Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Surgery 105 (2022) 106820

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Review

Economic evaluation of laboratory diagnostic test types in Covid-19 epidemic: A systematic review

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ARTICLE INFO

Keywords:
Cost-effectiveness analysis
Cost-benefit analysis
COVID-19 testing
RT-PCR tests
Systematic review

ABSTRACT

Background: Corona 2 virus (SARS-CoV-2) is known as the causative agent of COVID-19 disease; the World Health Organization (WHO) declared it an epidemic on March 11, 2020. The Joint Guidelines of the Centers for Disease Control and Prevention (CDC) and the WHO including social distancing, the use of face masks, emphasis on hand washing, quarantine, and using diagnosis tests have been used widely, but the value of diagnostic interventions to prevent the transmission of SARS-CoV-2 is unclear. We compared the economic evaluation of different laboratory diagnostic interventions with each other and also with implementing the conservative CDC & WHO guidelines.

Material and methods: Electronic searches were conducted on PubMed, Embase, Science Direct, Scopus, Cochrane Library, Web of Knowledge, NHSEED, NHS Health Technology assessment (CRD), and Cost-Effectiveness Analysis Registry databases. Related articles were reviewed from January 2020 to the end of November 2021.

Results: Out of 1791 initial studies, 13 articles had the inclusion criteria. According to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, ten studies were of excellent quality, and the remaining two studies were of very good quality. Most studies were cost-effectiveness analysis studies. The entered studies had different time horizons. Diagnostic tests reviewed in the studies included real-time polymerase chain reaction (RT-PCR) test, immunoglobulin G (IgG) & Antigen, point of care tests. Although polymerase chain reaction (PCR) testing improves the quality of life and survival for patients with infected Covid-19 based on its greater effectiveness compared to standard protection protocols, due to the high cost of this intervention, it has been considered a cost-effective method in some countries.

Conclusion: Since most studies have been conducted in developed countries, it unquestionably does not make sense to extend these results to low-income and developing countries. Therefore further studies are required in low-income and developing countries to evaluate the cost-effectiveness of laboratory-based diagnostic methods (RT-PCR) of covid-19 in variable prevalence of infectious cases.

1. Introduction

Acute Respiratory Syndrome (COVID-19), caused by the Corona 2 virus (SARS-CoV-2), emerged in Wuhan, China in December 2019 and is known as the causative agent of COVID-19 disease [1].The swift spread of the disease around the world propelled the World Health Organization to declare it an epidemic on March 11, 2020 [2].Global reports from 210 countries, as of April 30, 2021, revealed about 150 million infected cases and more than 3.2 million deaths [3]. And consequently, human-to-human transmission of the virus has produced immense challenges for healthcare systems especially in accurate and timely diagnosis. The Joint Guidelines of the Centers for Disease Control and Prevention (CDC) and the WHO have been implemented as the first step in coping with the disease in various countries, including social

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https://doi.org/10.1016/j.ijsu.2022.106820
Received 11 April 2022; Received in revised form 24 July 2022; Accepted 30 July 2022
Available online 17 August 2022

distancing, the use of face masks, emphasis on hand washing, and quarantine at the discretion of health systems [4,5]. Besides these protocols, the current reference laboratory test, known as the "gold standard" due to its high sensitivity and specificity, is the real-time polymerase chain reaction (RT-PCR). Despite the high diagnostic accuracy of this test, its high cost, the requirement of ribonucleic acid (RNA) extraction, the availability of specialized raw materials, necessitating specimen transport outside the hospitals in some times, and the relatively long execution time which usually lead RT-PCR results to a one-day delay in response, has generated some challenges for healthcare policymakers in different countries. Other diagnostic methods, although not as accurate as RT-PCR tests, are known as SARS-CoV-2 rapid antigen tests. They are inexpensive, can be used at a point of care (POC) test, and deliver results in less than half an hour [6]. However, the time of the patients' visit plays an important role in the right detection and filtering of the infected persons [7]. The advantage of rapid tests is that service providers could make decisions sooner, to put people into or release them from isolation. Although we could consider that one of the disadvantages of POC tests is their low accuracy compared to laboratory tests, they may play a double-edged sword. They could both overestimate the possibility of unnecessary isolation, consequently proliferate the costs, or by underestimating diagnosis elevate the prevalence of SARS CoV-2.

Therefore the wrong decision especially in care/nursing homes or university campuses, where the virus can spread rapidly due to overcrowding, could produce new challenges and problems [8]. In low-income countries such as sub-Saharan Africa, the risk and prevalence of pandemics in the region increases due to inadequate environmental infrastructures such as constraints, overcrowding, and less access to sanitation, and overcrowding [9].

On the other hand, their present health infrastructure such as testing capacity, observation facilities, isolated services, and intensive care units are scattered [10,11]. Sometimes resource constraints are not limited to low-income countries; for instance in some high-income countries, such as the United States, especially in the early days of the epidemic, limited testing capacity forced some states to test only those with severe symptoms and/or those who were known to be exposed [12]. To manage the Covid-19 epidemic before vaccination, low-income and middle-income countries have tried to implement WHO and CDC epidemic control programs [13]. Evaluation of epidemiological models of WHO-recommended interventions in studies from different countries has shown that the effectiveness of these interventions depends on the commitment of the countries and the dynamics of transmission [14,15]. Given the high shock of the epidemic and its high mortality rate, few studies have included resource costs to determine the cost-effectiveness of different diagnostic strategies for Covid-19, especially in low-income/middle-income countries. We aimed to evaluate the cost-effectiveness of different laboratory methods of Covid-19 conducted by the selected countries in entered studies.

2. Methods

2.1. Literature search strategy

This study is a systematic review in which all published English-language articles related to the cost-effectiveness of diagnostic test strategies for COVID-19 epidemic control are compared to determine the prevailing strategies from 2020 to 2021. Search strategy in this systematic review includes a combination of keywords and medical subject headings (MeSH). In order to find articles, internet search was performed in international databases consisting PubMed/MEDLINE, Embase Scopus,ISI/Web of Science, Database of Abstracts of Reviews of Effects (DARE), the Cochrane Library, Health Technology Assessment (HTA) Database, the Tufts Medical Center "Cost-Effectiveness Analysis Registry", "National Institute for Health and Care Excellence" (NICE), the Institute for Clinical and Economic Review (ICER), and National Health Service Economic Evaluation Database (NHS EED). Keywords of "Covid-19", "SARS-COV-2", "COVID-19 Testing", "COVID-19 Serological Testing", "Reverse Transcriptase Polymerase Chain Reaction", "Cost-utility analysis", "Cost-benefit Analysis", "Cost-effectiveness analysis", "CDC Guidelines" and "WHO Guidelines" were used to find relevant articles.

2.2. Selection of study

A systematic review according to the guidelines of the assessment of multiple systematic reviews (AMSTAR) and preferential reporting items for systematic review and meta-analysis (PRISMA) has been performed [16,17]. At first, any duplications were excluded from the initial search list by screening all titles and abstracts of retrieved articles. Each article was then inspected for its relativity in terms of its research contents in evaluating the cost-effectiveness and economic analysis of the Covid-19 diagnostic identification in epidemic control. After that, full-text articles of these selected titles were retrieved and criticized for further evaluation under the following inclusion and exclusion criteria. The screening of the articles was performed by two reviewers respectively and the results from each reviewer were compared. The agreement for any discrepancies between the two reviewers' results was reached through discussion with a third reviewer.

2.3. Inclusion and exclusion criteria

Articles that met the following criteria were independently selected by two reviewers:

1. Review of Covid-19 identification diagnostic methods.
2. Complete economic assessments, including cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis.
3. Quality of Adjusted Life Years Report (QALY), Lived Life Years (LYS), and Incremental Cost-Effectiveness Ratio (ICER), as well as articles published in English between 2020 and 2021. And the articles were excluded if the articles contain a partial economic assessment (cost of disease (CoI), cost analysis, cost-minimization analysis), the ones that were published in congresses and conferences, or review articles in the form of protocols, conference abstracts, commentaries and letters to editors.

2.4. Quality assessment of included studies

Two authors conducted the quality assessment of the studies based on CHEERS checklist. The international society for pharmacy-economics and outcomes research (ISPOR) in 2013 published it for the first time; since then, it has been widely used to help ensure report consistency This checklist consists of 24 questions, including the components of the article title, year of publication, journal name, place of the first author, funding, conflict of interest, the purpose of economic evaluation, main interventions and comparison, study population, economic evaluation perspective, time horizon, intervention cost data source, cost reference year, intervention outcome data source, health outcomes index, *discount rate*, and sensitivity analysis results. The "Y" sign indicated that the checklist item was completely consistent with the studied article and has received 1 score, the "P" sign with a score of 0.5 indicated items that were almost appropriate, and items that did not match were marked with "N" and a score of zero. The maximum score for each study was 24 points. Then the percentage score was calculated, and each study was classified into one of four categories: excellent (score $\geq$85%), very good (score 70% - <85%), good (score 55% - <70%) and poor (score <55%) [18,19].

2.5. Data extraction and analysis

The key features of studies which extracted are the following: first

author's, time of publication, number of included population and country, alternative comparators, outcome measurement, time horizon, model and perspective of the study, type of cost and sensitivity analysis, discount rate (cost/effectiveness) and incremental cost-effectiveness.

The extracted data through selected articles were evaluated. Derivation of the relevant information was done by the two authors independently. Regarding the uncertainty and heterogeneity of the different studies and qualitative analysis was implemented to the results of the selected studies.

3. Results

3.1. Literature search results

Initial search retrieved 1791 related citations, of which 561 were from PubMed, and the rest were from other databases. And after the removal of the 783 duplicate version, a detailed revision was made of the remaining 1008 studies on their abstracts and titles. Then 784 studies that did not meet the inclusion criteria were excluded. Abstracts of 224 studies were set for the full-text screen. Of those, 211 articles were excluded due to failure to meet the inclusion criteria and insufficient report or absence of adequate methodology evaluated by the CHEERS checklist. Finally, a total of 13 Studies were selected for study features and cost data analysis. Fig. 1 shows the review selection strategy based on the PRISMA guidelines [20].

3.2. Characteristics of the studies

13 selected studies were published from 2020 to the end of 2021. Two of the studies were cost-benefit analysis [21,22] and the other studies were cost-effectiveness analysis. Many of these studies have investigated the economic evaluation of Covid-19 laboratory diagnostic tests in their countries. One study in South Africa [23], six studies in the United States [24–27], two studies in the United Kingdom [8,28], one study in Germany [22], one study in Spain [21], one study in Uganda [29], and one study in China [30]. Table 1 details the characteristics of the studies.

In all the studies, except one [24], the perspective of the study was specified. Three studies from the perspective of the healthcare sector [23,31,32], two studies from the healthcare system [25,30], one study from healthcare contractor [21], one study from the health system and the societal [27], one study from the community [26], one study from the hospital [22], one study from the provider [29], and one study from the UK NHS [28], and one study from the UK NHS and personal social perspective [8].

Determining the time horizon in economic evaluation studies is essential to review and track intervention, related outcomes, and costs. The entered studies had different time horizons. One study with a 360-day [23], two studies with a 90-day [8,26], one study with a two-week [25], one study with a 200-day [28], one study with 10 days [22], a study with more than one year [27], and a study with one year [24]. One study had a time horizon of 180 days [31], and one study had with four months [32]. Also in three studies, the time horizon is not mentioned [21,29,30]. Table 1 shows the summary results of included studies.

Different discount rates have been used to discount costs and effectiveness outcomes in the studies. Three studies have used a 3% discount rate on effectiveness [23,24,31]. One study used a 3% discount rate on costs [21]. Two studies used a 3.5% discount rate [8,28], and two studies used a 3% discount rate on costs and outcomes [26,27]. Other studies have not considered the discount rate for a short period [22,25,29,30,32].

All studies have identified the type of diagnostic test. In nine studies RT-PCR test [21,23,26,27,29,31], in one study PCR & IgG & Antigen testing [24], and three studies the PCR tests & point of care tests (POCTs), that is known as the rapid tests, have been used [8,22,28].

In all but two studies [21,29], the model included the Markov model and the decision tree; five studies of dynamic micro-simulation model [8,23,25,28,31], four studies of analytical decision model [22,24,26,32], and two studies of Markov simulation model [27,30]. These models have been used to extrapolate long-term data.

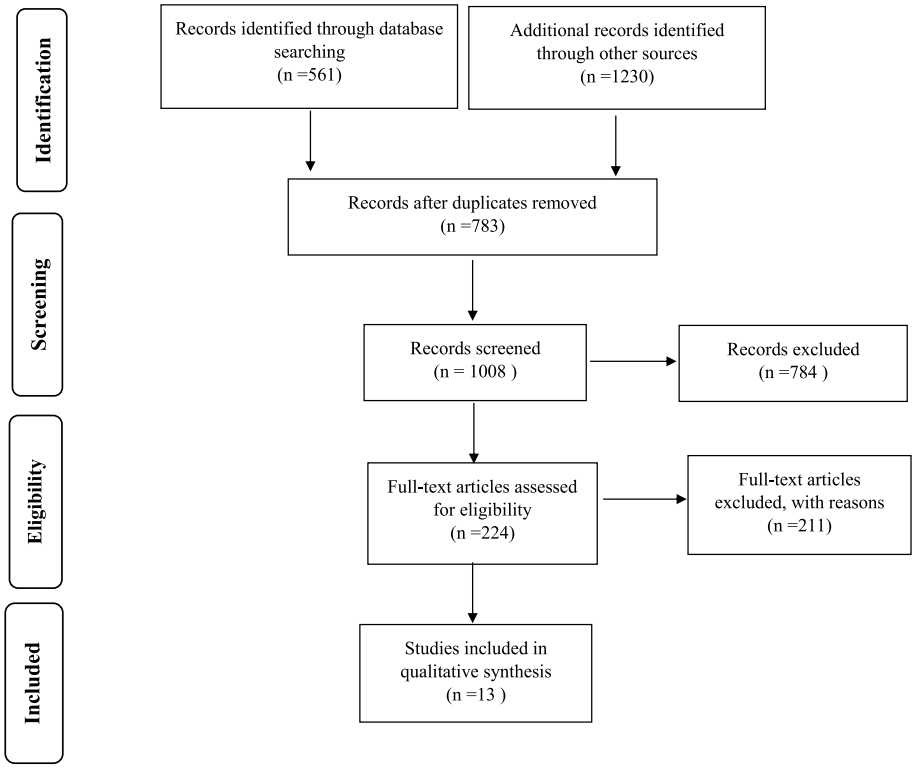

Fig. 1. Process of the systematic literature search, according to the preferred reporting items for systematic review.

Table 1
Characteristics of included studies in the review.

Study, Year	Country	Type of Study	Type of Test	Perspective	TimeHorizon	Health Outcomes	Research Question/Intervention	Sensitivity Analysis	Discount Rate	Types of Costs
K.P Reddy 2021(23)	South Africa	CEA	RT-PCR	health sector perspective	360 days	LYS LYL	HT, CT, IC,MS, and QC	One-way sensitivity analyses & PSA	Eff: 3%	health-care costs
Zhanwei Du 2021(25)	USA	CEA	RT-PCR	Healthcare sysytem	2 Weeks	QALY	testing strategies (daily to monthly) and isolation period (1 or 2 weeks) VS the status-quo strategy of symptom-based testing and isolation	One-way sensitivity analyses & PSA	–	-the expense of testing -the loss of salary -admissions to hospital
Matt Stevenson 2021(8)	UK	CEA	PCR & POCTs	NHS and Personal Social Services	90 days	the number of infections, the number of days spent in isolation, QALY	PCR and POC tests in variety of interval times for residents of home cares and the staff.	Multi-way sensitivity analyses	3.5%	Direct & indirect Costs
Matt Stevenson 2021(28)	UK	CEA	PCR & POCTs	UK NHS	200 days	Length of hospital stay, QALY	Thirty-two strategies involving different hypothetical SARS-CoV-2 tests	Multi-way sensitivity analyses	3.5%	Direct costs
R.Diel 2021 (22)	Germany	CBA	Point-of-care COVID-19 antigen testing	Hospital	10 days	Length of hospital stay	SARS Antigen FIA (Fluorescent Type) compared to the conventional clinical approach	probabilistic sensitivity analysis	–	Direct and indirect costs, with and without subsequent RT-PCR confirmation
Zafari 2021(26)	USA	CEA	RT-PCR	Community	90 days	QALY	1-implementing the CDC guidelines alone 2-implementing the CDC guidelines with: ā-a symptom-checking mobile application ṅ- university-provided standardized, high filtration masks X-thermal cameras for temperature screening Ǫ-one-time entry ('gateway') PCR testing ḫ-weekly PCR testing 3-A combination of all	one-way sensitivity analyses + Multi-way sensitivity analyses	3%	The direct and indirect costs
Guzman Ruiz 2021 (27)	USA	CEA	RT-PCR	health system, societal	over a one-year	number of deaths, QALY, ICU staying days	Test-Trace Isolate (TTI) programe VS no intervention	one-way sensitivity analysis + PSA	3%	The direct and indirect costs
Jiang 2020 [30]	China	CEA	RT-PCR	healthcare system	–	QALYs	RT-PCR tests three/RT-CR tests twice	One-way sensitivity analyses	–	Direct cost Costs/RT-PCR Test, Costs per hospital day of the fully quarantined individuals, Costs of the mixed profiles of the symptomatic and infective individuals
López Seguí 2021 [21]	Spain	CBA	RT-PCR	healthcare contractor	–	QALY	PCR&RAT	One-way sensitivity analyses	Cost: 3%	Direct cost daily cost; and the costs of hospitalization and admission to the ICU,Cost of permanent sequelae from COVID-19
Maya2021 [24]	US	CEA	PCR&IgG& Ag test	–	year one	new infections, quality-adjusted life years lost	PCR&IgG& Ag test	one-way& multi-way probabilistic	EFF: 3%	Direct cost:Testing costs for both IgG and PCR tests include cost of testing supplies (swabs, chemical reagents) and human resource costs.
Bogere 2021 [29]	Uganda	CEA	RT-PCR	provider's perspective	–	diagnostic accuracy (Positive& negative rate)	pooled sample testing/individual sample testing	–	–	cost of testing
Neilan 2021 (31)	Massachusetts	CEA	RT-PCR	healthcare sector	180-day	QALYs	[1] hospitalized: (PCR) only for patients with severe/critical symptoms warranting	one-way& multi-way	EFF: 3%	

(*continued on next page*)

Table 1 (*continued*)

Study, Year	Country	Type of Study	Type of Test	Perspective	TimeHorizon	Health Outcomes	Research Question/Intervention	Sensitivity Analysis	Discount Rate	Types of Costs
							hospitalization [2]; symptomatic: PCR for any COVID-19–consistent symptoms, with selfisolation if positive [3]; symptomatic + asymptomatic once: symptomatic and 1-time PCR for the entire population; and [4] symptomatic + asymptomatic monthly: symptomatic with monthly retesting for the entire population			Direct cost: cost of testing; and the costs of hospitalization and admission to the ICU
Baggett 2021 [32]	Massachusetts	**CEA**	RT-PCR	health care sector	4 months	Cumulative infections, hospital-days	Symptom screening, PCR, and ACS/Hybrid ACS/Universal PCR and ACS/No intervention/ Hybrid hospital/Symptom screening, PCR, and hospital/Universal PCR and hospital/Universal PCR and temporary housing compare no intervention	One&two-way sensitivity analyses	-	Direct cost daily costs, including medical supplies and personnel

RT-PCR: Real Time Polymerase Chain Reaction; Re: effective reproduction number; CEA: Cost-Effectiveness Analysis, CBA: Cost-Benefit Analysis, CN¥:Chinese yuan; QALD: quality-adjusted life day; QALY: quality-adjusted life year; NA: not applicable; NMB: net monetary benefit; YLS: years of life saved; LYL:Life years lost; HT: Health-Care testing alone; CT: contact tracing in households; IC: Isolation Centers; MS: mass symptom screening and molecular testing; QC: quarantine centers.

Studies have used different Health Outcomes to measure effectiveness outcomes. In one study, two outcomes of years of life saved (LYS), Life years lost (LYL) [23], and in eight studies, the outcome of QALY [21,25–28,30,31] was used. In addition to QALY, one study looked at the number of infections and days spent in isolation [8]. Two studies have reported length of hospital stay [22,28]. One study in addition to QALY reported the number of deaths, and ICU staying days [27]. One study also considered new infections, QALY lost as outcomes [24]. One study reported outcomes of cumulative infections and hospital days [32], and another study reported the outcomes of diagnostic accuracy (Positive & negative rate) [29].

3.3. Quality assessment results

All included studies met the CHEERS checklist items for background and aims, population group, comparative interventions, the horizon of time, discount rate, health outcomes, costs, resources, and measure of effect. Based on the quality of the CHEERS checklist, the one study that have been done in the Massachusetts by Neilan et al. had the highest score compared to other studies [31]. Out of 13, ten studies were of excellent quality [8,22–25,27,28,30,32], and the remaining two studies were of very good quality [21,29]. All cases clearly described the study population and competing options, while also having a well-defined research question (Tables1 and 2).

All but two studies referred to the study perspective [21,24]. Of all the studies, only one did not report sensitivity analysis [29], but the rest used one-way, two-way, and probabilistic sensitivity analysis to examine the effect of the changed parameters on cost-effectiveness results.

3.4. Cost outcomes

Different types of costs have been used in different studies. All studies have calculated direct costs. In addition to direct costs, four studies have also calculated indirect costs [8,22,26,29].

The cost of a weekly PCR test compared to using standardized masks was $9.27 million/QALY, resulting in cost savings of −77.36$ million [26]. Test-Trace-Isolate compared to non-intervention has reduced costs by $1045 and $850 per case, respectively, from a social and Colombian health system perspective. This amount was equivalent to twice Colombia's current health spending per year [27]. In the prevalence of 15.6% in Germany, the POCT tests reduced the average cost of hospitalized patients, by € 213 per patient [22], and in Spain, the cost of mass PCR testing was €125,865 €7,340 265 and the cost of each test after exposure was €58.32 [21]. The approximately results, in a low-income country has been extracted, they showed that the total cost of pooled testing was $161.28, while in individual testing it was $716.80, which means that pooled testing cost 77.5% less than individual testing in Uganda [29].

The results of a study in China showed that although hospital stay for receiving Covid-19 cares in Wuhan was relatively long and enhanced the medical costs, to control the Covid-19 epidemic could be considered a cost-effective strategy, and could save money if the sensitivity of the test be moderate and the test price be a fraction of the treatment's cost. Identifying more cases and quarantining them, not only increased the detected cases, but would reduce also the number of infected people, and consequently reduce health costs. In this study, the cost of RT-PCR test was about 260¥CN, while the daily cost of people staying in quarantine was1.332¥CN [30]. In another study, the cost of a PCR test was $51.37, the cost of a hospitalization and ICU stay was $1641 & $2683 per day respectively. In all epidemic scenarios (R_e from 0.9, to 1.3 to 2.6), daily symptom screening by PCR in individuals with positive screening results and COVID-19 management based on alternative care location was the most effective strategy, and compared to non-intervention, it was a cost savings method [32].

Table 2
Quality assessment of the selected studies.

Item	Item No	*Reddy* [23]	Du [25]	Stevenson [8]	Stevenson [28]	R. Diel [22]	Zafari [26]	Guzman [27]	Jiang [30]	Seguí [21]	Maya [24]	Bogere [29]	Neilan [31]	Baggett [32]
Title	1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Abstract	2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Background and objective	3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Target population and subgroup	4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Setting and location	5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Study perspective	6	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Comparators	7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time horizon	8	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y
Discount rate	9	Y	N	Y	Y	N	Y	Y	N	Y	Y	N	Y	N
Choice of health outcomes	10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness (single study-based estimates)	11a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness (synthesis-based estimates)	11b	–	–	–	–	–	–	–	–	–	–	–		–
Measurement and valuation of preference based outcomes	12	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Estimate resources and cost(single study-based economic evaluation)	13a	–	–	–	–	–	–	–	–	–	–	–		–
Estimate resources and cost (model-based economic evaluation)	13b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Currency,price date, and conversion	14	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Choice of model	15	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y
Assumptions	16	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	P
Analytic method	17	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Study parameters	18	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	Y
Incremental costs and outcomes	19	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Characterizing uncertainty(single study-based economic evaluation)	20a	Y	Y	Y	Y	P	P	Y	P	Y	Y	N	Y	Y
Characterizing uncertainty (model-based economic evaluation)	20b	–	–	–	–	–	–	–	–	–	–	–		–
Characterizing heterogeneity	21	P	P	P	P	P	P	P	Y	P	P	N	Y	N
Study funding. limitation, generalizability, and current knowledge	22	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Source funding	23	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Conflict of interest	24	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total percentage		23.5	22	23.5	23.5	22	23	23.5	21.5	19.5	23.5	17.5	24	21.5

Y fully reported (1 score), P partially reported (0.5 score), N no reported (0 score), – not applicable, a single study-based estimates, b synthesis-based estimates.

3.5. Uncertainty analysis

In all studies, except one study [29], sensitivity analysis was performed to ascertain the effect of input parameters on the consistency of ICER value in the study models. Studies have used a variety of one-way, multiple, and probabilistic sensitivity analyses (PSA).

In three studies one-way sensitivity analysis & PSA [23,25,27], two studies of multi-way sensitivity analysis [8,28], one study of PSA [22], four studies of one-way, and multi-way sensitivity analyses [24,26,32], and two studies only one-way sensitivity analysis [21,30] have been used.

The parameters that had the greatest impact on ICER were the cost of COVID-19 treatment and the cost of the prevalence of transmissible infection among asymptomatic individuals. For health care workers in

Table 3
Summary results of included economic evaluation studies.

Study, Year	Price/Year	Study Model	Threshold	Health Outcome	Cost	ICER	Is cost effective?
Reddy 2021 [23]	2019 US$	dynamic microsimulation model	US$ 3014.77	Re*, 1.5 HT*:450 940 HT, CT*, IC*,MS*, and QC*:27 220 HT and CT:322 970 HT, CT, IC,and MS:60 930 HT, CT, and IC:128 890 HT, CT, IC,and QC:60 190 **Re 1·2** HT, CT, IC,and QC:3890 HT, CT, and IC: 6850 HT, CT, IC,and MS:4260 HT, CT, IC,MS, and QC:2040 HT and CT:32 040 HT:97 600	Re, 1.5 HT:437 000 000 HT, CT, IC,MS, and QC:581 000 000 HT and CT HT, CT, IC,and MS:668 000 000 HT, CT, and IC:780 000 000 HT, CT, IC,and QC:965 000 000 **Re 1·2** HT, CT, IC,and QC:139 000 000 HT, CT, and IC:141 000 000 HT, CT, IC,and MS:183 000 000 HT, CT, IC,MS, and QC:190 000 000 HT and CT:276 000 000 HT:393 000 000	Re, 1.5 HT, CT, IC,MS, QC:340 HT, CT:Dominated HT, CT, IC,and MS: Dominated HT, CT, IC: Dominated HT, CT, IC,QC: Dominated **Re 1·2** HT, CT, IC: Dominated HT, CT, IC, MS: Dominated HT, CT, IC,MS, QC:27 590 HT, CT: Dominated HT: Dominated	Re 1·2–1·5: HT, CT, IC,MS, and QC **was cost-effective** With high epidemic growth (Re of 2·6): -no combination of the modelled interventions was cost-effective compared with HT.
Zhanwei Du 2021(25)	2020US$	dynamic microsimulation model	US$ 2 00 000	Assuming each test costs US$5 and assuming a societal willingness to pay per YLL* averted of $100000 Re → Test Intervals + Isolation = cost per test Re = 1·1 →every 28days +1 week = $75 Re = 1.2→every 28days+1week = $125 Re = 1·3→every 14days +1 week = $175 Re = 1·4→every 14days +1 week = $350 Re = 1·5→every 7days +1 week = $325 Re = 1·6→every 7days +1 week = $375 Re = 1·7→every 7days +1 week = $425 Re = 1·8→every 7days +1 week = $475 Re = 1·9→every 7days +2 weeks = $450 Re = 2·0→every 7days +2 weeks = $375 Re = 2·1→every 7days +2 weeks = $350 Re = 2·2→every 7days +2 weeks = $400 Re = 2·5→every 1day +2 weeks = $400 Re = 3→every 1day +2 weeks = $275	1-The most costly option we considered was daily testing coupled with a 2-week isolation period. 2-weekly testing coupled with 2-week isolation under high transmission scenarios (R_e: 2·2) = the optimal strategy 3-testing every 14 days with 1-week isolation = the optimal strategy under moderate transmission rates (R_e:1·3–1·4) 4-monthly testing with 1-week isolation = the optimal strategy for lower transmission scenarios (R_e:1·1–1·2)	Expanded surveillance is more cost-effective than the status-quo scenario if the price per test is less than $75 across all transmission rates.	The optimal strategy will depend on the transmission rate of the virus. 1-In high transmission: weekly testing coupled with a 2-week isolation period after a positive test is advisable and frequent surveillance testing at least monthly is preferred to the status quo of symptom-based would be an efficient use of resources. More frequent testing combined with reduced duration of isolation has a greater impact and is more cost-effective.
Matt Stevenson 2021 [8]	Great British pounds at 2020 values	dynamic microsimulation model	£20 000, £30 000 and £50 000,	in the seeded en suite model: Total QALY* loss for each 13 strategies respectively: 3.72 -2.15- 1.89- 2.50–2.27 -2.10- 2.10- 2.50- 2.82- 2.37- 2.97- 2.17- 2.89 in the seeded shared facility model: Total QALY loss for each 13 strategies respectively: 3.97- 3.19- 3.09- 3.03- 2.89- 3.16- 3.28- 2.99- 3.13- 3.37- 3.31- 3.23- 3.21	Strategy: in the seeded en suite mode 1-162 (£) 2–5500 (£) 3–5459 (£) 4-5677 (£) 5–5617 (£) 6–6099 (£) 7-6143 (£) 8–6323 (£) 9–6351 (£) 10-5298 (£) 11–5436 (£) 12-5521 (£) 13–5747(£) Strategy: in the seeded shared facility model	ICERs* for the en suite residential care facility: (A = Acceptable/D = Desirable) No early release permitted: POC* D& PCR* D = Dominating POC A& PCR A = 5621(£) POC A& PCR D = Dominated POC D& PCR A = Dominating Early release permitted: POC D& PCR D = Dominating POC A& PCR A = Dominated	1-NMB* of both POC & PCR tests of SARS-CoV-2 is greater than that of the acceptable TPPs*. 2- POCT with desirable TPP, there is potential benefit associated with SARS-CoV-2 POCT SARS-CoV-2 POCTs have considerable potential for benefit in residential care facilities, but it is dependent on the diagnostic accuracy and the costs of forthcoming SARS-CoV-2 POCTs.

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Table 3 (*continued*)

Study, Year	Price/Year	Study Model	Threshold	Health Outcome	Cost	ICER	Is cost effective?
					1-172(£) 2–5776(£) 3–5741(£) 4–5807(£) 5–5781(£) 6–6303 (£) 7–6314(£) 8–6343(£) 9–6337(£) 10–5601(£) 11–5820(£) 12–5579(£) 13–5834(£) Strategy: in the non-seeded en suite model 1-22(£) 2–4728(£) 3–4707(£) 4–4918(£) 5–4903(£) 6–5755 (£) 7–5771(£) 8–5972(£) 9–5977(£) 10–4208(£) 11–4730(£) 12–4297(£) 13–4943(£) Strategy: in the non-seeded shared facility mode 1-22(£) 2–4737(£) 3–4705(£) 4–4854(£) 5–4858(£) 6–5768 (£) 7–5757(£) 8–5909(£) 9–5926(£) 10–4201(£) 11–4726(£) 12–4269(£) 13–4899(£)	POC A& PCR D = Dominated POC D& PCR A = Dominating ICERs for the shared facilities residential care facility: No early release permitted: POC D& PCR D = Dominating POC A& PCR A = Dominated POC A& PCR D = Dominated POC D& PCR A = Dominating Early release permitted: POC D& PCR D = Dominating POC A& PCR A = Dominated POC A& PCR D = Dominated POC D& PCR A = Dominating	
Matt Stevenson 2021 [28]	Great British pounds at 2020 values	dynamic microsimulation model	£20 000, £30 000 and £50 000	The QALYs lost associated to each 28 strategies respectively: 33.81- 35.56- 39.53- 39.32- 35.86- 36.61- 38.86- 41.24- 41.23- 38.8- 35.78- 38.46- 35.80- 38.18- 37.15- 36.31- 38.25- 35.93- 38.68- 36.77- 38.56- 39.02- 40.64- 38.72- 40.52- 39.57- 38.08- 40.27	1- costs of tests performed (the cost of laboratory tests equal to the costs of POCTs) 2- the costs of additional intensive care unit requirement 3- the cost-per-QALY ratio	strategy 1, strategy 12 (£90 025) strategy 23 (£308 993) strategy 9 (£547 329) and strategy 8 (£52 577 110) strategy 24 Dominated strategy 25 (£ 25 625)	SARS-CoV-2 POCT with a desirable TPP: a relatively high NMB depending on the cost-per-QALY threshold SARS-CoV-2 POCT has the acceptable TPP: a lower NMB than a SARS-CoV-2 laboratory-based test To assess the cost-effectiveness of SARS-CoV-2 POCTs, we need further information on the costs, turnaround times and diagnostic accuracy
R.Diel 2021 [22]	2021 Euros	A decision-analytic model	German threshold	a negative POCT result one day earlier discharge results in a cost saving of €50. Reducing the base case value of 68.3 to60.0% (worst case) results in a further cost savings of €48.90 on top of the €212.57. performing POCT on each patient prior to hospitalization reduces the costs that occur when COVID-19 suspects are isolated based only on the conventional clinical approach, by €209.91	1-the costs of routine diagnostics (chest X-ray, routine laboratory values, physical examination) 2- the costs of POCT 3- Costs of RT-PCR performed in external laboratory 4- "opportunity costs"(Costs of productivity loss per day) 5- the administration of low-molecular weight heparin 6-Isolation Room 7- cost of Enoxaparin per day	Sofia SARS Antigen FIA* = 37.96 (€) (mean cost per patients) Conventional approach = 192.21 (€) (mean cost per patients) Incremental Cost for FIA= (€) 0 Incremental Cost for Conventional approach = (€) 154.25	POC test is likely to reduce hospital-related costs in cases of suspected COVID-19 in German emergency departments.
Zafari 2021 [26]	2020 US dollars	A decision-analytic model	$200,000 per QALY gained	Gateway testing plus CDC guidelines 0.55 (−0.16, 2.34) Weekly testing plus CDC guidelines 1.10 (0.14, 4.89)	Gateway testing plus CDC* guidelines-$4043021 (-$11416977,-$1863169) Weekly testing plus CDCguidelines$10235673 (-$2162557,$11062938)	Gateway testing plus CDC guidelines(-$7398283) Weekly testing plus CDC guidelines $9273023	At both a prevalence of 1% and 2%, the 'package' intervention saved money and improved health compared to all the other interventions
Guzman Ruiz 2021 [27]	2020 US dollars	A Markov simulation model	at any willingness-to-pay threshold	The social perspective: (annually) PCR: 0.44 *QALY* The healthcare perspective: (annually) PCR: 0.44 *QALY*	The social perspective: (annually) PCR: 1045.52 The healthcare perspective:	social, healthcare perspective ICER: Dominates	TTI* program as implemented in Colombia represents a cost-effective use of resources, even when the costs and disutility's

(*continued on next page*)

Table 3 (*continued*)

Study, Year	Price/Year	Study Model	Threshold	Health Outcome	Cost	ICER	Is cost effective?
					(annually) PCR: 850.19		associated with long COVID-19 were not included.
Jiang 2020 [30]	CN¥ (2020)	Markov model	CN¥64644	QALY: 850.1 QALDs:36 799	Two tests: 715.5 million Three tests: 666.4 million	−49.1 million	NMB (CN¥): 104.0 million
López Seguí 2021 [21]	€ (2021)	–	–	251 QALY	€8,372 265	Increase in costs: €4,609 943 Cost per QALY: €18,392	CBA*:1.20
Maya2021 [24]	$2020	decision model	-	Early clinical period, days 1–7: IgG* + PCR: 0.0003 Only Ag*: 0.09 IgG, if positive PCR: 1.39 No Test: 1.828 Only IgG: 1.826	Early clinical period, days 1–7: IgG + PCR: $404 Only Ag: $3660 IgG, if positive PCR: $59,664 No Test: $77,539 Only IgG: $77,863	ICER: Early clinical period, days 1–7: IgG + PCR: $1,081 393 Only Ag& IgG, if positive PCR& No Test&Only IgG: Dominated	Early clinical period, days 1–7: Only PCR, dominant Early clinical period, days 8–14: Only PCR, $34,000/QALY gained Late clinical period: No Test, dominant Asymptomatic: Only Ag, dominant
Bogere 2021 [29]	$2020	–	-	Pooledtesting(Positive:21,Negative:1259,Total:1280) Individual RT-PCR* testing(Positive:24 Negative:1256 Total:1280)	pooled sample testing:16 128$ individual sample testing:71 680 $	55 552 US$	pooled testing increases cost-effectiveness without much influence on the accuracy of PCR testing
Neilan 2021 [31]	$2020	dynamic state-transition microsimulation model	$100 000/QALY	Slowing scenario Symptomatic: 11 900)Hospitalized: 16 400 Symptomatic + asymptomatic once: 10 500 Symptomatic + asymptomatic monthly: 8900 (Intermediate scenario)Symptomatic: 18 300 Symptomatic + asymptomatic once: 16 100 Hospitalized: 36 100 Symptomatic + asymptomatic monthly: 11 400 (Surging scenario) Symptomatic:72 600 Symptomatic + asymptomatic once: 68 800 Hospitalized:97 200 Symptomatic + asymptomatic monthly 37 700 (	Slowing scenario Symptomatic: 342 787 000)Hospitalized: 439 495 000 Symptomatic + asymptomatic once: 605 505 000 Symptomatic + asymptomatic monthly: 2024106000 (Intermediate scenario) Symptomatic 488 896 000: Symptomatic + asymptomatic once: 727 290 000 Hospitalized: 849 882 000 Symptomatic + asymptomatic monthly: 2091084000 (Surging scenario) Symptomatic: 1608128 000 Symptomatic + asymptomatic once: 1831196 000 Hospitalized: 2090289000 Symptomatic + asymptomatic monthly 2757024 000)	Slowing scenario)Hospitalized: Dominated Symptomatic + asymptomatic once:194 000 Symptomatic + asymptomatic monthly:908 000(Intermediate scenario)Symptomatic + asymptomatic once:110 000 Hospitalized:Dominated Symptomatic + asymptomatic monthly:287 000(Surging scenario)Symptomatic + asymptomatic once: Dominated Hospitalized:Dominated Symptomatic + asymptomatic monthly:33 000(	
Baggett 2021 [32]	$(2020)	decision analytic model		Re, 2.6 Symptom screening, PCR, and ACS*: 1239 Hybrid ACS: 985 Universal PCR and ACS: 1681 No intervention: 1954 Hybrid hospital: 967 Symptom screening, PCR, and hospital:	Re, 2.6 Symptom screening, PCR, and ACS: 3 267 000 Hybrid ACS: 3 628 000 Universal PCR and ACS: 4 143 000 No intervention: 6 098 000 Hybrid hospital: 12 202 000	Re, 2.6 Hybrid ACS: 1000 Universal PCR and ACS/No intervention/Hybrid hospital/ Symptom screening, PCR, and hospital/Universal PCR and hospital: Dominated Universal PCR and temporary	Daily symptom screening with PCR testing of individuals who had positive screening results and ACS-based COVID-19 management was cost-effectiveness compared with no intervention.

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Table 3 (*continued*)

Study, Year	Price/Year	Study Model	Threshold	Health Outcome	Cost	ICER	Is cost effective?
				1133 Universal PCR and hospital: 1679 Universal PCR and temporary housing: 376 Re, 1.3 Symptom screening, PCR, and ACS: 137 Hybrid ACS: 103 Universal PCR and ACS: 207 No intervention: 538 Symptom screening, PCR, and hospital: 125 Hybrid hospital: 100 Universal PCR and hospital: 207 Universal PCR and temporary housing: 95 Re, 0.9 Symptom screening, PCR, and ACS: 85 No intervention: 174 Symptom screening, PCR, and hospital: 82 Universal PCR and ACS: 94 Hybrid ACS: 71 Universal PCR and hospital: 95 Hybrid hospital: 71 Universal PCR and temporary housing: 71	Symptom screening, PCR, and hospital: 12 620 000 Universal PCR and hospital: 12 914 000 Universal PCR and temporary housing: 39 119 000 Re, 1.3 Symptom screening, PCR, and ACS: 409 000 Hybrid ACS: 1 325 000 Universal PCR and ACS: 1 426 000 No intervention: 1 461 000 Symptom screening, PCR, and hospital: 1 604 000 Hybrid hospital: 2 368 000 Universal PCR and hospital: 2 631 000 Universal PCR and temporary housing: 38 974 000 Re, 0.9 Symptom screening, PCR, and ACS: 264 000 No intervention: 540 000 Symptom screening, PCR, and hospital: 1 113 000 Universal PCR and ACS: 1 226 000 Hybrid ACS: 1 240 000 Universal PCR and hospital: 1 901 000 Hybrid hospital: 2 004 000 Universal PCR and temporary housing:38 954 000	housing: 58 000 Re, 1.3 Hybrid ACS: 27 000 Universal PCR and ACS/No intervention/Symptom screening PCR, and hospital/Universal PCR and hospital: Dominated Hybrid hospital: 382 000 Universal PCR and temporary housing: 6 854 000 Re, 0.9 Hybrid ACS: 71 000 No intervention/Hybrid hospital/Symptom screening, PCR, and hospital/Universal PCR and ACS/Hybrid hospital/Universal PCR and temporary housing/Universal PCR and hospital: Dominated	

R_e: Effective Reproductive Number/HT: Health-care Testing/CT: Contact Tracing within households/IC: Isolation Centers/MS: Mass Symptom Screening/QC: Quarantine Centers/YLS:/Years of Life Saved/YLL: Years of Life Lost/ICER: Incremental Cost-Effectiveness Ratio/QALY: Quality Adjusted Life Years/POC or POCTs: Point-of-Care Tests/PCR: Polymerase Chain Reaction/NMB: Net Monetary Benefit/TPPs: Target Product Profiles/FIA: Sofia SARS Antigen/CDC: Centers for Disease Prevention and Control/TTI: Test-Trace-Isolate/CBA: Cost Benefit Analysis/IgG: Immunoglobulin G/Ag: Antigen or Rapid Antigen/RT-PCR: Real-Time Polymerase Chain Reaction/ACS: Alternative Care Site.

the first week of Covid-19 symptoms, PCR is likely to save 74% more QALY than antigen tests, but only 26% is likely to reduce costs. Both of these outcomes were more dependent on the sensitivity of PCR and antigen tests. In the second week of infection, PCR testing remained the preferred strategy. In the late phases of the disease, antigen testing and PCR were less cost-effective in QALY compared to no testing; but were not cost-effective due to very small health gains. Therefore, at this phase, no kind of laboratory testing remains as an optimal strategy [24].

In asymptomatic screening for the low prevalence of COVID-19, antigen tests always saved QALYs compared to no test, but when costs or prevalence of COVID-19 were low, antigen testing in simulations was 25% more expensive. In the comparison of PCR with antigen testing alone, PCR was 65% more likely to save on QALYs than antigen testing. However, it was not cost-effective due to its small health gains and increased net costs [24].

In another study, the results were sensitive to the cost and sensitivity of the impact of PCR and alternative care sites (ACS) in preventing transmission. It was also associated with changes in PCR sensitivity, cost and frequency of testing, and as well ACS effectiveness as with the most changes in an incremental cost per prevented case. The combined approach, including daily symptom screening with PCR, sensitivity analysis, was less expensive than daily symptom screening alone and reduced the incremental costs of $ 1000 to $ 3000 per case. Therefore, the results were correlated with increased PCR sensitivity and reduced PCR cost [32].

According to the results of the Reddy study on sensitivity analysis, a combination of all five interventions including healthcare testing, contact tracking, use of isolation, mass symptom screening, and use of quarantine centers in all scenarios, except in scenario with the effective reproductive number (R_e) R_e 2.6, was cost-effective contingent on increased PCR sensitivity to 90% and reduced the effectiveness of transmission in isolated and quarantine centers [23]. In another study, when the sensitivity of the tests was moderate and the tests' cost was a part of the treatment, increasing the frequency of tests to control the COVID-19 epidemic could be cost-effective [30]. In the Neilan study, when the costs of PCR testing were reduced, many of the combined programs and the costs of monthly strategies for symptomatic and asymptomatic cases would be cost-effective. It could not be considered a cost-effective intervention when the tests were performed more than every 30 days in the incremental scenario. However, by decreasing the cost of the test to less than $3, testing every 14 days would be cost-effective in all scenarios [31].

Based on the results of one study, a probabilistic sensitivity analysis in a POCT testing saves € 210 compared to a clinical judgment strategy alone. This cost savings of € 159, or 75.9%, was due to the high specificity of the POC test, which prevented unnecessary hospitalization, 21 times less [22].

3.6. Cost- effectiveness outcomes analysis

In a study under all considered epidemic extension scenarios (from R_e = 0.9, and 1.3 to 2.6), the symptomatic scenario was clinically preferable and cost-effective compared to hospitalization. In symptomatic and asymptomatic monthly strategies through incremental scenarios, ICER was less than $100,000/QALY compared to only symptomatic cases; and with a decrease in R_e in the incremental scenario, ICER has increased sharply [31]. In the screening of recently symptomatic health care workers (HCWs), only PCR testing was preferred strategy. This test saved money and improved health outcomes in the first week after the onset of symptoms and costs $83,000 per year of QALY in the second week of the symptoms. However, in screening HCWs at the late clinical phases of the disease, none of the test methods were cost-effective [24].

Performing RT-PCR tests three times for diagnosis and discharge in one of the studies, resulted in 850.1 QALYs, and net savings of CN ¥49.1 million healthcare costs, and consequently amounting to CN ¥ 104.0 million net monetary benefit (NMB) [30]. The results of a study showed that mass testing strategy by RT-PCR was a feasible and practicable option compared to an individual testing strategy in Uganda. In a pooled sample testing, the mean cost-effectiveness ratio was four times lower than individual sample testing (US $12.6 per test versus the US $56 per test, respectively) and required three positive tests to further identification, and the incremental cost-effectiveness of the individual test method was $55,552 [26]. In another of the studies, their results showed that the PCR test was more cost-effective than non-intervention [29] (Table 3).

4. Discussion

The Covid-19 epidemic, an acute respiratory syndrome of the Corona 2 virus (SARS-CoV-2), emerged in the early days of 2019 in Wuhan, China. Clinical symptoms include stunted breath, fever, pulmonary infiltration in radiological images, and dry cough. The WHO named this viral disease COVID-19; and more broadly, the world's health, economy, and social stability were followed by socio-economic threats, including global socio-economic welfare, health systems, pharmaceutics, aviation industry, tourism, media, information technology, nutrition and sports industries, the housing market, and R&D activities [33–35]. The Covid-19 pandemic, according to global reports from 210 countries, as of April 30, 2021, showed about 150 million infected cases and more than 3.2 million deaths, [3,36]. Moreover, global economic costs are estimated to exceed $ 21 trillion by 2020 [37].

Until medical reciprocal measures like vaccination or antiviral drugs become widely available, the world will deal with SARS primarily through unprecedented non-drug interventions, including the use of face masks, travel restrictions, and physical distancing measures that could produce drastic social and economic costs [38,39].

Despite the fact that in high-income countries with high test capacity, complex efforts have provide more accurate predictions for COVID-19 identification by creating artificial intelligence programs, and efforts are being made to process clinical data as well imaging techniques [40], immediate clinical decisions are still critical; laboratory results include changes in white and red blood cell types and immune system components, C-reactive protein, renal and serum function measures, and a rise in liver enzymes, and also procalcitonin levels may be considered a non-conclusive diagnosis. And to receive a definite confirmation of the diagnosis of COVID-19, more specific laboratory tests are required [41]; rapid and inexpensive laboratory tests, such as POCTs, can offer the potential to prevent unnecessary isolation, which is widely practiced as a conventional clinical approach. Even in high-income countries such as Germany, implementing a rapid Covid-19 POCT antigen test without any change in prevalence, where a sensitivity of clinical judgment and the POCT was estimated a range of 45–99% versus 80.0%, could be saved € 209.91 per patient and accounted less costly than the conventional clinical approach (based on symptomatic signs), as well as providing immediate results and facilitating the decision process in the setting of an emergency room before deciding whether a possible COVID-19 patient should be hospitalized or not [22]. The same findings with different sensitivity, are comprehended from the UK, which showed that the POCT strategy, where a sensitivity of clinical judgment and the POCT was estimated 80.6% versus 80.0%, avoids higher mortality and costs less than did RT-PCR testing ($140,000 versus $150,000 per prevented death) [42]. And also in the UK's residential facilities, it has been achieved that the POC tests have considerable potential benefit for use in residential care homes, but its monetary benefit depends on the diagnostic accuracy and costs of forthcoming SARS-CoV-2 point-of-care tests.

The study of Stevenson and their colleague assigned the cost-effective results of these tests, POCTs, by desirable and acceptable target product profiles (TPPs) based on diagnostic accuracy (post-infected) and symptomatic signs. They assumed neither the laboratory-based test nor the POCT could detect SARS-CoV-2 until 0.5 days after

infection. SARS-CoV-2 POCTs, with desirable & acceptable TPPs, had a sensitivity of 97% & 80%in symptomatic and 80.1% & 66% in asymptomatic residents respectively, and appeared to have high & low net monetary benefit values [8]. Through the study process of Jiang et al. it showed that the virus transmission rate determines the optimal strategy.

In the high prevalence of the disease, all interventions, including CDC guidelines alone and combined with PCR or rapid testing and, isolation of confirmed infected individuals were effective in preventing COVID-19 pandemic; and reimbursed resources from shorter isolation could be cost-effectively allocated to multiple tests. However, in the low prevalence, only standardized masks with high filtration offered value [27].

By focusing on implementing the hospital-based PCR testing in different scenarios and different prevalence Neilan et al. estimated that if PCR testing had been used widely during April 2020 in Massachusetts, 103.000–176.900 infected cases and 90–260 deaths would have been prevented. And at $R_e = 0.9$, both symptomatic & asymptomatic monthly PCR (S&A PCR) testing vs hospitalized showed a 64% decrease in infectious cases and a 46% decrease in mortality but entailed more than 66-fold tests per day with 5-fold higher costs. S&A PCR had an ICER <$100 000/QALY only when $R_e \geq 1.6$; when test cost was ≤$3, even shorter time testing (every 14-day) was cost-effective at all R_e results [31]. As mentioned above, even in low-income countries like South Africa, Reddy's study demonstrated that the conditions of epidemic growth determine the best timely diagnostic strategy. In high epidemic growth (R_e of 2·6), PCR testing alone strategy was the optimal one; and combined with providing isolation centers as housing facilities for confirmed infected individuals reduced the transmission rate from 50% to 5%. In such countries, a mix of all-intervention strategies would cost an additional $ 340 per YLS, which is cost-effective for many public health interventions; including TB diagnostic tests and cervical cancer screening [23]. In China, focusing on the number of PCR tests on asymptomatic and pre-symptomatic infectivity found that performing three RT-PCR tests for diagnosis and discharges resulted in 850.1 QALY of health benefits and a net saving of 49.1 million CNY in health care costs during the analytical period in Wuhan [27]. In Barcelona, a massive pilot screening of 125 865 people identified a total of 1724 positive cases. It prevented a total of 5429 additional infections, which in turn prevented 168 hospitalizations, 11 ICU admissions, 56 permanent complications, 33 deaths. The results of various studies show that the most effective interventions maximize the percentage of positive cases detected. And while effective resource management for mass screening policies in asymptomatic populations can generate high social returns, in the Seguí study, excluding monetary health value, the profit segment was estimated at 0.45, which seems to be of little value in the recommendation. However, early detection of cases reduces further transmission in the transmission chain, maximizing resource value depends on tracking screening strategies and focusing on targeting groups like high-risk subpopulations with the highest positive rates expected [21].

In health care worker (HCWs) covid-19 screening, Maya's study assessed the cost-effectiveness of six screening approaches for HCWs in the US using one-time PCR, Ag, and/or IgG assays based on clinical presentation and concluded that, in contrast with the other studies, even in low prevalence condition the best screening approach is PCR testing. And in their sensitivity analysis results, the Antigen testing was dominant in first-onset clinical disease (cheaper & more effective) over PCR. However, with ICER more than $ 30 million per QALY, IgG testing was no longer cost-effective in late-onset clinical illness due to the low prevalence [24]. In Baguette's study on the homeless, a timely diagnostic strategy was developed in a large Boston shelter, including various combinations of symptom screening, PCR testing, alternative care facilities (ACS), and relocation of all shelter residents to temporary accommodation. They found that daily screening for mild to moderate symptoms and using ACS results in a 37% reduction in infection and a lower cost compared to non-intervention ($ 6.10 million vs. $ 3.27 million) in R_e of 2.6; and estimated that in a growing epidemic, adding an RT-PCR test every 2 weeks would be associated with a further reduction in infections at a reasonable cost [32]. Although almost all selected studies considered ICER as a health outcome, some with a large number of strategies in their models adopted a net monetary approach in their models, their strategies stemming from the fact that when there are small differences between the health benefits and costs, ICERs can be misleading. However, with the adoption of NMB, the cost-effectiveness of diagnostic tests compared to other interventions has also been achieved [8,28].

Selected studies showed that in Covid-19 identification policies, various factors play a critical role in health outcomes and cost savings; some of these parameters are more prominent, such as the prevalence of infections in the community and the timing of referrals for laboratory tests. Except in one of the studies [24] that considered PCR testing as the dominant strategy even in low prevalence, when the prevalence is low and the transmission chain breaks, following the guidelines and protection protocols of the WHO and CDC can be the most cost-effective strategy.

In the high prevalence, it seems that testing methods such as PCR, rapid POC, and even IgG testing convert into a dominant and cost-effective strategy in detecting infected people and naturally reducing their hospitalization or isolation. However, the prominent test method depends on the socio-economic conditions, provider perspective, health expenditure portion from GDP, and the extent of disease transmission in that community.

4.1. Limitations

There were some limitations in evaluating the effectiveness, accountability, and cost of our study as below:

4.1.1. Effectiveness limitations

1. In cost-effectiveness analyses, uncertainty is always a concern, especially in the Covid-19 pandemic where we are encountered with limited information (clinical & epidemiological) due to the unknown nature of the disease.
2. Compared to molecular PCR tests with serological antibodies, the immunological complications of IgG and their probable transient protection time in Covid-19 may increase the false reassurance effect of the IgG test over time.
3. In some selected studies, there are some oversimplifications to the results of molecular tests, while in the real world, these test results are considered along with other medical records and patient medical situations that may affect health outcomes.
4. In this study, only English literature was reprocessed due to database access and language restrictions.

4.1.2. Accountability limitations

1. Some other factors may play a role in measuring the extent of effectiveness of diagnostic approaches, e.g. occupations predisposing to frequent contact with infected persons, comorbidity, access to health care and molecular and rapid diagnostic test.
2. The population of these studies and their specific characteristics, except for general characteristics such as their disease and different levels of treatment received, have provided some comparing problems.

4.1.3. Costs limitations

1. The selected studies are limited to some countries, mostly as the high-upper/middle-upper level of income ones.
2. Nonetheless, different countries have different levels of health care systems, medical insurance, reimbursement, drug costs, willingness-

to-pay thresholds, and so on. Therefore, there were certain limitations in extrapolating the data and further studies are required, especially in low-income countries to evaluate the cost-effectiveness of different diagnostic strategies in Covid-19 identification.

5. Conclusion

PCR testing was not reported as a certainly cost-effective intervention due to the high cost of the test in some of studies, although it has been more effective than standard protection protocols. And POC testing, in spite of its low sensitivity, was considered a prominent strategy due to their cost-saving. All studies emphasized that until a universal covering of vaccination, early diagnosis of Covid-19 has improved quality of life, increased survival in patients with infected Covid-19, and enhanced cost-saving indirectly.

Ethics approval and consent to participate

Not applicable.

Funding

This study was part of research project funded by the Ilam University of Medical Sciences (ethical code: IR.MEDILAM.REC.1400.056).

Authors' contributions

All authors contributed to the conceptual background and content of the publication.

Data statement

All data generated or analyzed during this study are included in the article.

Registration

This systematic review was registered in the International Futuristic Systematic Review Database (PROSPERO) with the code CRD42022324825.

Guarantor

Shahin Nargesi.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2022.106820.

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