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RESEARCH ARTICLE

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Estimating health care costs at scale in low- and middle-income countries: Mathematical notations and frameworks for the application of cost functions

Marc d'Elbée[1,2,3] | **Fern Terris-Prestholt**[1] | **Andrew Briggs**[4] | **Ulla Kou Griffiths**[1,5] | **Joseph Larmarange**[3] | **Graham Francis Medley**[1] | **Gabriella Beatriz Gomez**[1,6]

[1]Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, UK

[2]University of Bordeaux, National Institute for Health and Medical Research (INSERM) UMR 1219, Research Institute for Sustainable Development (IRD) EMR 271, Bordeaux Population Health Centre, Bordeaux, France

[3]Ceped UMR 196, Université Paris Cité, Research Institute for Sustainable Development (IRD), Inserm, Paris, France

[4]Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK

[5]Health Section, Program Group, UNICEF, New York, New York, USA

[6]IAVI, New York, New York, USA

Correspondence
Marc d'Elbée, London School of Hygiene and Tropical Medicine, 15-17 Tavistock Place, Kings Cross, London WC1H 9SH, UK.
Email: marc.delbee@u-bordeaux.fr

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Abstract

Appropriate costing and economic modeling are major factors for the successful scale-up of health interventions. Various cost functions are currently being used to estimate costs of health interventions at scale in low- and middle-income countries (LMICs) potentially resulting in disparate cost projections. The aim of this study is to gain understanding of current methods used and provide guidance to inform the use of cost functions that is fit for purpose. We reviewed seven databases covering the economic and global health literature to identify studies reporting a quantitative analysis of costs informing the projected scale-up of a health intervention in LMICs between 2003 and 2019. Of the 8725 articles identified, 40 met the inclusion criteria. We classified studies according to the type of cost functions applied—accounting or econometric—and described the intended use of cost projections. Based on these findings, we developed new mathematical notations and cost function frameworks for the analysis of healthcare costs at scale in LMICs setting. These notations estimate variable returns to scale in cost projection methods, which is currently ignored in most studies. The frameworks help to balance simplicity versus accuracy and increase the overall transparency in reporting of methods.

KEYWORDS
cost functions, econometrics, health economics, low- and middle-income countries, microeconomics, production costs

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1 | INTRODUCTION

The research in implementation science for intervention scale-up in low- and middle-income countries (LMICs) is gaining interest in the field of health economics (Pitt et al., 2016). Whether it is related to changes of the donor landscape where LMICs are transitioning to more reliance on domestic funding (e.g., HIV epidemic), or an evolution to decentralized health services delivery systems aiming to increase access to care (or in response to the COVID-19 pandemic), stakeholders need robust estimates of program costs at scale to better inform decisions. Additional considerations in intervention scale-up are related to the growing use of costs modeling in planning health care interventions, with a greater interest in equity of access.

Two systematic reviews have looked at conceptual frameworks for the successful scale-up of health interventions in LMICs (Milat et al., 2015; Subramanian et al., 2011), both highlighted the misevaluation of resource needs as a major challenge to scale-up. Milat and colleagues ranked the appropriate costing and economic modeling as the second most important success factor, after establishing monitoring and evaluation systems, based on the literature review citations (Milat et al., 2015).

The constraints to scale-up differ between high-income countries and LMICs, in terms of human resources, infrastructures, and health system organization. In LMICs, these constraints are often related to data scarcity (weak routine cost accounting systems and patient-information systems) (Victora et al., 2012), shortages of human resources (Perez-Escamilla et al., 2012), the health financing system in countries with high out-of-pocket expenditures (Prata et al., 2010), and weak governance (Bhandari et al., 2008).

According to the World Health Organisation, scaling up in the health sector means "doing something in a big way to improve some aspect of a population's health" (World Health Organization, 2008). This broad definition encompasses multiple dimensions including inputs/resources (mobilizing more funds), outputs (providing more services), outcomes (reaching more people), and/or impact (reducing morbidity or mortality). We distinguish "costs at scale"—assessing resource needs at various quantities of outputs, from "costs of scaling-up"—estimating all costs incurred in the process of increasing the quantity of outputs of an intervention.

Originally, the production function, developed by Cobb and Douglas in 1927, describes the relationship between outputs and factors of productions (inputs) (Cobb & Douglas, 1928). Cost functions are derived then from the production function and estimate the total cost of production given a specific quantity of output produced. The simplest cost function multiplies a single unit cost by a quantity—the commonly used "simple cost multiplier" (SCM) (Vassall et al., 2017). This linear cost function always assumes the same unit cost regardless of the scale, which is a key issue in cost modeling of health interventions because we know it is not a good representation of reality. Accounting cost functions (ACF)—also called accounting identity cost functions (Meyer-Rath & Over, 2012)—are broad in nature because they aim to follow step-by-step the intervention production process as close as possible to the reality (Meyer-Rath & Over, 2012; Vassall et al., 2017). ACF identify fixed and variable costs, typically assumed to vary linearly with the scale of output produced, such as that used in input-output analysis as originally developed by Leontief (Kuznets, 1941) (e.g., *total costs of scaling up HIV testing = cost of a HIV testing site* (fixed cost) + *HIV testing session cost*number of person to test* (variable cost*scale)) (Gomez et al., 2020). In contrast to accounting approaches, econometric cost functions (ECF) do not follow the production process and apply statistical inference to project costs. The challenge of ECF is to reflect the complexity of real-world production process with a relatively simple statistical model of dependent (costs) and independent variables (input prices, output quantities, and other variables).

The applications of cost functions have developed largely independently in the context of budgeting, medium- and long-term financial planning, technical efficiency analyses, and priority setting. These applications differ regarding their economic assumptions, complexity and data requirements, ultimately resulting in disparate cost projections.

In 2005, as part of the WHO CHOICE project (CHOosing Interventions that are Cost-Effective), Johns and colleagues systematically reviewed factors affecting costs as coverage increased. The authors outlined various methods used and identified accounting methods, projections from budget expenditures, and econometric models from 37 studies (Johns & Torres, 2005). In 2008, Kumaranayake systematically reviewed methods used in 34 studies to estimate costs at scale for HIV/AIDS interventions and identified that the majority of methods were using either an ACF where costs were modeled with or without adjustment for scale, empirically estimated, or using econometric models (Kumaranayake, 2008). Studies were used for cost-effectiveness analysis or resource needs estimates.

We conducted a scoping review of methods used to estimate the costs at scale of interventions in LMICs and the purpose for which those estimates have been produced. This review aims to update and expand previous works to identify potentially innovative approaches for projecting costs at scale, better accounting for variable returns to scale (Johns & Torres, 2005; Kumaranayake, 2008). Since the relationship between the choice of cost function and the intended use of the estimates produced is unclear, we also aim to assess how the choice of methods used and the purpose of the cost estimate are related to draw lessons on the suitability of different methods for each purpose. Specifically, the objectives of the review are: (1) to synthesize the

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literature on methods used to estimate costs of health interventions at scale in LMICs, (2) to summarize key factors considered by researchers for the fitting of cost functions, (3) to critically review quality of studies and validity of cost projections, (4) to propose new algebraic formula for cost functions based on the synthesized literature, and (5) considering the above findings, to propose a mathematical framework for the estimation of costs at scale for health interventions in LMICs based on the intended use of the cost estimates.

2 | METHODS

2.1 | Search strategy

Research questions in scoping reviews are broad in nature as the focus is on summarizing breadth of evidence (Levac et al., 2010). We followed the Arksey and O'Malley methodological framework for scoping studies revised by Levac et al. and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (Arksey & O'Malley, 2005; Levac et al., 2010; Tricco et al., 2018). Seven databases covering the economic and global health literature were reviewed: Pubmed, Embase, Global Health, Econlit, The Cost-Effectiveness Analysis Registry, Global Health Cost Consortium unit cost database and the Latin American and Caribbean Health Science Literature database.

We included studies reporting a quantitative cost analysis to inform the scale-up of an intervention in at least one LMIC between 2003 (corresponding to the end of Johns' review; Johns & Torres, 2005) and 2019 without language restrictions. Eligible studies in other development economic sectors than health, such as agriculture and education were also included in the search (Econlit database) to capture the broader scale-up literature available across economic fields, allowing for cross fertilization across disciplinary foci. The intended readers of this review are researchers or planners tasked with generating information for financial planning decisions, conducting economic evaluations at scale and technical efficiency analyses for estimating costs at scale. Therefore, program budgeting methods used by health managers for routine health services, funding application, price setting methods (e.g., in the insurance sector), and technical efficiency analyses not used for estimating costs at scale (performance analysis such as frontier models, data envelopment analysis or stochastic frontier approach)—are judged beyond the scope of the review. Only studies using a provider perspective were included (e.g., health system, health facility) because we focus on health sector planning. User costs are important to understand demand and access, they inform different decisions. Finally, we excluded studies using only the commonly found SCM approach because our focus was improving upon the SCM approach. However, we report the SCM approach in the cost function algebra section to allow for comparison between methods.

We looked at the first 50 hits (i.e., results in Google) of our search in additional key economics sources, such as the World Bank (WB), and sources for health research in developing countries, including the World Health Organisation, The Joint United Nations Programme on HIV/AIDS, Clinton Health Access Initiative and Médecins Sans Frontières, with the aim of including approaches not captured with our database search. No additional studies were found with the gray literature search (Supporting Information S1: Table A1).

The concept of costing at scale is broad, therefore the search strategy covered a wide range of research areas, these can be found in Supporting Information S1: Table A2. The search strategy was composed of three dimensions: (1) costs: including economic evaluations, ECF, program financing, expenditure analysis, efficiency analysis, cost sharing analysis; (2) research areas: related to implementation sciences, program organization/evaluation, health service assessment/monitoring, health planning, management of health resources, delivery of care, operational and organizational research; and finally (3) setting: LMICs as per the 2020 WB classification (World Bank, 2020). We validated our search strategy using a list of fourteen pre-identified research articles applying diverse cost projection methods that we knew should be included in the review to ensure our search strategy was capturing studies of interest. Our final search strategy identified all of these research articles.

2.2 | Data extraction and analysis

We conducted two types of data extraction (Supporting Information S1: Table A3). One approach was more descriptive, related to the article information (e.g., name of first author, year of publication), the intervention setting and scale-up (e.g., countries, study objectives), and the cost projection method (e.g., accounting or econometric, fixed/variable costs, uncertainty measure).

The second data extraction phase was more analytical and synthesized the factors explicitly presented by the authors, that were considered when fitting the cost functions. The approach taken extracted text and summarized data as bullet points, which were then categorized as factors (Supporting Information S1: Tables A4 and A5).

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The search results, study characteristics, and data extraction from the literature review are presented in the result section and in Supporting Information S1 (Table A6). The critical review is reported in Supporting Information S1 (Supporting Information S1: Text A1, and Supporting Information S1: Tables A7a & A7b). These findings constituted our knowledge base for understanding current practices by researchers and identifying research areas where the use of cost functions should be improved. We defined the criteria for the critical review on the assessment of method transparency. Based on these findings, we developed new mathematical notations and cost function frameworks for the analysis of healthcare costs at scale in LMICs settings.

3 | RESULTS FROM THE LITERATURE REVIEW

In this section, we present key concepts related to cost functions, followed by the results of the literature review, the presentation of key features of the extracted studies, and findings from the data analysis on the applications of cost functions.

3.1 | Key concepts

3.1.1 | Fixed and variable costs

As a rule of thumb, most capital costs can be considered as fixed costs whereas recurrent costs usually compose the variable costs (Vassall et al., 2017). However, the treatment of costs as fixed or variable will depend on the type of intervention (costs that are considered fixed in a study can be considered variable in another study), the magnitude of intervention scale-up (high coverage of the population), the intervention level (more variable costs at service delivery level than above service delivery level), the intervention phase (development, start-up, and implementation), and whether the analysis is conducted in the short- or long-run. Fixed costs can be a total cost (e.g., initial set up of a hotline at national level) or an average cost (average capital costs at primary care health facility level for a specific intervention). Fixed costs can be both related to health program costs and cross-cutting health system costs following the OneHealth costing tool classification (Cantelmo et al., 2018). Consideration of fixed costs depends on the intervention, some interventions have a small proportion of fixed costs (Rodrigues et al., 2014), or considered insignificant (Abdullah et al., 2012; Cantelmo et al., 2018; Prinja et al., 2018; Verguet et al., 2015).

3.1.2 | Intervention levels

Intervention levels refer to health system levels such as health facility, district, central, etc. Intervention level is the level at which the intervention is implemented (and where costs incur), and it is possible for an intervention to be implemented at several levels. They are context-specific and consideration of costs and resources at each level depends on data availability, and the level of planning (e.g., national or district level). There is a need to acknowledge the considerable data challenges in LMICs because of the lack of routine cost data collection through accountancy systems or a simple way to extract these data. Consideration of different intervention levels also reflect the degree of integration of an intervention within the existing healthcare system. One should note that the composition of fixed and variable costs will depend on the intervention level.

3.1.3 | Scale variables

Following the World Health Organisation classification, we classify scale variables into areas related to *inputs*, *outputs*, and *outcomes* (World Health Organization, 2008). We also identify a new area related to *setting*.

Scale variables (s) can be classified in the following areas:

1. *Inputs (or resources)*: hospital bed, per field officer, lab reagent, diagnostic test (Deo et al., 2019)
2. *Outputs*:
   a. per service (e.g., dose of vaccine delivered or administered, hospital visit with/without admission, home visit, medical consultation, screening or diagnostic test for HIV or tuberculosis, treatment administered, surgical operation, long-lasting insecticide-treated bed-net delivered) (Barasa et al., 2012; Castaneda-Orjuela et al., 2013; Deo et al., 2019; Ensor et al., 2012; Marschall & Flessa, 2008; Turner et al., 2016; Verguet et al., 2015; Winskill et al., 2017)

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b. per health intervention as a package or not (e.g., primary health care: health promotion, sanitation and environment health, maternal and child health and family planning, nutrition, immunization and communicable diseases control, and treatment of common illness) (Cantelmo et al., 2018; Marschall & Flessa, 2008)

3. *Outcomes*: per beneficiary/target individual (e.g., general population, patient, pregnant woman, child under 5 years old, fully vaccinated child, school child) (Abdullah et al., 2012; Castaneda-Orjuela et al., 2013; Deghaye et al., 2006; Prinja et al., 2018; Rodrigues et al., 2014; Terris-Prestholt et al., 2006; Winskill et al., 2017)
4. *Setting*: per administrative structure (e.g., village, district, block, ward, health center) (Abdullah et al., 2012; Prinja et al., 2018; Terris-Prestholt et al., 2006; Verguet et al., 2015)

These variables are used as a combination of variables in half of the studies to follow closely a production process (e.g., input/setting/outcome or setting/output) (Barasa et al., 2012; Prinja et al., 2018).

3.1.4 | Treatment of the dependent cost variable in econometric cost functions (total/average costs, inclusion/exclusion of above service level costs)

In studies included in this review, researchers are either using total costs or dividing it by total output in a specified time period to obtain average costs. The choice to use average costs might be made to avoid the higher error terms due to heteroscedasticity in the estimated regression. Sometimes, standardized unit costs can be used across studies, such as cost per bed-day (Adam et al., 2003; Barnum & Kutzin, 1993; Breyer, 1987). In other cases, an average cost function on cost per sexual health consultation at a clinic could use cost per HIV test conducted or cost per sexually transmitted disease treated as the dependent variable. However, average cost functions vary according to which of many outputs are used in the denominator and if this is arbitrarily chosen, it might lead to ambiguous results. For instance, an average cost function can ignore the effect of economies of scope associated with the chosen output variable. The Breusch–Pagan test of heteroscedasticity can potentially help to assess whether to use total or average costs as a dependent variable (Bautista-Arredondo, Sosa-Rubi, et al., 2018) or a heteroscedastic robust estimator can be applied.

The inclusion of program cost should also be considered carefully. As many above service level costs are intuitively fixed and invariant with the scale of production, such as management or information system set up, their inclusion or exclusion might have a big impact in the estimation of economies of scale, as discussed by Lepine and colleagues in the Avahan HIV prevention program in India (Lepine et al., 2016). Their results highlight the importance of ensuring that above service level costs are considered when examining optimal operational size. In cases where the proportion of above service level costs is substantial, the allocation method to the unit of analysis should also be clearly reported. In these cases, two cost functions can be estimated, with and without inclusion of above service level costs (Lepine et al., 2016).

3.2 | Search results

The screening process is presented in Figure 1. The database searches identified 8725 published studies for screening. A total of 40 articles were included (Table 1).

3.3 | Study characteristics

Most studies are conducted in Sub-Saharan Africa (n = 19, 48%), followed by South Asia (n = 10, 23%), multiple regions (n = 6, 15%), East Asia & Pacific (n = 4, 11%), and Latin America & Caribbean (n = 1, 3%)—see Table 1. Nine studies are multi-country analyses ranging from 2 to 188 countries (20%) and another nine studies are conducted in India (20%). Although we included other development economics interventions in our review, most studies are in the health sector (n = 39, 97%) and one study is related to waste management research (n = 1, 3%). Finally, a third of studies are related to HIV (n = 16, 38%), followed by health-related expenditure analysis (n = 5, 12%), packages of primary health care services (n = 6, 14%), and maternal and childcare (n = 3, 7%).

We observe an increasing number of relevant studies over time, and half of the studies (48%) are published in the five most recent years (Supporting Information S1: Table A6). Studies are published in a wide range of journals in the fields of health economics (n = 7, 19%); health management, policy, and planning (n = 5, 13%); health service delivery (n = 27, 65%); and

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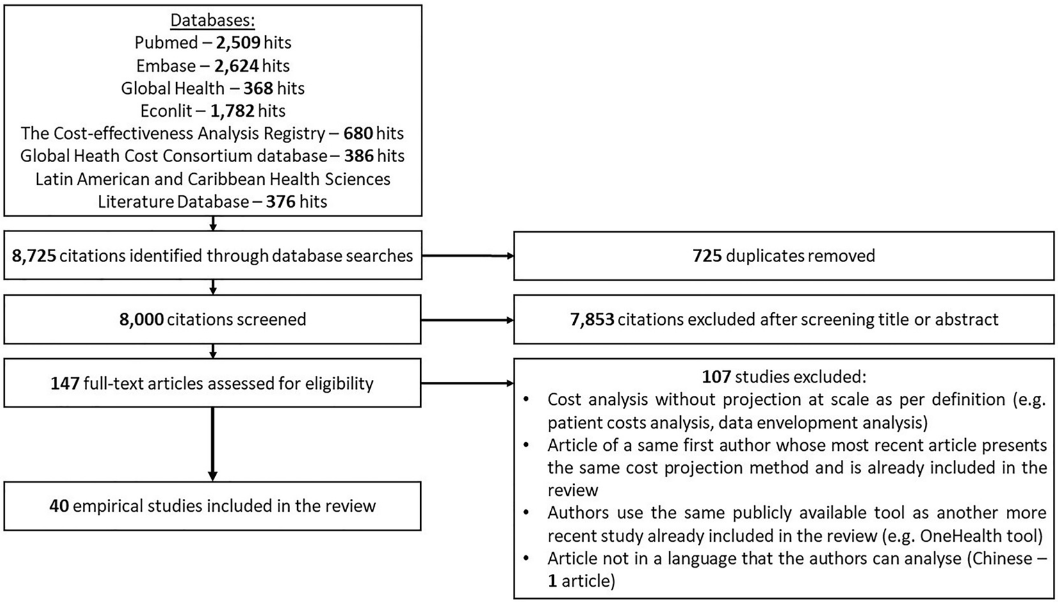

FIGURE 1 Database search and screening process.

waste management research ($n = 1$, 3%). The most common publication journals are PloS one ($n = 6$, 12%), Cost Effectiveness and Resource Allocation ($n = 4$, 11%), Health Policy and Planning ($n = 3$, 7%) and The Lancet journals ($n = 3$, 7%).

3.4 | Applications of cost function

Several factors are considered by researchers when selecting the type of cost function for projecting costs at scale. These are presented by projection approach in Supporting Information S1: Figure A1. The intended use of cost projections is the major factor considered, other motivators are scope of analysis, complexity of cost function, data-related considerations, method being easy to use, transparent, replicable, or whether the analysis tool is available online (Supporting Information S1: Text A2). ACF have a broader range of motivators suggesting its wider range of applications; the main motivators are the intended use of the cost projection, scope of analysis, and the complexity of the cost function.

A synthesis of study objectives by cost projection approach is presented in Figure 2 and follow the classification proposed by the Global Health Costing Consortium reference case (Vassall et al., 2017). In summary, most studies informing short- and medium-term financial planning use ACF with one exception (Adam et al., 2003). Long-term financial planning present nuanced approaches with either accounting, econometric or mixed approaches (Berman et al., 2018; Castro, 2017; Global Burden of Disease Health Financing Collaborator, 2018; Verguet et al., 2015). For technical efficiency analyses, a few studies specifically explore how to measure the efficient scale of operation (Bollinger et al., 2014; Guinness et al., 2007; Lepine et al., 2015; Meyer-Rath & Over, 2012; Weaver & Deolalikar, 2004), while other studies analyze drivers of technical efficiency between sites more broadly, and all use ECF. Only a few studies conduct an economic evaluation at scale using cost functions as per our inclusion criteria (excluding SCM) (Kerr et al., 2015; Marseille et al., 2012; Turner et al., 2016; Winskill et al., 2017). We report a descriptive analysis of these applications in Supporting Information S1: Text A3.

4 | DERIVED ALGEBRA AND FRAMEWORKS FOR RECOMMENDATIONS

In their review, Johns et al. provide general guidance on factors to consider when adjusting costs to account for scale, including: calculating separate unit costs for urban/rural setting; identifying (dis)economies of scale, separating the fixed and variable components of the costs; assessing the availability and capacity of health human resources; and including above service level costs (Johns & Torres, 2005). We identified similar factors through the classification of fixed/variable costs at various intervention levels for ACF and the classification of regressors for ECF. In this section, we further explore how to consist-

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TABLE 1 Overview of individual study characteristics ($N = 40$).

First author, year	Study objective	Cost function	Intervention field	World region	Country
Kerr et al. (2015)	Econ. Eval.[a]	Accounting	HIV	Multiple regions	Not reported
Turner et al. (2016)	Econ. Eval.	Accounting	Parasitology—helminthiasis	Sub-Saharan Africa	Uganda
Winskill et al. (2017)	Econ. Eval.	Accounting	Malaria	Sub-Saharan Africa	Unknown
Marseille et al. (2012)	Econ. Eval.	Econometric	HIV	Sub-Saharan Africa	Zambia
Abdullah et al. (2012)	Fin. Plan.[b]	Accounting	Basic package of health services	East Asia & Pacific	Indonesia
Barasa et al. (2012)	Fin. Plan.	Accounting	Maternal and child care	Sub-Saharan Africa	Kenya
Cantelmo et al. (2018)	Fin. Plan.	Accounting	Basic package of health services	East Asia & Pacific	Cambodia
Castaneda-Orjuela et al. (2013)	Fin. Plan.	Accounting	Vaccination	Latin America & Caribbean	Colombia
Deghaye et al. (2006)	Fin. Plan.	Accounting	HIV	Sub-Saharan Africa	South Africa
Deo et al. (2019)	Fin. Plan.	Accounting	Tuberculosis	South Asia	India
Ensor et al. (2012)	Fin. Plan.	Accounting	Basic package of health services	East Asia & Pacific	Indonesia
Marschall and Flessa (2008)	Fin. Plan.	Accounting	Basic package of health services	Sub-Saharan Africa	Burkina Faso
Prinja et al. (2018)	Fin. Plan.	Accounting	Maternal and child care	South Asia	India
Rodrigues et al. (2014)	Fin. Plan.	Accounting	HIV	South Asia	India
Terris-Prestholt et al. (2006)	Fin. Plan.	Accounting	Adolescent health	Sub-Saharan Africa	Tanzania
Verguet et al. (2015)	Fin. Plan.	Accounting	Surgery	Multiple regions	88 countries
Castro (2017)	Fin. Plan.	Econometric	Health care expenditures	Multiple regions	156 countries
Global Burden of Disease Health Financing Collaborator (2018)	Fin. Plan.	Econometric	Health care expenditures	Multiple regions	188 countries
Berman et al. (2018)	Fin. Plan.	Mixed	Basic package of health services	Sub-Saharan Africa	Ethiopia
Adam et al. (2003)	Fin. Plan.	Econometric	Hospital expenditures	Multiple regions	6 countries
Ameli and Newbrander (2008)	Tech. Eff. An.[c]	Econometric	Basic package of health services	South Asia	Afghanistan
Bautista-Arredondo, Colchero, et al. (2018)	Tech. Eff. An.	Econometric	HIV	Sub-Saharan Africa	Nigeria
Bautista-Arredondo, Sosa-Rubi, et al. (2018)	Tech. Eff. An.	Econometric	HIV	Sub-Saharan Africa	4 countries
Bollinger et al. (2014)	Tech. Eff. An.	Econometric	HIV	Sub-Saharan Africa	6 countries
Chandrashekar et al. (2010)	Tech. Eff. An.	Econometric	HIV	South Asia	India
Dandona et al. (2005)	Tech. Eff. An.	Econometric	HIV	South Asia	India
Galarraga et al. (2017)	Tech. Eff. An.	Econometric	HIV	Sub-Saharan Africa	Kenya
Guinness et al. (2007)	Tech. Eff. An.	Econometric	HIV	South Asia	India
Johns et al. (2013)	Tech. Eff. An.	Econometric	Maternal and child care	Sub-Saharan Africa	Malawi
Lepine et al. (2015)	Tech. Eff. An.	Econometric	HIV	South Asia	India
Lepine et al. (2016)	Tech. Eff. An.	Econometric	HIV	South Asia	India
Menzies et al. (2012)	Tech. Eff. An.	Econometric	HIV	Multiple regions	6 countries
Meyer-Rath and Over (2012)	Tech. Eff. An.	Econometric	HIV	Sub-Saharan Africa	South Africa

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TABLE 1 (Continued)

First author, year	Study objective	Cost function	Intervention field	World region	Country
Mujasi and Puig-Junoy (2015)	Tech. Eff. An.	Econometric	Pharmaceutical expenditures	Sub-Saharan Africa	Uganda
Obure et al. (2016)	Tech. Eff. An.	Econometric	HIV	Sub-Saharan Africa	2 countries
Parthan et al. (2012)	Tech. Eff. An.	Econometric	Solid waste management	South Asia	India
Pitt et al. (2017)	Tech. Eff. An.	Econometric	Malaria	Sub-Saharan Africa	Senegal
Schneider and Hanson (2007)	Tech. Eff. An.	Econometric	Health insurance	Sub-Saharan Africa	Rwanda
Weaver and Deolalikar (2004)	Tech. Eff. An.	Econometric	Hospital expenditures	East Asia & Pacific	Vietnam
Ahanhanzo et al. (2015)	Tech. Eff. An.	Econometric	Vaccination	Sub-Saharan Africa	2 countries

[a]Economic Evaluation: use of cost estimates in analytical approaches to assess allocative efficiency of investment and policy decisions.

[b]Financial Planning: use of cost estimates to predict expenditures in the medium (3–5 years) and longer term.

[c]Technical Efficiency Analysis: use of costs to explore differences and drivers of technical efficiency between providers and/or modes of delivery for health interventions or services.

Source: (Vassall et al., 2017).

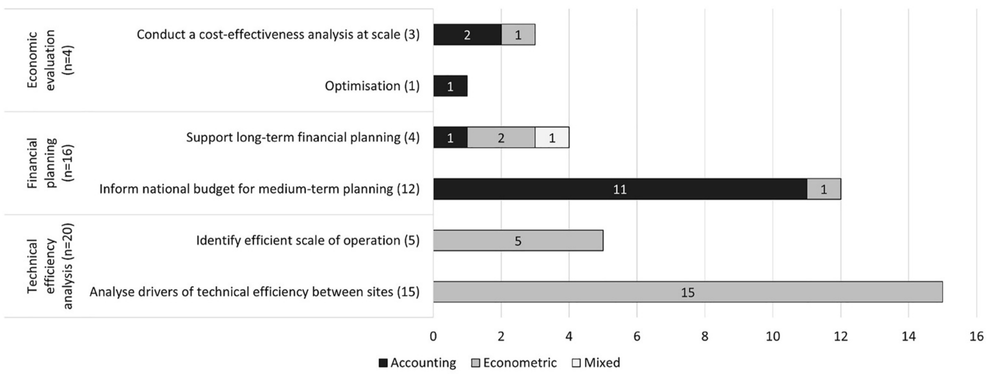

FIGURE 2 Synthesis study objectives by type of cost function ($N = 40$).

ently apply these factors and we derive the algebra for each cost function that encompass all reported methods. The algebra is presented in Table 2 and applied examples are provided in Supporting Information S1: Table A8. Finally, we propose frameworks to guide the decision process of fitting the ACF and ECF by study objective (Figure 3a,b). The development of these frameworks is based on the synthesis of cost function algebra from our study sample, the analysis of authors' motivators guiding the fitting of a cost function, and complemented by the methodological literature on healthcare cost data analysis. We propose an approach to estimate variable returns to scale in cost projection methods, which is currently ignored in most studies. We also report on the SCM (linear cost function) as a basis for comparison with ACF and ECF.

4.1 | Simple cost multiplier (linear cost function)

As the review is broad in nature, and the aim is to synthesize information on the most innovative approaches, we excluded the commonly found SCM method from the search. However, we recognize the usefulness of this simplified approach for two reasons: (1) its simplicity and transparency desirable for certain types of analysis, and (2) although intuitively less accurate as it assumes constant returns to scale, there is no method obviously superior to another, that is, no defined gold standard for each study objective. In this review, we only found one study related to development economics using an alternative approach to SCM (waste management research), suggesting that more complex cost projection methods (beyond SCM) are mostly found in health care interventions in development studies.

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TABLE 2 Cost functions—Derived mathematical notations.

Simple cost multiplier (comparator)	Accounting cost function	Econometric cost function
$C = s \cdot \text{UC}$ with $\text{UC} = \sum_i P_i \cdot Q_i$	$C = \sum_j c_j + \sum_k \left\lceil \frac{s_k}{D_k} \right\rceil \cdot c_k + \sum_l s_l \cdot c_l + \sum_m s_m \cdot \left(\left(\frac{s_m}{S_m^{\text{full}}} \right)^x \cdot \left(C_m^{\text{full}} - c_m \right) + c_m \right)$ with $c_j = f(P_j, Q_j)$ in the short run, with $c_k = f(P_k, Q_k)$; $c_l = f(P_l, Q_l)$; $c_m = f(P_m, Q_m)$, with $\left\lceil \frac{s_k}{D_k} \right\rceil$, where [] is the rounded-up value to the nearest higher integer and is >0	$C = \sum_v C_v$ with $C_v = \beta_0 + \sum_w \beta_{vw} \cdot X_{vw}$ OR $C = \sum_v \text{UC}_v \cdot s_v$ with $\text{UC}_v = \beta_0 + \sum_w \beta_{vw} \cdot X_{vw}$
Where: C: Total cost s: Scale variable to reach desired number of outputs UC: Unit cost per output i: Input (building, personnel, supplies, etc.) differentiated by intervention level (health facility, district office, central, etc.) P_i: Price of an input i Q_i: Quantity of input i required for one output	Where: c: Cost by type of input (building, personnel, supplies, etc.) differentiated by intervention level (health facility, district office, central, etc.) s: Scale is defined as a number of outputs c and s vary by type of input. We differentiate the type of inputs into j, k, l, m defined by their behavior at scale (j = fixed, no variation to scale; k = semi-variable, increasing returns to scale; l = variable, constant returns to scale; m = variable, decreasing returns to scale) P: Price of an input Q: Quantity of input required for one output D_k: Maximum capacity per input k C_m^{full}: Input cost m when outputs are produced at full scale-up S_m^{full}: Number of outputs at full scale-up for an input m x: Scale factor—varies typically from 2 to 5	Where: β_0: Model intercept v: Unit of analysis: District, facility, catchment area of health facility w: Number of regressors introduced in the model β_{vw}: Model coefficients computed using empirical dataset X_{vw}: Regressors introduced in the model—Quality variables, organizational characteristics of the unit v, characteristics of the population reached by v, environmental characteristics, and observed scale variable

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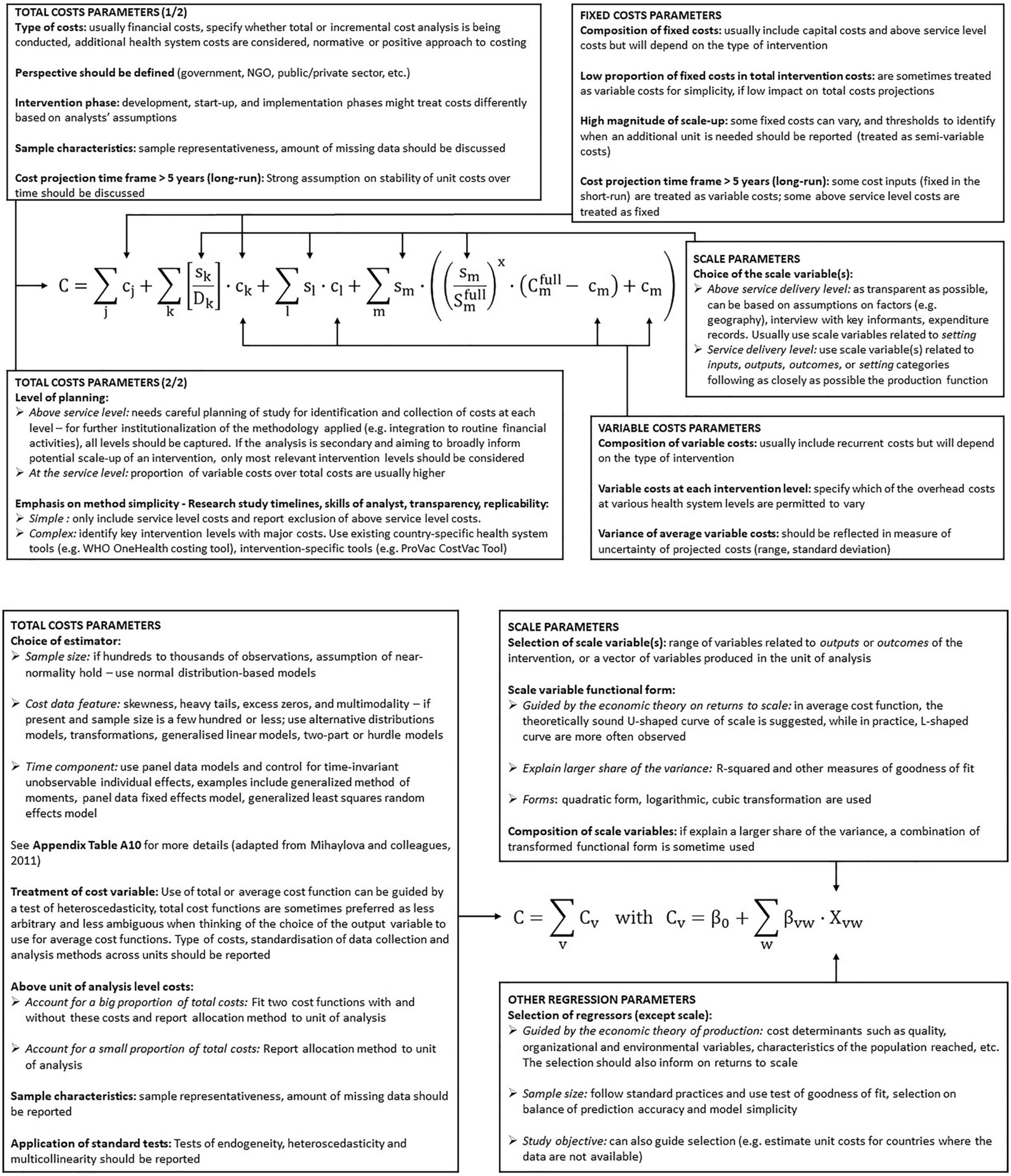

FIGURE 3 (a) Framework—Fitting of Accounting cost functions. (b) Framework—Fitting of econometric cost functions.

As presented in Table 2, the SCM approach estimates total costs at scale (C) using a unit cost per output (UC) multiplied by a scale variable to reach a desired number of outputs (e.g., number of HIV test to conduct). The UC is the sum of multiplied input prices (P_i) by input quantities (Q_i) for one output, for each cost input (i), identified at different intervention levels—

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national, regional, district, health facility, community, etc. SCM, following our definition, imposes a linear relationship between variable inputs and output quantities: a given percentage increase in inputs leads to the same percentage increase in output. Therefore, SCM only accounts for constant returns to scale, and (dis)economies of scale cannot be evaluated.

4.2 | Accounting cost functions—Application for medium- and long-term financial planning, economic evaluation at scale

4.2.1 | Derived algebra

In this section, we describe the terms of the accounting cost function (Table 2) and analyze the 15 included papers that use this approach. Derived notations with detailed extractions by study are presented in Supporting Information S1: Table A9. The costs (C) are total program costs at scale for one or more interventions, regardless of whether scale-up happens at sub-national, national, or international level.

The cost inputs j, k, l, and m are defined by their behavior as scale changes, where: j = fixed cost, no variation with scale; k = semi-variable cost, exhibiting increasing returns to scale; l = variable cost, exhibiting constant returns to scale; m = variable cost, exhibiting decreasing returns to scale; as illustrated in Figure 4. Inputs k are categorized as "semi-variable" because they are the fixed costs for a given level of production and become variable after a certain production level is reached.

The studies identified inputs at various intervention levels and differentiated between: (1) *service delivery:* health facility—primary health center ($n = 6$, 15%) or secondary hospital health center ($n = 2$, 5%), the entire site or part of it related to the intervention (e.g., operating room) ($n = 1$, 3%); outreach (community, village) ($n = 3$, 8%); and (2) *above service delivery*: government/central or health system level ($n = 3$, 8%), state ($n = 1$, 3%), district ($n = 3$, 8%), block ($n = 1$, 3%), ward ($n = 1$, 3%), department ($n = 1$, 3%), municipality ($n = 1$, 3%), community council, etc.—depending on the country's administrative structure (Supporting Information S1: Table A9).

Fixed cost inputs j are identified at different intervention levels. Fixed costs include a broad range of costs related to intervention start-up phase ($n = 1$, 3%), sensitization ($n = 1$, 3%), production of information, education, and communication material ($n = 3$, 8%), training ($n = 2$, 5%), meetings, workshops ($n = 1$, 3%), capital goods (building, vehicle, equipment) ($n = 1$, 3%), administrative central cost, central/national/sub-national/overheads ($n = 3$, 8%), personnel (management/program, supervision, monitoring, data management) at sub-national level, health facility level ($n = 7$, 18%) (Supporting Information S1: Table A9).

Almost all variable costs from these studies are assumed to exhibit constant returns to scale (input l) and include a broad range of inputs. These costs can be varied depending on the intervention and magnitude of scale-up. Most commonly, these costs

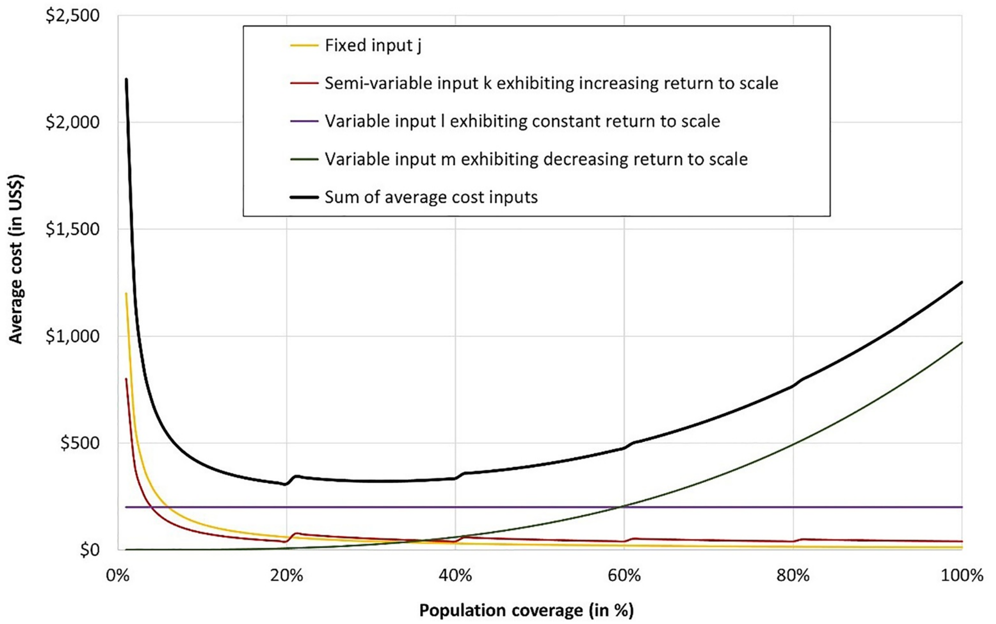

FIGURE 4 Average cost of inputs j, k, l, m, and sum of inputs by % population coverage. [Colour figure can be viewed at wileyonlinelibrary.com]

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include medical personnel costs ($n = 4$, 10%), and medical supplies such as drugs or biological tests ($n = 8$, 20%). Only two studies account for variable returns to scale, for instance related to delivery costs, increasing with scale to account for diminishing marginal returns associated with a higher unit cost at high levels of coverage ($n = 2$, 5%) (Supporting Information S1: Table A9).

The following three parameters need to be defined by the analyst (observed or arbitrarily): $\boldsymbol{D_k}$ (maximum capacity per input k), $\boldsymbol{C_m}^{\mathbf{full}}$ (input cost m when outputs are produced at full scale-up), and $\boldsymbol{S_m}^{\mathbf{full}}$ (number of outputs at full scale-up for an input m).

Finally, the scale factor x applied for cost inputs m defines how steep the slope of the curve is, that is, the lower the power, the stronger the assumed effect of decreasing returns to scale (e.g., transport costs are rapidly increasing at scale-up if roads are in a bad state and require 4 × 4 with high petrol consumption) (Supporting Information S1: Figure A2).

In the short run, ACF identifies fixed input costs. As output increases, fixed costs are spread across more units of output and the average cost per output is decreasing, exhibiting increasing returns to scale. After a certain point in scale, average cost increases related to either the law of diminishing marginal returns (short run), or theoretical diseconomies of scale, such as management challenges at large scale (long run) (Bishai et al., 2006; Elbasha & Messonnier, 2004; Sloman et al., 2018). However, the literature on cost functions usually agrees on a L-shaped average cost curve against scale, rather than the U-shaped curve as diseconomies of scale are rarely empirically measured (Guinness et al., 2007; Lave & Lave, 1984; Lepine et al., 2016).

It is increasingly relevant to account for decreasing returns to scale for the application of cost function formula to epidemics, such as HIV and malaria because it costs more to reach the last percentage of the target population (remote areas, groups harder to reach, etc.). Winskill and colleagues applied a fixed delivery cost of malaria prevention technologies per person reached at a baseline amount and after a given threshold, derived a logarithmic relationship between coverage and delivery costs to account for higher costs of reaching the last percentage of the population (Winskill et al., 2017). Therefore, because of the flexibility in fitting non-linear relationship between output and input costs, ACF can account for variable (increasing then decreasing) returns to scale contrary to SCM.

4.2.2 | Best practice guidance

The proposed framework (Figure 3a) provides recommendations on how to fit the ACF. A major assumption with ACF using average fixed/variable costs is that for each intervention levels, we assume similar costs between units (e.g., health facility, district) ignoring efficiency considerations (economies of scale and scope). Another issue relates to the consideration of joint costs and methods to allocate them to average costs; this is further explained in the Global Health Cost Consortium reference case (Vassall et al., 2017). The formula assumes that average costs are constant over time, which might be acceptable in the medium-term, but a limitation in long-term planning. Meyer-Rath and Over showed with the modeling of antiretroviral treatment costs at scale in South Africa that delivery costs can significantly change depending on how services are delivered and the rate of scale-up (Meyer-Rath & Over, 2012). A measure of variability, such as range or standard deviations should be reported, which is currently not done in most studies.

Scale variables correspond mostly to input, output and outcome variables at the service delivery level, but might be less intuitive for above service levels where *setting* is more commonly used. The diversity of variables used implies a necessary choice from the authors that replicate as realistically as possible a scale unit that follows the production process.

However, one should note that multiple output variables can act as proxies for scale. The choice of output variables also defines the composition of the relevant average variable cost and might lead to wide variation in the estimation of total costs. It also ignores the concept of quality of health care services, which influences both scale and costs (Donabedian, 2005; Meyer-Rath & Over, 2012).

4.3 | Econometric cost functions—Application for technical efficiency analysis for estimating costs at scale, economic evaluation at scale

4.3.1 | Derived algebra

The costs are represented by total program costs (C) or total cost at the unit of analysis v (C_v) ($n = 9$, 23%) or unit costs per unit of analysis (UC_v) ($n = 15$, 38%), single or a set of cost dependent variables ($n = 8$, 20%), and log transformed or not ($n = 10$, 25%) (Table 2).

Broadly, several groups of w regressors (X_w) are identified in this review, including scale, quality, and organizational variables, following the classification proposed by Lepine et al. (2016): (1) quality: share of management staff in total staff,

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proportion of drugs out of stock during observation period; (2) unit organizational characteristics: type of hospital, cost inputs (labor, drug costs), experience of medical staff/non-governmental organization; (3) environmental time-variant factors: growth domestic product, target population size within unit of analysis; (4) environmental time-invariant factors: country, urban/rural setting, geographical characteristics (e.g., distance to nearest health facility); (5) characteristics of population targeted: socio-economic status, clinical characteristics (e.g., proportion of high-risk population reached).

The functional form is normal, quadratic (assuming U-shaped following the economic theory), log transformed (L-shaped), or cubic, and several forms are sometimes included in the equation ($n = 6$, 15%). The scale variable is a combination of variables defining scale-up of simultaneous interventions or a single variable in the equation ($n = 15$, 38%). The functional form of the scale variable(s) is either normal, squared, cubic, or log transformed, and sometimes, several forms are included in the same equation ($n = 9$, 23%). The classification of scale variables follows the one proposed for ACF. The most common categories of scale variables are related to *outcomes* (e.g., number of clients tested) ($n = 15$, 38%) or *outputs* (beneficiaries or coverage of eligible population) ($n = 9$, 23%). Other scale variables related to *inputs*, and *setting* are less commonly used. Only one category of scale variable is used in each cost function, with one exception ($n = 1$, 3%) (Supporting Information S1: Table A9).

The unit of analysis v is broad, the most commonly observed units are health facility ($n = 14$, 35%), non-governmental organization ($n = 4$, 10%), country ($n = 3$, 8%). The unit of analysis is sometimes time-dependent, affecting the choice of estimator for time series and/or panel data models ($n = 5$, 13%) (Supporting Information S1: Table A9).

For ECF, the relationship between inputs and outputs is specific to each unit of analysis. Observed constant or variable returns to scale are identified by looking at the entire sample of sites. The values of scale can be transformed to improve the goodness of fit in the regression model—in theory, log-transformation provides the best fit as it accounts for some increasing returns to scale (economies of scale), and is often observed in the literature (Bautista-Arredondo, Colchero, et al., 2018; Berman et al., 2018; Bollinger et al., 2014; Lepine et al., 2016). A combination of transformed scale variables is sometimes found (e.g., logarithmic and quadratic), potentially accounting for increasing then decreasing returns to scale. The sign and value of the scale variable coefficient allow to measure (dis)economies of scale, other things being equal. Other cost determinants in the model (e.g., percentage of hard-to-reach group tested) can be varied as scale is increasing to account for variable returns to scale.

4.3.2 | Best practice guidance

The proposed framework (Figure 3b) provide recommendations on how to fit the ECF. Challenges in finding the right specifications for regression models are well documented in the literature and choosing the best estimator for health care cost analysis is not simple (Basu et al., 2004, 2006; Chen et al., 2013, 2016; Gebregziabher et al., 2013; Li et al., 2016; Manning et al., 2005; Mazumdar et al., 2020; Montez-Rath et al., 2006; Powers et al., 2005; Yoon et al., 2019). Several literature reviews and comparative studies exist to guide the choice and specification of a regression model (Basu et al., 2011; Franklin et al., 2019; Malehi et al., 2015; Manning, 1998; Manning & Mullahy, 2001; Mantopoulos et al., 2016; Mullahy, 1998). We find the review by Mihaylova and colleagues particularly useful (Mihaylova et al., 2011). We summarize in Supporting Information S1: Text A4 the features of cost data to consider for model selection and in Supporting Information S1: Table A10 the different estimators that can be used based on Mihaylova's review and empirical applications from our study sample (Mihaylova et al., 2011). However, in LMICs, most of studies are conducted on relatively few sites where data access is sometimes limited, posing a major challenge for the validity of statistical methods applied in this context. More than half of the econometric analyses in our review are conducted with a sample below one hundred. The feature of cost data is guiding the choice and specification of the regression models. Cases where there is a need to back transform to produce inferences on the original cost variable, rather than on the transformed cost variable are complex, and are out of the scope of this review.

A challenge in developing cost prediction models is the presence of many covariates. Therefore, variable selection methods should be applied to achieve a balance of prediction accuracy and avoid over fitting the model (Franklin et al., 2019; Mihaylova et al., 2011; Yoon et al., 2019). However, in economics, independent variable selection should be based on theory and not on fit, making model fitting challenging. In LMICs, the availability of good proxy variables is sometimes limited due to data scarcity and may require a less than optimal choice of covariates, for instance, when assessing quality proxied by a share of supervisory team or how well a site reached target groups of an intervention (e.g., sex workers for HIV care services). The purpose of the cost projection exercise can also guide the choice of explanatory variables. For instance, when the aim is to estimate average costs for countries where the data are not available, the chosen explanatory variables must be available in the out-of-sample countries (Adam et al., 2003). Efficiency, or "economies of scope" parameters can be included as an independent variable to assess their impact on site-level costs. Ideally, incentives for increasing service efficiency (e.g., financial incentives paid to health providers) should also be captured in the cost function.

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When there is no commonly agreed measure as a proxy of scale (e.g., doses of vaccines delivered), the choice of variable(s) defining scale can sometimes be arbitrary (as for accounting methods) and can use a wide range of variables related to *outputs* or *outcomes*. The economic theory can guide the choice of how to transform the scale variable. A number of studies have shown that when using average cost as dependent variable, the cost function may be more consistent with an L-shaped curve in practice (Guinness et al., 2007; Lepine et al., 2016), rather than the theoretical U-shape (Lave & Lave, 1984). In addition, the scale can be tested to see whether a logarithmic form versus a quadratic, cubic functional form, or normal form explains a larger share of the variance. The issue of endogeneity for the estimation of unbiased economies of scale also needs to be addressed. It can arise from key independent variable omission, simultaneous relationship between scale and costs, and random measurement error, and has been described empirically by Lepine et al. (2015).

The analysis of costs at scale should account for the notion of time and application of economic concepts related to short and long run situations. In the short run, at least one input is fixed, whereas, in the long run, all inputs can vary (Sloman et al., 2018). Based on the algebra, SCM is therefore applied only in the long run, ACF in both the short run (if some inputs are fixed) and the long run, and ECF ignores the notion of time because it does not use inputs in the regression model to project costs at scale.

5 | CONCLUSIONS, LIMITATIONS, AND FUTURE RESEARCH

The proposed notations and frameworks can offer a more consistent use of cost functions in LMICs by guiding the choice of the relevant approach based on the intended use of the cost estimate. We hope to facilitate the decision process of balancing simplicity versus accuracy when needed and to increase the overall transparency in the reporting of methods.

Our study has a few limitations. First, the review is in majority based on the published peer-reviewed literature potentially missing other innovative methods. However, the aim was to select studies which already passed a peer-review process. Second, this review excluded technical efficiency analyses, such as frontier models, data envelopment analysis or stochastic frontier approach. Although these approaches are not used to estimate costs at scale per se, we recognize that they contribute to insights on efficiencies and therefore, on the estimation of more accurate costs at scale. Nevertheless, we believe that these approaches would not be a first choice for the estimation of costs at scale, and are, therefore, less central in this review. Third, we only included studies using a provider perspective. We recognize this limitation because researchers should aim to include societal costs whenever possible. However, we think this is a distinctly different area of research (patient cost analyses), and outside the scope of this review. Fourth, for ECF, the interpretation of coefficient of cost determinants, including scale, can be challenging (related to issues of back transformation), and is not discussed in this review because it is specific to each study. Fifth, since we almost never have information on observed costs at scale to compare with projected costs, the validation of cost projection approach in each study cannot be done and only transparency in methods reporting and expected validity of cost projections were assessed in our critical review.

Areas of future research include comparative analysis of these various cost functions based on empirical data to further characterize similarities and differences between approaches, further integration of cost functions into theoretical economics textbooks and applied economic evaluations, development of a validated reporting checklist for study transparency and validity, and the development of econometric approaches that can address the issues specific to LMICs, including working with a small sample of sites and restricted access to routine information and financial data.

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CONFLICT OF INTEREST STATEMENT

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Marc d'Elbée https://orcid.org/0000-0002-8827-019X
Andrew Briggs https://orcid.org/0000-0002-0777-1997

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