, preparedness and response measures in averting and/or responding to COVID-19 pandemic in this setting.

METHODS

Search strategy and selection criteria

A systematic review was conducted to identify peer-reviewed articles published from 1 January 2020 through 22 April 2021 in Ovid MEDLINE and EMBASE. The review is reported adhering to the PRISMA framework (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[14] available in online supplemental appendix 1. Two sets of inclusion criteria were used to determine the eligibility of the studies based on the two objectives; however, a single search strategy was used to capture eligible studies. The complete search strategy and search terms are available in online supplemental appendix 2.

To summarise the total direct and indirect costs of the COVID-19 pandemic, the inclusion criteria for Objective 1 were as follows:

- Population: EU/EEA/UK and remaining OECD countries.
- Exposure: COVID-19 outbreak or public health preparedness measures or interventions.
- Outcome measures: direct and indirect costs for disease and preparedness and/or response.
- Study designs: We included all relevant analytical epidemiological designs which estimate cost, including partial cost evaluation studies, cost studies, cost-outcome description studies, cost-description studies, and economic modelling studies.
- Perspective: All direct and indirect costs were considered pertaining to all relevant perspectives (eg, individual, health and social care, and societal including national and regional).

In particular:

- The individual perspective refers to considering the costs and outcomes experienced by individuals directly affected by the issue being studied. It focuses on understanding how the issue impacts individuals in terms of their personal expenses, quality of life and health outcomes.
- The health and social care perspective involves examining the costs and outcomes associated with healthcare services and social support systems. It considers the financial implications and health-related consequences for healthcare providers, institutions, and social care organisations involved in addressing the issue.
- The societal perspective considers the broader societal impact of the issue under investigation. It considers not only the direct costs and outcomes for individuals and healthcare systems but also the economic costs to society as a whole. This perspective includes factors such as productivity loss, resource allocation and the overall impact on the well-being and functioning of society at large.

To contrast with the costs and the cost-effectiveness of public health surveillance, preparedness and response measures in averting and/or responding to COVID-19, the inclusion criteria for Objective 2 were as follows:

- Population: EU/EEA/UK and remaining OECD countries.
- Intervention: Public health preparedness measures or interventions.
- Comparator: (i) No intervention (cost of inaction) or current practice; (ii) cost of preparedness versus cost

of response (for studies reporting cost and benefit of public health preparedness).

- Outcome measures: Cost-benefit and cost-effectiveness outcomes (eg, cost per life-year saved). Studies that use other methods to formally combine cost and clinical outcome data (pertinent to infectious diseases) were also included. Typical outcome measures of economic evaluations include: Life years gained (or cost per life-year achieved with the intervention under investigation when incremental costs are combined), Quality-Adjusted Life Years (QALY; cost per QALY gained), Cases averted (eg, cost per case that is averted with the intervention vs the comparator) and monetary outcomes (in the case of a cost-benefit analysis). Where available, the incremental cost-effectiveness ratio (ICER) was also provided.
- Study designs: We included all designs specific to cost-benefit questions either as full economic evaluation studies, including cost-minimisation, cost-effectiveness, cost-utility and cost-benefit analyses; cost-outcome and economic modelling studies; or partial economic evaluations.
- Perspective: All direct and indirect costs were considered pertaining to all relevant perspectives (eg, individual, health and social care, and societal, a detailed explanation of which is provided in the inclusion criteria for Objective 1).

Data analysis and extraction

Studies identified from the searches were uploaded into a bibliographic database (Covidence) in which duplicate entries were removed. Initially, a random sample of 100 titles and abstracts were screened independently for eligibility by two reviewers to enable consistency in screening and identify areas for amendments in the inclusion criteria. Since a high measure of inter-rater agreement was achieved (inter-rater agreement=88.7%), the remaining titles and abstracts were screened for eligibility by one reviewer. Full-text articles of potentially eligible studies were retrieved and screened independently by two reviewers (inter-rater agreement=89.3%). Data were extracted with the use of a predefined data extraction sheet. Initially, two reviewers piloted the data extraction template independently on a random sample of five included studies and given the high consistency in data extraction, the remaining studies were extracted only by one reviewer. Disagreements in every step of the process were subsequently discussed with a third reviewer and agreed on.

Appraisal of methodological quality

The Consensus on Health Economic Criteria (CHEC) checklist was used[15] to evaluate the methodological quality of full health economic evaluations, which comprises 19 questions with answers of 'Yes' or 'No'. For each positive response of full health economic evaluations, a single point was assigned for the methodological quality, with a maximum score of 19. For the quality appraisal of partial economic evaluations, we used items from the CHEC checklist that were applicable—hence the maximum score was 17. In cases of insufficient information or details reported in both full and partial economic evaluation studies, with regard to a specific item, no point was awarded for that question. Studies were categorised as high (>80%), good (60%–80%), medium (40%–60%) or low (<40%) quality. The quality appraisal process was completed by one reviewer since piloting of three studies by two independent reviewers had an inter-rater agreement of 85.6%.

Comparative economic analysis approach

All cost data were adjusted to a common currency (Euro in 2021) and price year, using the Campbell and Cochrane Economics Methods Group–Evidence for Policy and Practice Information and Coordinating Centre cost converter.[16] A two-stage computation is used, where the 2021 implied conversion factor is US$1=€0.88. The 2021 implied conversion factor of British pounds is £1=€1.18. In our study, we first inflated the cost from the original price year to 2021, using a GDP deflator index (GDP values), obtained from the International Monetary Fund World Economic Outlook Database GDP deflator index data set. After that, we converted the original currency to the next rounded 2021 Euros, using conversion rates based on Purchasing Power Parities for GDP (PPP values). For studies that did not state the year of cost calculation, the costs were calculated 1 year before the publication year.

Synthesis of cost-effectiveness

The Dominance Ranking Matrix (DRM) was used to assess the cost-effectiveness of the interventions noted within the identified studies.[17] The DRM is a three-by-three matrix with the following classification options:

1. Strong dominance for the intervention when the incremental cost-effectiveness measure shows that the intervention versus the comparator is (a) more effective and less costly; or (b) as effective and less costly; or (c) equally costly and more effective. Strong dominance suggests that under similar circumstances, the intervention is preferable to the comparator.
2. Weak dominance for the intervention versus the comparator is noted when the measure shows the intervention as (d) equally costly and effective; or (e) more effective and more costly; or (f) less effective and less costly. In principle, weak dominance indicates that no conclusion can be drawn and hence judgement by policymakers is required on whether the intervention is preferable when taking into consideration whether the cost/benefit trade-offs are worth the introduction of the intervention within the particular context.
3. Non-dominance for the intervention versus the comparator when the measure shows the intervention as (g) more costly and less effective; or (h) equally as costly and less effective; or (i) more costly and as effective. In this case, the comparator is preferable to the

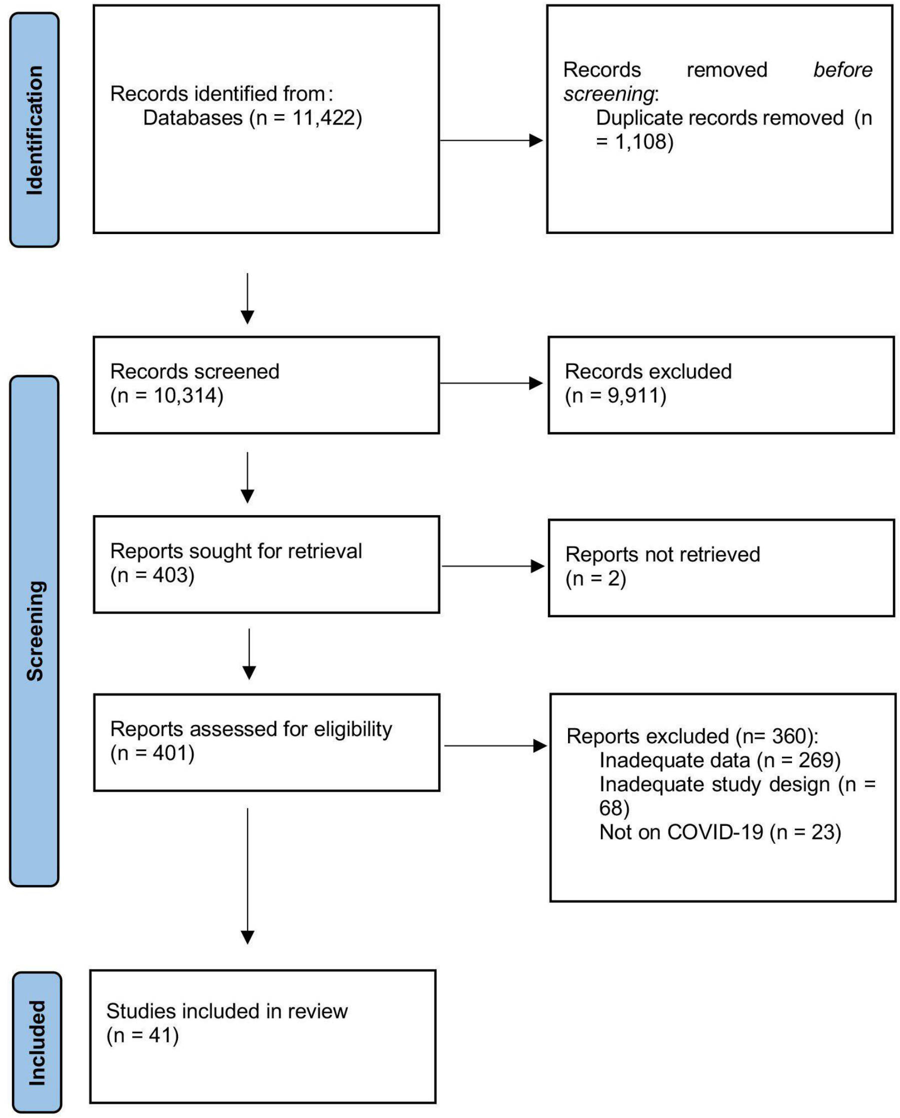

Figure 1 PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) flow chart of the search strategy.

measured intervention, at least under the circumstances of the specific study.

Patient and public involvement

This study was performed under contract for the ECDC. Patients or the public were not explicitly involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

A total of 10314 non-duplicate studies were identified, of which 403 proceeded to full-text screening with 362 full-text studies were excluded for the following reasons: inadequate data on costs and/or cost-effectiveness (n=269), reviews/editorials/perspectives/views/opinion papers (n=68), not referring to outbreaks of COVID-19 infectious disease (n=23) and no full text available (n=2). Subsequently, 41 studies met all inclusion criteria and were included in the systematic review (figure 1).

Approximately half of the studies (20/41) were of high methodological quality, 10 had good quality and the remaining 11 studies were of medium quality (online supplemental appendix 3). Lower scores were mainly due to missing information relating to the comparative intervention, lack of sensitivity analysis and not reporting incremental costs among comparative interventions (since in some studies alternative strategies were not included).

Objective 1: economic impact of COVID-19 infection on healthcare systems and societies

Ten studies evaluated the cost of the COVID-19 pandemic within EU/EEA/UK and OECD countries (table 1), among which eight studies used a cost of illness analysis approach.[18–25] The direct medical costs were presented in 7 out of 10 studies,[18–20 22 23 25 26] while in 8 studies the costs were estimated for a time horizon shorter than 1 year,[19–21 23–27] and specific discount rates were not applied in 7 studies.[18–20 23 25–27] With

Table 1 Overview of included studies evaluating the economic impact of COVID-19 pandemic in EU/EEA/UK and OECD countries (n=10)

Study/ publication year	Country	Population	Study design	Economic evaluation method	Costs calculation	Perspective	Funding
Degeling *et al*, 2021[18]	Australia	65 415 cases—2020 Australian incident breast cancer, colorectal cancer, lung cancer and melanoma patient populations	Modelling study	Cost of illness analysis	Direct medical costs	Public healthcare payer	No funding
Czernichow *et al*, 2021[19]	European countries	720 547 hospitalisations	Modelling study	Cost of illness analysis	Direct medical costs	Healthcare system	Yes
Bain *et al*, 2021[20]	European countries	720 547 hospitalisations	Modelling study	Cost of illness analysis	Direct medical costs	Healthcare system	Yes
Mallow, 2021[27]	USA/Ohio	6429 Ohioans deaths	Retrospective cohort study	Partial economic evaluation	Not clearly specified	Not clearly specified	No funding
Nurchis *et al*, 2020[21]	Italy	Italian population	Observational study	Cost of illness analysis	Indirect costs	Societal	No funding
Bartsch *et al*, 2020[22]	USA	USA population	Simulation study	Cost of illness analysis	Direct medical costs	1. Health system. 2. Third-payer.	Yes
Lee *et al*, 2020[23]	Korea	145 hospitalised children with COVID-19	Retrospective cohort study	Cost of illness analysis	Direct medical costs	Third payer	Not clearly specified
Kirigia and Deborah Muthuri, 2020[24]	UK	UK population	Retrospective cohort study	Economic impact analysis/cost of illness	Indirect costs (using human capital approach)	Societal	No funding
Gedik, 2020[26]	Turkey	459 patients—393 clinical patients 66 intensive care unit patients	Retrospective cohort study	Cost analysis	Direct medical costs	Third payer	Not clearly specified
Di Fusco *et al*, 2021[25]	USA	173 942 hospitalised COVID-19 patients	Retrospective cohort study	Cost of illness analysis	Direct medical costs	Healthcare system	Yes

EEA, European Economic Area; EU, European Union; OECD, Organisation for Economic Co-operation and Development.

regard to the country of origin, 5 out of the 10 studies took place in the European region, including in the UK and Turkey,[19–21 24 26] 3 were from the USA,[22 25 27] 1 from Korea[23] and 1 from Australia.[18] Six of the 10 studies were observational,[21 23–27] while a few used modelling techniques[18–20] or simulation methods.[22] Furthermore, it should be noted that the healthcare system perspective was included in the analysis of four studies,[19 20 22 25] the societal in two,[21 24] the third payer perspective was assessed in three[22 23 26] and one study[18] assessed data from the public health payer perspective. The perspective considered within one study was unclear.[27]

Overall economic burden on the population and to the healthcare system

Overall, the economic burden of the COVID-19 pandemic was found to be substantial (online supplemental appendix 4). The socioeconomic implications of COVID-19 in Italy, appraised by Nurchis *et al*[21] through a cost of illness analysis of indirect costs, showed a temporary productivity loss reaching €114 120 531 for 110 868 cases (€1029 per case). Individuals at the age of >40 years old were found to be affected the most. Furthermore, the permanent productivity losses were estimated at €333 063 591 for 3926 deaths (€84 836 per death) with ages >50 years old to consistently having higher indirect costs due to death. Bartsch *et al*[22] at the start of the pandemic, when no vaccines were available showed that the more people infected, the higher medical costs are presented using a Monte Carlo simulation model to highlight the devastating impact of the pandemic on the US healthcare system and third payers. In the case that 20% of the US population were to be infected with SARS-CoV-2 over the course of the pandemic (and not accounting for reinfections), the total costs accrued were estimated at €129.8 billion and reaching €170.3 billion including post-discharge costs after 1 year. In the case that 80% of the US population were to be infected, the direct medical costs reached an estimated €519.4 billion, and €682.6 billion with the post-discharge costs after 1 year of infection. Mallow[27] assessed the value of statistical life in a total of 6429 deaths in Ohio, USA, where the economic burden of premature deaths was estimated at €13.8 billion as of 30 November 2020. Additional analyses have been performed by Kirigia and Deborah Muthuri[24] using the human capital approach to estimate the total present value of human lives lost due to COVID-19 in the UK as of 2 July 2020. Notably, the value for 43 906 lives lost approached €7.8 billion at a 3% discount rate with, approximately 76.2% of the total present value sustained by those aged 30–79 years. Lee *et al*[23] aimed to determine the hospitalisation periods and medical costs among 145 hospitalised children with COVID-19 in Korea. According to the results, the estimated medical expenses reached €252 389 in total and increased per age as 54 patients in the ages of 16–19 accounted for €156 738 (more than 60% of the total cost) and per patient at €2903 for a mean hospitalisation period of approximately 10 days, indicating that these ages contributed to higher costs than younger ages included in the study.

Di Fusco *et al*[25] by conducting a cost of illness analysis to estimate the direct medical costs of inpatient setting for a time horizon of 8 months, showed that the total mean of hospital costs related to COVID-19 was €19 513 for 8.3 mean hospital length of stay days (LOS) (SD 9.1). Higher costs were presented for those people treated in the intensive care unit (ICU), reaching a mean cost of € 20 400, which represent €21 850 in case of ICU usage without invasive mechanical ventilation (IMV) for a mean LOS of 9.1 days and estimated at a mean cost of €62 139 if both ICU and IMV are used for mean LOS of 18.6 days.

Moreover, Gedik[26] performed a simple cost-analysis of COVID-19 patients in Turkey and showed that the mean cost per ICU patient was much higher than clinical patients in wards and particularly estimated at €2322 for mean hospitalisation days of 14.7 compared with €700.0 for nine mean hospitalisation days.

Overall economic burden to specific population subgroups

With regard to the costs for specific subpopulations, Degeling *et al*[18] estimated the health and economic impacts of delays in treatment initiation of 65 415 cancer cases (breast cancer, colorectal cancer, lung cancer and melanoma) due to COVID-19 infection in Australia. Apart from the excess deaths and life-years lost, costs to the healthcare system exceeded more than €6 million for the 3-month delay while more than €25 million for a 6-month delay. Czernichow *et al*[19] identified a strong relationship between obese and overweight patients (body mass index (BMI) 25.0 to ≥40) with increased direct medical costs of secondary care related to COVID-19 across the EU, UK and European Free Trade Association (EFTA) countries, with 44% of the total treatment costs of COVID-19 in Europe to be associated with those populations (due to the higher probability of being hospitalised, a longer length of stay and higher risk of severe outcomes). The total costs of €14.2 billion were the total secondary medical care costs for a 6-month time horizon analysis, with cases with a BMI≥40 accounting for the highest direct costs per case. In a similar study conducted by Bain *et al*,[20] whose aim was to estimate the impact of diabetes on the total secondary care costs of COVID-19 and for the same time frame and population numbers in regard to the same European countries, poor glycaemic control was associated with excess direct medical costs of secondary care due to COVID-19, estimated at €400.4 million for 6869 hospitalisations of type 1 diabetes cases and €1498 billion for 31 701 hospitalisations of type 2 diabetes cases.

Objective 2: economic evaluation of strategies for the mitigation of COVID-19 virus transmission

Our systematic review identified 31 studies assessing the cost-effectiveness of interventions for reducing SARS-CoV-2 transmission within EU/EEA/UK and OECD countries (online supplemental appendix 5). We identified studies that assessed isolation, lockdown policies, physical distancing scenarios,[28–38] testing/screening policies,[39–45] personal protective equipment intervention,[46] vaccinations[47–50] and pharmaceutical treatment strategies (n=4).[50–53] Multiple strategies were evaluated by four studies,[54–57] which mainly assessed the combination of testing, isolation and vaccinations, and one study[58] that analysed an ICU bed provision scenario.

Concerning study characteristics, 13 out of 31 studies were from the USA,[28 29 39 41 43 44 47–49 51 53 55 57] seven from the UK,[33–36 45 52 56] three from Germany,[31 54 58] one from Switzerland,[50] Israel[37] and Wales,[40] while five studies included analyses from multiple OECD countries.[30 32 38 42 46] The societal perspective was followed in 14 studies,[29 31 33 34 36 37 39 42 44 46 54 55 57 58] while ten studies performed an analysis via a healthcare perspective.[28 30 40 41 43 45 49 50 52 56] Various perspectives were included in four studies,[47 48 51 53] including the payer for some of them,[48 51 53] while the perspective considered was unclear in three studies.[32 35 38]

Seven studies (online supplemental appendix 6) assessed the cost-effectiveness of testing and screening interventions, a synthesis of which is in figure 2. Stevenson *et al*[45] compared 30 interventions and found that the least costly testing intervention was testing on hospital admission, and routine retesting following hospital admission. The authors noted that strategies with shorter times to

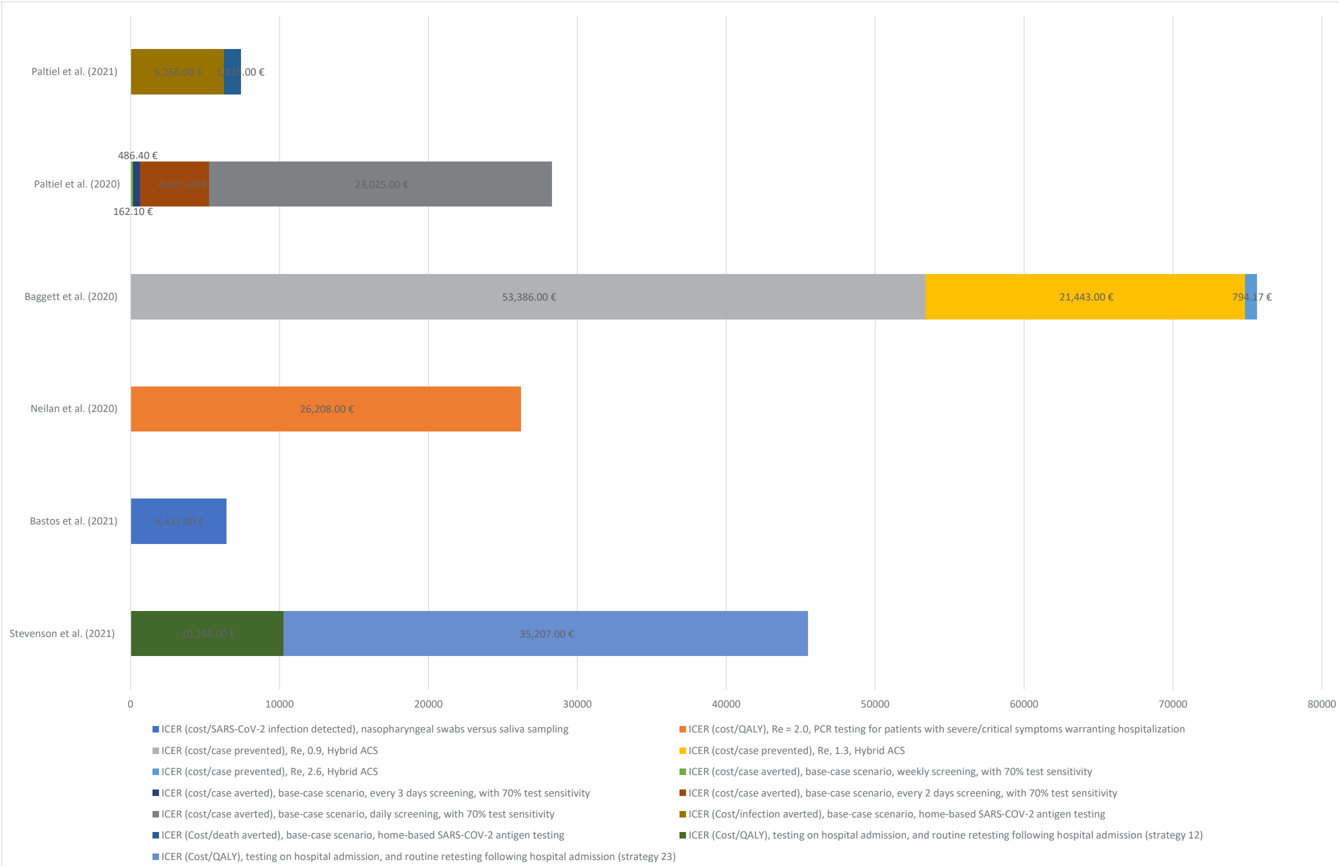

Figure 2 ICER results for testing and screening strategies. ACS, alternative care site; ICER, incremental cost-effectiveness ratio; QALY, Quality-Adjusted Life Years.

test results were more cost-effective, all other things being equal, as were SARS-CoV-2 tests with greater diagnostic accuracy. Strategies that included saliva sampling and nasopharyngeal have been assessed within the systematic review and meta-analysis by Bastos *et al*.[42] The incremental cost per additional SARS-CoV-2 infection detected with nasopharyngeal swabs versus saliva sampling was €6427 if the prevalence was 1%, and the cost-savings of saliva sampling were estimated at €505 177 € (95% CI 371 217 to 660 568) if 100 000 persons are tested. The clinical and economic value of PCR testing was investigated by Neilan *et al*,[41] who showed that under all epidemic growth scenarios considered, testing people with any COVID-19-consistent symptoms would be cost-saving compared with restricting testing to only those with symptoms severe enough to warrant hospital care, leading to lower costs and reducing infections and deaths. According to their results, and within the context of the first wave of the pandemic, the symptomatic and asymptomatic monthly testing scenario was a cost-effective strategy only with an (R_e)>1.6 but would be no longer a cost-effective option for lower reproduction scenarios, unless testing cost was lower. A cost-minimisation analysis performed by Currie *et al*[40] comparing community testing undertaking *swabbing of suspected cases in Wales* with standard hospital testing showed that community testing for COVID-19 was a superior strategy, resulting in significant benefits for the healthcare system. Two studies appraised the cost-effectiveness outcomes of different testing strategies within specific settings. Baggett *et al*[43] investigated the clinical outcomes, costs and cost-effectiveness associated with strategies for COVID-19 management among adults experiencing sheltered homelessness in Boston, USA. Daily symptom screening with subsequent PCR testing of individuals who screened positively was the most efficient strategy and was cost-saving relative to no intervention in all epidemic scenarios.

Paltiel *et al*[44] examined the SARS-CoV-2 screening performance standards that would permit the safe return of students to US residential college campuses for the fall semester of 2020 and noted that screening with a less expensive, less sensitive test dominated the intervention of screening with more expensive, more accurate tests. Paltiel *et al*,[39] assessed the clinical and economic effects of widespread home-based SARS-CoV-2 antigen testing and noted that the cost per infection averted was €6266.

Cost-effectiveness of quarantine, isolation, physical distancing and physical restriction policies

Twelve studies were included to assess the cost-effectiveness across different strategies to prevent or mitigate SARS-COV-2 transmission (online supplemental appendix 6).

Kouidere *et al*[38] conducted a mathematical compartmental modelling to assess three different strategies for diabetics and concluded that awareness programmes and quarantine for those infected having symptoms as well as those having complications in hospital treatment was the most effective strategy and was associated with an ICER of −0.6951 (cost per infection averted) compared with sensitisation and prevention.

The cost-effectiveness of comparing the national lockdown policy for the susceptible population with the isolation of those infected or being at high risk in Israel returning to the workforce under social distancing measures after a 14-day isolation period was appraised by Shlomai *et al*.[37] The national lockdown of the susceptible population was associated with a higher economic burden but contributed to a reduction in deaths making this intervention superior to the comparator only in terms of health outcomes but was not cost-effective since it contributed to high economic costs, estimated at €36 568 451 costs per death averted, and €3.6 million costs per QALY gained. Furthermore, Keogh-Brown *et al*[36] assessed the direct and indirect costs of three different strategies in the UK and indicated that although mitigation and suppression policies contribute to lower mortality rates, the economic impact of COVID-19 is likely to be dominated by public prevention measures rather than the direct health costs of the disease and indicated that a 3-month mitigation scenario resulted in a prediction of 13.5% loss to GDP with the direct-health related economic impact of 2% of the GDP while the suppression scenario was associated with an approximately 22% loss in GDP. Furthermore, Miles *et al* within the context of a cost-benefit analyses[35] noted that a full lockdown policy for 4 months followed by an extension for 3 months showed that net extra economic costs of the lockdown relative to the easing of restrictions were estimated at €116.2 billion with the best scenario of lives not lost at €96.5 billion. The main factors of the substantial costs of the lockdown policy were associated mainly with employment restrictions and physical restrictions. Miles *et al*[34] also conducted an additional modelling and simulation study to assess a few physical restriction scenarios in a time frame of 6 months in the UK and found that the strategy of relatively slowly easing restrictions comes at a cost in terms of GDP reduction of up to €697 121/life-year saved. Moreover, the cost per life-year saved with a short transition physical restriction policy (8 weeks medium then 18 weeks low) was associated with a cost of per life-year saved at €206 888 while keeping the policies strict for 26 weeks was estimated at a cost of per life-year saved of €1 553 988.

Suppression and physical distancing interventions were assessed by Zala *et al*[33] and Barnett-Howell *et al*.[32] Zala *et al*[33] noted that suppression policies compared with an unmitigated scenario strategy were associated with an ICER below €56 972, while all of the four suppression policies presented ICER results. Barnett-Howell *et al*[32] investigated five physical distancing strategies, including an unmitigated intervention, to assess the value of statistical life lost. Full lockdown policies were associated with lower Value of Statistical Life (VSL) in the USA, UK and Mexico countries (USA: €23 billion, UK: €4.76 billion, Mexico: €794 million) while the no-action scenario, which was the unmitigated spread of COVID-19, contributed to higher VSL in those countries (USA: €38.9 billion, UK: €7.1 billion, Mexico: €1.58 billion).

Additional studies focusing on policies related to stay-home and shutdown orders were investigated by Gandjour[31] and Thom *et al*.[30] Gandjour[31] assessed the clinical and economic cost of a shutdown during the SARS-CoV-2 pandemic in Germany to estimate the cost of life-years gained per capita estimating the indirect costs for 1 year. The results showed that the economic cost of the lockdown intervention was associated with €3472 or extrapolated to the total population, 8% of Germany's GDP in 2019 (ranging from 1% to 12% in the sensitivity analysis). Thom *et al*[30] provided an exploratory comparison of health-related benefits and costs saved by government mitigation measures across European countries (UK, Ireland, Germany, Spain and Sweden) over a time frame of 7 months, where the authors concluded that the benefit of government COVID-19 responses might outweigh their economic costs, saving millions of QALYs (0.5 million for Sweden to approximately 5 million for Germany) and ideally those countries with more mask-wearing and testing, had better outcomes.

The last studies focusing on stay-home policies were by the same authors, Chen *et al*.[28 29] Their first study, Chen *et al*[28] estimated the total medical costs by keeping the US economy open and assessed 13 interventions with different stay-home isolation and voluntary home isolation compliance rates for 1 year. Without mitigation, the total medical costs would be 5% of the US GDP. In their second study, Chen *et al*[29] compared the epidemiological and economic impact of SARS-CoV-2 spread in the USA under different mitigation scenarios, comprising NPIs including stay-home with varying compliance rates.

Cost-effectiveness of vaccination measures

Three included studies[47–49] focused on vaccination interventions and used modelling and simulation methods to assess the cost-effectiveness of the included interventions (online supplemental appendix 6) and synthesised in figure 3. Shaker *et al*[47] appraised the universal COVID-19 vaccination versus the risk-stratified vaccination approach over the time frame of 1 year, and they found that the universal COVID-19 vaccination dominates the risk-stratified approach, making it a cost-effective strategy for the US population from the societal perspective and the healthcare perspective. ICER analyses indicated that in the case of societal perspective, the universal approach presents a cost of €52 033 per death averted compared with the risk-stratified vaccination, with cost-savings estimated at €395 million. When considering the healthcare perspective, the cost per death averted by the risk-stratified approach was €52 575 making it the dominant option. Bartsch *et al*[48] noted that NPI implementation before vaccination was associated with less total costs compared with the case of non-implementation of NPIs.

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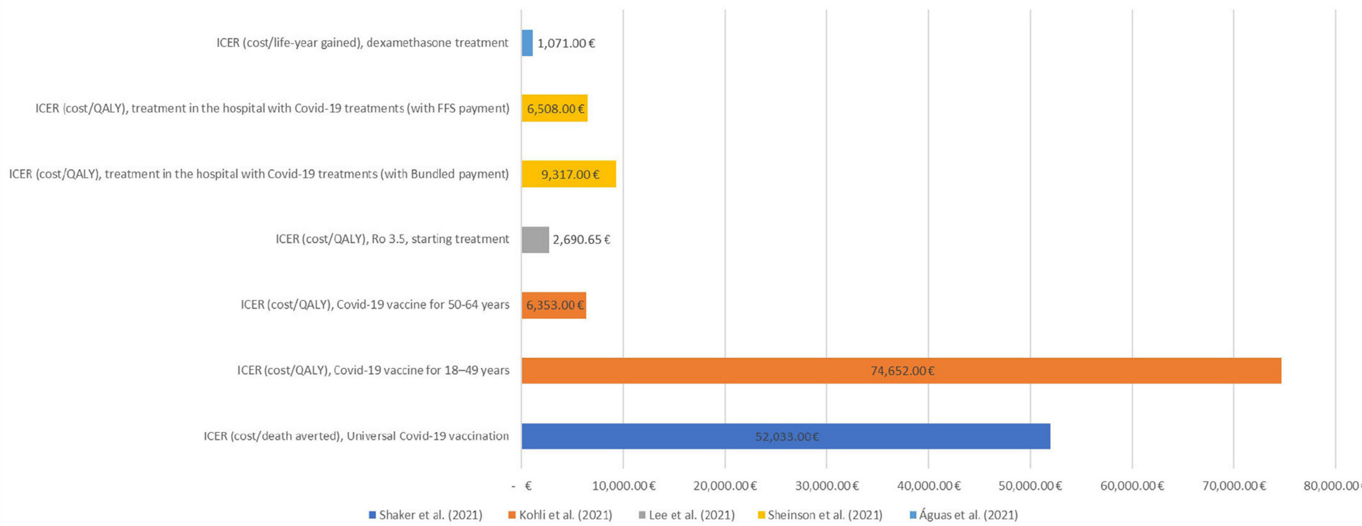

Figure 3 ICER results for vaccination and treatment strategies. FFS, fee for service payment; ICER, incremental cost-effectiveness ratio; QALY, Quality-Adjusted Life Years.

Finally, Kohli *et al*[49] conducted a cost utility analysis (CUA) to assess the COVID-19 vaccine versus no vaccine for the US population over 1 year. Base case analysis presented good value for money outcomes where the ICER per age was found to be €74 652 for ages 18–49 years, €6353 for 50–64 years, while for ages 65+ the COVID-19 vaccine dominates. This strategy was also cost-effective under additional scenarios, such as with the per-risk-based prioritisation scheme.

Cost-effectiveness of treatment measures

Our analysis included four studies[50–53] assessing pharmaceutical interventions (online supplemental appendix 6). Lee *et al*[51] simulated the transmission spread of SARS-CoV-2 and the economic and clinical impact of the spread in the USA over 1 year. The authors noted that starting treatment at an of R_e 3.5 was cost-effective and provided ICER results of €2690/QALY saved from the societal perspective when treating 75% of symptomatic cases and treatment course cost €397, and ≤€6267/QALY saved from the third-payer perspective when at least 50% of all patients were treated. The study also concluded that treating 25% or 50% of symptomatic patients at R_e 2.5 and at a treatment cost of €397, was also cost-effective. Across all R_e assessed, the net cost-savings were high from the third-payer perspective and even higher from the societal perspective. Sheinson *et al*[53] assessed the cost-effectiveness of treating hospitalised COVID-19 patients with COVID-19 treatment versus treating them with the best supportive care (BSC). Under the payer perspective, treatment of patients with COVID-19 was more cost-effective than BSC as it was associated with €15 784 with a fee for service payment (FFS) and €18 593 (with a bundled payment). The ICER results from a societal perspective were even better, making the COVID-19 treatment process a dominant strategy as treatment of patients with COVID-19 was associated with a cost of €6508 (with FFS payment) and €9317 (with bundled payment).

With regard to specific pharmaceutical regiments, Águas *et al*[52] estimated that the incremental cost per life-year gained for dexamethasone treatment was €1071 compared with no treatment. On the contrary, Vernaz *et al*[50] performed a cost-analysis study and compared standard care among pharmaceutical interventions including lopinavir/ritonavir and hydroxychloroquine (a pharmaceutical discussed early in the pandemic but not a legitimate treatment) for hospitalised patients with SARS-CoV-2 in Switzerland. The results highlighted the additional costs attributable to the length of stay that presented a mean cost of €648 102 for 93 patients.

Cost-effectiveness of bed provision policies

We identified one study indicating the scenario of increasing ICU bed availability. Gandjour[58] performed a cost-effectiveness and return-on-investment analysis and estimated that the provision of a staffed ICU bed reserve capacity was cost-effective even for a low probability of bed usage and estimated that the provision of one ICU bed would cost €14 306 to €22 986 per life-year gained, while the addition of 10 000 ICU beds provided a cost of €18 389 to €29 627 per life-year gained.

Cost-effectiveness of personal protective equipment strategies

Risko *et al*[46] conducted a cost-effectiveness analysis indicating that investing in personal protective equipment (PPE) was a cost-effective option for 166 million simulated workers over a period of 7.5 months (online supplemental appendix 6). In general, they found that an investment of US$9.6 billion (€7.62 billion in 2021) concerning the purchasing and distribution of PPE to allow for adequate protection of all healthcare workers (HCWs) was cost-effective and led to an ICER of cost per case averted at €57, and an ICER of cost per death averted of €4159, which translates to €41.1 billion (95% CI 39.6 to 42.6) in economic gains.

Cost-effectiveness of other combined strategies

The review included four studies[54–57] that assessed multiple combined interventions related to testing, isolation, vaccination and physical distancing strategies (online supplemental appendix 6). Sandmann *et al*[56] assessed the clinical and economic value of COVID-19 vaccination in the UK and estimated that without the initial lockdown, vaccination and increased physical distancing, 3.1 million (0.84–4.5) deaths would have occurred in the UK over a 10-year period at a cost of €169 million. The introduction of vaccination provided estimations of incremental net monetary values ranging from €13.7 billion to €381.4 billion in the best-case scenario and from €1.25 billion to €64.8 billion in the worst-case scenario compared with no immunisation—under the healthcare perspective. With regard to the wider societal perspective, where GDP income loss was included in the relevant analyses, the incremental net monetary value of introducing vaccination versus no vaccination was found to be extremely positive across physical distancing scenarios. Du *et al*[57] assessed the cost-effectiveness of eight testing measures in conjunction with isolation measures over a time frame of 5 months. In cases of an R_0=2 and assuming a test cost of approximately €4 and the societal willingness-to-pay per year-life lost averted of €79 417, the optimal strategy was daily testing plus a 2-week isolation. On the contrary, at a lower R_0 (1.5–1.8) weekly testing plus 1-week isolation was found to be the optimal cost-effective strategy. Furthermore, the weekly testing plus 2-week isolation was also optimal if R_0>2 (under the same assumptions and when the test costs <€318).

The combination of over 3.5 months of isolation with laboratory testing and self-screening in college campuses was assessed by Losina *et al*,[55] who concluded that a comprehensive physical distancing policy with a mandatory mask-wearing policy can prevent most COVID-19 cases on college campuses and is relatively cost-effective. The last study that assessed multiple interventions was that of Ebigbo *et al*[54] that appraised the use of low versus high-risk PPE (masks, goggles, gloves and apron and centralised laboratory-based testing) applied during routine pre-endoscopy procedures. The authors noted that routine pre-endoscopy testing combined with high-risk PPE was more cost-effective during rising prevalence rates of COVID-19 while during lower prevalence rates, the dominant cost-effective strategy appeared to be the use of point-of-care antigen testing without the routine use of high-risk PPE.

DISCUSSION

This systematic review aimed to assess the economic burden of the COVID-19 pandemic to societies and healthcare systems and to assess the strategies used to prevent and mitigate COVID-19 outbreaks in the EU/UK/EEA and OECD countries from studies published through 22 April 2021. Our findings indicate that the overall economic impact of the virus is substantial for individuals, healthcare systems and payers, while our review identified that NPIs and pharmaceutical measures, including ICU bed provision implemented within the context of the COVID-19 pandemic from both healthcare and societal perspectives and within 1-year time horizon are cost-effective response and mitigation measures.

Overall, in the studies identified, the economic burden of the COVID-19 pandemic was found to be substantial in all studies included in the current systematic review, with both direct and indirect costs playing a significant role. Direct costs were primarily attributed to medical expenses from hospitalisations and ICU admissions while the indirect and societal costs yielded by NPIs, mainly from stay-home and isolation strategies, contributed to the further increase of economic costs and also resulted in a decrease in GDP. Moreover, the delays in treatment initiation of other diseases (eg, cancer) were also found to have a substantial economic impact. At the patient level, increased medical costs were also related to comorbidities such as obesity and diabetes. Regarding indirect costs, temporary and permanent productivity loss, as well as human lives lost due to COVID-19 were substantial.

The NPIs implemented for the pandemic control led to a benefit in life years in an individual or societal level compared with the no-intervention scenario, although the cost-benefit of such interventions differed depending on the perspective, the time frame, the setting and the epidemiological situation of the pandemic. Considering the testing strategy, results were dependent on the cost per test and the R_0 at the time of assessment. Overall, low-cost repeated community screening was a cost-effective approach, in combination with other NPIs, especially when the cost of testing remains low and at higher R_e. As for lockdown strategies, studies showed that if performed early in the pandemic for a limited period of time and with sufficient compliance, they substantially could reduce the medical costs of COVID-19 from a healthcare perspective—especially prior to population immunisation. In general, mitigation scenarios resulted in less GDP loss compared with suppression ones. Finally, quarantine and physical distancing strategies were found to be effective for the containment of the COVID-19 pandemic, while it was indicated that with an increasing R_e, a combination of NPIs, including screening, physical distancing and quarantine of contacts would be more efficient. With regard to PPEs, they showed a benefit both in health and costs when used by HCWs, as also was the provision of ICU beds. Regarding pharmaceutical measures, vaccination was consistently found to be cost-effective, with the universal COVID-19 vaccination dominating the risk-stratified approach. Additionally, pharmaceutical treatments were also cost-effective when provided in scenarios of high transmissibility (high R_e). Finally, the combination of testing, vaccination, physical distancing measures and mask wearing was found to be cost saving, with a significant number prevented cases and deaths.

A systematic review on previous respiratory infectious disease outbreaks prior to COVID-19[59] concluded to similar results by pointing out the significant burden of both direct and indirect medical costs for management and response activities. Most direct costs occurred from the additional personnel hours, the response planning and contact tracing activities, the provision of training and educational materials and the laboratory costs. Indirect costs were greater than direct ones, particularly when school closures and/or workplace closures were implemented, due to lower productivity.[59] However, given the strictness of the NPIs in the COVID-19 pandemic, the economic burden has been found to be high for primary production sectors including industries associated with raw material extraction activities, secondary industrial sectors involved in the production of finished products and tertiary sectors encompassing service provision industries.[60]

This systematic review provides a wide range of cost-effective options across comparative strategies implemented to prevent or mitigate virus transmission. Strategies, including vaccination measures (ideally universal vaccinations), screening policies (with the saliva sampling to be a cost-saving option compared with nasopharyngeal swabs) and expanding a staffed ICU bed reserve capacity were found to be dominant strategies against SARS-COV-2 transmission, indicating the cost-savings as well as the economic value of their implementation. An earlier systematic review by Vandepitte *et al*[61] also showed that frequent and universal testing activities are a cost-effective strategy, highlighting that these could have a greater impact if enacted in a setting with a high R_e. Moreover, they noted that personal protective measures (PPM) were another cost-effective strategy that was dependent on compliance, context and R_e.[61] Similarly in another review, contact tracing and isolation of cases were important cost-effective NPIs, along with adequate surveillance, PPM for healthcare professionals and vaccination.[62] In contrast, physical distancing strategies including school and workplace closures were found to be effective but costly, making them the least cost-effective options.[62] Finally, combined NPIs were more cost-effective than individual ones, while the significance of early implementation was emphasised.[62]

Strengths and limitations

This review provides several strengths, including covering within one review both the economic burden of COVID-19 and the cost-effectiveness of the strategies and programmes implemented to mitigate the pandemic. Moreover, this review followed a systematic approach to study identification, data extraction and quality appraisal with most of the included studies of good or high quality. Furthermore, this study used the DRM approach, which summarised and interpreted the results of economic evaluation studies. On the other hand, there are some limitations, as publication bias can not be excluded and as our search was performed up to the end of April 2021 it only reflects the cost-effectiveness of interventions assessed during the first waves of the pandemic when the majority of the populations were unvaccinated, and while most of the included studies have a short duration on which modelling was performed. A further limitation is that most studies estimate costs and benefits based on a healthcare perspective, excluding wider societal effects, with a time horizon of 1 year. As we restricted our search to EU/UK/EEA/USA and OECD countries, the studies primarily refer to high-income countries. In addition, our literature search was conducted through two databases, Ovid MEDLINE and EMBASE and consequently any information available in other databases or in the grey literature may have been overlooked. Finally, as costs and resources varied between different countries, different pandemic settings and over time, and as indicated in this review depended on multiple other factors including population vaccination status, pre-existing healthcare capacity and the infectivity of the SARS-CoV-2 variant at each time point, the comparison of cost-effectiveness measures is a complex process to interpret and the cost-effectiveness of each intervention should be weighed by policymakers against the regional circumstances. Moreover, as the complete economic and health consequences are yet unknown, further research is needed on the cost-effectiveness of NPIs, while the cost of the long-term effects of COVID-19 (both physical and mental) should also be assessed in future analyses.

CONCLUSION

This systematic review assessed economic evaluation studies concerning COVID-19 and the cost-effectiveness of strategies to prevent and mitigate SARS-CoV-2 spread within the EU/UK/EEA and OECD country context. Results of this study are based primarily on the first wave of the pandemic and mostly from a healthcare perspective with a short time horizon; particularly within 1-year time horizon. Our review showed that the COVID-19 pandemic is associated with substantial economic costs to healthcare systems, payers and societies, both short-term and long-term, while interventions including testing and screening policies, vaccination and physical distancing policies were identified as those presenting cost-effective options to deal with the pandemic—dependent on population vaccination and the R_e at the stage of the pandemic. Policymakers could benefit from these findings as they indicate the value of both pharmaceutical and non-pharmaceutical interventions to mitigate and respond to the ongoing COVID-19 pandemic and in preparation for future respiratory pandemics.

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