Title: Economic evaluation of pharmacy services: A systematic review of the literature (2016-2020)

Abstract:

Background: Economic evaluation is a crucial tool for healthcare decision makers to select effective interventions. An updated systematic review of the economic evaluation of pharmacy services is essential for proficient management.

Aim: To conduct a systematic review of literature on economic evaluation of pharmacy services. This is done in global settings.

Method: A literature (2016-2020) was searched through PubMed, Web of Sciences, Scopus, ScienceDirect, and SpringerLink. An additional search was conducted in five health economic-related journals. The studies performed economic analysis which described pharmacy service and settings were considered. The reviewing checklist for economic evaluation was used for quality assessment. Incremental cost effectiveness ratio and willingness-to-pay threshold were the main measures for cost-effective analysis (CEA) and cost-utility analysis (CUA), while cost-saving, cost-benefit-ratio (CBR), and net-benefit were for cost-minimization analysis (CMA) and cost-benefit analysis (CBA).

Results: Forty-three articles were reviewed. The USA (n=6), the UK (n=6), Canada (n=6), and the Netherlands (n=6) were the major practice settings. Twelve studies had good quality according to the reviewing checklist. Cost utility analysis (CUA) was used most frequently (n=15), followed by CBA (n=12). There were some inconsistent findings (n=14) among the included studies, most agreed (n=29) that pharmacy services contributed economic impacts to all levels of health service: hospital-based (n=13), community pharmacy (n=13), and primary care (n=3). The key findings were similar among both developed (n=32) and developing countries (n=11).

Conclusion: The increased use of economic evaluation of pharmacy services confirms that pharmacy services are worth improving patients' health outcomes in all settings. These methods should be incorporated in developing the future innovative pharmacy service.

Keywords: economic evaluation, pharmacy service, systematic review, hospital, community pharmacy, primary care

Impact of findings on practice statements

- Pharmacy services contribute clinical benefits, save costs, and are cost-effective. They are thus be acknowledged as a part of healthcare services.
- An increased trend of economic evaluation for pharmacy service underlines its importance for policy making decision, thus should be incorporated in developing the future innovative pharmacy services globally.
- Economic evaluation of pharmacy services in other primary care settings is still limited. A further study is needed to confirm the benefit in such area.

Introduction

Economic evaluation of healthcare is a comparison of alternative options in terms of costs and consequences [1]. This assessment has become increasingly used by policymakers as it helps to decide which intervention or technology should be included in health benefit schemes. Alternative options refer to a range of new ways to increase population health outcomes [2]. Four economic evaluation methods that are currently used include cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), and cost-utility analysis (CUA). Each method is used for a different purpose. The CMA is appropriate when the equivalence of healthcare alternatives has already been proven. The CBA uses a welfarist approach which concern about the individual judgement on how a particular consequence affects his or her wellbeing [3]. The outcome of CBA has to be transformed into monetary units. CEA is frequently considered when comparing effectiveness using the clinical outcomes of interventions. Cost utility analaysis (CUA) is commonly used for policy decision making and considers health-related quality of life (Quality-adjusted life-year; QALY) as part of its measure of effectiveness [4].

A systematic review of the literature on the economic evaluation of pharmacy services between 2010 and 2015 found that the pharmacy services tend to be cost- effective in improving medication-related outcomes and quality of life [5]. After 2015, two similar systematic reviews were published that only focused on community pharmacy. One reported benefit of the community pharmacist in improving clinical outcomes of patients with chronic diseases [6]. However, these findings contradict the European-based review indicating insufficient evidence to prove the cost-effectiveness for community settings [7].

This study explores global literature on economic evaluation for pharmacy services as well as their economic impacts. This is to provide a wider perspective by covering pharmacy

service in all settings and to update findings from a previous systematic review on the topic [5].

Aim

To conduct a systematic review of literature on economic evaluation of pharmacy services. This is done in global settings.

Method

A standard approach for conducting systematic reviews, PRISMA, was employed [8].

A literature search was performed through PubMed, Web of Sciences, Scopus, ScienceDirect, and Springerlink. Five health economic-related journals were searched: Health Policy, Expert Review of Pharmacoeconomics and Outcomes Research, Journal of Health Economics, Pharmacoeconomics, and The European Journal of Health Economics. Moreover, PlosOne, PlosMedicine, and Nature were searched. For the economic journals, the only keyword used was "pharmacy service". A manual search of the references for the included articles was also performed. The search was limited to English language. The search was limited from January 1, 2016, to December 31, 2020. The following search terms were used: "health economics" and "evaluation" "assessment" or "appraisal," "methods," "hospital" or "community" or "residential care," "pharmacy" or "pharmacy services" and "cost-minimization analysis" or "cost-utility analysis" or "cost-effectiveness analysis" or "cost-benefit analysis" (Supplementary material 1). The systematic review web application (rayyan.qcri.org) was used to screen and select the recruited articles [9]. This review obtained the PROSPERO registration number CRD42021266620 prior to conducting the study.

Selection of studies

Identified studies were selected based on the following inclusion and exclusion criteria. *Inclusion criteria*: (1) economic analysis undertaken using a modelling approach or

along with experimental studies such as randomized controlled trials, non-randomized controlled trials, cross-sectional studies, and retrospective studies. (2) Studies must describe the details of pharmacy services, and the setting of services must be specified. *Exclusion criteria*: Review articles, case reports, news reports, editorials, commentaries, and opinions were excluded. The PICO elements that framed selection criteria is listed in Table 1.

Article selection and data extraction

Two authors independently reviewed the titles and abstracts according the inclusion criteria. Conflicts were resolved by a senior author. The full texts of the selected articles were reviewed by two researchers. Eligible articles were then evaluated and extracted using tabulating the following items: authorship, year of publication, location/region of study, economic evaluation method, study design, study perspective, time horizon, discounting, clinical outcomes and economic outcomes. A third opinion was sought if disagreements arose between the two researchers.

Study quality assessment

The quality assessment of individual studies was performed using a tool - 'Reviewing economic evaluations: a checklist', which contains fifteen review questions with thorough descriptions for assessment [10]. All studies were first evaluated by KS, then a random sample of 9 manuscripts (~20%) was re-evaluated by PS to confirm and validate [11]. We used 80% of the total items [12] ('yes' given to at least 12 items) to primarily indicate 'good quality' for individual studies.

Analysis of included studies

The results from the base-case analysis were primarily drawn and considered to indicate the value for money. The measure used for CEA and CUA was the incremental cost-effectiveness ratio (ICER). Pharmacy interventions which demonstrated 'lower cost better effects' for economic outcomes were considered cost-effective. Conversely, the intervention

was not cost-effective if demonstrated the lower effects. The willingness-to-pay (WTP) threshold was used to indicate cost-effective intervention for CEA and CUA results that fell within the costlier and more effective range; thus, the WTP threshold value must be specified. Intervention was deemed cost-effective when the ICER was below the threshold. The study was indicated as CEA, however QALY was an outcome hence this study should be classed as CUA analysis. The measures used for CMA and CBA were cost-saving, cost-benefit ratio (CBR), and net-benefit. The results were interpreted as cost-saving or cost-beneficial whichever appropriate. If the above information was not specified, the interpretation was deemed unclear. The included studies were grouped by a set of pharmacy services and setting for delivery to summarize their economic impacts. The findings are described by a narrative synthesis approach.

Results

Characteristics of included studies

The search identified 2,261 potential articles. Two hundred and seventy-eight (278) articles were excluded as they were duplicate articles. All titles and abstracts were screened, and a further 1,837 articles were excluded for the following reasons: (1) an incorrect design or outcomes used (n=970), not pharmacy-related (n=674), had a wrong publication type (n=120), were background articles (n=71), and the publication date was not during 2016-2020 (n=2). Finally, 146 articles were screened. Ultimately, 43 full-text articles were included in the study (Figure 1).

The number of publications by year was plotted to show the growth of economic evaluation studies. The number of published studies was between eight–ten annually between 2016-2020 (Figure 2). Based on the review of 43 publications, the economic evaluation of pharmacy services was predominantly based in the US (n=6) [13–18], the UK (n=6) [19–24], Canada (n=6) [25–30], and the Netherlands (n=6) [31–36]. Pharmacy services in the studies

were delivered via three settings: hospital (n=20, Table 2) [13,15,39–48,16,23,24,31,33,34,37,38], community pharmacy (n=20, Table 3) [17,18,29,30,32,35,36,49–53,19–22,25–28], and primary care (n=3, Table 4) [14,54,55]. Various perspectives were focused, the healthcare provider's or hospital's perspective was mostly taken (n=22) [13,15,34,38,41–44,48,50,52,54,16,55,17,18,20,23,26,28,29] while four studies did not specify this [31,37,46,47]. The time horizon varied from the shortest of 24 hours after discharge [31] to the longest being lifetime [14,21,22,28,30,43,53] or reached 100 years [19]. Thirteen studies applied discounting to the analysis: both costs and outcomes (n=9) [14,16,21,22,25,28,30,53,55], and only cost (n=4) [18,19,26,40] with the discounting value ranging from 1 to 5%. The national consumer price index was used in five studies [26,32,48,52,54], whereas one study used price discounts and inflation rates [38].

Quality of included studies

Twelve studies adhere well to the reviewing checklist [10], they followed to at least 12 assessment questions [14,16,53,55,19,21,22,26,28,30,32,40]. Time horizon was stated vaguely in seven studies [17,20,27,33,37,47,48], but one did not specify this. Only four studies accounted for equity consideration by undertaken subgroup analysis [21,28,32,53]. Four studies did not apply discounting to their analysis though the time horizon were longer than one year [24,39,43,54]. Seven studies lacked performing the sensitivity analysis [17,18,35,37,38,41,45]. (Supplementary material 2)

Methods used for economic evaluation of pharmacy services

Cost Utility Analysis (CUA)

Cost Utility Analysis (CUA) was used in fifteen studies to evaluate the cost-utility of a range of pharmacy services: pharmaceutical care [14,24,40,45,46], health screening or diagnostic testing [19,30,53], medicines use review [52], medication therapy management [16,28], new medicine service [21,22], prescribing [25], and minor ailments [49]. All these

studies presented QALY as the main outcomes. Model-based analysis was conducted to predict cost-effectiveness for a longer time horizon [14,16,19,21,25,30,40,53], while a trial-based was often used when it taken less than one year [24,45,46,49,52].

Cost Effectiveness Analysis (CEA)

Cost Effectiveness Analysis (CEA) was used in nine studies to evaluate cost-effectiveness of pharmaceutical care [17,54,55], health screening or diagnostic screening [26], medication use review [36,42], medication therapy management [13], prescribing [43], and smoking cessation [20]. Six studies performed economic evaluation alongside randomised trial [13,17,36,42], quasi-experimental [54], or retrospective observation [20]. Modelling was used in only three studies [26,43,55] Outcomes were mainly the number of patients achieved the clinical goal: for example, patient's blood pressure controlled in the year [54], a person achieved good refill adherence [17], and others. Six studies observed the economic outcomes for at least one year [13,36,55] or up to lifetime [43].

Cost Utility Analysis (CUA) and Cost Effectivesy Analysis (CEA) Studies

Five studies performed both CEA and CUA. These studies include cost-effectiveness and cost-utility of pharmaceutical care [32], medication management therapy [18,35], and prescribing in community pharmacy. Only one study evaluated hospital-based pharmaceutical care [33]. Four studies collected cost and outcomes alongside the randomised trial [32,33] and quasi-experiment [18,35], while one study utilised a model-based [29]. Three studies reported an incremental analysis properly, stating incremental cost per one unit of achieving clinical outcomes and per one QALY gained [18,32,33].

Cost Benefit Analysis (CBA)

Twelves studies used CBA. These studies evaluated cost-benefit of pharmaceutical care [37,39,41,47], health screening or diagnostic testing [50], medicine use review [44,51], medication reconciliation [15,23,31], antibiotic stewardship [38], and home medicine use

review [48]. CBA was frequently used for evaluating hospital-based pharmacy services [15,23,31,37–39,41,44,47,48], only two were based in community pharmacy [50,51]. Five studies observed outcomes retrospectively, the rest collected data alongside the randomised trial [48,51], quasi-experiment [31,38], cross-sectional study [50], and prospective cohort [39], whereas one done through the modelling [15]. All studies reported clinical and economic outcomes with appropriate CBA measures: NB or CBR. Nevertheless, none of these studies focused on patients nor societal perspective.

Cost Minimisation Analysis (CMA)

The use of CMA was found in two studies: one hospital-based parenteral injection preparation [34] and one strep-throat testing in community pharmacy [27]. Both studies used a model approach for analysis, conducting from payer [27] and provider perspective [34]. Neither of them provided evidence of effectiveness equivalence between the comparators and alternatives.

Economic impacts of pharmacy services

It is clear that pharmacy services contributed economic impacts to all levels of health service. The studies based in developed countries (n=32) mainly evaluated hospital-based and community pharmacy services. The rest from developing countries (n=11) predominantly examined hospital-based and primary care pharmacy services.

Hospital-based pharmacy services

Hospital-based pharmaceutical care provided was the major service [24,37,39,40,46,47], followed by medication reconciliation [15,23,31] – most of these services contributed a good value of money. Among 20 hospital-based studies, 13 demonstrated that hospital-based pharmacy services were cost-effective and resulted in cost-saving. Pharmaceutical care provided to outpatients in the UK [24] and to patients using

warfarin in Taiwan [40] was cost-effective, reporting the incremental cost per QALY being under the national WTP threshold.

Pharmaceutical care in Taiwan [41], South Korea [47], and China [37] also reported a net-benefit when delivered to patients with haematologic diseases, having liver transplant, and at outpatients clinics. Medicine use review provided for chemotherapy prescription in South Korea were also found beneficial [44]. Medication management provided for elderly with acute coronary syndrome [16] was cost-effective. Medication reconciliation delivered to cardiovascular disease [15], intensive care [31] and internal medicine [23] was a cost-saving alternative compared to the usual care. Antibiotic stewardship [38], home medicine use review [48], and injection preparation [34] were also cost-saving. Nonetheless, several studies reported contradicted results (Table 2).

Community pharmacy service

Health screening or providing diagnostic testing was the service frequently explored in economic evaluation [19,26,27,30,50,53], followed by medicine use review [36,51,52] and medication therapy management [18,28,35]. Community pharmacist delivered screening for diabetes in Japan [53] and testing for hepatitis C virus in the UK [19], both were found to be cost-effective.

A rapid diagnostic test performed by community pharmacist to identify malaria and strep throat also contributed a net-benefit in Nigeria [50] and Canada [27]. Medicine use review for Italian asthmatic patients [52] and Spanish polypharmacy [51] was cost-effective and costs were saved as a result of it. Medication management therapy in the US for HIV [18] and in Canada for cardiovascular disease [28] were found cost-effective. The UK-based studies examined the new medication service for chronic disease and minor ailments, and they were also found to be cost-effective [21,22]. Canadian pharmacy prescribing [25], Australian

minor ailment service [49], and UK smoking cessation [20] were also found to be cost-effective. However, few other studies showed inconsistent findings. (Table 3)

Primary care pharmacy service

One study was performed using CUA [14] and the two employed CEA [54,55] for pharmacy services in primary care. Several studies reported that pharmaceutical care was cost-effective for chronic diseases. This was observed in Jordan [55] in the US [14] and in Brazil [54]. (Table 4)

Discussion

This systematic review demonstrated that the number of published studies on the economic evaluation of pharmacy services noticeably increased between 2010 and 2020, compared to previous years [5]. Although some studies reported varied findings (14 out of 43 studies), most included studies in this review (29 out of 43) agreed that pharmacy services would result in improving health outcomes and they are "value for money". The results in this review are consistent with those of previous reviews of pharmacy interventions. [56–58]

Uaviseswong *et al*. reported that pharmacist interventions provided economic benefits and saved the cost of preventable adverse drug events [56]. This was due to a reduction in medication errors. Antimicrobial management, chronic disease management, and multidimensional clinical pharmaceutical services in China were associated with cost-saving and improved patient outcomes [57]. US-based clinical pharmacy services including pharmacotherapy, disease management, ambulatory care, and community pharmacy settings, have been shown to be more effective at a lower cost [58].

Evidence is also well established that optimal hospital pharmacy is cost-saving and community pharmacy services are cost-effective. Hospital pharmacy services are often

related to providing as pharmaceutical care [24,37,40,41,47] and medication reconciliation [15,23,31]. This is also evident form a Jordanian home medication use review. This has shown that the review provided by hospital pharmacist could result in cost-saving [48]. This also indicates the possibility of hospital pharmacist's involvement in primary care.

Community pharmacies are involved in improving medication use such as medicine use review [51,52], medication therapy management [18,28], and new medication service [21,22]. They also screen for issues such as health-related risks of chronic [53] and infectious diseases [19,27,50]. These findings reiterate that pharmacy service is increasingly acknowledged as an important part of health service system.

In many countries, such as the UK [59], Canada [60], Europe and others [61], some pharmacy services are part of the national health benefit package, which means they are remunerated by the public payer [62]. Although the number of studies from the developed countries were about three-times higher than that from the developing ones, they have similar findings showing cost-effectiveness or cost-saving of pharmacy services across the board.

Regarding the use of economic evaluation method, Costa *et al*. reported that CEA is the most common type of economic analysis used, followed by CUA [62]. However, in community pharmacy setting, CUA is the most common used approach. This approach typically uses QALY as an outcome, making the cost-effectiveness results comparable to other interventions for any disease.

Cost benefit analysis is often used to evaluate hospital-based pharmacy service using the monetary outcomes e.g. cost avoidance of adverse events [47], cost of inappropriate prescription [37]. Several tools/checklists are available for assessing quality of economic evaluation for example the Drummond checklist, the BMJ checklist (15.8%), CHEERS statement [12]. We used the one proposed by the Centre for Epidemiology and Evidence, Australia because of its thorough definition for assessment [10]. Nonetheless, the items

contained in those tools/checklists are very similar. Only about one-third (12 out of 43) of the included studies were found to be of good quality studies.

The previous reviews have also shown that challenges emerged for evaluating pharmacy services due to methodological complexities [62,63]. All studies in this review addressed well to three criteria, namely: (1) a well-defined objective; (2) the target group clearly stated; (3) the relevant costs and outcomes were identified. Transferability was found to be difficult to judge since the pharmacy intervention is specific to each country and the resource inputs vary from one setting to another.

Strengths and weaknesses

This review synthesize global literature regarding the use of economic evaluation methods and covers pharmacy service in broader settings, distinguishes from the previous ones which focused on one particular aspect: cost-effectiveness of pharmacy service in community setting [7] and clinical pharmacy service. [57] While other two reviews focused on economic evaluation methodologies [62,63].

This review has the strength that it gathered a large number of economic evaluation studies. The review does not include unpublished studies. As various databases and specific journals were searched, however few other databases were not part of the search (e.g. NHS EED, CRD, EBSCO). This may lead to missing few articles.

Interpretation and future research

There is an increasing trend to use economic evaluation for pharmacy services globally, this underlines its importance for policy making decision. This also implies that it should be incorporated in developing the future innovative pharmacy service models. However, performing economic evaluation is challenging due to its methodological complexities and training and lack of workforce in this area. Additionally, performing economic evaluation is specific to context of each country. Although similar intervention is

used, the evaluation results may differ between countries. Therefore, researchers must appraise quality in individual studies.

Conclusion

The increased use of economic evaluation of pharmacy services confirms that pharmacy services can improve patients' health outcomes in all settings: hospitals, community pharmacies, and primary care. Cost utility analysis and cost benefit analysis were found to be the common approaches used to assess pharmacy services. Economic evaluation underlines its importance for policy-making decisions and thus should be incorporated in developing the future innovative pharmacy services.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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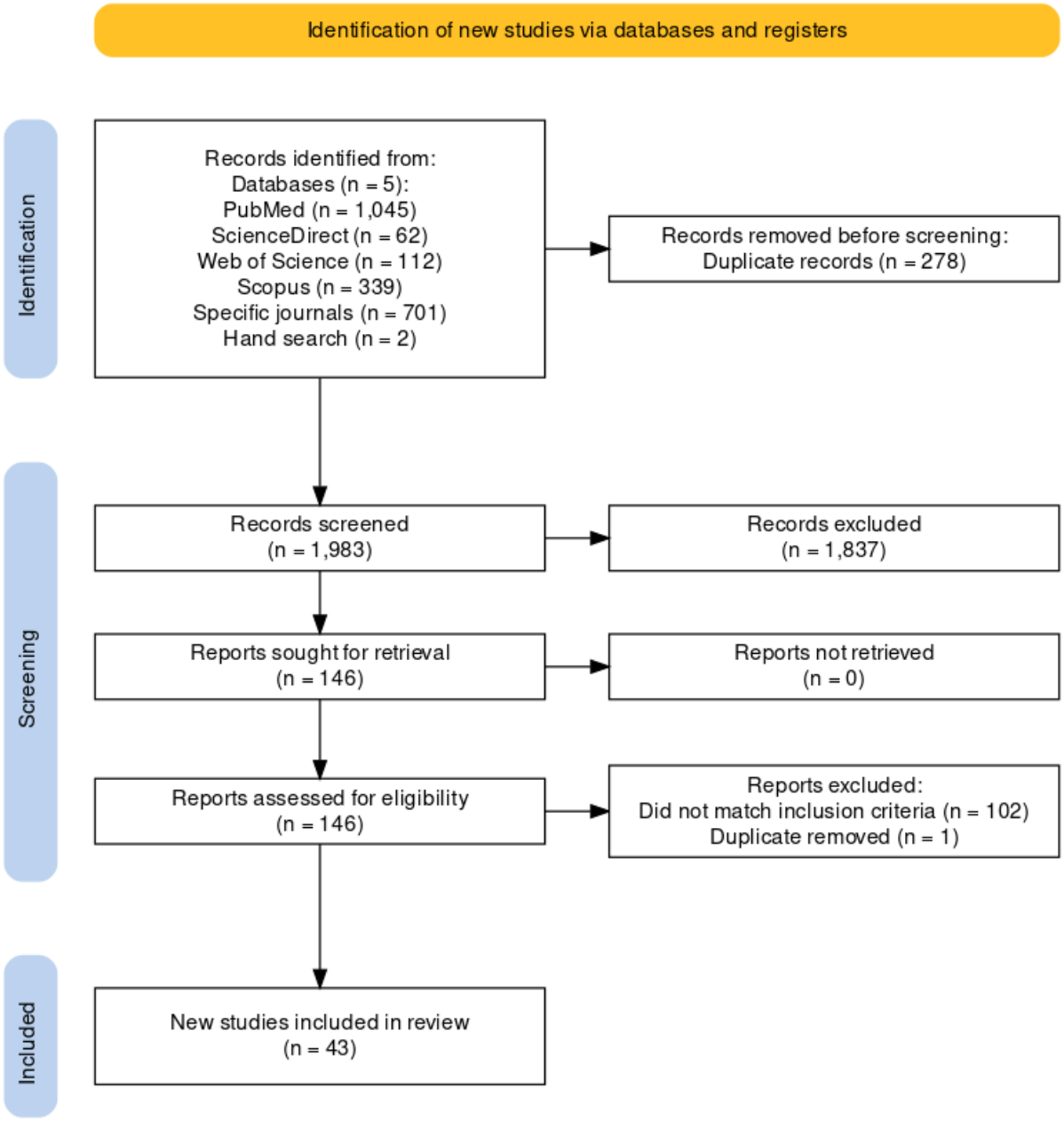

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509 **Figure 1.** A PRISMA flow diagram describing the process of studies selection.[64] Reasons

510 to exclude 1,837 records were: wrong designs or outcomes (n = 970); not pharmacy-related

511 (n = 674); wrong publication types (n=120); background articles (n = 71); published

512 before/after 2016 -2020 (n = 2).

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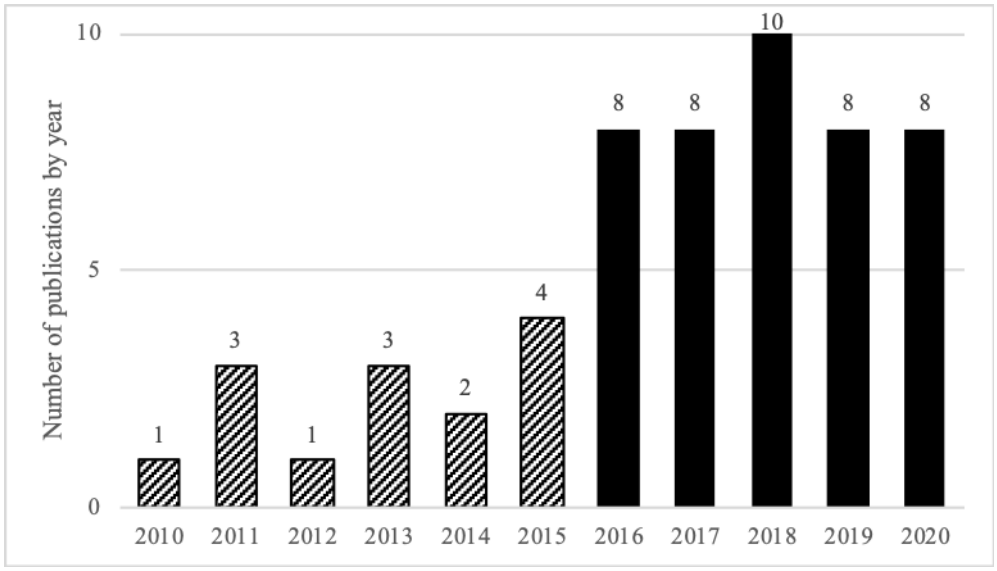

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516 **Figure 2** Number of publications by year (Note: Data of year 2010-2015 drawn from the

517 previous work by Gammie et al, 2017)

518

519 **Table 1** The PICOS elements for study selection

Participants (P)	-
Intervention (I)	Pharmacy service: any pharmacy service delivered by pharmacist via any pharmacy setting: hospital, community pharmacy, primary care
Comparator (C)	Usual care, no intervention, or other pharmacy service
Outcome (O)	Clinical outcomes and economic outcomes
Study design (S)	Economic evaluation: cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), and cost-utility analysis (CUA).

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Table 2 Characteristic of studies performed economic evaluation of hospital-based pharmacy service (n=20)

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
36 Dehmer et al. 2018 [13] US	CEA Healthcare	I: Medication therapy management (MTM) by pharmacist telemonitoring of blood pressure H: Hypertension	12 months	n/a	n/a	MTM by pharmacist costed US$7,337 per person achieving hypertension control and US$139 or US$265 per mmHg reduction in systolic or diastolic blood pressure, respectively. WTP threshold: n/a	Unclear
37 Najafzadeh et al. 2016 [15] US	CBA Hospital	I: Pharmacist-led medication reconcile H: Cardiovascular disease	30 days	n/a	Pharmacist-led medication reconciliation at hospital discharge could reduce medication errors by 52%. The number of rehospitalizations and emergency department visits related to preventable adverse drug events were reduced to 199 and 215.	At hospital discharge, pharmacist-led medication reconciliation had a significant net-benefit of US$206 (95% CI US$73 to US$373) per patient.	Cost-saving
4 Okere et al. 2018 [16] US	CUA Healthcare	I: (1) Dual antiplatelet therapy (DAPT) + point-of-care phenotypic and genetic testing (POCP);	21 years	3.5% both costs and outcomes	n/a	Relative to MTM - clopidogrel, MTM-POCP and MTM-ticagrelor had an ICER of US$14,140.80 and US$41,345.99, respectively, per QALY.	Cost-effective

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
		(2) DAPT + Medication therapy management (MTM) with POCP (MTM-POCP); (3) MTM-clopidogrel; (4) MTM-ticagrelor H: Acute coronary syndrome and elderly				WTP threshold: US$50,000 per QALY	
38 Onatade and Quaye 2018 [23] UK	CBA Healthcare	I: Pharmacy-led medication reconciliation (run by pharmacist and pharmacy technician) H: Internal medicine	n/a	n/a	There were 118 preventable adverse drug events averted as a result of medication reconcile over the 12 half-hospital days (6 full days); 98% (116/118) of the averted events were rated for clinical significance.	Conducting 6 days of all medication reconciliations had a net-benefit of £29,604 – £68,718: £34 – £80 per one medication reconcile. The benefit-cost ratio was 5.53:1 – 11.51:1.	Cost-saving
61 Twigg et al. 2019 [24] UK	CUA NHS	I: Pharmacy care plan service - medication review using relevant guidance and clinical	12 months	n/a	Pharmacist intervention improved medication adherence (mean difference 0.26; 95% CI 0.14-0.4), systolic blood pressure (mean	ICER for pharmacy care plan service was £8,495. WTP threshold: £20,000 per QALY	Cost-effective

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
		tools to provide personalized care plans H: Outpatient			difference BP -2.90 mmHg; 95%CI -4.7 to -1), diastolic blood pressure (mean difference -1.81 mmHg; 95%CI -2.8 to -0.8), patient activation score (mean difference 5.39; 95% CI 3.9-6.9), and EQ-5D-5L score (mean difference 0.029; 95% CI 0.015–0.044)		
59 Bosma et al. 2018 [31] Netherlands	CBA n/a	I: Medication reconcile by pharmacist H: Intensive care	24 hours	n/a	The proportion of patients with at least 1 medication transfer errors (MTEs) at ICU admission was reduced from 45.1 to 14.6% (OR_{adj} 0.18, 95%CI 0.11-0.30) and after discharge from 73.9% to 41.2% in the post-intervention phase (OR_{adj} 0.24, 95%CI 0.15-0.37). The proportion of patients with a preventable adverse drug reaction at ICU admission was reduced from	Medication reconciliation showed a cost-benefit ratio of 2.48, a net cost-benefit was €103 per patient.	Cost-saving

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
					34.8 to 8.0% (OR_{adj} 0.13, 95%CI 0.07-0.24).		
24 Karapinar-Çarkit et al. 2017 [33] Netherlands	CEA/CUA Societal	I: Continuity of Appropriate pharmacotherapy, patient Counselling and information transfer in Healthcare (COACH) H: Internal medicine	n/a	n/a	There was no significant difference in the proportion of patients with unplanned rehospitalizations (21.4% COACH vs. 20.5% usual care). Mean difference of QALY between pharmacist intervention and usual care was -0.0085 (95% CI -0.0170 to 0.0001).	For unplanned rehospitalization and drug-related rehospitalization, ICER were -€627,251 and -€128,804 respectively. This indicates COACH had lower cost but higher undesired outcomes. For CUA, ICER was €137,059 per QALY gained in the control group in comparison with the intervention group. WTP threshold: €50,000 per QALY	Not cost-effective
3 Larmené-Beld et al. 2019 [34] Netherland	CMA Provider	I: Ready to administer prefilled sterilized syringe (PFSS) produced by pharmacy H: n/a	1 year	n/a	n/a	Conventional preparation method by nurses yielded an annual total cost of €14.0 million, while PFSSs yielded €4.1 million. PFSSs saved €9.9 million compared to the conventional method.	Cost-saving
113 Bao et al. 2018 [37] China	CBA n/a	I: Pharmacists intervened in inappropriate prescriptions (IPs) real-	n/a	n/a	Pharmacist interventions decreased the percentage of inappropriate prescriptions year by year,	The benefit of pharmacist intervention, which expressed as total cost of all inappropriate issues, decreased from	Cost-saving

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
		time, and summarized and analyzed the information monthly. H: Outpatients			decreased from 1845 (year 2011) to 238 (year 2016).	US$43,500.30 to US$8,978.16. The benefit was higher than the cost, and the benefit-to-cost ratio was greater than 1.	
48 Borde et al. 2016 [38] Germany	CBA Provider	I: Antibiotic stewardship H: Hip, knee and shoulder	1 month	n/a	Overall use of anti-infective substance in the post-intervention period was reduced from 334.9 to 221.4 recommended daily doses/1000 patient days. The drug use density of daptomycin dropped by 75%.	A monthly cost savings due to changes in antimicrobial prescribing were estimated at €4,563 ($p<0.001$) because of a decrease in daptomycin consumption.	Cost-saving
17 Maurilio de Souza Cazarim et al. 2020 [39] Brazil	CBA Provider and healthcare	I: Pharmacotherapeutic follow-up and identification of drug related problems for inpatients H: Neurological diseases	36 months	n/a	Of all pharmacist interventions, the percentage of acceptance by the health team was 70%. Of the 506 interventions, medication introduction was the frequently provided (29%).	Pharmacist intervention contributed no monetary benefit from hospital perspective: benefit-cost-ratio equated to zero and net-benefit was negative. However, benefit-cost-ratio was 3.0 with net-benefit of US$51,049 from the public health system viewpoint.	Not cost-benefit
27 Chang et	CUA	I: Pharmacist-assisted	20 years	3% for cost	n/a	ICER for PAWM was NT$410,749 per	Cost-

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
al. 2017 [40] Taiwan	Payer	warfarin monitoring (PAWM) H: Warfarin therapy				QALY gained. WTP threshold: Taiwanese GDP per capita in 2012 (NT$631,142). (NT = New Taiwanese dollars)	effective
112 Chen et al. 2020 [41] Taiwan	CBA Healthcare	I: Revisions in medication orders and active recommendations (orders: order modification, monitoring of drug therapy, key-in error, and violation of regulations) H: Hematology	12 months	n/a	After clinical pharmacist involvement, the intercepted preventable adverse drug events increased from 58 to 230. Average length of hospitalization reduced from 19.27 to 16.69 days.	Intervention had cost savings (NT$37,080 and NT$252,280), cost avoidance (NT$582,100 and NT$2,304,600), and benefit–cost ratio (0.77 and 3.19) increased after clinical pharmacist deployment. (NT = New Taiwanese dollars)	Cost-saving
56 Gallagher et al. 2016 [42] Ireland	CEA Provider	I: Structured Pharmacist Review of Medication Clinical Decision Support Software (SPRM/CDSS) Intervention H: Elderly	3 months	n/a	The effectiveness measures favored the intervention strategy. The odds ratio for experiencing an adverse drug reaction was 0.655 (95% CI 0.431 to 0.994); p=0.047) when comparing pharmacist intervention with usual care.	The intervention was linked with an €807 reduction in mean health costs and a -0.064 reduction in the mean number of adverse drug reaction occurrences per patient as compared to usual care. WTP threshold: only hypothetical threshold is indicated.	Unclear

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
19 Hale et al. 2018 [43] Australia	CEA Healthcare	I: Doctor-pharmacist Collaborative prescribing H: Venous thromboembolism	Lifetime	n/a	n/a	Pharmacist prescribing was non-significantly less costly than doctor prescribing by AU$31 (95% CI: -AU$97, AU$160) per patient compared with usual care and produced 0.02 (95% CI: -0.01, 0.05) QALYs per patient. ICER is not shown. (AU = Australian dollars) WTP threshold: AU$40,000 per QALY	Unclear
7 Han et al. 2016 [44] South Korea	CBA Provider	I: pharmacists reviewed chemotherapy prescriptions H: Chemotherapy preparation	1 year	n/a	Among the 631 pharmacist intervention cases, the acceptance rate was 72.1%. Of 455 cases which accepted pharmacist interventions, 362 cases (79%) were related to preventing adverse drug event.	The cost-benefit analysis of pharmacists review prescription showed a net cost-benefit of US$116,493 and a cost-benefit ratio of 3.64:1.	Cost-saving
25 Mateti et al. 2018 [45] India	CUA Patient	I: Pharmaceutical care - motivation and patient education about medication, diseases and	1 year	n/a	n/a	ICER of pharmaceutical care compared with usual care was 86,230 Indian Rupee (INR) per QALY. WTP threshold: n/a	Unclear

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
		life-style modification for CKD/ESRD patients H: Hemodialysis					
14 Tanaka et al. 2019 [46] Japan	CUA n/a	I: Pharmacist counseling for breast cancer outpatients H. Breast cancer	6 months and 1 year	n/a	The EQ-5D score across the timepoints were 0.831, 0.757, and 0.791 for the control group, and 0.882, 0.883, and 0.921 for the pharmacist counseling group.	ICER of the pharmacist counseling group over six months was performed for three points: before the second chemotherapy was 860,711 Yen per QALY, before the third course was 279,351 Yen per QALY, and the mean of before the second and third courses was 511,141 Yen per QALY. WTP threshold: n/a	Unclear
6 Ah et al. 2016 [47] South Korea	CBA n/a	I: Providing pre/post-transplant medication education, counseling and monitoring medication use in the outpatient clinic, reviewing inpatient pharmacotherapy, participating in medical	n/a	n/a	There were 489 interventions (26%) related to cost avoidance.	Pharmacist-led intervention had a net-cost benefit of €94,900 and cost-benefit ratio of 3.8.	Cost-saving

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
		round, coordinating the development drug protocol H: Liver transplant					
16 Al-Qudah et al. 2020 [48] Jordan	CBA Provider	I: Treatment-related problems and home medication management review (HMMR) H: Chronic disease	n/a	n/a	A number of treatment-related problems identified by pharmacist intervention was 158 times: diabetes (18.4%), hyperlipidemia (18.6%), hypertension (9.5%), asthma (9.5%), pre-diabetes (6.3%).	Monthly cost of pharmacist intervention was JD764, and the total monthly benefit was JD4,570. A benefit-to-cost ratio was 5.98. (JD = Jordanian dollars)	Cost-saving

Note: 95%CI: 95% Confidence interval, CBA: cost-benefit analysis, CEA: cost-effectiveness analysis, CMA: cost-minimization analysis, CUA: cost-utility analysis, ICER: Incremental cost effectiveness ratio, QALY: Quality adjusted life year, n/a: not applicable

Table 3 Characteristic of studies performed economic evaluation of community pharmacy service (n=20)

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
28 Shireman and Svarstad 2016 [17] US	CEA Provider	I: Pharmacists and pharmacy technicians using novel tools for improving adherence and feedback to hypertensive patients and physicians H: Hypertension	n/a	n/a	The 6-month blood pressure control was achieved in 53.8% and 36.7% in the intervention and control group respectively ($\chi2 = 14.19$, df = 1, $p<0.001$). Patients achieved good refill adherence was significantly higher for the intervention than that of the control (59.7% versus 36.1%; $\chi2 = 24.78$, df = 1, $p<0.001$).	The cost of helping one more person achieved the blood pressure goal (< 140/90 mmHg) was US$665.2 ± 265.2; the cost of helping one more person achieved good refill adherence was US $463.3 ± 110.7. WTP threshold: n/a	Unclear
30 Shrestha et al. 2020 [18] US	CEA/CUA Provider	I: Medication therapy management by pharmacist H: HIV	1 year	3% for cost	A total of 200 patients were virally suppressed post intervention, with the incremental number of patients virally suppressed of 45. The intervention averted 2.75 HIV transmissions and saved 12.22 QALY.	For CEA, medication therapy management by pharmacist had an incremental cost per patient virally suppressed for US$5039. For CUA, ICER of the intervention was -US$86,157 (less costly, greater QALY). WTP threshold: US$100,000 per QALY	Cost-effective

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
62 Buchanan et al. 2019 [19] England	CUA Patient	I: Dry blood spot (DBS) testing for hepatitis C virus in community pharmacies H: Hepatitis C	reached age of 100 years	3.5% for costs	Of 186 tests were conducted over 24 months, 13 were positive for hepatitis C virus RNA, 10 were current or former PWID. All were either genotype 1a (32%) or genotype 3a (68%).	ICER for the intervention was £3,689 per QALY gained. WTP threshold: £20,000 per QALY	Cost-effective
58 Csikar et al. 2016 [20] England	CEA provider and NHS	I: Smoking cessation H: Smoking	12 weeks	n/a	Percentage of quits by carbon monoxide verified for NHS stop smoking services, pharmacy, dental, are 31.66%, 36.36%, 33.33%.	From the NHS perspective, pharmacy-based smoking cessation was a dominant option with ICER of -£2.31 per quit compared to the NHS stop smoking services. WTP threshold: n/a Note: cost-effectiveness was compared to a conventional NHS service.	Cost-effective
13 Elliott et al. 2017 [21] UK	CUA NHS	I: New medicine service by pharmacist H: Antiplatelet/ anticoagulant drugs, asthma/ COPD,	Lifetime	3.5% both costs and outcomes	n/a	New medicine service dominated a normal practice with an ICER of -£3,166 per QALY. WTP threshold: £20,000 per QALY	Cost-effective

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
		Hypertension, type II diabetes					
49 Elliott et al. 2020 [22] UK	CUA NHS	I: New medicine service led by pharmacist H: Minor ailment condition	Lifetime	3.5% both costs and outcomes	57.1% and 65.6% patients were adherent in normal practice and new medicine service arms, respectively (OR_{adj}=1.50; 95% CI 0.93 to 2.44, p=0.095).	At 26-week follow-up, ICER for new medicine service led by pharmacist was −£2,847.5 per QALY compared to the normal practice. WTP threshold: £20,000 per QALY	Cost-effective
52 Al Hamarneh et al. 2019 [25] Canada	CUA Payer	I: Community pharmacist prescribing H: Cardiovascular disease	30 years	1.5% both costs and outcomes	Over 30 years, pharmacist care would prevent more than 8.9 million CV events compared to usually care if applied to only 15% of the eligible adults.	Community pharmacist prescribing would gain 0.19 QALY, experience 0.10 fewer cardiovascular events, and accrue Can$2,149 less in direct medical costs compared to not receiving intervention. This indicates that the intervention is dominant. WTP threshold: n/a	Cost-effective
34 Coronado et al. 2016 [26] Canada	CEA Healthcare	I: Pharmacy-based teleophthalmology program H: Diabetic retinopathy	5 years	5% for costs	Pharmacy-based tele-ophthalmology increased screening compliance from 51.1% to 56.2%. Intervention group correctly	The ICER of Pharmacy-based tele-ophthalmology was $314.10 per additional case detected and $73.24 per additional case correctly diagnosed. the	Unclear

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
					additional detected and diagnosed of 136 and 688 cases, compared with in-person examination only.	programs were nondominant; hence, the program was always costlier but was more effective than in-person examination alone. WTP threshold: n/a	
29 Lathia et al. 2018 [27] Canada	CMA Payer	I: Pharmacy offering strep throat (rapid antigen detection test; RADT) H: Strep throat	n/a	n/a	n/a	Mean cost per patient of treating severe sore throat at community pharmacy was lowest compared to other settings (range from Can$19.18 to Can$21.83 in five participated provinces).	Cost-saving
2 Tam-Tham et al. 2019 [28] Canada	CUA Healthcare	I: Medication therapy management review, laboratory assessment, individualized CV risk assessment and education, prescription H: Strep throat	Lifetime	1.5% both costs and outcomes	At 3 months, there was a statistically significant difference in the change in HbA1c between intervention and usual care groups (-0.92%, 95% CI -1.12% to -0.72%, P<0.001)	Intervention saved cost of Can$4,770 per patient over lifetime while gained 0.18 QALY (less costly, greater QALY). The intervention dominated usual care across all time horizons. WTP threshold: n/a	Cost-effective
21 Sanyal et al. 2019 [29]	CEA/CUA Healthcare	I: Pharmacists examined patients with symptoms of	1 month	n/a	n/a	Pharmacist-initiated management was lower cost (Can$78.70) and lower	Unclear

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
Canada		uncomplicated UTI and initiated antibiotic treatment (community pharmacist-initiated) H: Uncomplicated urinary tract infection				effects (0.75232 QALMs) when compared to family and emergency physician-initiated management. WTP threshold: n/a	
55 Tarride et al. 2017 [30] Canada	CUA Payer	I: Atrial fibrillation screening by pharmacist H: Atrial fibrillation	Lifetime	1.5% both costs and outcomes	n/a	The pharmacist intervention would result in higher expected costs (Can$26), more life-years (0.0032) and more QALYs (0.0035) over a lifelong time horizon, yielding an incremental cost per QALY gained of Can$7,480. WTP threshold: n/a	Unclear
57 Bosmans et al. 2019 [32] Netherland	CEA/CUA Societal	I: pharmacist-led Cardiovascular medication non-Adherence Tailored Intervention (CATI) H: Hypertension	3, 6 and 9 months	n/a	There were no statistically significant differences in any of the effect outcomes (self-reported adherence: Medication Adherence Report Scale; MARS, and Specific Beliefs about Medicines	There were no significant differences in costs or effects between the intervention program and usual care. WTP threshold: €20,000 per QALY	Not cost-effective

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
					Questionnaire; BMQ) between the group.		
22 Van Der Heijden et al. 2019 [36] Netherlands	CEA Societal	I: Clinical medication review by pharmacist H: Vulnerable older patients	1 year	n/a	After 12 months of follow-up, the intervention group had a statistically significant decreased in drug related problems (mean difference -0.2, 95% CI -0.4 to 0.0) compared to the control group.	Cost of the intervention group were €1,654 higher than in the control group but not statistically significant. The incremental cost of reducing one drug related problem by a clinical medication review amounted to €8,270. WTP threshold: n/a	Unclear
39 Van Boven et al. 2016 [35] Netherlands	CEA/CUA Payer and societal	I: Medication Monitoring and Optimization targeted COPD intervention (MeMO) H: COPD	1 year	n/a	Medication adherence and exacerbation between pre- and post-intervention were not different.	The cost differences between two groups were not significant, and not all health outcomes (such as the Clinical COPD Questionnaire; CCQ score and QALYs) were influenced by pharmacy intervention.	Unclear
15 Dineen-Griffin et al. 2020 [49] Australia	CUA Societal	I: Minor ailment service by pharmacist H: Minor ailments	14 days	n/a	n/a	ICER of pharmacist intervention was AU$2,277 per QALY. WTP threshold: AU$28,033 per QALY	Cost-effective

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
12 Ezennia, Nduka, and Ekwunife 2017 [50] Nigeria	CBA Provider	I: Rapid diagnostic test by pharmacist H: Malaria	n/a	n/a	82.2% of respondents (suspected cases of malaria) preferred rapid diagnostic test before malarial treatment.	The average willingness to pay for rapid diagnostic test was US$1.23. The benefit-cost ratio of the test-based malaria treatment was 6.7 (95% CI 6.4 to 7.0).	Cost-benefit
9 Malet-Larrea et al. 2017[51] Spain	CBA NHS	I: Medication review with follow up by pharmacist H: Aged polypharmacy	6 months	n/a	The number of uncontrolled health problems decreased in the intervention group was higher than 50% (p>0.001), similar to the control group. Emergency department visit or hospitalization decreased in the intervention group significantly.	Medication review with follow-up yielded the estimated savings of 273 € per patient-year. The cost-benefit ratio ranged from €3.3 to €6.2 for every €1 invested in the pharmacist intervention.	Cost-saving
1 Manfrin et al. 2017 [52] Italy	CUA Healthcare and societal	I: 9 months Italian medication use review H: Asthma	9 months	n/a	Intervention group provided an odds ratio for improved asthma control of 1.76 (95% CI 1.33 to 2.33) and number needed to treat of 10 (95% CI 6 to 28). Adherence improved by 35.4% at 3 months	Difference in yearly patient costs from healthcare perspective was -€122.63 in intervention group and -€113.29 in control group. Difference in QALY was 0.02 and 0.10 respectively. ICER value is not shown but the cost-effectiveness	Cost-effective

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
					post-intervention and 40.0% at 6 months (p<0.01).	plane is presented. WTP threshold: €30,000 per QALY	
23 Shono et al. 2018 [53] Japan	CUA Societal	I: Fingertip HbA1c testing by pharmacist H: Diabetes	Lifetime	3% both costs and outcomes	n/a	HbA1c testing at community pharmacies saved a total cost of $527 (JPY52,722) per individuals aged 40–74 years while 0.0203QALY gained . (less costly, greater QALY) compared with the usual care. (JPY = Japanese Yen) WTP threshold: US$50,000 (JPY 5,000,000)	Cost-effective

Note: 95%CI: 95% Confidence interval, CBA: cost-benefit analysis, CEA: cost-effectiveness analysis, CMA: cost-minimization analysis, CUA: cost-utility analysis, ICER: Incremental cost effectiveness ratio, QALY: Quality adjusted life year, n/a: not applicable

Table 4 Characteristic of studies performed economic evaluation of primary care pharmacy service (n=3)

Author Country	**Method Perspective**	**Intervention (I) Health issues (H)**	**Time-horizon**	**Discounting**	**Clinical outcome**	**Economic outcome**	**Interpretation**
32 Kulchaitanaroaj et al. 2017 [14] US	CUA Payer	I: Pharmacists collaborated intervention to physicians and provided counseling about medications and lifestyle therapy to patients H: Hypertension	5, 10 years and lifetime	3% both costs and outcomes	n/a	The ICER of the physician–pharmacist collaborative intervention was US$26,807.83 per QALY gained. In shorter horizons of 5 and 10 years, the ratios were US $78,547.07 and US $39,084.65, respectively. WTP threshold: US$50,000 per QALY	Cost-effective
20 Maurı´lio de Souza Cazarim and Pereira 2018 [39] Brazil	CEA Healthcare	I: Pharmacist conducted the consultations, which occurred monthly for hypertensive patients (follow-up, blood pressure measurement, review medications, education) H: Hypertension	2 years	n/a	The pre-pharmaceutical care (PC) year and post period years were more effective than conventional treatment.	The ICER equated to US$478.41 and US$42.95 per year in the pharmaceutical care and in the post period respectively. Even the highest ICER, the values were below the cost effectiveness threshold, which means that PC was a cost-effective strategy. WTP threshold: US$ 30,721.28 (3 times GDP per capita) per patient's blood pressure control in the year	Cost-effective

Author Country	Method Perspective	Intervention (I) Health issues (H)	Time-horizon	Discounting	Clinical outcome	Economic outcome	Interpretation
26 Mousa and Hammad 2021[55] Jordan	CEA Provider	I: Pharmaceutical care services and therapy optimization from a trained clinical pharmacist in preventing cardiovascular diseases in diabetes H: Asthma/chronic obstructive pulmonary disease, hypertension, type 2 diabetes, anticoagulant/antiplatelet agent	1 and 10 years	4.75% both costs and outcomes	n/a	The pharmacist-led care resulted in an incremental cost of JD1,238.78 (US$1,747.24) and with incremental life years gained of 0.29 as compared to the usual care group. WTP threshold: US$4,241.79 (JD3,008.36) (very cost-effective) to US$12,723 (JD9,023.23) (cost-effective) per one health benefit	Cost-effective

Note: 95%CI: 95% Confidence interval, CBA: cost-benefit analysis, CEA: cost-effectiveness analysis, CMA: cost-minimization analysis, CUA: cost-utility analysis, ICER: Incremental cost effectiveness ratio, QALY: Quality adjusted life year, n/a: not applicable