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Review Article

Cost-effectiveness of Public Health Strategies on COVID-19 Control: A Systematic Review

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Abstract: The COVID-19 pandemic has been one of the greatest public health challenges imposing significant economic and societal costs. A wide range of public health interventions (PHIs) have been implemented to control the virus, with many aggressive measures that led to economic downturn and social calamity. However, evidence concerning their impacts in terms of costs and benefits of the best buy strategy is limited. This systematic review aimed to provide a critical summary of full economic evaluations (EEs) to inform decisions concerning their adoptions. A systemic search in 7 relevant databases and other sources were conducted. Out of 11,584 and 11 records identified from databases and other sources, a total 31 full EEs focusing on PHIs were included. Majority of studies included were in good quality and from the US and upper-middle, and high-income countries whereas only 6 studies were from low and middle-income countries. Suppression/containment was the most deployed strategy (n=19), followed by screening/detection (n = 8), and protection (n = 4). Aggressive elimination strategy usually results in more lives or QALYs saved compared to mitigation strategies but at a very high cost. The trade-off between aggressive and loose suppressions depends on several factors including timing of implementation, duration, epidemiological characteristics of the virus, and the healthcare capacity. Tight and timely adoption of effective intervention at the early stage of pandemic is key in shrinking the number of cases. Using a combination approach is generally more cost-effective compared to a single intervention. Personal protective measure is highly cost-effective in protecting healthcare workers in a high prevalence scenario and when it is adopted together with social distancing strategy. Future studies to address the flaws of current evidence are warranted. This review provides important insights regarding adoption of PHIs and their cost-effectiveness which would be useful to inform policy decisions in response to COVID-19 and future pandemics.

Keywords: Systematic review; COVID-19; SARS-CoV-2; public health intervention; cost-effectiveness

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1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was first reported in Wuhan, China in December 2019[1], and declared a global pandemic on March 11, 2020[2] has spread to every corner of the world and become one of the greatest public health challenges globally with over 503,000,000 confirmed cases and 6,218,000 deaths worldwide as of April 15h, 2022[3]. Recent evidence has shown exhibition of neurological, gastrointestinal, and long-term complications among post COVID-19 survivors[4-6]. The possible mechanism of which is the use of the angiotensin-converting enzyme 2 (ACE-2) receptors which are expressed in the central nervous system and various organs for SARS-COV-2 entry to the host cell[5], and the inflammatory responses caused by the virus[6].

Various public health strategies to slow the infection have been implemented[7]. Despite the success in virus containment, many of extreme non-specific measures have also inadvertently resulted in substantial economic and social costs[8, 9], of which those with lower socioeconomic status or scarce resource settings are disproportionally impacted[10-12]. As such, policymakers need to design a low-risk yet cost-effective method for managing this pandemic.

To date, there have been several epidemiological models of these interventions published. However, most previous reviews mainly focused on clinical outcomes without considering the costs and the effectiveness of interventions[13]. The evidence concerning cost-effectiveness is limited with conflicting findings. This systematic review was conducted to update the results from two previous systematic reviews on the cost-effectiveness and feasibility of such public health measures[14, 15] with a significant distinction in including only full economic evaluations focusing on public health interventions (PHIs) for the COVID-19 pandemic. The findings would be essential to inform decisions for practical approaches to slowing down the infection and minimizing the economic impact.

2. Materials and Methods

The study reporting was done according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[16, 17]. The study protocol was registered in PROSPERO under protocol number CRD42021243848.

2.1. Search strategy

We performed a systematic search in relevant databases including CINAHL, The Cochrane Library, ECONLIT, EMBASE, Medrivx, PubMed, and Web of Science using Medical Subject Headings (MeSH) terms "((COVID* OR COVID-19 OR COVID19 OR (SARS-CoV-2)) AND (economic OR cost-effectiveness analysis OR cost-benefit OR cost-utility OR cost-effectiveness)" without language restriction from 2019 up until 19 March 2021 (online supplementary Appendix 1). The search results from all databases were merged and duplicates were removed. Additional references were sought by scanning the reference lists.

The primary outcome was incremental cost-effectiveness ratio (ICER) per any health outcome unit gain or averted. An incremental cost-effectiveness ratio (ICER) is a summary of measures representing the economic value of an intervention, compared with an alternative, calculated by dividing the difference in total costs by the difference in the total health outcome measure[18]. The ratio presents additional cost incurred per one more health unit gained which is useful to inform policy decisions. Articles were included if they contained a full economic evaluation (EE) on PHIs in response to COVID-19 control and prevention; included the comparison of PHIs with do nothing or other alternative strategies; and had one of outcome of interests. Systematic review, meta-analysis, review, and editorial letters were excluded.

2.2. Study selection and data extraction

PC performed searching and initial screening. The screened articles were rechecked against the inclusion and exclusion criteria which were independently reviewed by AR and SLL. Data extraction was performed by AR and SLL and checked for accuracy by SWHL. Any disagreement was discussed until consensus was reached. In case, there was more than one publication of the same study identified, the most recent publication would be referred to.

Information including study setting, study design, intervention, comparisons, perspective, an incremental cost-effectiveness ratio (ICER)/Net monetary benefit (NMB), willingness to pay (WTP) threshold, time horizon, and main findings were extracted.

The original currency of costs was converted into 2020 international dollars (I$) according to methods recommended by Turner et al.[19]. Briefly, local currencies were inflated to 2020 value using the local consumer price indices (CPIs) and later converted to international dollars using the purchasing power parity (PPP) using the average exchange rate for the year 2020[20].

2.3. Risk of bias assessment

The quality of studies included was assessed according to the Drummond 10-point checklist guidelines, the standard tool for appraisal the methodological quality of cost-

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effectiveness analysis[21, 22]. Each item in the checklist has a potential score of 1. The aggregate results reflect the overall study quality ranging from poor quality (score of 1 to 3), average quality (score of 4 to 7), and good quality (score of 8 to 10)[23]. AR and SLL independently appraised the quality of the included economic evaluations, and all ratings were checked for accuracy by SWHL.

3. Results

3.1. Study selection

We identified 11,584 records from searches in seven relevant databases. After duplicates were removed, there were 10,183 articles. After title and abstract screening, 10,135 irrelevant articles that did not meet the inclusion criteria were excluded. Of 48 articles reviewed for full-text eligibility, twenty-five were excluded, leaving 23 studies included in the review. Additionally, eleven articles were identified from other sources (7 articles from websites, 4 articles from citation searching) and reviewed in full text, of which three studies were excluded. Therefore, 31 studies were finally included (23 from databases and 8 from other sources) in the systematic review[24-54] (Figure 1). The details of 28 studies excluded after full-text evaluation were presented in the online supplementary Appendix 3.

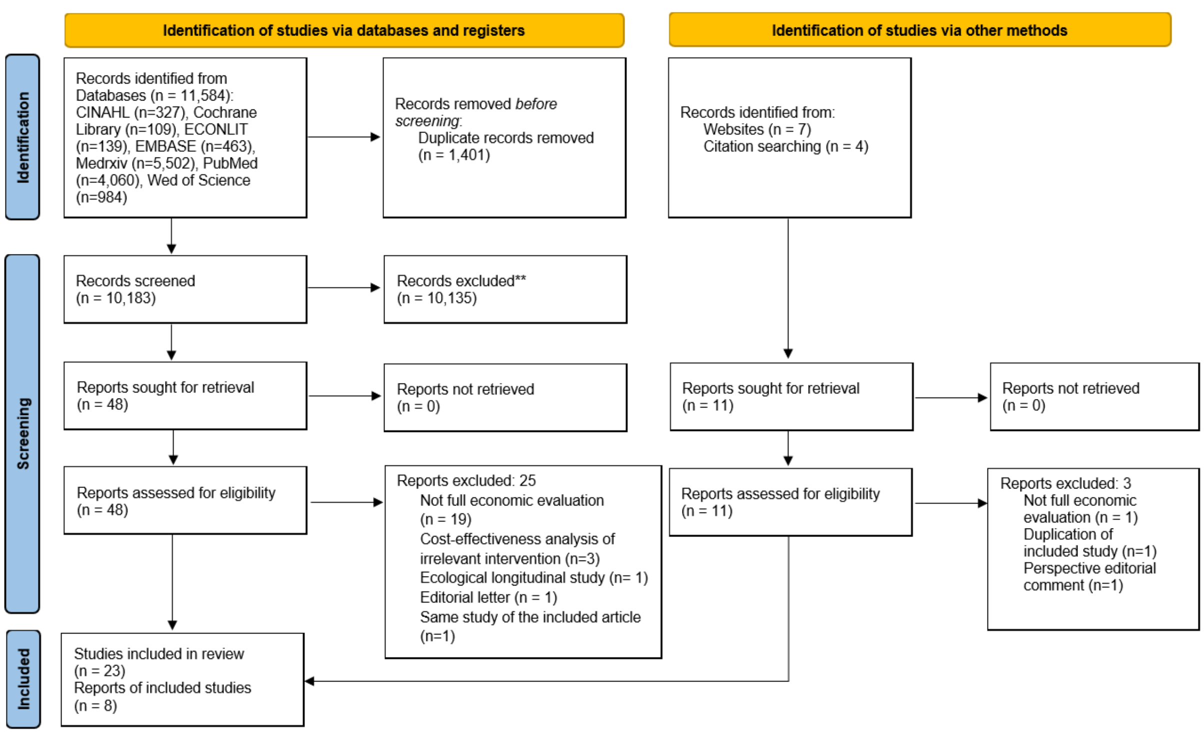

Figure 1. Flow diagram of search strategy and study selection.

3.2. Study characteristics

All included studies were published between 2020 and 2021. Thirteen studies were from the US[29, 31, 36-38, 40, 41, 43, 47-49, 51, 52], four studies were from China[28, 34, 44, 45], three were from India [32, 42, 50], and two studies each were from Germany [33, 46] and the United Kingdom[53, 54] while one study each was from Australia[24], South Africa[26], Israel[27], Ghana[30], Morocco[35]. One study evaluated data from Sweden and Denmark[25] and one study was an EE that investigated the cost-effectiveness of personal protective equipment (PPE) in 139 low and middle-income countries (LMICs)[39]. A summary of study characteristics is presented in Table 1.

3.3. Study design and time horizon

Thirteen studies conducted cost-effectiveness analysis using life-years saved[25, 26, 33], number of human protected[28], positive patients detected[46], infection or cases[30, 35, 38-40, 44, 51], and years of life lost averted[47] as health outcome measures. Eight studies performed a cost-utility analysis in which six studies reported outcomes in terms of quality-adjusted life years (QALYs)[29, 34, 36, 37, 53, 54] while one each reported the outcome in terms of health-adjusted life years (HALYs)[24] and disability-adjusted life-year (DALYs) saved[45]. Seven studies focused only on cost-benefit analysis [31, 32, 41-43, 48, 49]. Three study employed both cost-utility and cost-effectiveness analysis[27, 50, 52] using the number of death[27, 50], infection averted and QALYs[52] as outcome measures.

Three studies used a stochastic agent-based model (ABM)[24, 28, 47], a computational model for simulation that capture the behavior of individuals in the model (agents) and their interactions with other agents and the environment[55]. Fourteen studies applied the Susceptible-Exposed-Infected-Recovered (SEIR) or SIR model, a compartment disease model computing how SARS-CoV2 infects the population[27, 32, 34, 36-38, 43-45, 49, 51-54]. A decision-tree analytic model was implied in four studies[33, 39, 40, 42]. The others used different approaches including a dynamic COVID-19 microsimulation model[26], a decision-analytic model deploying a Monte Carlo simulation[29], multi-region discrete-time mathematical modeling[35], the Institute for Health Metrics and Evaluation (IHME) model[31], and the Penn Wharton model[41].

The time horizon ranged from 30 days to 30 years. Nine studies projected the outcomes ranging from 30 to 150 days[29, 31, 34, 38, 44, 45, 47, 52, 54] while twelve studies used the time span from 6 months to 1 years[24-27, 33, 36, 37, 39, 42, 46, 50, 53]. The time duration of 30 years was assumed in a CBA[43]. The other studies did not report the duration. The discount rate was not applied in most studies due to a short timeframe while discounting rates ranging from 3% to 5% were reported in 8 studies[24, 31, 32, 36, 37, 41, 43, 45].

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3.4. Willingness-to-pay thresholds

Different willingness to pay (WTP) thresholds were used ranging from $3,250 to $200,000 depending on country-specific context and health outcomes. Studies from the US generally employed thresholds spanning from $8,500 to $200,000 per QALY, YLL or infection averted [29, 36-38, 40, 41, 47, 52] except a CBA in which the threshold of $10 million per value of statistical life (VSL) was used[43]. Thresholds adopted by Chinese studies were lower, at $15,000 to $47,000 per QALY or DALYs saved[28, 34, 45], while one study applied a cost-effectiveness threshold of three times of GDP per capita[28]. Similarly, an EE from India applied a cost-effectiveness threshold of 1 to 3 GDP per capita[50] based on the WHO guideline for WTP threshold[56]. Two studies from the UK used WTP thresholds of £20,000-£30,000 per QALY ($28,589-$42,884), as recommended by the National Institute for Clinical Excellence (NICE)[53, 54]. The threshold was not stated in 11 studies[30-32, 35, 39, 42, 44, 46, 48, 49, 51].

3.5. Perspectives

Twelve studies used a societal perspective[25, 28, 29, 31, 33, 37, 39, 42, 46-48, 52] and six studies used a health system perspective[26, 27, 34, 36, 50, 51] in their analyses. Three studies used both the health system and societal perspective[24, 45, 53], of which one study adopted a partial societal perspective using gross domestic product (GDP) cost in addition to healthcare expenditure[24]. Ten studies did not specify the perspectives used in their analyses[30, 32, 35, 38, 40, 41, 43, 44, 49, 54].

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Table 1. Summary of study characteristics.

No	Author, Year	Country	Study design	Population	Interventions	Comparison	Perspective	Unit of ICER	WTP threshold	Time horizon	Discount rate
Screening/detection											
1	Atkeson et al. 2021[48]	USA	CBA	General population	Strategy 1. 10-day screening testing Strategy 2. 5-day screening testing Strategy 3. 3-day screening testing	No additional screening test	Societal	NR	NR	NR	NR
2	Baggett et al. 2020[51]	USA	CEA, Extended SEIRD (CEACOV) model	Adults residing in homeless shelters	• Symptom screening, PCR, and hospital • Symptom screening, PCR, and ACS • Universal PCR testing and hospital • Universal PCR and ACS • Universal PCR and temporary housing • Hybrid hospital • Hybrid ACS	No intervention: only basic infection control practices are implemented in shelters	Healthcare sector	Cost/case prevented	NR	4 months	NA
3	Du et al. 2021[47]	USA	CEA (A stochastic individual-based chain-binomial model)	General population	Strategy 1: Daily antigen test plus 1-week isolation Strategy 2: Daily antigen test plus 2-week isolation Strategy 3: Antigen test every 7 days plus 1-week isolation. Strategy 4: Antigen test every 7 days plus 2-week isolation. Strategy 5: Antigen test every 14 days plus 1-week isolation. Strategy 6: Antigen test every 14 days plus 2-week isolation. Strategy 7: Antigen test every 28 days plus 1-week isolation. Strategy 8: Antigen test every 28 days plus 2-week isolation.	Symptom-based testing and isolation (status-quo strategy)	Societal	Cost/YLL	$100 000 per YLL averted	150 days	NA
4	Jiang et al. 2020[34]	China	CUA (SALIRD model)	Suspected people with COVID-19 and COVID-19 patients being discharged	Three reverse transcription-PCR (RT-PCR) tests	Two reverse transcription-PCR (RT-PCR) tests	Health system	Cost/QALY	64,644 RMB ($15,444.37)	43 days (23 January - 6 March 2020)	NA
5	Losina et al. 2020[52]	USA.	CUA, Extended SEIRD (CEACOV) model	University students, faculty and community members	4 NPIs include social distancing, mask-wearing policies, isolation, and laboratory testing in various combinations	No intervention	Modified societal	Cost/infection prevented; Cost/QALY	$150,000 per QALY	105 days	NA

No	Author, Year	Country	Study design	Population	Interventions	Comparison	Perspective	Unit of ICER	WTP threshold	Time horizon	Discount rate
6	Neilan et al. 2020 [36]†	USA	CUA, Extended SEIRD (CEACOV) model	General population	Strategy 1. PCR-severe-only Strategy 3 (Symptomatic + asymptomatic-once): Symptomatic and one-time PCR for the entire population Strategy 4: Symptomatic + monthly testing	Strategy 2 (Symptomatic): Hospitalised and PCR COVID-19-consistent symptoms with self-isolation	Healthcare system	Cost/QALY	$100,000 per QALY	180 days (May 1-Nov 1, 2020)	3%
7	Paltiel et al. 2020[38]	USA	CEA (SEIR model)	University students aged < 30 years old	1. Weekly screening 2. Screening every 3 days 3. Screening every 2 days 4. Daily	Symptom-based screening	NR	Cost/ infection averted	$8,500 per infection averted	80 days	NA
8	Zafari et al. 2020[29]	USA	CUA, Decision-analytic model deploying a Monte Carlo simulation (the Columbia COVID-19 model)	Columbia University students and staff	CDC guidelines +additional screening and preventive measures include: 1. Symptom-checking mobile application 2. Standardizing mask 3. Thermal imaging camera 4. One-time testing for SARS-CoV2 on entry 5. Weekly testing for SARS-CoV2 6. Upgrades to ventilation systems or installation of far-ultraviolet C lighting systems	CDC guidelines (social distancing, protective measures, and maintaining a healthy environment) alone	Societal	Cost/QALY	$200,000 per QALY	91 days	NA
Suppression/containment											
9	Asamoa et al. 2020[30]	Ghana	CEA (A deterministic model)	General population	Strategy 1, u1 only (The effective testing and quarantine when borders are opened. Strategy 2, u2 only (Intensifying the usage of nose masks and face shields through education.) Strategy 3, u3 only (Cleaning of surfaces with home-based detergents.) Strategy 5, u5 only (Fumigating commercial areas such as markets. Strategy 6, combines the use of control ui, i = 1,..,5	Strategy 4, u4 only (Safety measures adopted by asymptomatic and symptomatic individuals such as practicing proper cough etiquette)	NR	Cost/ infection averted	NR	NR	NR
10	Blakely et al. 2021[24]	Australia (Victoria)	CUA, An agent-based model (ABM)	General population	The four policy options: 1. Aggressive elimination strategy 2. Moderate elimination strategy 3. Tight suppression strategy 4. Loose suppression strategy	Business-as usual or no COVID-19	Health system and partial societal	Cost/HALY	$15,000 per HALY	12 months	3%

No	Author, Year	Country	Study design	Population	Interventions	Comparison	Perspective	Unit of ICER	WTP threshold	Time horizon	Discount rate
11	Broughel et al. 2021[31, 57]†	USA	CBA, model from the Institute for Health Metrics and Evaluation (IHME)	General population	Suppression policies enforced by the U.S States. (Government suppression scenario)	Only targeted "mitigation" was practiced including case isolation, household quarantine, and social distancing among elderly and high-risk populations	Societal	NR *__Note:__* Net mortality benefit (NMB) was reported	NR	42-65 days	5%
12	Dutta et al. 2020[32]	India	CBA (Susceptible-Infected-Recovered (SIR) model)	General population	National lockdown	Without lockdown	NR	NR *__Note:__* Reported in net benefits	NR	NR	4%
13	Gandjour 2020[33]	Germany	CEA (Decision tree)	General population	Successful lockdown: ICU capacity exceeded by 50%, 100%, 200%, and 300%	No intervention	Societal	Cost/LYs gained	€101,493 ($136,133) per life years gained	1 year	NA
14	Khajji et al. 2020[35]	Morocco	CEA (A multi-region discrete-time mathematical modeling)	General population	Strategy 1: protecting susceptible individuals from contacting the infected individuals in the same region 1 Strategy 2: protecting and preventing susceptible individuals from contacting the infected individuals in the same region or in other regions Strategy 3: protecting susceptible individuals, preventing their contact with the infected individuals, encouraging the exposed individuals to join quarantine centers Strategy 4: protecting susceptible individuals, preventing their contact with the infected individuals, encouraging the exposed individuals to join quarantine centers and the disposal of the infected animals	Strategy 3: Protect susceptible individuals, prevent their contact with infected individuals, and encourage the exposed individuals to join quarantine centers.	NR	Cost/case averted	NR	NR	NR
15	Miles et. al. 2021[54]	United Kingdom	CUA, extended SEIRD (Imperial College COVID-19 Response Team Model)	General population	Lockdown	Do nothing	NR	Cost/QALY; Cost/LYS	£30,000/QALY ($42,884); £20,000/ LYS ($28,589)	3 months	NA
16	Mol and Karnon 2020[25]	Sweden and Denmark	CEA	General population	Strict lockdown strategy (Denmark)	Flexible social distancing strategy (Sweden)	Societal	Cost/LYS	$100,000 per life-year saved	6 months	NA

No	Author, Year	Country	Study design	Population	Interventions	Comparison	Perspective	Unit of ICER	WTP threshold	Time horizon	Discount rate
17	Padula et al. 2020[37]	USA	CUA (Markov model using SEIR structure)	General population	1. Social distancing 2. Treatment 3. Vaccination	Do nothing	Societal	Cost/QALY	$50,000 per QALY	365 days	3%
18	Reddy et al. 2021[26]	South Africa (KwaZulu-Natal)	CEA (Markov)	General population	Public health intervention strategies below: 1. HT+CT 2. HT+CT+IC 3. HT+CT+IC+MS 4. HT+CT+IC+QC 5. HT+CT+IC+MS+QC	Healthcare Testing (HT)	Health sector	Cost/LYS	$3250 per life-year saved	360 days	NA
19	Scherbina 2020[49]	USA	CBA (SIR Model)	General population	Suppression policy extended by 6, 10, 12, 15, 18-week	Suppression extended by 2-week	NR	NR *Note:* Reported in NMB	NR	NR	NR
20	Schonberger et al. 2020[41]	USA	CBA (The Penn Wharton model)	General population	Limited reopening with social distancing	Full reopening and reduced social distancing	NR	Cost/QALY	$125,000 per QALY	NR	3%
21	Sharma and Mishra 2020[42]	India	CBA (Decision tree)	General population	National lockdown	No lockdown	Societal	Cost/case averted	NR	1 year	NA
22	Shlomai et al. 2020[27]	Israel	CEA and CUA (SEIRD model)	General population	Non-selective nationwide lockdown	Focused isolation of individuals at high exposure risk	Health sector*	Cost/death averted; Cost/QALY	$15,243-$17,366 per QALY	200 days	NA
23	Thunstrom et al 2020[43]	USA	CBA (SIR model)	General population	Social distancing policy	No social distancing policy	NR	Cost/ live saved (VSL)	$10 million/live saved (VSL)	30 years	3%
24	Wang et al. 2020[28]	China	CEA, The stochastic agent-based model (ABM)	General population	Single strategies: 1. Personal protection 2. Isolation-and-quarantine 3. Gathering restriction 4. Community containment Combination of public health measures: 1. Personal protection (mask wearing and hand washing) and isolation-and-quarantine program (Program A) 2. Gathering restriction and isolation-and-quarantine, program (Program B) 3. Personal protection and community containment (Program C) 4. Personal protection, isolation-and-quarantine, and gathering restriction (Program D)	No intervention	Societal	Cost/human protected	ICER < 3 times of per capita GDP ($47,155.59)	NR	NA
25	Xu et al. 2020[44]	China	CEA (A Spatial-Temporal	General population	1. Epidemiological control including identification of infected cases, tracing their close contact tracing 2. Local social interaction control	No restrictions	NR	Cost/ infection averted	NR	30 days	NA

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No	Author, Year	Country	Study design	Population	Interventions	Comparison	Perspective	Unit of ICER	WTP threshold	Time horizon	Discount rate
			Explicit SEIR Model)		3. Inter-city travel restriction						
26	Zala et. al. 2020[53]	United Kingdom	CUA, extended SEIRD (Imperial College COVID-19 Response Team Model)	General population	1. Mitigation policy: individual case isolation, home quarantine, social distancing advice for people aged > 70 years old 2. Suppression 1: mitigation+social distancing+school closure, triggered "on" when there are 100 ICU cases/week, and "off" when weekly cases halve to 50 cases 3. Suppression 2: Suppression 1 triggered "on" when there are 400 ICU cases/week, and "off" when weekly cases halve to 200 cases	Unmitigated (Do nothing)	NR *Note:* Societal perspective could be assumed based on costs included.	Cost/QALY	NICE WTP: £20,000-30,000 ($28,589-42,884) More general estimates of the social value: £10,000-70,000 ($42,883-100,061)	1 year	NA
27	Zhao et al. 2021[45]	China	CUA (SIER model)	General population	Strategy B: 1 week delay movement restriction Strategy C: 2 weeks delay movement restriction Strategy D: 4 weeks delay movement restriction	Strategy A: Rapid implementation of movement restriction	Healthcare and societal	Cost/DALY	70,892 RMB per disability-adjusted life-year saved ($16,937)	100 days	3%
Protection											
28	Bagepallyet al. 2021[50]	India	CEA, and CUA (A decision tree and Markov model)	General population	1. Surgical mask 2. N-95 respirator (fit and non-fit tested) 3. hand hygiene 4. surgical mask + hand hygiene	Do nothing	Health system	Cost/case prevented; Cost/QALY	146,709.29 INR ($6671.77)	1 year	NA
29	Ebigbo et al. 2021[46]	Germany	CEA	Patients presenting for endoscopy	Strategy 2: No routine pre-endoscopy virus test; additional use of FFP-2 and water-resistant gowns for all procedures Strategy 3: Decentralized point of care antigen test; use of surgical masks, goggles, gloves and apron for all procedures Strategy 4: Decentralized point of care antigen test; additional use of FFP-2 and water-resistant gowns for all procedures irrespective of test result. Strategy 5: Centralized laboratory-based rapid PCR test; use of surgical masks, goggles, gloves and apron for all procedures Strategy 6: Centralized laboratory-based rapid PCR test; additional use of FFP-2 and water-resistant gowns for all procedures irrespective of test result. Strategy 7: Centralized laboratory-based standard PCR test; use of surgical	Strategy 1. No routine pre-endoscopy virus test; use of surgical masks, goggles, gloves and apron for all procedures	NR *Note*: Societal perspective could be assumed based on costs included	Cost/ number of patients who tested positive	NR	1 year	NA

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No	Author, Year	Country	Study design	Population	Interventions	Comparison	Perspective	Unit of ICER	WTP threshold	Time horizon	Discount rate
					masks, goggles, gloves and apron for all procedures Strategy 8: Centralized laboratory-based standard PCR test; additional use of FFP-2 and water-resistant gowns for all procedures irrespective of test result.						
30	Risko et. al. 2020[39]	LMICs	CEA (Decision tree)	HCWs	Full personal protective equipment (PPE) supply per the WHO best practice guidelines to maintain a low rate of HCW infection	Inadequate PPE with absence of one or more PPE elements	Societal	Cost/HCW life saved; Cost/HCW case averted	NR	30 weeks	NA
31	Savitsky, et al. 2020[40]	USA	CEA (Decision tree)	HCWs on labor and delivery	Universal Screening	Universal PPE	NR	Cost/HCW case averted	$25000 per HCW case averted	NR	NR

ACS, Alternative care site; CDC, the Centers for Disease Control and Prevention; CT, Contact Tracing; HT, Healthcare Testing; IC, Isolation Center; MS, Mass Symptom Screening; QC, Quarantine Centres; CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; DALY, Disability adjusted life years; HCW, healthcare worker, ICER, Incremental cost-effectiveness ratio; LMICs, Low-middle income countries; NA, Not applied; NPIs, Nonpharmaceutical interventions; NR, Not reported; QALY, Quality adjusted life years; RMB, The Renminbi or Chinese Yuan (¥); SEIR, Susceptible-Exposed-Infected-Recovered; SALIRD, Susceptible-asymptomatic-pre-symptomatic-symptomatic-recovered-deceased; USA, The United States of America; VSL, Value of Statistical Life; WTP, Willingness to pay; YLL, years of life lost; YLS, years of life saved; *Not reported by the authors but interpreted from methodology and key findings; †The most recent publication was cited.

3.6. Public health interventions and cost-effectiveness results

3.6.1. Screening strategies

Of the 31 studies, eight explored cost-effectiveness of screening strategies[29, 34, 36, 38, 44, 47, 48, 51, 52]. Key findings are presented in the online supplementary Appendix 4. Three studies examined the cost-effectiveness of antigen testing[38, 47, 48]. Atkeson et al.[48] compared the costs and benefits of a 10-day, 5-day, and 3-day nationwide COVID-19 screening testing regime coupled with self-isolation among those testing positive vs. no federal testing program. The net economic benefits were found to be greater with early introduction and projected to avert between 28,000 to 91,000 deaths with an increased in GDP ranging between $8 to $46 billion[48]. Du et al.[47] assessed eight antigen testing strategies with different testing frequencies in combination with 1 or 2-week isolation vs. symptom-based testing and isolation. They found that weekly testing following with 2-week isolation upon a positive test result was preferred at the reproduction number (R0 or Rt) of 2.2 (ICER = $31,267 per YLL averted, median NMB = $2,378 billion) while monthly testing followed by 1-week isolation was the most cost-effective under low transmission scenarios at R0 of 1.2 (ICER = $52,500 per YLL averted, median NMB $257 billion)[47]. Paltiel et. al.[38] reported screening every 2 days with a 70% sensitivity rapid test as the optimal strategy vs. symptom-based screening under a university setting to keep Rt below 2.5 (ICER = $5,700 per infection averted). Another two EEs of COVID-19 mitigation strategies in college settings implied the added value of nonpharmaceutical interventions (NPIs) in combination with laboratory testing (LT)[29, 52]. Losina et. al.[52] examined the cost-effectiveness of 24 COVID-19 mitigation strategies in various combinations compared with no intervention and found that extensive social distancing and mandatory mask-wearing policies were very cost-effective (ICER = $224/infection prevented, $25,485/QALY). Adding routine laboratory testing would further decrease infections at a relatively higher cost (ICER = $482/infection prevented, $121,643/QALY) while keeping campuses closed may result in more infections due to the lack of structured programs to enforce mask-wearing and social distancing. Zafari et. al.[29] compared additional control measures to the Centers for Disease Control and Prevention (CDC) guidelines and found that the effectiveness of interventions varied greatly according to the COVID-19 prevalence rate. At a low prevalence rate of 0.1%, a symptom checking application was cost-saving relative to CDC guidelines alone whereas using a symptom checking application and 2-ply mask-wearing was cost-saving at a prevalence rate of 2.0%. However, the latter approach would result in university closure after 18 days due to many COVID-19 cases.

Three EEs compared the use of RT-PCR strategies in identifying potential COVID-19 cases. The Chinese study[34] comparing 3 RT-PCR vs. 2 RT-PCR strategy concluded that the 3-test strategy was cost-saving compared to the 2-test strategy resulting in 850 QALYs gain and a net monetary benefit of CN¥ 104 million ($4.86 million). Neilan et al.[36] compared different PCR testing approaches and demonstrated cost-saving of PCR testing with any COVID-19-consistent symptoms compared to the hospitalized strategy (PCR testing only severely symptomatic individuals) while symptomatic + asymptomatic monthly approach resulted in the most favorable outcomes in reducing infections and deaths but would be cost-effective only in the surging scenario at Re of 2.0 (ICER = $33,000/QALY).

An American study[51] assessing 7 different combinations of symptom screening, PCR, hospital-based COVID-19 care, alternative care sites (ACS), and temporary housing strategies relative to no intervention among adults residing in homeless shelters showed that daily symptom screening paired with ACS strategy and universal PCR every 2 weeks (hybrid ACS) was the optimal strategy compared with no intervention in all scenarios (ICER = $-2,549.02/prevented case).

3.6.2. Suppression/containment

Nation-wide lockdown/aggressive suppression policies

A total of 19 studies reported the cost-effectiveness of suppression or containment strategies with conflicting findings. Ten studies compared a strict lockdown strategy or suppression policy to a flexible social distancing policy or no intervention as a reference strategy[24, 25, 27, 31-33, 42, 49, 53, 54]. Among these, 4 studies reported the substantial costs of the lockdown which far exceeded its benefits and did not justify its value[25, 27, 32, 54]. In contrast, the other studies found lockdown to be cost-effective/saving[24, 31, 33, 42, 49, 53] depending on the context.

Two studies[25, 27] showed that a strict lockdown measure could potentially save more lives or life-year saved but was not cost-effective compared to a more focused approach (ICERs = $45,104,156/death averted or $4.5m/QALY; ICER = $137,285/LYS) while a CBA conducted in India[32] reported the negative net benefits of lockdown vs. no lockdown under all scenarios varying from -9,125 to -23,232 Rs. billion ($-415 to $-1,052 billion). On the contrary, another CBA from the same country[42] concluded that lockdown was a cost-saving intervention compared to no lockdown in saving 2.74 Rs. trillion ($1.25 trillion) equating to an annual GDP of 1.86%.

Two CUAs from the UK using the NICE guideline as the WTP threshold (£30,000 or $42,884 per QALY) reported inconsistent findings[53, 54], of which one study[54] demonstrated significant fewer benefits of 3-month lockdown compared to its costs accounting for the net extra economic costs of £59 billion ($84 billion) relative to the easing restrictions even on the most conservative assumption. In contrast, another study[53] showed the ICERs of suppression policies vs. an unmitigated (do nothing) to be below the threshold.

In line, a CUA conducted in Australia compared 4 COVID-19 strategies; aggressive and moderate elimination, tight suppression and loose suppression to a no COVID-19 scenario, which favored elimination (moderate and aggressive) strategies over a 1-year pandemic[24]. Broughel et. al.[31] and Gandjour[33] focused on national lockdown/suppression policies compared with mitigation strategies or no intervention also demonstrated the positive net benefits of suppression policies on economic impact and flattening the curve.

Timing and duration of policy implementation

Zhao et. al.[45] examined the cost-effectiveness of early movement restriction policies (MRPs) relative to delayed MRPs by 1, 2, and 4-week in China and identified the rapid MRP as the “dominant” strategy vs. all other approaches. Consistently, another Chinese study[44] comparing three anti-epidemic policies for COVID-19 emphasized the high cost-effectiveness of comprehensive epidemiological control measures at the early stage. At the same time, in-city, inter-city travel restrictions had minimal impact with high costs. Scherbina[49] assessed the costs and benefits of suppression policy extension by 6, 10, 12, 15, and 18-week compared with lifting the lockdown after 2-week. The optimal duration of lockdown suggested ranges between 10 and 19 weeks depending on its effectiveness in reducing the number of new cases.

3.6.3. Social distancing policy

The benefits of the social distancing policy were noted in three studies from the U.S.[37, 41, 43]. Padula et. al.[37] compared three interventions: social distancing, COVID-19 treatment, and vaccination vs. do nothing, of which all the three options dominated the do-nothing approach. Thunstrom et. al.[43] estimated the net benefits of social distancing policy relative to the uncontrolled scenario to be $5.16 trillion. Schonberger et. al.[41] considered cost-benefit of a full reopening with reduced social distancing, and a return to Shelter-in-Place (SIP) relative to continued limited reopening with social distancing. A limited reopening with partial mitigation dominated a full reopening and SIP policies in terms of QALYs gained and GDP costs under the condition that an effective treatment/vaccine could be deployed within 11.1 months

3.6.4. A wide range of interventions

Four CEAs[26, 28, 30, 35] compared a range of strategies using a stepwise approach across the general population regarding the number of infections prevented or life-year saved, and costs. Wang et. al.[28] compared single strategies of either personal protection (mask-wearing and hand washing), isolation-and-quarantine, gathering restriction, community containment or a combination of public health measures with no intervention in two scenarios (1 imported case, and 4 imported cases). Among all strategies, the joint strategy of personal protection and isolation-and-quarantine was optimal among all strategies. However, all interventions except personal protection and gathering restriction were cost-effective if cases were low. Reddy et. al.[26] evaluated various PHIs vs. healthcare testing only among those presenting at healthcare centers (HT) in South Africa at different epidemic growths (Re 1.2, 1.5, and 2.6). At base case (Re 1.5), strategies involving healthcare testing, contact tracing, isolation center, mass symptom screening, and quarantine center (HT+CT+IC+MS+QC) was the most cost-effective (ICER $340/YLS), followed by HT+CT+IC+MS (ICER = $590/YLS) whereas HT+CT+IC+QC was the optimal strategy at a low prevalence scenario (Re 1.1-1.2). The cost-effectiveness was sensitive to epidemic growth that all combinations of control measures were outpaced and ineffective at Re 2.6.

Another study from Morocco[35] compared 4 different preventive strategies by progressively adding more restrictions in a stepwise manner ranging from implementing awareness campaigns to prevent population movement, encourage contacts to join quarantine centers, and dispose of the infected animals. Among all strategies considered, awareness/security campaigns to avoid exposure to the infected population and encourage the exposed individual to join quarantine centers was the most preferred strategy.

According to a study from Ghana[30], safety measures including social distancing, hand washing, and cough etiquette were the most cost-effective strategy and dominated the other 5 interventions considered while a combination of all strategies was dominated (less effective and more costly).

3.6.5. Protection

Four economic evaluations focused on personal protective equipment (PPE) as protective measures[39, 40, 46, 50], of which two CEAs found that that PPE was highly cost-effective in maintaining a low rate of infection among HCWs[39, 40]. Risko et. al.[39] demonstrated cost-effectiveness of full PPE supply defined as supply availability allowing full adherence to the World Health Organization (WHO) best practice guidelines[58] compared with an "inadequate" scenario in 139 LMICs with a mean ICERs of $59, and $4,309 per HCW case averted and life saved respectively, and the societal return of 7.93%. Savitsky et. al.[40] compared PPE with universal screening to prevent COVID-19 transmission among HCW and reported that universal screening was generally the preferred option. In contrast, universal PPE was cost-effective under the high prevalence scenario (29.5 to 34.3%) and cost-saving for planned cesarean delivery.

A German CEA[46] examined the cost-effectiveness of eight different combinations of pre-endoscopy virus testing and protection strategies including additional use of FF-2 masks, water-resistant gowns, POC antigen test, PCR vs. routine protective measures with no pre-endoscopic virus testing among asymptomatic patients presenting at endoscopy unit. The study suggested that the ICER values were lowest when a strategy of POC antigen testing without the use of high-risk PPE was implemented whereas at higher prevalence rates of 1% and 5%, the lowest ICERs were achieved with rapid POC antigen testing paired with high-risk PPE use. In contrast, Bagepally et. al.[50] conducted CEA and CUA in India comparing the use of 5 different protective measures (surgical mask, N-95 respirator fit tested and non-fit tested, hand-hygiene, surgical mask+hand hygiene) vs. do-nothing approach and found that none of the interventions were cost-effective while hand hygiene appeared to be less expensive compared to other interventions.

3.7. Sensitivity Analysis

Most studies performed one-way sensitivity analysis, three of which[28, 40, 51] also conducted 2-way sensitivity analyses. Probabilistic sensitivity analyses (PSAs) were carried out in 10 studies[26, 27, 29, 36, 37, 39, 40, 45, 46, 50]. Nineteen studies[24, 28, 29, 32, 33, 38-40, 43, 44, 46-49, 51-54, 57] used scenario analyses in which only two[24, 47], and one studies[43] provided cost-effectiveness acceptability curves (CEACs) and break-even analysis respectively. Sensitivity analyses used were not reported in 3 studies[35, 41, 42] (Table 2).

Table 2. Sensitivity analyses.

No	Author, Year	Country	1-way	2-way	3-way	PSA	CEAC	Scenario
1	Atkeson, A. et al 2021[48]	USA	●					●
2	Baggett, TP. et. al. 2020[51]	USA	●	●				●
3	Du, Z. et al. 2021[47]	USA					●	●
4	Jiang, Y. et al. 2020[34]	China	●					
5	Losina, E. et al. 2020[52]	USA	●					●
6	Neilan, AM. et al. 2020[36]	USA	●			●		
7	Paltiel, AD. et al. 2020[38]	USA						●
8	Zafari, Z. et al. 2020[29]	USA	●			●		●
9	Asamoah, JKK. et al. 2020[30]	Ghana	●					
10	Blakely, T. et al. 2021[24]	Australia	●				●	●
11	Broughel, J. et al. 2021[31, 57]	United States						●
12	Dutta, M. et al. 2020[32]	India						●
13	Gandjour, A. 2020[33]	Germany	●					●
14	Khajji, B. et al. 2020[35]*	Morocco						
15	Miles, DK. et al. 2021[54]	UK						●
16	Mol, B and Karnon, J 2020[25]	Sweden and Denmark	●					
17	Padula, WV. et al. 2020[37]	USA	●			●		
18	Reddy, KP. et al. 2021[26]	South Africa	●			●		
19	Scherbina, A. 2020[49]	USA						●
20	Schonberger, RB. et al.2020[41]*	USA						
21	Sharma, N. et al. 2020[42]*	India						
22	Shlomai, A. et al. 2020[27]	Israel	●			●		
23	Thunstrom, L. et al 2020[43]	USA	●					●
24	Wang, Q. et al. 2020[28]	China	●	●				●

No	Author, Year	Country	1-way	2-way	3-way	PSA	CEAC	Scenario
25	Xu, L. et al. 2020[44]	China	●					●
26	Zala, D. et al 2020[53]	UK	●					●
27	Zhao, J. et al. 2021[45]	China	●			●		
28	Bagepally, BS. et al. 2021[50]	India	●			●		
29	Ebigbo, A. et al. 2021[46]	Germany				●		●
30	Risko, N. et al. 2020[39]	LMICs				●		●
31	Savitsky, LM. et al. 2020[40]	USA	●	●		●		●

Note: CEAC, cost-effectiveness acceptability curve; LMICs, Low- and Middle-income Countries; PSA, probability sensitivity analysis; *Not reported

3.8. Risk of Bias Assessment

The risk of bias was assessed in all studies (Table 3). According to the Drummond 10-point checklist, 21 of economic evaluations[24-29, 34, 36-40, 43, 45, 47, 49-53, 57] included were rated 8 to 10 indicating the methodology and analyses used were of high quality. The others were rated a score of 4 to 7 and classified as average quality. A summary of the rating and the checklist detail is provided in the online supplementary Appendix 5.

Table 3. Summary of rating using the 10-item Drummond's checklist.

No	Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Screening/detection											
1	Atkeson et al 2021[48]	+	+	?	?	+	+	−	+	+	−
2	Baggett et al. 2020[51]	+	+	+	+	+	+	−	+	+	+
3	Du et al. 2021[47]	+	+	−	+	+	+	−	+	+	+
4	Jiang et al. 2020[34]	+	+	−	?	+	+	+	+	+	+
5	Losina et al. 2020[52]	+	+	+	+	+	+	−	+	+	+
6	Neilan et al. 2020[36]	+	+	+	?	+	+	+	+	+	+
7	Paltiel et al.2020[38]	+	+	−	+	+	+	−	+	+	+
8	Zafari et al. 2020[29]	+	+	+	+	+	+	−	+	+	+
Suppression/containment											

No	Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
9	Asamoah et al. 2020[30]	+	+	+	−	−	−	−	+	−	−
10	Blakely et al. 2021[24]	+	+	+	+	−	+	+	−	+	+
11	Broughel et al. 2021[31, 57]†	+	+	+	+	+	+	+	+	+	−
12	Dutta et al. 2020[32]	+	+	+	-	+	+	+	−	+	−
13	Gandjour 2020[33]	+	+	−	?	+	+	−	+	+	+
14	Khajji et al. 2020[35]	+	+	−	?	+	+	−	+	−	−
15	Miles et al. 2021[54]	+	+	+	-	+	+	−	+	+	−
16	Mol and Karnon 2020[25]	+	+	+	+	−	+	−	+	+	+
17	Padula et al. 2020[37]	+	+	+	+	+	+	+	+	+	+
18	Reddy et al. 2021[26]	+	+	+	+	+	+	−	+	+	+
19	Scherbina et. al. 2020[49]	+	+	-	+	+	+	−	+	+	+
20	Schonberger et al. 2020[41]	+	+	?	?	+	?	+	+	−	−
21	Sharma and Mishra 2020[42]	+	+	?	?	+	+	−	−	−	−
22	Shlomai et al. 2020[27]	+	+	+	+	+	+	−	+	+	+
23	Thunstrom et al 2020[43]	+	+	+	?	+	+	+	−	+	+
24	Wang et al.2020[28]	+	+	−	+	+	+	−	+	+	+
25	Xu et al. 2020[44]	+	+	−	−	+	−	−	−	+	+
26	Zala et. al. 2020[53]	+	+	-	+	+	+	−	+	+	+
27	Zhao et al 2021[45]	+	+	+	+	+	+	+	+	+	+
Protection											
28	Bagepally et al. 2021[50]	+	+	+	+	+	+	−	+	+	+
29	Ebigbo et al. 2021[46]	+	+	−	?	+	+	−	+	+	+
30	Risko et. al. 2020[39]	+	+	+	+	+	+	−	+	+	+
31	Savitsky et al. 2020[40]	+	+	+	+	+	+	−	+	+	+

Note: Plus signs represent yes (low risk of bias); minus signs, no (high risk of bias); question marks, unclear (unclear risk of bias).

4. Discussion

This systematic review summarizes the cost-effectiveness of full economic evaluations on public health interventions in response to COVID-19. We identified 31 full EEs focusing on PHIs regarding COVID-19 prevention, of which majority are in good quality. The number of included studies is slightly more than the 2 previous reviews[14, 15] , possibly due to the extensive inclusion of several databases and other sources including citation searching. The findings concerning cost-effectiveness results, assessment of methodological quality, strengths and limitations would provide invaluable insights for policymakers regarding optimal strategies under different contexts and health economists concerning existing evidence gaps to be addressed in future EEs.

Suppression/containment strategies were most frequently examined among the included studies (n =19), followed by screening/detection (n = 8), and protection (n = 4). Using a combination strategy is generally more cost-effective than a single intervention approach. However, certain conditions including the number of infected cases, timing, effectiveness, and adherence to intervention should be considered. Wang et. al.[28] reported a combination of PHIs involving personal protection and isolation-and-quarantine as the optimal strategy compared to isolation-and-quarantine alone in both 1 and 4 imported cases scenarios. In contrast, neither personal protection nor gathering restriction was cost-effective when there was more than 4 imported cases were imported. The decline in the effectiveness of isolation and quarantine was more pronounced as decreasing quarantine probability and increasing delay time especially in sporadic outbreak scenario. In a South African study[26], joint strategies involving healthcare testing, contact tracing, isolation center, mass symptom screening, and quarantine center dominated healthcare testing alone across the general population at Re 1.5. However, the efficacy of isolation and quarantine markedly decreases at high epidemic growth (Re 2.6). A high prevalence with many cases can lead to a higher probability of contacting with the infected population among susceptible individuals resulting in exacerbation of the infection.

A nationwide lockdown usually results in more LYS and QALYs compared to mitigation strategies or loose suppression but with tremendous costs[25, 27, 49]. The effectiveness of this extreme measure has been controversial with concerns regarding basic human rights and limited healthcare facilities[59]. The primary purpose of lockdown is to flatten the pandemic curve, allowing time for preparing the healthcare infrastructure before replacing it with less restrictive measures to delay the growth of new cases. The trade-off between aggressive and relaxing control measures depends on several factors, including the health system capacity, virus mutation, vaccine effectiveness, timing, and duration. The optimal time of lockdown before its incremental benefits fall below the incremental costs ranges between 10 to 19 weeks[49] which largely relies on the policy's effectiveness in reducing the number of new cases. Contact tracing and isolation would be most effective when there is a relatively small number of cases. As the number of infections increases, susceptible individuals are more likely to be exposed to the virus resulting in a rapidly rising of infected population in the community. These epidemiological measures would be insufficient to control the transmission and can lead to an overwhelming health system. Therefore, the timely and effective suppression strategy at the early stage of transmission at sufficient duration would be critical for a significant reduction in the number of new cases and a reversal of the epidemic whereas alternating suppression strategy would be economically inefficient[49].

Comprehensive testing and identification of the infection have a significant impact on reverse the pandemic trend. More frequent testing prevents more infections but at a relatively high cost[52]. Expanding screening strategies provides greater benefits in reducing infections as Re increases whereas ICERs significantly rise as Re decreases but reduce as costs decline. At a high prevalence rate with rapid disease transmission, periodic universal screening combined with 1-2 week isolation subsequently to a positive test result is potentially to be cost-effective[36, 38, 47] while at a low prevalence rate, restricting testing to those with COVID-19 symptoms combining with self-isolation and other protective measures is likely to be economically preferred strategy[29, 36, 51]. Specificity, the turnaround time, and the test cost are also important factors in determining cost-effectiveness. High specificity is matter far more than sensitivity in controlling the outbreak which can result in overwhelming number of false positives and quarantine center capacity[38]. Lowering the test cost would enable more frequency and expansion of testing capacity for cases detection with a lower ICER value. A rapid turnaround time would facilitate timely isolation of infected individuals while a longer turnaround time over a day period imposes a higher number of new cases and costs[51]. Laboratory screening and contact tracing are tedious and exhaustive work. This epidemiological approach requires extensive manpower and heavily relies on the health system capacity. In limited-resource settings, particularly LMICs with underfunding of the health system, elimination strategies may need to be deployed for sufficient transmission control.

The utilization of ACS is helpful in COVID-19 management among the homeless and socioeconomic disadvantaged population. This approach would avoid the fixed costs and avert hospitalizations to preserve beds for those exhibiting severe conditions. The hybrid ACS strategy among those with pending test results or mild to moderate symptoms is associated with substantially reduced infections at a lower cost than hospital care management in achieving similar clinical outcomes[51].

Personal protective measures, including PPE, FFP-2, N-95 respirator, surgical masks are potentially cost-effective in high prevalence situations especially when combined with rapid antigen testing among HCWs[39, 40], and patients undergoing specific conditions procedures[40]. In contrast, applying such preventive measure broadly across the general population is unlikely to be cost-effective particularly in low-resource settings[50]. The usage of surgical/2-ply mask in combination with other PHIs including symptom screening, extensive social distancing was suggested to be cost-effective in college settings[29, 52]. Social distancing reduces contact hours between infected and susceptible individuals while masks decreases infectivity among cases[52]. Therefore, a protection strategy should be enforced among high-risk groups e.g., HCWs or implemented alongside with social distancing strategy to optimize the benefits.

High cost-effectiveness interventions exist at the beginning of the endemic. This involves tight and timely comprehensive epidemiological measures to contain the virus whereas a travel ban or lockdown which impose substantial economic and societal costs may have minimal impact at this stage. Therefore, in a low prevalence scenario, stringency, and enforcement of effective PHIs in minimizing exposed individuals is more important than implementing aggressive policies that paralyze the whole society.

No intervention or mediocre stringency of social distancing is generally the worst choice and not an acceptable option unless there is sufficient evidence to justify or achievement of herd immunity, which is unlikely to be the case under the current situation. As the transmission progresses with the increasing number of infected cases, aggressive policies may be necessary to reverse the spread in reaching the turning point and clearance of cases, of which strong enforcement is essential as the stricter the control, the lower number of cases[44, 60].

Due to a large stochastic variation in SARS-CoV-2 infection, there is no universal optimal strategy. The success of PHIs depends on epidemiological characteristics of the disease (Re), policy enforcement, and stringency, vaccine, and treatment effectiveness, and the health system capacity. The fact that major sources of infections and mortality are concentrated in elderlies and vulnerable populations reinforces the need for more focused PHIs targeting on high-risk individuals. Despite the widely available of COVID-19 vaccines and treatment[61], evidence has shown that vaccination alone is not sufficient to control the virus. With emerging variant of concerns which spread more rapidly with higher transmissibility[62] and disproportionate COVID-19 vaccination uptake and acceptance, effective PHIs are still essential to curtail the spread of the infection.

This systematic review has notable limitations. First, the studies included in the review were widely different in terms of study design, setting, perspective, time horizon, population, WTP thresholds, and type of interventions. Therefore, direct comparison of the findings would be limited. The fact that majority of included EEs are from the US and upper-middle, and high-income countries with only 6 studies from LMICs (India, Ghana, Morocco, and 139 LMICs) may impede transferability of findings especially in low-resource settings. However, most studies were of good quality which could be attributable to our stringent criteria in explicitly including only full EE focusing on PHIs. None of the included studies accounted for the impacts from long COVID-19 and irreversible medical conditions. The costs of lockdown including disruption in education, maternal and child health programs, increased domestic violence, and the benefits including the environment rebound and decreased road traffic accidents/injuries were not captured in the analyses. Therefore, the estimations might have been underestimated. In addition, the results are largely based on estimations from the first wave of the COVID-19 pandemic which may not reflect the current pandemic situation concerning evolving variants of concerns, and the immunity developed against the virus through past infection and vaccination, wanning of vaccine efficacy and the extent of booster vaccines administration and protection[63]. With the constantly growing COVID-19 literature, an updated review could be carried out to capture new evidence. Finally, most included studies assumed a homogenous population and employed static models which can lead to overestimation of SARS-COV2 prevalence[36, 38]. Therefore, future EEs considering on these limitations from a societal perspective is warranted.

5. Conclusion

Tight and timely implementation of PHIs is essential to flatten the curve of the pandemic. The cost-effectiveness of epidemiological control measures depends on the stringency, enforcement, timing, and adherence to interventions. A combination of strategies focusing on specific targets is likely to be more cost-effective than non-selective widescale measures or a single strategy. The epidemiological characteristics of the virus, the health system capacity, and local contexts should be considered in adopting PHIs. More EEs particularly in LMICs to address existing evidence gaps should be mandated.

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