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Cost-Effectiveness of Health Systems Strengthening Interventions in Improving Maternal and Child Health in Low- and Middle-Income Countries: A Systematic Review

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ABSTRACT

Maternal and child health (MCH) remains a major health concern in low- and middle-income countries (LMICs). Despite impressive progress made during the millennium development goals era, low efficiency of health systems significantly delays the efforts in getting effective health interventions to populations in need. Recognizing the strong need to strengthen health systems in addressing MCH, health systems strengthening interventions have been increasingly implemented in LMICs in the last decade. This study reviews global literature on cost-effectiveness of health systems strengthening interventions in improving MCH.

A systematic review was carried out. Key words for searching articles were developed based on the WHO's framework on health systems and prior studies. Articles were searched from four bibliographic databases (PubMed, Econlit, Academic Search Premier, and Web of Science), one database for grey literature (Popline), as well as the web through Google Scholar. Additional efforts were taken to review references to identify more articles. Articles that estimate cost-effectiveness of health systems interventions in LMICs were included in the analysis. All selected studies were assessed in terms of quality and biases using the Cochrane's criteria. Review Manager and an Excel template were used to extract data and synthesize findings. Study characteristics and cost-effectiveness of interventions were reported.

24 publications were identified from 15 countries. Most studies were undertaken in Africa. Health systems strengthening interventions were primarily concentrated on service delivery, health financing and human resources, which included community mobilization, quality improvement, pay for performance, voucher schemes, and training to health providers. Among the 24 studies, 15 studies were rated as high quality, 5 as medium and 4 as low quality. A majority of studies reported cost per disability-adjusted life year (DALY) averted or cost per quality-adjusted life year (QALY) gained; other studies reported cost per life saved or life year gained. However, studies used mixed perspectives of analyses. Compared to gross domestic product per capita, interventions in studies reporting cost per DALY averted or QALY gained were all cost-effective, including performance based financing, health insurance, and quality improvement.

This review shows the diversity of health systems strengthening interventions in improving MCH, and their potential cost-effectiveness. However, the different perspectives employed in the studies, costing components included in the analyses, and heterogeneous measures of effectiveness and outputs, made it challenging to compare cost-effectiveness across all studies. For policy making, it is critical to examine long-term cost-effectiveness of programs and cost-effectiveness of synergistic demand and supply side interventions.

INTRODUCTION

Maternal and child health (MCH) remains a major health concern in low- and middle-income countries (LMIC). During the Millennium Development Goals (MDGs) era, strong international commitment was directed to MCH: MCH services expanded substantially to poor and venerable populations and equity of reproductive and maternal health services continuously improved[1]. Globally, the under 5 mortality rate (U5MR) was reduced from 90.6 in 1990 to 42.5 per 1,000 live births in 2000 (53% reduction)[2], and the maternal mortality rate (MMR) from 282 in 1990 to 196 per 100,000 live births in 2015 (30% reduction)[3]. These declines are impressive. However, only a few countries achieved all of MDGs health-related goals. For example, only ten countries achieved MDG 5 on reduction of maternal mortality rate[3]. To maintain the momentum of reducing maternal and child mortality rates, international communities developed the Sustainable Development Goals (SDGs) aimed to sustain health gains in combating MCH-related illnesses.

The reduction of MMR and U5MR significantly benefited from increased financial commitments from donors though official development aid (ODA). Since 2002, ODA has tripled from $54.8 billion in 2001 to $167 billion in 2013[4]. ODA funding for health during the same period increased more than five-times, rising from $4.4 billion to $22.8 billion[4]. A substantial amount of donor support was allocated to combating HIV/AIDS, malaria, and tuberculosis, as well as for providing MCH services. In spite of the increase in resources, there is a great need to continue investing in health programs to sustain health gains. In the last decades, the international community has increasingly realized that treatment expansion efforts have been slowed by insufficient health infrastructure and inefficient health systems. To accelerate the pace of delivering effective and available prevention and treatment to populations in need, donors are paying increasing attention to health systems strengthening (HSS), calling for interventions for building a more efficient and effective health system [5]. Taking projects funded by USAID as an example, there have been multiple global flagship projects on HSS awarded to implementation partners, including a, $209 million health governance and finance project (2012-2017)[6], for strengthening health finance and governance systems, a health policy plus (HP+) project of $185 million for generating evidence for policy making[7], and DELIVERY Project for enhancing supply chains. Similarly, The Global Fund has gradually switched its funding from disease-specific interventions to HSS. Thirty-seven percent ($362 million) of the Global Fund Round 8 funding was allocated for HSS [8]. HSS becomes a critical element to catalyze efforts to expand service coverage.

Along with improving MCH services, many HSS programs, with the support from donors and governments, have been designed. For example, performance based financing (PBF) programs provide financial incentives to health facilities for delivering MCH services. With support from the Health Results Innovation Trust Fund (HRITF), 35 PBF programs have been implemented in 29 countries since 2007, with a total of commitment of $385.6 million as of September 2016[9]. PBF aims to improve MCH through improving the management and financial situation of health facilities. Voucher programs incentivize pregnant women to seek essential maternal care, and have been implemented widely[10]. Initial impact evaluation shows positive impact of these programs in improving the use of MCH services[10,11]. However, there is little evidence concerning cost-effectiveness of these programs[12,13].

Many of such programs have been supported by donors initially, with the expectation that they will be transferred to governments as programs mature. This raises an important question as to whether the governments can afford to take on and sustain the programs. Each government has to operate programs within its budget, and when multiple programs are available, governments must wisely choose among them. Additionally, with substantial investment in HSS, both donors and governments call for value for money to maximize the impact of available resources[14]. A study in the United States showed that using cost-effectiveness information to allocate resources had the potential to improve a population's health status[15]. Thus, it is critical to include costs in assessing the range of available programs and in evaluating programs' impact, to understand better economy, efficiency, and effectiveness of programs[14].

Recognizing the critical role of health systems in improving MCH, this study aims to provide a systematic review of cost-effectiveness of HSS interventions in addressing MCH. The term cost-effectiveness in this review is used in a more generic way, and it includes any studies linking costs to the impact of programs, encapsulating cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). Through this review, we hope to provide a more complete picture of HSS interventions in order for countries to make informed decisions, to identify gaps in existing economic evaluations of HSS interventions.

METHODS

This review concentrated on the cost-effectiveness of HSS interventions. World Health Organization (WHO) developed a framework with six building blocks (Figure 1), providing a common understanding of what a health system is and what constitutes health systems strengthening[16]. Building on this framework, HSS interventions, in this review, are defined as activities aiming to improve the six building blocks of a health system (leadership/governance, health financing, human resources, medical products and technologies, health information, and service delivery). This definition is consistent with what Warren et al. used to analyze Global Fund funding for health system strengthening[8].

Figure 1. Six building blocks of a health system (Source: WHO, 2007.)
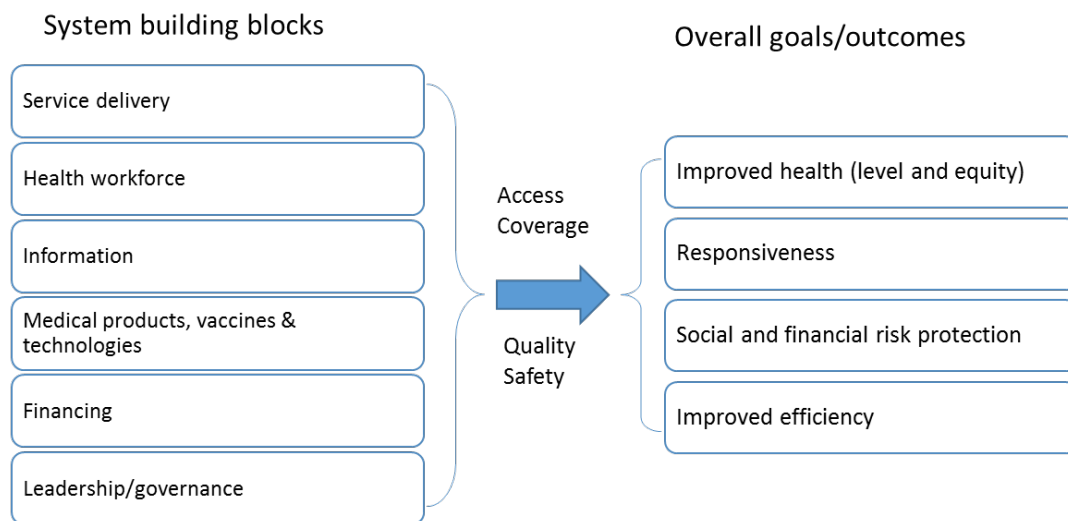
Service delivery, among the six building blocks, is slightly different from the other five blocks. Service delivery is regarded as an immediate goal of a health system, while the remaining building blocks serve as inputs for effective, safe, quality service provision. Given that service delivery is often measured by access, coverage, and quality of care and that one of WHO's priorities in responding to health system challenges on service delivery is to develop effective service delivery models[16], HSS interventions on service delivery are limited to activities for improving quality of care, enhancing engagement of the demand side, and developing innovative service delivery models (e.g., community engagement, public-private partnerships, and social marketing). Activities directly targeted to patients or potential patients for preventive and curative purposes are regarded as clinical interventions (e.g., screening, testing, and treatment), rather than HSS interventions, and thus excluded from the review.

Desk research strategy

To identify articles for review, we used the combination of terms in the following three areas to conduct the desk research: (1) cost-effectiveness; (2) maternal and child health; and (3) the six building blocks. For cost-effectiveness, we used the terms of "cost-effectiveness", or "cost-benefit", or "economic evaluation". To capture maternal and child health, the search terms were "reproductive", or "maternal", or "neonatal", or "child" or "motherhood program" or "prenatal care". As to key words for the six building blocks, given the wide variation of health system interventions for MCH, we first reviewed an article that synthesized key innovative interventions addressing MCH [17], and developed key words for searching articles. Table 1 shows the terms that we used for each of the six building blocks to conduct the search. In general, the key words started with terms or synonyms of the building blocks, and proceeded with more specific interventions within the block.

Table 1. Key search terms on the six building blocks of the health system

	Service delivery	Health workforce	Information	Medical products	Financing	Leadership/governance
Search words	Quality improvement Community Public-private partnership	Human resources Human workforce Training Education	Information	Supply chain Technology	Financing Cash transfer Incentives Voucher Health insurance User fees Performance based financing Results based financing Pay for performance	Governance Leadership Health policy Regulation

We conducted searches in four major electronic bibliographic databases on public health and economics: PubMed, EconLit, Academic Search Premier, and Web of Science, on Jan 12, 2017 and updated the search on Feb 10, 2017. We also conducted a search for grey literature through Popline database. All searches were conducted in English. With an additional three articles collected by authors, the initial search identified 4,197 non-duplicate publications that were eligible for title and abstract

screening (Figure 2). To include more grey literature for review, we also searched through Google Scholar using the same key words as those applied to bibliographic databases. The research team reviewed the first 100 records from the search and compared them with those obtained from electronic databases. We further checked their eligibility and found no additional articles that could be included in the review from Google Scholar.

Figure 2. Flow diagram for study identification
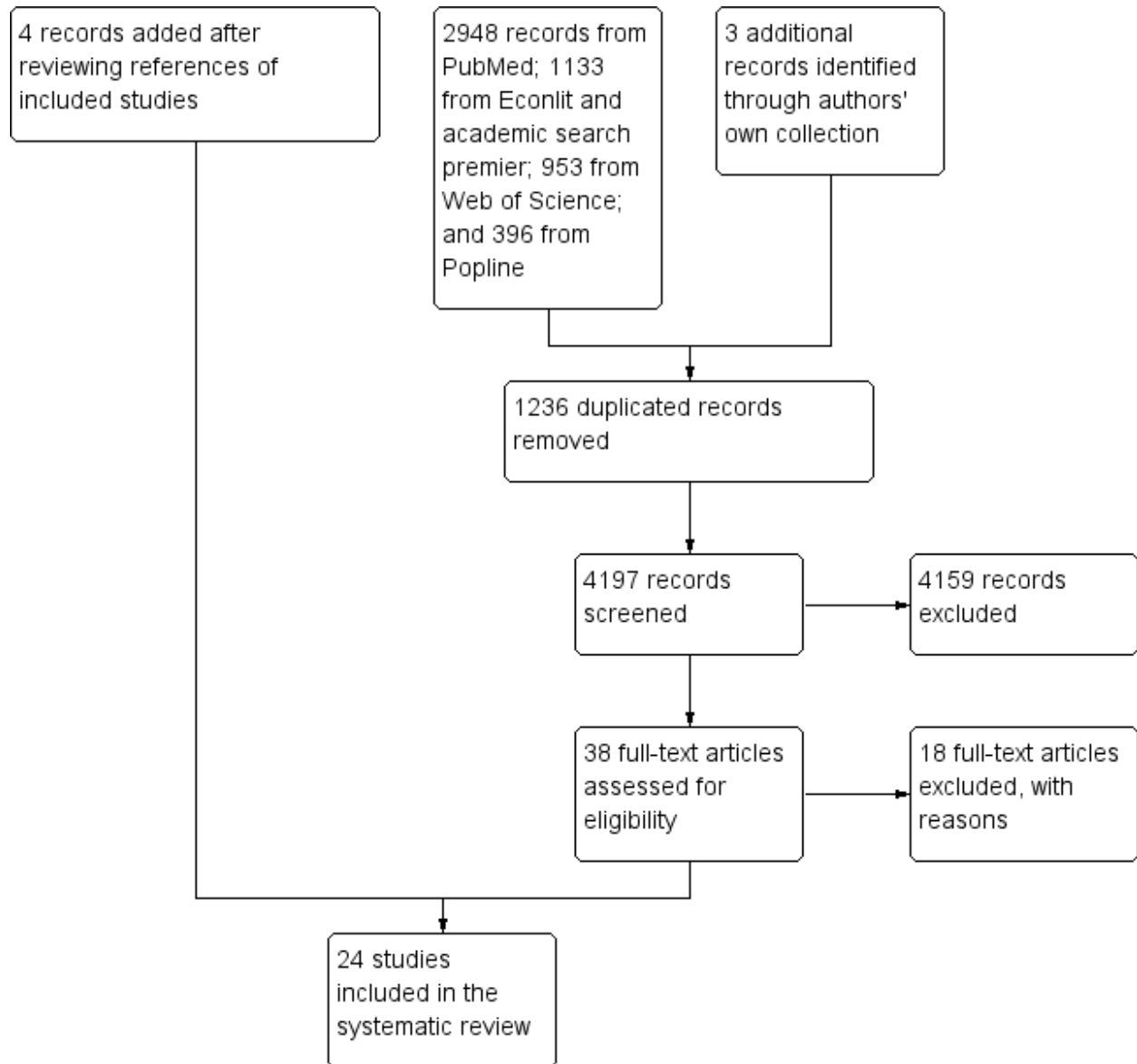
Exclusion criteria

All the search records were first uploaded in Endnote X8 and independently screened by two reviewers (WZ and HA). We used Endnote to eliminate duplicated records (1236 records). The remaining records (4197 records) were first reviewed through titles and abstracts to assess their relevance: (1) studies focused on maternal and child health; (2) interventions concerned with HSS: (3) studies that reported on

cost-effectiveness measures; and (4) studies conducted in LMIC. Articles that met these inclusion criteria and those that possibly met the criteria were included in the full-text review. As a result, 38 articles were selected for full-text review. Articles were excluded if they met one of the following exclusion criteria:

- Studies not related to maternal and child health;
- Studies not conducted in low- and middle-income countries;
- Studies where interventions did not fall in any of the six building blocks of a health system;
- Studies where interventions were direct preventive and curative services;
- Qualitative studies;
- Studies synthesizing prior studies;
- Studies evaluating programs that had not been implemented;
- Studies where the final effectiveness in the economic evaluation was not measured in terms of health outcome (e.g. life years saved, disability adjusted life years (DALYs) averted, quality adjusted life years (QALYs) gained, lives saved or deaths averted);
- Studies reporting average cost-effectiveness ratio without any comparison group, rather than incremental cost-effectiveness ratio (ICER); and
- Studies published prior to 1990.

The full text review was conducted independently by WZ and HA for all 38 articles, and 18 articles were excluded based on exclusion criteria. We further reviewed references from the remaining 20 articles, and included 4 more articles. In the end, 24 articles were selected in the final review for synthesizing findings. Table 2 shows the reason for exclusion for the 18 articles.

Table 2. Reasons for exclusion of 18 out of 38 articles

Number of articles	Reasons for exclusion
10	Cost-effectiveness measures not in terms of cost per outcome measures
2	No empirical data, CEA purely based on assumptions and secondary data
2	Reporting average cost-effectiveness ratio
1	Duplication
1	Not related to MCH
1	Not conducted in LMIC
1	Synthesis of prior studies

CEA denotes cost-effectiveness analysis; MCH denotes maternal and child health; LMIC denotes low- and mid-income countries.

Study selection and data extraction

An Excel template was developed to extract data from the 24 articles. The collected information included: (1) characteristics of studies: publication year, interventions under examination, research design for impact evaluation, outcome measures of impact evaluation, along with other relevant study characteristics; and (2) components of economic evaluation: perspective of cost analyses, cost components, length of assessment, year in which costs were assessed and expressed, cost-effectiveness

measures, value of cost-effectiveness, whether sensitivity analyses were conducted, and the like. For each article, corresponding information was extracted. Data extraction was primarily carried out by one researcher, while another researcher reviewed and checked collected data. If information (e.g. year in which costs were assessed and expressed) was not available in the main text, two researchers discussed and made best guesses.

Quality assessment or risk of bias in individual studies

The final 24 studies were then imported into Review Manager software 5.3 (RevMan) (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) and subsequently evaluated for quality of evidence or risk of bias using the Cochrane Effective Practice and Organisation of Care (EPOC) risk of bias criteria and study quality guide [18,19].

The quality of evidence was assessed through examining the risk of bias of each study. There were seven major biases assessed using the checklist based on the Cochrane criteria, and we assigned scores to each study on the following seven categories: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other risks of bias, including publication bias.

For each category, a study received a rating of low, high, or unclear risk. Numerical rating codes were assigned to each of the three ratings: low risk was assigned a numerical code of 1, high risk a numerical code of 0, and unclear risk a numerical code of 0.5. A composite quality score for each study was calculated by averaging the seven numerical rating codes. We then rated each study based on the overall quality score: low (<60%), medium (an average 60-80%), or high (> =80%).

Data synthesis

Consistent with the Excel template, the data analyses focus on two dimensions. The first dimension concerned characteristics of overall study and impact evaluation, which examined HSS strategies, building blocks to which interventions/strategies belong, study design of impact evaluation, primary measures for impact evaluation, and impact of interventions/strategies if this was reported. It should be noted that sometimes, there were overlaps when categorizing a particular intervention/strategy into building blocks. For example, comprehensive quality improvement programs (block of service delivery) sometimes incorporated training of health providers (block of human workforce). When encountering such circumstance, core research members (WZ and HA) further examined the overall intervention and categorized it based on the key components and purposes of the intervention. For example, if a training program was a single intervention for an existing and conventional delivery approach, we categorized it into the block of human workforce. If the training was part of a quality improvement package, or the training of human resources was for implementing a new service delivery model, then it was categorized into the block of service delivery.

The second dimension of the analysis was for characteristics of economic evaluation/cost-effectiveness for each article. The major characteristics included perspectives of cost-effectiveness, cost components, measures and value of cost-effectiveness, and use of sensitivity analysis, as well as length of cost-

effectiveness assessment (long-term [>=4 years] or short-term assessment [<4 years]). The cost-effectiveness was reported as US Dollars (USD) per effectiveness measure in the year when costs of programs were expressed and evaluated in the article. To standardize cost-effectiveness measures, we also listed gross domestic product (GDP) per capita in the same year for comparison. For cost-effectiveness of strategies that reported as cost per DALY averted or cost per QALY gained, the WHO's Commission on Macroeconomics and Health considers interventions/strategies to be highly cost effective if they are less than one times GDP per capita, and being cost-effective if they are less than three times GDP per capita [20,21].

RESULTS

Overview of studies

Of the 24 selected articles, 21 were obtained from peer review articles, and three from grey literature; 23 were published since the year 2000, and one published a few years prior. The 24 studies were conducted in 15 countries, with four in Zambia, three each in Uganda and India, two each in Bangladesh and Malawi, and one in each of remaining countries (Argentina, Gambia, Kenya, Myanmar, Nepal, Niger, Nigeria, Papua and New Guinea, Ukraine, and Zimbabwe). Geographically, there were 14 studies conducted in Africa, 7 in Asia, 1 in Oceania, 1 in Eastern Europe, and 1 in Central America. Table 3 provides detailed information of the selected studies.

Table 3. Interventions, study design and impact evaluation of included studies

Last name of the first author	Publication year	Building Block	Country	Region	Interventions	Study design for impact evaluation	Key measures of the impact evaluation	Impact of intervention
Shepard[22]	2017	Financing	Zimbabwe	Africa	Provide financial incentives to health providers for maternal and child health services	Pre-post controlled design	Quality indictors; institutional delivery, post-partum care	RBF increased the share of institutional deliveries by 13.4%, and post-partum tetanus vaccinations by 20.0%.
Zeng[23]	2017	Financing	Zambia	Africa	Provide financial incentives to health providers for maternal and child health services	cRCT	Institutional delivery, family planning, and quality of care	Compared to INP, RBF improved utilization of Hib vaccination (15.0%) and family planning (21.8%), and resulted in quality of care changes ranging from -0.8% to +4.9%. Compared to CON, RBF improved quality of care, ranging from 2.3% to 9.7%, and significantly increased utilization of postnatal care (7.8%), institutional delivery (12.2%),Hib (19.1%) and family planning (19.5%)
Wang[24]	2016	Financing	Zambia	Africa	Provide 'Mama kit' incentives to mothers conditional on delivering baby in facilities	cRCT	Use of institutional delivery	The odds of delivering at a facility were increased by 63% (29%-106%), or an increase of 9.9 percentage points.
Bishai[25]	2015	Service delivery	Myanmar	Asia	Add oral rehydration salts and Zinc (ORS-Z) as an additional product line in an existing social franchise program.	Pre-post controlled design	Use of ORS	7.6% increase in zinc and ORS use, which would translate to 2.85 (SD = 0.29) incremental deaths averted in a total community population of 1 million.
Colbourn[26]	2015	Service delivery	Malawi	Africa	1. Mobilize community around maternal and neonate health through women's group (CI). 2. Improve quality of health facilities through training staff, implementing change packages focused on obstetric and newborn care, conducting death reviews, leadership training and protocol-based clinical trainings (FI)	cRCT	Neonatal mortality rate; maternal mortality rate	The neonatal mortality rate was 22% lower in FI + CI than control clusters (OR = 0.78, 95% CI 0.60–1.01), and the perinatal mortality rate was 16% lower in CI clusters (OR = 0.84, 95% CI 0.72–0.97). No intervention effects on maternal mortality.

Gomez[27]	2015	Financing	Nigeria	Africa	Implement a health insurance program, which provided access to comprehensive health care.	Cohort study	Use of antenatal care and institutional delivery	Access to antenatal care increased from o.65 to 0.85; institutional delivery from 0.50 to 0.675, with an estimated 47 deaths averted per 10,000 deliveries.
Saya[28]	2015	Financing	Uganda	Africa	Implement community health insurance schemes covering immunizations and curative services, as well as transport for pregnant women to and from contracted facilities.	Health insurance: Assumption based on prior study	Use of facility delivery	1% insurance increase in the health insurance enrollment rate of the entire population would raise the proportion of facility deliveries by 0.9% from its initial value
Gerler[29]	2014	Financing	Argentina	Central America	Provide financial incentives to health providers for maternal and child health services	Pre-post controlled design	Neonatal mortality rate	Beneficiaries' probability of low birth-weight is estimated to be reduced by 19 percent. Beneficiaries have a 74 percent lower chance of in-hospital neonatal mortality in larger facilities.
Alfonso[30]	2013	Financing	Uganda	Africa	Provide eligible pregnant women with a health vouchers for a subsidized price of US$1.40 covering four ANC visits, delivery care, referral and treatment of eventual complications, and a postnatal care visit.	Pre-post controlled design	Use of institutional delivery	The demand for births at HFs enrolled in the voucher scheme increased by 52.3 percentage points. Out of this value, conservative estimates indicate that at least 9.4 percentage points are new HF users. This 9.4% bump in IDC implies 20 deaths averted
Broughton[31]	2013	Service delivery	Niger	Africa	Implement quality improvement program through clinical and improvement capacity-building sessions for participants; coaching visits to participating sites; learning sessions; office personnel and administrative support; and other resources used to coordinate these activities	Pre-post design	Postpartum hemorrhage; adherence to newborn care standards; maternal mortality ratio	Probability of postpartum hemorrhage decreased from 0.0202 to 0.00216; probability of adherence to newborn care standards increased from 0.185 to 0.975; maternal mortality ratio decreased from 7.11 to 0.98 per 10,000 births.
Fottrell[32]	2013	Service delivery	Bangladesh	Asia	Convene women's groups for participatory learning and action cycle in which they prioritize issues that affected maternal and neonatal health, and design and implement strategies to address these issues.	cRCT	Neonatal mortality rate	The neonatal mortality rate was significantly lower in the intervention arm (21.3 neonatal deaths per 1,000 live births vs 30.1 per 1,000 in control areas), a reduction in neonatal mortality of 38% (risk ratio, 0.62 [95% CI, 0.43-0.89]) when adjusted for socioeconomic factors.
LeFevre[33]	2013	Service delivery	Bangladesh	Asia	1. Recruit and training community health workers (CHWs) to conduct home visits during pregnancy and post-natal period.	cRCT	Neonatal mortality rate	Neonatal mortality was reduced in the home-care arm by 34% (adjusted relative risk 0.66; 95% CI 0.47–0.93) during the last 6 months versus that in the comparison

							2. Conduct other health system strengthening activities: train facility-level providers in MNH care, distribute drugs & supplies, and establish system for tracking neonatal care.			arm. No mortality reduction was noted in the community-care arm (0.95; 95% CI 0.69–1.31).
Lewycka[34]	2013	Service delivery	Malawi	Africa	1. Recruited and trained facilitators to convene women's groups. Women's groups encouraged to identify and adopt local strategies to improve maternal and child health. 2. Volunteer peer counsellors made home visits during pregnancy and post-birth to support breastfeeding and infant care.	Factorial cluster randomized trial	Neonatal mortality rate	After adjustment for parity, socioeconomic quintile, and baseline measures, effects were larger for NMR (0.85, 95% CI 0.59–1.22) and MMR (0.48, 95% CI 0.26–0.91). Because of the interaction between the two interventions, a stratified analysis was done. For women's groups, in adjusted analyses, MMR fell by 74% (0.26, 95% CI 0.10–0.70), and NMR by 41% (0.59, 95% CI 0.40–0.86) in areas with no peer counsellors, but there was no effect in areas with counsellors (1.09, 95% CI 0.40–2.98, and 1.38, 95% CI 0.75–2.54). Factorial analysis for the peer counselling intervention for years 1–3 showed a fall in IMR of 18% (0.82, 0.67–1.00) and an improvement in EBF rates (2.42, 1.48–3.96)
Barasa[35]	2012	Service delivery	Kenya	Africa	Implement quality improvement through employing guidelines, training, supervision, feedback, and facilitation, called the Emergency Triage and Treatment Plus (ETAT+) strategy.	cRCT	14 process measures (e.g. child's weight documented)	The impact was assumed that the intervention produced a 1%-10% relative reduction of mortality rate of 7%.
Sabin[36]	2012	Health Work-force	Zambia	Africa	Conduct 4-day sessions of training to traditional birth attendants (TBAs) to perform interventions targeting birth asphyxia, hypothermia, and neonatal sepsis, followed by 1–2 day refresher trainings approximately every 3–4 months for the duration of the trial.	cRCT	Neonatal mortality rate	Neonatal mortality was 45% lower among live born infants delivered by intervention birth attendants than control birth attendants (rate ratio 0.55, 95% CI 0.33 to 0.90). Deaths due to birth asphyxia were reduced by 63% among infants delivered by intervention birth attendants (0.37, 0.17 to 0.81) and by 81% within the first two days after birth (0.19, 0.07 to 0.52).
Manasyan[37]	2011	Health Work-force	Zambia	Africa	Offer the essential newborn care course, which included universal precautions and cleanliness; routine neonatal care; initiation of breathing and resuscitation; prevention of hypothermia; early and exclusive breastfeeding; kangaroo (skin-to-skin) care; small	Pre-post design	Neonatal mortality rate	All-cause 7-day (early) neonatal mortality decreased from 11.5 per 1,000 to 6.8 per 1,000 live births after ENC training of the clinic midwives (relative risk: 0.59; 95% confidence interval: 0.48–0.77; 40 615 births).

					infant care; counseling on infant care; and danger signs, recognition, and initial management of illnesses.			
Somigliana[38]	2011	Service delivery	Uganda	Africa	Use an ambulance within a hospital-/community- based reproductive health service.	Cohort study	Referrals	Ninety-two obstetrical referrals were recorded. Eleven (12%) were considered effective, corresponding to 611.7 years saved.
Nizalova[39]	2010	Service delivery	Ukraine	Eastern Europe	Implement a comprehensive mother and infant health project (MIHP). The MIHP promoted new evidence-based medicine (EBM) standards: partner deliveries; avoidance of unnecessary C-sections, amniotomies and episiotomies; use of free position during delivery; immediate skin-to-skin contact; early breastfeeding; and the rooming-in of mothers and newborns.	Pre-post controlled design	Maternal and infant deaths	The number of C-sections in the MIHP participating Rayons decreases by 4.71% or by 132.17 deliveries on average per year. The estimates suggest that the MIHP participation on average translates into 1.69 fewer maternal deaths per maternity per year and 5.63 fewer infant deaths resulted from deviations in perinatal period
Tripathy[40]	2010	Service delivery	India	Asia	1. Recruit and train facilitators to convene monthly women's group meetings, and encourage women's groups to adopt strategies to improve maternal and neonatal health. 2. Implement other health system strengthening activities (including training in newborn care, equipment & supplies)	cRCT	Neonatal mortality rate	NMR was 32% lower in intervention clusters adjusted for clustering, stratification, and baseline differences (odds ratio 0.68, 95% CI 0.59-0.78) during the 3 years, and 45% lower in years 2 and 3 (0.55, 0.46-0.66). Although we did not note a significant effect on maternal depression overall, reduction in moderate depression was 57% in year 3 (0.43, 0.23-0.80).
Bang[41]	2005	Service delivery	India	Asia	1. Train female village health workers (VHWs) to diagnose and manage birth asphyxia (when supported by TBAs at delivery) in comparison with current practice with TBAs trained to manage birth asphyxia.	Pre-post design	Incidence of mild birth asphyxia; case fatality of neonates with severe asphyxia	The incidence of mild birth asphyxia decreased by 60%, from 14% in the observation year (1995 to 1996) to 6% in the intervention years. The incidence of severe asphyxia did not change significantly, but the CF in neonates with severe asphyxia decreased by 47.5%, from 39 to 20% and ASMR by 65%, from 11 to 4%. Mouth-to-mouth resuscitation reduced the ASMR by 12%, tube–mask further reduced the CF by 27% and the ASMR by 67%.

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Bang[42]	2005	Service delivery	India	Asia	Train village health workers to provide neonatal care	Pre-post controlled design	Neonatal mortality rate	The NMR in the intervention area decreased from 62 to 25. The reduction in comparison to the control area was 70%. The reduction in the NMR was created by the reduction in both the early NMR (24 points) and the late NMR (20 points). The SBR decreased by 49%; the PMR decreased by 56%.
Borghi[43]	2005	Service delivery	Nepal	Asia	Training community facilitators to work with women's groups to develop strategies for improvement of maternal and neonatal health	cRCT	Neonatal mortality rate and maternal mortality	Intervention group achieved a 29% reduction in neonatal mortality and a substantial reduction in maternal mortality during 33 months
Duke[44]	2000	Service delivery	Papua and New Guinea	Oceania	Introduce minimal standards of neonatal care in 10 areas	Pre-post design	Neonatal mortality rate	The in-hospital neonatal mortality in the 30-month period after the interventions began was 44% lower (relative risk (RR) 0.56). After adjustment for a higher number of neonates <1.5 kg in the pre-intervention period, the relative risk was 0.59. The mortality in the intervention phase for very low birthweight babies was 56% lower (RR 0.44) and for moderate low birthweight (1.5-2 kg) 50% lower (RR 0.50)
Fox-Rushby[45]	1996	Service delivery	Gambia	Africa	Conduct mobile outreach services, with two midwives providing antenatal and family planning care for 22 villages, and visiting villages regularly.	Pre-post controlled design	Neonatal mortality rate and maternal mortality rate	Neonatal mortality rate was reduced from 32.2 to 16 per 1000 live births, and maternal mortality rate from 7 to 3.1 per 1000 live births.

Notes: cRCT denotes cluster randomized control trial, RBF denotes results-based financing, INP denotes input financing, Hib denotes haemophilus influenza type b vaccine, SD denotes standard deviation, CI confidence interval, ANC denotes antenatal care, CHW denotes community health worker, NMR denotes neonatal mortality rate, MMR denotes maternal mortality rate, IMR denotes infant mortality rate, SBR denotes stillbirth rate, PMR denotes perinatal mortality rate, EBF denotes exclusive breastfeeding, TBA denotes traditional birth attendant, ASMR denotes asphyxia-specific mortality rate, CF denotes case fatality.

Strategy of health system strengthening

Using the six building blocks to categorize the studies, 15 were on enhancing service delivery[25,26,31-35,38-45], 7 on financing[22-24,27-30], and 2 studies on workforce[36,37]. However, we found no studies on cost-effectiveness of the building blocks of leadership/governance, information, and medical supplies.

For service delivery, strategies were taken at both community- and health-facility levels. At the community level, five studies examined community mobilization through participatory women's groups or peer counselors to develop strategies to improve maternal and neonatal mortality rate[26,32,34,40,43]; three studies investigated training to community health workers for providing MCH services (e.g. conducting home visits) [33,41,42]; and one study used a social marketing approach to distribute oral rehydration salts and zinc (ORS-Z)[25].

At the health-facility level, strategies undertaken included quality improvement[26,31,35,39,44] through training health providers, coaching visits, supporting administrative management, and strengthening adherence to treatment guidelines and standards. In one study, conducted in The Gambia, health providers were also encouraged to conduct more outreach activities to expand services to pregnant women and infants who would otherwise be neglected[45]Strategies to provide transportation were undertaken[38] to remove a barrier for pregnant women to access MCH services.

Similarly, various approaches on financing strategies were also implemented. From the supply side, there were three articles on PBF[22,23,29] conducted in Zambia, Zimbabwe and Argentina respectively, where health providers were offered financial incentives for providing MCH services. From the demand side, two articles concerned health insurance[27,28]; one examined voucher schemes that offerred financial incentives to pregnant women for seeking MCH services[30]; and one from Zambia reported offering "Mama kit", a non-financial incentive conditional on giving birth in health facilities.

On strategies concerning workforce, the major intervention was providing training to health personnel. As mentioned earlier, there existed overlap of training health providers between the block of human resources and service delivery. The two studies categorized in the block of workforce were for capacity building only and did not have other complementary activities. Sabin et al. examined the cost-effectiveness of training traditional birth attendants in Zambia[36], while Manasyan focused on training related to health providers on essential newborn care[37].

Study design and assessment of study quality

Of the 24 articles, 10 applied cluster randomized control trial (cRCT) design; 7, pre-post controlled design; and 4, pre-post design without a control group. There were two studies using cohort study design, following up research subjects over a certain period and observing health outputs or outcomes. The last study used parameters from another country to estimate effectiveness[28].

Based on the grading process described in the methods section, the average quality score for the 24 articles was 82%, with 15 articles were rated as high quality, 5 as medium quality, and 4 as low quality. The primary reasons for low quality grade were defected study design in assessing the program's impact, inappropriate approaches to convert health outputs to outcomes, or missing some cost components.

Depending on perspectives of the studies, cost components of the 24 articles varied substantially. Four studies examined costs from the project/program's perspective[37,39,40,43], which did not account for costs occurred in health facilities, either in public or private settings. Nor did it account for costs borne by households. As most interventions intended to improve utilization of MCH services, without considering potential increased costs due to improved use of services, cost-effectiveness of interventions may be overestimated. One study only costed equipment and suppliers[44], which might substantially inflate the cost-effectiveness of the intervention.

Measures of cost and effectiveness

Table 4 provides detailed information on cost-effectiveness from the 24 articles. In total, 38 cost-effectiveness values were obtained. Only five values provide the long term cost-effectiveness of the program (Length of assessment >= 4 years). As to study perspectives, 22 values (57.89%) were from the health provider's perspective, eight (21.05%) from the program/project's perspective, and eight (21.05%) from the societal perspective.

Table 4. Characteristics of cost-effectiveness analysis of included studies

Last name of the first author	Perspective	Year of dollar expressed	Lengthen of assessment (months)	Intervention	Comparator/scenarios	CE value	CE measure	Sensitivity analysis	GDP/capita (USD)Δ	Times of GDP/capita
Colbourn[26]	Health provider	2013	27	Community mobilization	CI vs SQ	79	DALY averted	Yes	317	0.249
Colbourn[26]	Health provider	2013	27	Quality improvement	FI vs SQ	281	DALY averted	Yes	317	0.886
Colbourn[26]	Health provider	2013	27	CI+FI	CI+FI vs SQ	146	DALY averted	Yes	317	0.461
Gomez[27]	Health provider	2012	144	Health insurance	Int vs SQ	46	DALY averted	Yes	2,798	0.017
Saya[28]	Health provider	2013*	Not clear	Health insurance	Int vs SQ	298	DALY averted	No	681	0.438
Gerler[29]	Health provider	2005	60	PBF	Int vs SQ	814	DALY averted	Yes	5,164	0.158
Bang[42]	Health provider	2003*	84	VHWs training	Int vs SQ	6.8	DALY averted	No	572	0.012
Broughton[31]	Health provider	2008	30	Quality improvement	Int vs SQ	147	DALY averted	No	382	0.385
Barasa[35]	Health provider	2011	18	Quality improvement	Int vs SQ (Best case)	40	DALY averted	Yes	1,062	0.037
Barasa[35]	Health provider	2011	18	Quality improvement	Int vs SQ (Worst case)	398	DALY averted	Yes	1,062	0.375
LeFevre[33]	Program	2010	30	CHWs training	Int vs SQ	103	DALY averted	Yes	808	0.128
Alfonso[30]	Program	2010	37	Voucher scheme	Int vs SQ	338	DALY averted	Yes	594	0.569
Manasyan[37]	Program	2005	24	Midwife training	Int vs SQ	5.2	DALY averted	No	692	0.008
Alfonso[30]	Societal	2010	37	Voucher scheme	Int vs SQ	302	DALY averted	Yes	594	0.508
LeFevre[33]	Societal	2010	30	CHWs training	Int vs SQ	105	DALY averted	Yes	808	0.129
Bishai[25]	Societal	2010	10	Social marketing	Int vs SQ	214	DALY averted	Yes	997	0.215
Sabin[36]	Societal	2011	120	TBAs training	Int vs SQ	74	DALY averted	Yes	1,636	0.045
Shepard[22]	Health provider	2013	27	PBF	Int vs SQ	662	QALY gained	Yes	1,005	0.659
Zeng[23]	Health provider	2013	27	PBF	Int vs input financing	1,350	QALY gained	Yes	1,840	0.734
Zeng[23]	Health provider	2013	27	PBF	Int vs pure control	809	QALY gained	Yes	1,840	0.440
Lewycka[34]	Health provider	2010	72	Community mobilization	Int vs SQ	33-114	LYS	No	443	0.075-0.257
Somigliana[38]	Health provider	2009	3	Ambulance service	Int vs SQ	16	LYS	Yes	565	0.028
Tripathy[40]	Program	2007	36	Community mobilization	Women's group vs SQ	33	LYS	Yes	1,081	0.031
Tripathy[40]	Program	2008	36	Community mobilization	women's group + HSS vs SQ	48	LYS	Yes	1,081	0.044

Study	Perspective	Year		Intervention	Comparison		Outcome			
Borghi[43]	Program	2003	33	Community mobilization	Int vs SQ	211	LYS	Yes	254	0.831
Fottrell[32]	Health provider	2011	24	Community mobilization	Int vs SQ	330	LYS	No	857	0.385
Fox-Rushby[45]	Societal	1991	24	Mobile outreach	Int vs SQ (Best - Worst case)	42.9-459.0	Discounted LYS	Yes	486	0.088-0.944
Nizalova[39]	Program	2005	72	Quality improvement	Int vs SQ	0.01	Dollar gained	No	1,910	-
Wang[24]	Health provider	2013*	11	Mama kit	Int vs SQ	5,183	Life saved	No	1,840	2.817
Bang[41]	Health provider	2003*	84	VHWs training	Int vs SQ	13	Life saved	No	572	0.023
Bang[42]	Health provider	2003*	84	VHWs training	Int vs SQ	150.5	Life saved	No	572	0.263
Duke[44]	Health provider	1998*	30	Quality improvement	Int vs SQ	445	Life saved	No	1,158	0.384
Alfonso[30]	Health provider	2010	37	Voucher scheme	Int vs SQ	22,933	Life saved	Yes	594	38.608
Fottrell[32]	Health provider	2011	24	Community mobilization	Int vs SQ	10,053	life saved	No	857	11.730
Manasyan[37]	Program	2005	24	Midwife training	Int vs SQ	208	Life saved	No	692	0.301
Alfonso[30]	Societal	2010	37	Voucher scheme	Int vs SQ	20,575	Life saved	Yes	594	34.638
Bishai[25]	Societal	2010	10	Social marketing	Int vs SQ	5,955	Life saved	Yes	997	5.973
Fox-Rushby[45]	Societal	1991	24	Mobile outreach	Int vs SQ (Best - Worst case)	206.3-2,134.0	Life saved	Yes	486	0.424-4.391

*Best guess; Δ source: international monetary fund, available at http://www.imf.org/external/pubs/ft/weo/2016/02/weodata/index.aspx.

CE denotes cost-effectiveness, GDP denotes gross domestic product, Int denotes intervention, SQ denotes status quo, HSS denotes health system strengthening, CI denotes community intervention, FI denotes facility intervention, TBAs denotes traditional birth attendants, VHWs denotes village health workers, PBF denotes performance based financing, LYS denotes life year saved, DALY denotes disability adjusted life year, QALY denotes quality adjusted life year.

Of the 38 values of cost-effectiveness, 17 were measured with DALYs averted, followed by 10 using lives saved, 6 using life year saved, 3 using QALYs gained, 1 using discounted life year saved, and 1 using dollars gained.

If cost-effectiveness were examined using the same perspective, for the studies reporting DALY or QALYs, the values could be compared. Compared to the benchmark of GDP per capita, all 13 cost-effectiveness values reported as cost per DALY averted or QALY gained from the health provider's perspective were less than one times GDP per capita (Table 5), suggesting that associated interventions were highly cost-effective. Among them, the training of village health workers in India had the lowest cost-effectiveness ratio and the lowest relative cost-effectiveness to its GDP/capita. The three PBF programs had cost-effectiveness ratios ranging from $662 to $1350/DALY averted or QALY gained. Their relative values to GDP per capita spanned from 0.158 to 0.734, indicating that PBF was among the highly cost-effective interventions in addressing MCH.

Table 5. Cost-effectiveness reported as cost/DALY averted or QALY gained from health provider's perspective

Last name of the first author	Intervention	Comparator/scenarios	Cost/DALY averted or cost/QALY gained	Times of GDP/capita
Bang[42]	VHWs training	Int vs SQ	6.8	0.012
Gomez[27]	Health insurance	Int vs SQ	46.4	0.017
Barasa[35]	Quality improvement	Int vs SQ (Best case)	39.8	0.037
Gerler[29]	PBF	Int vs SQ	814.0	0.158
Colbourn[26]	Community mobilization	CI vs SQ	79.0	0.249
Barasa[35]	Quality improvement	Int vs SQ (Worst case)	398.3	0.375
Broughton[31]	Quality improvement	Int vs SQ	147.0	0.385
Saya[28]	Health insurance	Int vs SQ	298.0	0.438
Zeng[23]	PBF	Int vs pure control	809.0	0.440
Colbourn[26]	CI+FI	CI+FI vs SQ	146.0	0.461
Shepard[22]	PBF	Int vs SQ	662.0	0.659
Zeng[23]	PBF	Int vs input financing	1,350.0	0.734
Colbourn[26]	Quality improvement	FI vs SQ	281.0	0.886

Notes: DALY denotes disability adjusted life year, QALY denotes quality adjusted life year, GDP denotes gross domestic product; VHWs denotes village health workers, Int denotes intervention, SQ denotes status quo, CI denotes community intervention, FI denotes facility intervention, PBF denotes performance based financing.

DISCUSSION

This systematic review identified 24 articles on cost-effectiveness of HSS interventions for improving MCH. The major HSS interventions concern service delivery, health financing, and human workforce. None of the articles reported on governance/leadership, supply chain, or information systems.

Consistent to what had been synthesized before on cost-effectiveness of overall strategies in improving MCH[46], this review of HSS strategies has also found that countries take diverse approaches to address their health system gaps in responding to MCH concerns. For example, in Bangladesh, where awareness of MCH services is low and there exists a dynamic non-governmental organization sector[47], community mobilization programs are piloted and tested[32,33]. In contrast, in countries such as Kenya and Nigeria, where quality of health care is a major concern, quality improvement programs through training personnel and strengthening adherence to protocol are implemented[31,35]. To address financial barriers for pregnant women, strategies such as health insurance and voucher schemes, as well as providing ambulance services, are carried out to improve MCH service coverage and outcomes[27,28,30,38]. Each country has its own health system concerns. To design cost-effective health system interventions, it is important to conduct health system diagnosis to identify health system malfunctions[48], in order to design more targeted and effective interventions.

We also found that the diversity of HSS strategies lies in both the supply- and demand-side interventions. From the supply side, HSS strategies targeting health services providers (e.g. hospitals, health clinics, and medical personnel) take the form of, for example, training health personnel, direct provision of equipment, and incentivizing health providers, and they are instrumental in ensuring quality of care and reaching out to targeted populations to deliver services. Donors play an important role in supporting supply interventions[4]. On the other hand, demand-side strategies are directly targeted to users of health care services, such as pregnant women and children. Community engagement and providing financial or non-financial incentives to service users are the most common demand side interventions[10]. As demand for health services increases, it is expected that the use of needed services would increase. A review shows that, overall, demand-side interventions increase the use of health services, but do not necessarily improve health outcomes.[10] To address MCH more effectively, it is critical to leverage strengths of both supply- and demand-side strategies. In Cambodia, it was reported that the effects of PBF on MCH services quadrupled when it was implemented simultaneously with a voucher scheme[49]. Similarly, Colbourn et al. examined cost-effectiveness of combined demand side and supply side interventions and found a lower cost-effectiveness ratio for the combined approach than supply side intervention alone[26], suggesting strong synergy between demand and supply side interventions. When designing comprehensive programs, policy makers should take a holistic approach that considers synergies among programs in order to achieve better outcomes with lower costs. The complementarities among HSS interventions may preclude a league table approach to report their cost-effectiveness.

We extracted cost-effectiveness values from the 24 articles, in the hope of making a comparison among them. However, the studies used different cost-effectiveness measures, took different perspectives of analysis, and applied different assumptions for modelling, which significantly limited the comparability among studies. Even though some studies under the review used the same cost-effectiveness measures and took the same perspective, some results were still not comparable, due to, for example, cost components included in the analysis, as mentioned in the Results section. In addition, cost effectiveness comparisons were difficult because of the inconsistency in approaches used in measuring effectiveness. Some studies used measures of changes of mortality rate, from which DALYs averted or QALYs gained could be derived directly. Other studies collected changes of utilization of health services as impact

measures. Thus, modelling was needed to convert utilization of services to health outcomes for cost-effectiveness analyses. Often modelling relies on international literature, which may not provide accurate parameters for the country where the program was implemented. With only 24 articles found on economic evaluation of HSS interventions for MCH, it is critical to generate more relevant evidence through conducting cost-effectiveness/benefit studies, in order to help donors and governments make HSS investments.

Specifically for PBF, one of the major HSS interventions applied in LMICs, impact evaluation of PBF programs generally demonstrates a positive impact of financial incentives on quality and coverage of MCH services[11,22,23,29,50,51], such as prenatal care, institutional deliveries, and postnatal care. When combining with associated costs, although costly, PBF programs prove to be highly cost-effective, whether they are modelled through health outcomes[22,23] or through direct examination of maternal and neonatal mortality rates[29]. As the coverage of services increases through PBF, PBF programs may need to switch their focus to the improvement of quality of care in the future. Given the challenge in modelling the health impact of quality of care, direct examination of changes of mortality rates attributable to PBF would be more appropriate when conducting cost-effectiveness analysis or the impact evaluation of future PBF programs[52]. Table 5 shows that there are three HSS interventions, such as training of village health workers[42], health insurance[27], quality improvement[35], having a lower relative cost-effectiveness ratio than the PBF program with the lowest relative cost-effectiveness ratio[29]. Those three studies were conducted on a relatively smaller scale (e.g. coverage population) than was the RBF program. It is likely that as those programs scale up, their cost-effectiveness ratio may increase given diminishing returns to investment.

It should also be noted that among the 24 articles, only a few studies examined long-term cost-effectiveness of interventions. Perhaps, due to time and budget constraints, most cost-effectiveness studies included in this review were for short-term assessment with the length of assessment less than four years. Given that some start-up costs could be shared for a longer period and that program management and implementation skills improve over time, cost-effectiveness of a mature program with a long implementation period tends to be lower. Bang et al. estimated that over the seven years of their study, the cost-effectiveness ratio for training village health workers in India was only 0.12 times of GDP per capita[41], one of the lowest cost-effectiveness ratios among all the interventions. More studies should be conducted to examine long-term cost-effectiveness of a program for informed policy-making. At the same time, policy makers should also be aware of the length of cost-effectiveness assessments, and gauge the program's long-term cost-effectiveness when making decisions.

Several limitations of this review should be acknowledged. First, although we endeavored to obtain as many studies as possible for screening, we were not able to review all records from the large amount of search results from Google Scholar. Missing some relevant studies is possible. Second, most interventions were cost-effective, and some studies had a very low cost-effectiveness ratio, which may suggest under reporting of negative results. Third, given the broad definition of health systems, we had to limit the scope of interventions to some domains of the health system, particularly around service delivery, where we limited the search to quality improvement and innovative delivery models. In spite of

these limitations, this review assembled evidence on HSS interventions, contributing to a better understanding of HSS in addressing MCH and evidence-based decision making.

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