The costs of introducing a vaccine in sub-Saharan Africa: a systematic review of the literature

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Abstract

Purpose – This study provides a systematic literature review and categorization of the costs reported in the literature for the introduction of new vaccines, focusing on sub-Saharan Africa within LMICs, where vaccines are highly needed, financial resources are scarce and data are lacking and scattered.

Design/methodology/approach – A systematic literature search of PubMed and Web of Science databases was conducted according to the PRISMA requirements. Searches also included the relevant grey literature. In total, 39 studies were selected and nine cost categories were investigated to build a comprehensive framework.

Findings – The paper considers nine cost categories that cover the whole life of the vaccine, from its initial study to its full implementation, including for each of them the relevant subcategories. The systematic review, besides providing specific quantitative data and allowing to assess their variability within each category, points out that delivery, program preparation, administration and procurement costs are the most frequently estimated categories, while the cost of the good sold, costs borne by households and costs associated to AEFI are usually overlooked. Data reported on R&D costs and investment in the production plant differ significantly among the selected contributions.

Originality/value – The literature contributions on cost estimation tend to focus on a precise vaccine, a specific geographic area, or to adopt a narrow approach that captures only a subset of the costs. This article presents a rich and inclusive set of the economic quantitative data on immunization costs in limited-resource countries.

Keywords Public health, Evidence-based practice, Emerging health economies, Quantitative research

Paper type Literature review

Introduction

Even before COVID-19, immunization has proven to be one of the most cost-effective medical interventions to defeat diseases worldwide (Berkley, 2014), having a great impact on human health and contributing to increase life expectancy and quality (WHO, 2013; Black, 2013). Indeed, vaccines are one of the most successful public health initiatives in eliminating or reducing the impact of infectious diseases (Timmis *et al.*, 2017).

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The recent pandemic has made the value of vaccines even clearer due to the substantial impact they had on mitigating COVID-19 outbreaks (Polack *et al.*, 2020; Moghadas *et al.*, 2021). Nowadays, the fast-track development and large-scale production of safe and effective COVID-19 vaccines (i.e. Pfizer BioNTech, Moderna, Janssen) would not have been possible without a renewed business vision and model characterized by both accelerated innovation and strong partnerships. The COVID pandemic has demonstrated that it is possible to develop, test and review multiple safe and effective vaccines against a new disease in less than a year. This should also be a paradigm to enhance access and rollout to vaccines, in particular in low-income and middle-income countries, since the COVID-19 pandemic may have worsened the already existing and wide gaps in healthcare services. The Ebola vaccine is another example of how solidarity, science and cooperation between international organizations and the private sector to save lives can help scaled rollout throughout sub-Saharan Africa.

Furthermore, as highlighted by Tatar and Wilson (2021), the COVID-19 campaign is a unique and valuable opportunity to advance public health and improve public trust in the healthcare system and decreasing global disparities in health outcomes.

However, despite this clear evidence, the goal of providing the needed vaccination programs, in line with the Sustainable Development Goal 3 (Good Health and Well-Being) of the UN-2030 Agenda, has not been achieved yet (UN, 2021), especially in lower-middle-income countries (LMICs), where vaccine-preventable diseases are still a relevant cause of morbidity and mortality. Furthermore, some infectious diseases are still lacking a vaccine: approximately 60% of the current all age burden of infectious diseases, there is no registered vaccine, especially in developing countries (Saul and O'Brien, 2017). Moreover, prevalence rates or the size of affected populations may be impeding the investment of discovery and industry development for many of the diseases that are currently missing a vaccine.

Therefore, the need of new vaccines and greater diffusion of those already existing is evident, especially in LMICs, where greater difficulties arise in facing the relative costs and there are more fragile health conditions. Hence, a reliable and well-founded forecast of costs is of fundamental importance and an essential prerequisite for further sustainability analysis, in order to decide among different competing health needs, prioritize the allocation of resources and attract the necessary funding. As highlighted by Bloom (2015): "looking at vaccination with an economic lens is meaningful because it communicates in the language of decision makers who have the power of the purse".

In line with this, a greater attention has been progressively paid both in estimating the immunization costs and in valuing vaccination's benefits. In 2008, WHO developed a special "Guide for Standardization of Economic Evaluations of Immunization Programmes" to provide guidance to those who conduct or critically appraise economic evaluations of immunization programmes at local, national and global levels (the document was updated in 2019). However, as underlined in the same preface of the WHO guide: "the emphasis is on what to do, rather than how to do it".

To support this last step, the literature is providing a growing number of examples. Often, however, they focus strictly on a precise vaccine (Nichol, 2003; Termrungruanglert *et al.*, 2012) and a specific geographic area (Rose *et al.*, 2017; Haidari *et al.*, 2016) and they mainly adopt a narrow approach that captures only a subset of the costs (Gouglas *et al.*, 2018) and benefits (Bärnighausen *et al.*, 2014) of vaccination campaigns.

The purpose of this research is to collect and cluster the main different quantitative information obtainable from the published literature to support economic evaluations of immunization programs. In particular, the present study focuses on the costs of vaccine introduction and aims at providing a systematic review of the costs reported in the literature for the introduction of new vaccines, focusing on sub-Saharan Africa within LMICs.

The reason for the choice of such a focus is because, in these countries, vaccines are highly needed; financial resources are scarce, and data are lacing and scattered. This makes it very difficult to elaborate complete cost estimations to support reliable sustainability analysis and, consequently, investments both in the development and in the delivery of vaccines.

Despite the information variety of the contributions analyzed, all the relevant cost categories with a significant impact on vaccine introduction were included. Hence, this article aims at providing an inclusive and quantitative review of the costs of vaccine introduction in limited-resource countries. The final aim is to make cost estimations more trustworthy and, thus, to provide valuable information to stakeholders involved in the introduction of a novel vaccine in sub-Saharan Africa.

Methods

Authors have been involved in studying the existing literature regarding economic evaluations of introducing a vaccine in LMICs – especially in sub-Saharan Africa – since 2017, when they have been engaged in the S-AFRIVAC project (under the coordination of Achille Sclavo Foundation and the scientific direction of Rino Rappuoli), whose focus was the introduction of a vaccine against invasive non-typhoidal salmonella (iNTS) disease in sub-Saharan Africa. In particular, the authors were involved in drawing up the sustainability plan of the project.

For this reason, a remarkable amount of materials have been analyzed throughout the almost four years of study, following a well-defined process (Muka *et al.*, 2020; Tawfik *et al.*, 2019) summarized in Table 1.

Data collected from these contributions concern several diseases, among which meningitis, rotavirus, cholera, malaria and typhoid. Despite the variety of the contributions analyzed, an effort to embrace all the relevant cost categories that have a significant impact on the introduction of a new vaccine in sub-Saharan countries was made.

Results

Economic quantitative data on immunization costs were extracted from the selected contributions. Data were divided into cost categories that cover the whole life of the vaccine, from its initial study to its full implementation, including procurement costs. For each category, subcategories were identified in order to rationalize the different cost estimations that can be found in the literature, understand their peculiarities and seize their comparability. The division in subcategories has been carried out in such a way as to provide detailed quantitative economic data on the most relevant components.

The main cost categories included in this review were identified distinguishing them according to the particular phase of the introduction process to which they refer. Table 2 describes the nine cost categories included. Within the 39 selected contribution, the most analyzed and discussed cost categories are delivery, administration and procurement costs (they are present in 14, 19 and 15 contributions, respectively), while little quantitative information can be retrieved on the cost of the good sold, costs borne by households and on costs associated to adverse events following immunization (they are present in 1, 2 and 1 contribution, respectively). Costs related to R&D, program preparation and investment in the production plant can be found in 8, 7, 3 contributions respectively.

Table 3 briefly describes the main findings for each cost category, while Table 4 summarizes the quantitative data collected (reported as in the reviewed articles, without converting them back to the same year, in order to leave freedom of elaboration and computation to stakeholders who will benefit from the cost classification and data collected of this systematic review). Supplementary files from 2 to 9 collect the information for each cost

Search strategy	A systematic literature search of both scientific and economic databases was conducted according to the PRISMA requirements (Preferred Reporting Items or Systematic reviews and Meta-Analyses; Moher *et al.*, 2009). Figure 1 shows the different phases of the search process Web of Science and PubMed databases were systematically searched and the following restrictions were applied: English was the only language selected; the dates of the publications ranged from January 1, 2001 to July 15, 2021; only peer-reviewed articles were included; only studies related to LMICs were included, due to the research question we intend to address. Moreover, articles pertaining to non-humans, abstract-only papers as preceding papers, conference, editorial or articles without available full text available were excluded. The list of excluded studies is available upon request The search was preformed using appropriate text words and thesaurus terms for papers relating to the costs of immunization program in LMICs, particularly in sub-Saharan Africa. As for keywords, for both databases, we combined "vaccination cost/s", "immunization cost/s" and "vaccine cost categories" with each of the following research strings: "Africa", "sub-Saharan Africa" and "LMICs". Thus, no search was performed using one keyword only, since our research question concerns the introduction of a vaccine in low-middle income countries and, in particular, in sub-Saharan Africa We collected all references in a single file for each database (2.269 references for PubMed and 848 for Web of Science). After merging the references in a unique file, 481 duplicates were removed. The titles first and the abstracts afterward of each reference were screened for relevance by the authors, who judged the relevance of the abstract if the title was found to be relevant. The authors worked independently and then the references screened were collected and compared. The overlapping references were selected to be considered for the next step, the analysis of the full text. The non-overlapping references were discussed and a common final decision was reached. Our search strategy returned 441 articles to be screened for full-text review. We excluded 411 articles since they were not relevant for the purpose of the present study and/or they did not provide quantitative reliable information about the costs of introducing a vaccine in poor countries. We were left with 30 articles eligible for our study. The references of the 30 selected articles were carefully screened and so doing 4 more contributions were selected to be included Due to the comprehensive approach this study aims at embracing, by providing quantitative information on different cost categories in order to cover the different phases required by the vaccine introduction, searches were also undertaken by hand focusing on references from identified papers, authors' own collections and review articles. Google and the bibliography of the main international agencies (as WHO, GAVI, UNICEF etc.), as well as reports from the World Bank, were searched for the relevant grey literature and 5 crucial contributions were included
Study outcomes	Data were extracted and stored in an Excel sheet containing the economic information reported in each publication, on the basis of their availability. Variables collected included article information (title, authors, year and journal of publication) and economic quantitative information on the costs of the immunization programs

Table 1.
The research process

category from the selected papers. These results are separately discussed in the following sections.

Discussion

This cost review takes a broad perspective, considering also those costs that accompany and follow the actual administration of the vaccine, such as the costs borne by household. The results found point out that quantitative data are lacking and more research and quantitative studies are highly needed in order to account for the costs that have to be faced to introduce a vaccine in LMICs.

Some cost categories are particularly characterized by an indefinite estimation. For instance, for the R&D category, this review clearly identifies a relevant gap in the literature: few studies contain quantitative data and most of them just provide total costs without

Cost category				Description
1	Research and Development (R&D), clinical studies (pre- and early-), and registration costs	Pre-licensure		Vaccine R&D consists in identifying candidate vaccines, test safety and efficacy and evaluate efficacy in human beings. Vaccine R&D is a lengthy – it lasts more than 10 years (Serdobova and Kieny, 2006) − complex and risky process, involving high opportunity costs (Lightet al., 2009). ▪ R&D activities are followed by preclinical and clinical phases that can be divided into (Light *et al.*, 2009; UNICEF, 2018): • phase I (preclinical), enclosing adverse effects, safety, consistency, trial and efficacy assessment studies; • phase II (clinical), with age calculation, target population dosing and clinical trial studies; • phase III (advanced development), including dose optimality tests, larger samples and scaling up.
2	Investments in production plant	Pre-licensure		They include all costs supported in order to establish the vaccine production, including a full new plant or an already existing one.
3	Cost of goods sold	Pre-licensure	Post-licensure	They concern all costs concerning the production of the goods sold and costs incurred throughout the product cycle life of a vaccine
4	Vaccine delivery costs	Before immunization	Post-licensure	They concern the supply through the health system network, the storage and transport within the country to the different vaccination sites, aiming at preserving stability and reaching the entire population (WHO, 2013). They include all cold chain costs for storing vaccines and transportation logistics. They are particularly significant in Equatorial countries, where climate issues are relevant and communication routes are poorly developed. Vaccine delivery costs can be divided into service delivery costs, including personnel, program management, training, social mobilization and disease surveillance, and vaccine delivery costs, including storage, cold chain equipment, vehicles and transport.[10]
5	Vaccination program preparation costs	Before immunization	Post-licensure	They include micro-planning activities, training of personnel, community sensitization, social mobilization and other costs prior to vaccine implementation (Mogasale *et al.*, 2016). Micro-planning activities mainly consist of initial planning, remuneration and allowances for planners and management staff, costs sustained for planning meetings, equipment needed for planning and transportation costs. The training of personnel requires updated training material and should be targeted both to front-line health workers and to managers: hence, technical knowledge about vaccines and their administration, management competences and communication skills are needed (Berlier *et al.*, 2015). Community sensitization activities includes all the actions undertaken to enhance communication on the disease, contributing to target society and Stakeholder engagement. These are linked to social mobilization activities and organization of promotion campaigns. All communications activities in support of a novel immunization program need to be implemented in a strategic way in order to support in facing the challenge of how to present the need for a vaccine, as recently showed by the MenAfrivac case (Berlier *et al.*, 2015).
6	Vaccine administration costs	Before immunization	Post-licensure	They refer to administration costs sustained to provide vaccination to individuals. (Mogasale *et al.*, 2016). They include materials and supplies (i.e. cups for water, soap for hand wash, vaccination cards and supplies), site preparation (i.e. venue rental, cleaning and vaccination booth setup), vaccine administration (i.e. personnel costs, per diem and other allowances, including food and refreshment), supervision, monitoring and waste management. Transportation and logistics to vaccination field sites may also be included in vaccine administration costs (Mogasale *et al.*, 2016).
7	Vaccine procurement costs	Before immunization	Post-licensure	They refer to the vaccine price, costs of freight, insurance, taxes, clearance charges and pre-clearance storage cost (Mogasale *et al.*, 2016).
8	Costs borne by households	Before immunization	Post-licensure	They refer to the costs that households have to face to receive the immunization.
9	Costs associated with AEFI (Adverse Events Following Immunization)	After	Post-licensure	They concern reactions that can affect the health of vaccine recipients (Mogasale *et al.*, 2016) and should include, for example, the salary of the personnel involved, transportation, delivery costs, medicine and laboratory costs.

Table 2. Description of the cost categories included in this review

distinguishing among the different phases (Serdobova and Kieny, 2006; Phelps *et al.*, 2017; Pronker *et al.*, 2013). Since each phase has its own peculiarity (for instance, failure risk lies mostly in early stages, while most costs are incurred during Phase III), it would be important to have more precise costs, achieving more transparency and disclosure. Moreover, it is not always clear whether the costs provided incorporate failed attempts or not. Actually, detailed

Table 3.
Main findings for each cost category

R&D, preclinical, early clinical and registration costs	With regards to R&D costs (8 out of 39 contributions selected contained details on costs related to vaccine R&D), most of the studies just report total costs, which range from US $100 million estimated for Ebola vaccines (Phelps *et al.*, 2017) to 2 billion (Oyston and Robinson, 2012) that refer to some common estimates for a single vaccine, based on development costs for new drugs previously elaborated (Light *et al.*, 2009) However, only little R&D costs estimation is present in the literature (Waye *et al.*, 2013). Furthermore, no clear detail is provided about the methodology used to come up with the total figure, pointing out the need to improve the R&D costs data. The only exception among the selected articles is represented by the study from Light *et al.* (2009) that, comparing two different rotavirus vaccines, provides information on estimated trial and development costs, finely distinguishing also among Phase I, II and III and considering both a low and a high estimate scenario. For both vaccines, in the low scenario, Phase III accounted for more than 98% of total costs (99.3 and 98.6%). Still, in the high estimation, which included US $200 million for possibly setting up new manufacturing capacity, Phase III covered around 50% of costs (50.3 and 48.4%)
Investments in production plant and Cost of goods sold	The next two categories are usually overlooked when estimating cost of vaccine introduction (respectively, 3 and 1 out of the 39 contributions contain related information). As for production plant, there are two main scenarios to be considered: one in which the vaccine requires the construction of a new production plant and the other in which only an incremental cost for an already existing plant is required. A range between US $50 to 700 million is reported (Plotkin *et al.*, 2017) and includes facilities and equipment capitalized costs that depreciate over time, considering a period of 10 (Aguado *et al.*, 2015) and 15 years (Light *et al.*, 2009). According to Light *et al.* (2009), in the first scenario, the cost is about US $200 million. Examined studies do not provide cost estimations for the second scenario As for the cost of goods sold, precise estimations are lacking. The per-dose cost of goods sold to develop a meningococcal group A vaccine for a US manufacturer is estimated between US $0.35–1.35, considering volumes of 25–50 million doses annually and depending on composition, doses/vials number and formulation type (Aguado *et al.*, 2015)
Vaccine delivery costs	Among the 39 analyzed studies, 14 contain quantitative information on delivery costs. Most of them provide overall costs, without distinguishing between service and vaccine delivery costs, but dividing them according to the following variables: vaccine type, doses, immunization campaigns, country and immunization site (facilities, urban and rural settings) As reported in Table 4, when estimated as a unique figure, mass vaccination campaigns costs range from US $0.30 to 2.09 (Cravioto *et al.*, 2012). Range estimation is much wider for routine immunization: US $0.50 is the lowest bound (Diop *et al.*, 2015), while US $8.07 is the highest (Schütte *et al.*, 2015) Unit delivery cost per fully immunized individual with mass vaccination campaign against cholera ranges from US $0.53 to 2.09 (Cravioto *et al.*, 2012). Unit delivery cost per fully immunized child of new and underutilized vaccines is significantly higher and it is also affected by the hospital where immunization takes place. Estimations for Ghana range from US $23.64 for urban reproductive and child health facilities to US $80.94 for rural community health-based planning and services facilities (Le Gargasson *et al.*, 2015). Some articles, focusing on vaccine supply chain per dose costs, report a range between US $0.43 and 1.21 (Mvundura *et al.*, 2015). Others provide specific components estimations, such as cold chain (Constenla, 2015; Vaughan *et al.*, 2020; Memirie *et al.*, 2020), transportation (Cravioto *et al.*, 2012), vehicles, gas price per liter and personnel costs (Vaughan *et al.*, 2020; Portnoy *et al.*, 2015). Some contributions interestingly distinguish between urban and rural facilities (Schütte *et al.*, 2015): delivery costs to rural centers, on average, are almost three times the costs of urban centers. Only one study explicitly provides delivery costs as an estimated incremental cost per dose (US $0.50), assuming that existing immunization program staff are involved (Diop *et al.*, 2015)

(*continued*)

Vaccination program preparation costs	Seven out of the 39 contributions analyzed contain information on program preparation costs. As shown in Table 4, estimation for overall program preparation costs range between US $0.42 and 1.22 (Mogasale *et al.*, 2016). Some articles provide specific information on the subcategories described in Table 2. In particular, costs for microplanning ranges from US $0.040 per dose in supplementary activities for measles (Cravioto *et al.*, 2012) to $0.53 per fully immunized child in South Sudan with oral cholera, expressed in 2014 dollars (Mogasale *et al.*, 2016) The lower bound for training preparation costs is US $0.040 per dose, estimated for measles (Cravioto *et al.*, 2012), while the upper bound is US $0.53 for a child fully immunized against cholera in Tanzania (Mogasale *et al.*, 2016). Sensitization and social mobilization are often estimated together and range from US $0.05 for a child fully immunized against cholera to US $0.069 (Mogasale *et al.*, 2016). Program preparation costs include training as well: sometimes the cost of training is computed as a separate element (Memirie *et al.*, 2020), while in other papers it is computed with other components, Gosset *et al.* (2021) estimate the cost of planning, budgeting, training, for the introduction of the Hepatitis B birth dose, in Senegal as equal to US $0.00535 Preparation costs are sometimes included in operating costs and considered as direct costs together with cold chain maintenance and vaccine administration costs (Carias *et al.*, 2015) or they are not distinguished from service delivery and monitoring and surveillance costs (Colombini *et al.*, 2015)
Vaccine administration costs	Nineteen studies out of those selected contain information on materials and supplies costs, either in percentage or in monetary terms. As reported in Table 4, costs per dose of vaccine supplies range from US $0.06 (Schütte *et al.*, 2015) to US $0.19 (Antillón *et al.*, 2017). Here vaccine injection and other supplies costs are also distinguished between urban and rural facilities (Antillón *et al.*, 2017). Some studies estimate vaccine and injection material costs together with others: mean costs per dose of meningococcal routine vaccination equal to US $0.90 and 0.73 when computed on the projection period 2015–2035 are reported (Colombini *et al.*, 2015) No specific information can be retrieved on site preparation costs, while detailed costs are provided for personnel's costs. Some contributions contain useful data on hourly wage in specific African countries (Portnoy *et al.*, 2015). The personnel's cost per dose ranges from US $0.05, which is the minimum immunization-specific, routine recurrent personnel cost per dose, estimated for 94 countries by Portnoy *et al.* (2015) to US$ 4.44 for routine immunization in rural health centers in Zambia (Schütte *et al.*, 2015). Salaried labor routine immunization costs per dose differentiate according to facility type and location (Schütte *et al.*, 2015): in urban health center cost per dose is US $1.00, while in rural health center the same cost rises up to US $4.44. Interestingly, the opportunity cost of volunteers' time is equal to US $0.80 per dose. Some estimates include not only the time cost per dose of health workers, but also transport costs: using this classification, costs of US $0.99 (0.82) and US $2.15 ($1.64) are reported in Kenya and in Tanzania, respectively (Mvundura *et al.*, 2015) Supervision and monitoring costs range from US $0.006 for Hepatitis B birth dose (Gosset *et al.*, 2021) to 0.12 (Irurzun-Lopez *et al.*, 2016) including personnel, transportation, laboratory, office and recurrent and capital costs. Erondu *et al.* (2019) focus their systematic review on vaccine preventable disease surveillance, which includes the on-going collection, analysis and dissemination of health data and report per-capita costs ranging from US $0.02 to 0.16 Specific estimations on waste management are lacking, as they are often included in overall vaccine administration costs. The evaluation of the resources needed for effective waste management, including both capital costs (i.e. incinerators and any buildings required) and recurrent costs (i.e. incinerator fuel and maintenance, training and salaries) is actually difficult (WHO, 2002)

(*continued*)

Table 3.

	In some studies, vaccine administration costs are included into operational costs (Carias *et al.*, 2015). Values range from US $0.30 for operational cost per dose of cholera vaccines in Bangladesh, including logistics, social mobilization, training, monitoring and surveillance, and personnel costs, to US $3.61 for typhoid conjugate vaccines in Kenya, both for routine and catch-up vaccination (Cravioto *et al.*, 2012) when transportation costs and injection materials are included as well (Antillón *et al.*, 2017) When costs are distinguished among different facility types (Le Gargasson *et al.*, 2015), costs per routine dose administered appear to be higher in rural community health-based planning and services facilities (US $8), and lower in urban clinics (US $2.16), emphasizing the additional costs associated with reaching children in various settings. When vaccine administration costs are computed as a unique figure, costs per dose range from US $0.41, in the case of pre-emptive vaccination in a refugee rural camp in Uganda, to US $5.10 when referring to pre-emptive vaccination, taken in a rural and urban setting in Tanzania (Mogasale *et al.*, 2016)
Vaccine procurement costs	Fifteen studies report information on vaccine FOB price (Freight on Board, i.e. the vaccine price before shipping, insurance and customs costs are added). In the initial phases of production, when there is often only one producer, the public sector has limited information and the initial price tends to be high. Then, price declines overtime due to improvements in production capacity, economies of scale and potential competition (Kulkarni *et al.*, 2015). In developing countries, vaccine price strategy differs from the one usually applied in developed countries, where the price derives from the amount the market will bear rather than from the cost (Diop *et al.*, 2015) As Table 4 shows, the literature provides a wide range of estimations on vaccine prices per dose, from US $0.09 for tuberculosis computed as an average price for 73 GAVI eligible countries between 2011 and 2020 (Portnoy *et al.*, 2015), to US $7.00 for rotavirus and pneumococcal vaccine in Ghana (Le Gargasson *et al.*, 2015; Atherly *et al.*, 2009). Estimations for oral cholera range from US $1.00 to US $6.70 (Mogasale *et al.*, 2016). For pneumococcal, the low estimate of the vaccine price is US $2.60 and the high one 7.00 (Le Gargasson *et al.*, 2015), while the estimates for the initial price for rotavirus vaccine are around US $2.50 in Kenya, Uganda and Ghana (Sigei *et al.*, 2015).Estimates below or around US $0.50 can be found for measles (Le Gargasson *et al.*, 2015; Portnoy *et al.*, 2015) and meningitis A (Le Berlier *et al.*, 2015; Portnoy *et al.*, 2015) Specific information on customs, insurance and freight can be found in IVI (International Vaccine Institute) Report (Cravioto *et al.*, 2012). IVI includes infectious disease experts, health professionals and humanitarian leaders and its mission reads: "Discover, develop and deliver safe, effective and affordable vaccines for global public health" (https://www.ivi.int/). Hence, there is a clear lack of information in the literature concerning additional costs to be applied to vaccine price in order to be able to compute full procurement costs, the so-called CIF (Cost, Insurance and Freight). These additional costs per dose of oral cholera are estimated as being equal to $0.22 for shipping and handling, corresponding to 15% of the vaccine price Mogasale *et al.* (2016) report estimations on total procurement costs for fully immunized individual against oral cholera in Guinea, South Sudan and Uganda, pointing out that this category accounts for the highest proportion of total vaccination program costs. Results range from $0.29 for Dukoral oral cholera vaccination, in rural Uganda, in a refugee camp and in a pre-emptive vaccination setting, to $7.96 for Shancol oral cholera vaccination, in South Sudan, in the case of a pre-emptive vaccination setting
Costs borne by households	This review includes also the costs borne by households to obtain the vaccination that, although being a minor cost category, should be considered in order to provide a more cost accountability (Cravioto *et al.*, 2012). This cost category, mainly referring to time and transportation needed to reach the vaccination point and get the vaccination, tends to be overlooked because of poor data and information availability. Among the analyzed contributions, the 2012 IVI Report (Cravioto *et al.*, 2012) estimates such cost as being equal to US $0.11. Other studies attempt at analyzing the travel time for households to the nearest public hospital, which is a useful piece of information to assess the costs borne by households (Marsh and Rouhani, 2018)
Costs associated with AEFI	In the contributions analyzed, Adverse Events Following Immunization are widely described and their occurrence explained (Enwere *et al.*, 2015; Gessner and Halsey, 2017) but a quantitative evaluation of the costs associated with their management is lacking. The latter should include salary of trained staff engaged in monitoring, food and transportation costs, medical and advisory service provision and laboratory investigation (Mogasale *et al.*, 2016). The only estimation found is computed for India (Mogasale *et al.*, 2016) as reported in Table 4

Table 3.

Table 4. Lowest and highest values identified for each cost category and subcategories

	Cost category and subcategory	Lowest value, $	Highest value, $
1	Research and development	100 million (Ebola, Phelps *et al.*, 2017)	2 billion (generic vaccine, Oyston and Robinson, 2012)
	- Phase I	- 0,9 million (Rotavirus – GSK, Light *et al.*, 2009)	- 126 million (Rotavirus – Merck, Light *et al.*, 2009)
	- Phase II	- 0.1 million (Rotavirus – Merck, Light *et al.*, 2009)	- 3.6 million (Rotavirus – Merck, Light *et al.*, 2009)
	- Phase III	- 0.9 million (Rotavirus – Merck, Light *et al.*, 2009)	- 398,5 million (Rotavirus – Merck, Light *et al.*, 2009)
2	Investments in the production plant	50 million (Facilities and equipment capitalized costs that depreciate over time, such as land, buildings, machinery, on-going costs of upkeeping repairs, maintenance and utilities, Plotkin *et al.*, 2017)	700 million (Facilities and equipment capitalized costs that depreciate over time, such as land, buildings, machinery, on-going costs of upkeeping repairs, maintenance and utilities, Plotkin *et al.*, 2017)
3	Cost of goods sold (per dose)	0.20 (Meningitis A vaccine, cost for a US vaccine manufacturer, considering volumes of 25–50 million doses annually, depending on composition, number of doses/vials and type of formulation, liquid or lyophilized, in case facilities and fill/finish lines are already available, Aguado *et al.*, 2015)	1.35 (Meningitis A vaccine, cost for a US vaccine manufacturer, considering volumes of 25–50 million doses annually, depending on composition, number of doses/vials and type of formulation, liquid or lyophilized, Aguado *et al.*, 2015)
4	Delivery costs (per dose)	0.30 (Oral polio, mass vaccination campaign in Bangladesh, IVI 2012) 0.50 (Rotavirus, routine campaign, Senegal, Diop *et al.*, 2015)	2.09 (Oral cholera, mass vaccination campaign, urban slum, Mozambique 2004, IVI 2012) 8.07 (Rural health center, routine campaign, Zambia, 2011; Schütte *et al.*, 2015)
	- Cold chain cost	- 0.15 (Measles, catch-up campaign, Cravioto *et al.*, 2012)	- 5 (Malaria, Constenla, 2015)
	- Supply chain cost	- 0.43 (Kenya 2012; Mvundura *et al.*, 2015)	- 1.21 (Mozambique, Mvundura *et al.*, 2015)
5	Program preparation costs (per dose)	0.42 (Full immunization, Mozambique, 2003 pre-emptive vaccination, urban setting, oral cholera, Mogasale *et al.*, 2016)	1.22 (Full immunization, Tanzania, 2009, pre-emptive vaccination, urban and rural settings, oral cholera, Mogasale *et al.*, 2016)
	- Microplanning activities	- 0.040 (Measles, Cravioto *et al.*, 2012)	- 0.53 (Full immunization, South Sudan, 2013, pre-emptive vaccination, refugee camp, rural setting, oral cholera, Mogasale *et al.*, 2016)
	- Training of personnel	- 0.040 (Measles, Cravioto *et al.*, 2012)	- 0.53 (Full immunization, Tanzania, 2009, pre-emptive vaccination, urban and rural settings, oral cholera, Mogasale *et al.*, 2016)
	- Community sensitization and social mobilization	- 0.05 (Full immunization, South Sudan, 2013, pre-emptive vaccination, refugee camp, rural setting, oral cholera, Mogasale *et al.*, 2016)	- 0.69 (Full immunization, Tanzania, 2009 pre-emptive vaccination, urban and rural settings, oral cholera, Mogasale *et al.*, 2016)
	- Other costs	- 0.067 (Full immunization, Mozambique, 2003, pre-emptive vaccination, urban setting, oral cholera, Mogasale *et al.*, 2016)	- 0.58 (Full immunization, South Sudan, 2013, pre-emptive vaccination, refugee camp, rural setting, oral cholera, Mogasale *et al.*, 2016)

(*continued*)

Table 4.

	Cost category and subcategory	Lowest value, $	Highest value, $
6	Administration costs (per dose)	0.65 (Oral polio vaccine program across 94 low- and middle-income countries, Portnoy *et al.*, 2015)	5.51 (Rural health centers, Ghana, 2011 dollars, Le Gargasson *et al.*, 2015)
	- Materials and supplies	- 0.05 (Syringes and safety boxes, Ethiopia, Memirie *et al.*, 2020)	- 0.19 (Kenya, typhoid conjugate vaccines, Antillón *et al.*, 2017)
	- Personnel cost	- 0.05 (Estimated for 94 low- and middle-income countries, 2010 dollars, Portnoy *et al.*, 2015)	- 4.44 (Rural health centers, routine immunization in Zambia, Schütte *et al.*, 2015)
	- Supervision	- 0.006 (Supervision, monitoring and surveillance, Hepatitis B birth dose, Senegal, 2016 dollars, Gosset *et al.*, 2021)	- 0.12 (Surveillance, including personnel (e.g. salaries), transport (e.g. vehicles), laboratory (e.g. microscopes) and office (e.g. buildings) and comprised recurrent and capital costs, meningitis, Niger, 2012 dollars, Irurzun-Lopez *et al.*, 2016)
7	Procurement costs (per dose)		
	- Cholera	- 1.00 (Reported price per dose of Shanchol procurement costs, Mogasale *et al.*, 2016)	- 6.70 (Dukoral oral cholera vaccination, 2009, urban and rural Tanzania, pre-emptive vaccination setting, Dollars 2014, Mogasale *et al.*, 2016)
	- Rotavirus	- 0.94 (Kenya, Sigei *et al.*, 2015)	- 7.00 (Initial price, Atherly *et al.*, 2009)
	- Meningitis A	- 0.41 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)	- 0.52 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)
	- Typhoid	- 0.50 (Uganda, Carias *et al.*, 2015)	- 2.91 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)
	- Yellow fever	- 0.65 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)	- 0.80 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)
	- Tuberculosis	- 0.09 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)	- 0.10 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)
	- Papilloma virus	- 3.50 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)	- 4.41 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)
	- Malaria	- 4.26 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)	- 4.85 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)
	- Measles	- 0.19 (Ghana, Le Gargasson *et al.*, 2015)	- 0.30 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)
	......	......	......

(continued)

	Cost category and subcategory	Lowest value, $	Highest value, $
7	Procurement costs (per dose)	. . . . . .	. . . . . .
	. . . . . .		
	- Pneumococcal conjugate	- 2.60 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)	- 7.00 (Ghana, Le Gargasson *et al.*, 2015)
	- Pentavalent	- 0.79 (weighted average price in 2019, UNICEF, 2018)	- 3.00 (Ghana, Le Gargasson *et al.*, 2015)
	- Diphtheria, tetanus, pertussis	- 0.15 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)	- 0.22 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, (2015)
	- Inactivated polio	- 0.85 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)	- 0.97 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)
	- Oral polio	- 0.12 (Average price computed for 73 GAVI countries between 2011 and 2020, US $2010, Portnoy *et al.*, 2015)	- 0.13 (Ghana, Le Gargasson *et al.*, 2015)
8	Costs borne by households (per dose)	0.11 (Measles, economic opportunity cost corresponding to transport and time cost for households, Cravioto *et al.*, 2012)	
9	Adverse events associated with the vaccine	No numerical estimation found for sub-Saharan Africa 4.24 (per dose survey reported cost, oral cholera vaccination, pre-emptive rural campaign, India, Mogasale *et al.*, 2016)	4.28 (per dose cost adjusted for country level inflation and converting to 2014 US $, oral cholera vaccination, pre-emptive rural campaign, India, Mogasale *et al.*, 2016)

Table 4.

R&D costs are not easily disclosed by pharmaceutical companies for obvious reasons of protection of competition. There is a clear trade-off between informative needs of researchers and decision makers on the one hand and pharmaceutical companies on the other. Sometimes this is covered by referring to drug development, but there is no clear-cut agreement on the relationship between vaccine and drug R&D costs (Light *et al.*, 2009; Oyston and Robinson, 2012). Moreover, clinical phases appear to be different in required resources, while remaining phases seem more similar in process but not in resource intensity (Waye *et al.*, 2013). Furthermore, technological and scientific progress poses a challenge on the generalizability of vaccine R&D cost estimation, making the understanding of the peculiarities of each vaccine even more relevant. As a result, R&D costs should be reported more frequently and openly, possibly using a common methodology (Light *et al.*, 2009).

As for production plant costs, more research is needed, especially for incremental costs, as the setting up of a completely new plant to produce a new vaccine is infrequent. Furthermore, the reviewed literature appears to be lacking also in information on the cost of goods sold.

Moving to delivery costs, the review points out that they should be distinguished between service and vaccine delivery costs and the latter from distribution costs that can be defined as the cost to transport the vaccine from the site of production to the country of vaccination, when the two are different. In the case of limited-resource countries, these are often covered, totally or partially, by GAVI (Portnoy *et al.*, 2015): hence, in their computation the amount paid by GAVI and the eventual co-payment requested to the country is critical. In some studies, delivery costs are not distinguished and are included in routine immunization costs as operational costs (Antillón *et al.*, 2017) or simply shown as percentages of total immunization costs. Moreover, delivery cost data are often fragmented, and, consequently of variable quality (Vaughan *et al.*, 2019).

The evaluation of program preparation costs would definitely benefit from clearer estimations of incremental costs. This would contribute to the implementation of appropriate donor policies and to domestic and external resource mobilization for vaccination programs (Brenzel *et al.*, 2015). The objectives of immunization programs definitely require a careful planning of activities, in order to guarantee successful implementation, especially for new vaccines. Many studies confirm the growing importance of non-vaccine delivery costs, among which program preparation costs (Gandhi *et al.*, 2013; Lydon *et al.*, 2014). This category includes different subcategories: it is important to evaluate costs separately, in order to estimate their different weights and requirements in economic and financial terms. Moreover, the challenge is that they tend to be country specific and differ according to the vaccination campaign (routine vs. catch up).

Estimation of administration costs is complex because their different subcategories present specific characteristics to be taken into account. For example, many cost items are likely to represent incremental rather than full costs (Le Gargasson *et al.*, 2015; Brenzel *et al.*, 2015). No personnel unit will exclusively work on a new vaccine, and hence, percentage time's allocation should be provided. Similarly, surveillance and monitoring activities require incremental costs in terms of additional staff costs, training, data management, communications and transport (WHO, 2019; Brenzel *et al.*, 2015). Moreover, several data sources are needed for this cost estimations. Information on salary levels can be obtained from health ministry payrolls, while other data through surveys only – i.e. the percentage of time allocated to the new vaccine administration (WHO, 2019). Volunteer labor should also be included and computed in terms of opportunity costs (Le Gargasson *et al.*, 2015). Furthermore, vaccine administration costs closely depend on the adopted vaccination strategy but not much on the vaccine type. Other key cost considerations include wastage rates and the need to be able to minimize the number of doses remaining in vials. Unfortunately, specific cost estimations on waste management are lacking, as they are often included in overall vaccine administration costs. Moreover, the fact that the vaccination is integrated with existing

Expanded Program on Vaccination (EPI) schedules affects this cost category significantly, since the vaccine could be co-administered, leading to a cost reduction. Being part of the EPI schedules improves vaccination coverage by enhancing and facilitating its distribution, reduces inequalities in accessing immunization and leads to a decrease in child mortality. This is particularly relevant in the sub-Saharan Africa region where under-five mortality rate is the highest globally. Vaccines that are not part of the EPI system require different approaches to distribution (e.g. school-based clinics instead of health facility-based vaccine days, as in the case of the HPV).

The present review points out that a remarkable amount of work has been done on estimation of vaccine prices and also taking a long-run perspective, while more data need to be collected on the computation of additional costs that affect the overall vaccine price. Actually, while Freight on Board (FOB) estimations are available for different vaccines and countries, data on the Cost, Insurance and Freight (CIF) vaccine process are lacking. Moreover, vaccine development can/could be quite understandably affected by price considerations: the foreseen profitability of the immunization can be crucial in determining which vaccines are actually developed. However, for diseases that are unique to poor countries, this business model might not be applicable. In this regard, MenAfrivac was a successful example of how a group of African countries can come together and stipulate what price point (US$0.50/dose) they are willing to pay for a given vaccine. This greatly affected the development phase and ultimately the composition of who was involved in the effort, establishing a public-private partnership that led to relevant public health achievements in fighting MenA. It could be an inspiring model of action for future developments in global public health (Kulkarni *et al.*, 2015). The vaccine price is a relevant component of the overall cost computation and it is also an important parameter for potential sensitivity studies.

The estimation of the costs borne by households appears to be very challenging. The component concerning transport costs is quite country specific and differs in rural villages with respect to urban settings. Moreover, it is extremely difficult to reasonably estimate the distance households have to face, on average, to reach the vaccination point. Surveys should be administered to gain more insights and information on the costs endured by households. The same applies to the evaluation of the costs associated with AEFI management that suffer from the lack of data and the objective difficulty of distinguishing adverse events from coincidental health events that can randomly follow immunization but are unrelated to it (WHO, 2013). Actually, they are generally overlooked and we found no quantitative estimation for this category referred to sub-Saharan countries.

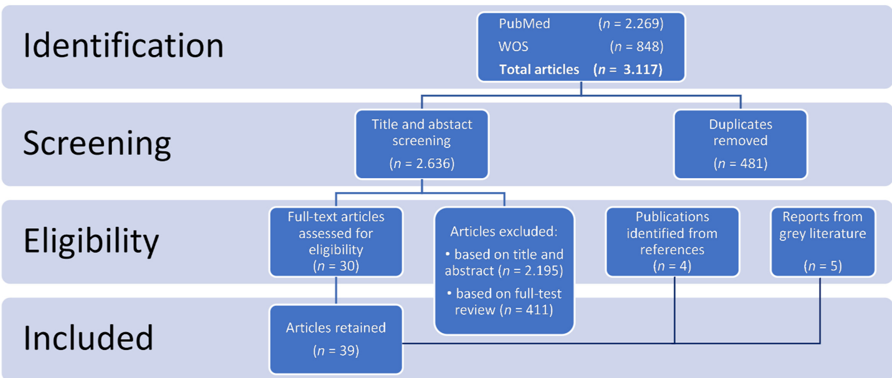

Figure 1.
PRISMA flow diagram

Summing up, among the various cost categories mapped in these contributions, most studies deal with delivery, administration and procurement costs, while only a lower number of publications were found on investments in production plant, costs borne by households to get the vaccination and costs due to AEFI, although they should be taken into account in order to provide a complete cost accountability for new vaccines in developing countries. Moreover, a clear definition of the components of cost categories is highly needed, in order to enhance comparability among different settings.

Conclusions

Economic valuations of immunization programmes are one of the key issues to be considered before deciding to introduce a vaccine (WHO, 2014). This calls for further studies to offer a useful support to decision makers in evaluating the major economic challenges linked to new vaccines introduction in LMICs.

In line with this, our paper aims at providing a systematic literature review of the costs that have to be faced when a vaccine is introduced in sub-Saharan Africa. In these countries, due in particular to the strong necessity of new vaccines to defeat diseases and to the competing health needs (Madhi and Rees, 2018) and the fairly widespread need to identify different financing strategies for their introduction, it is highly relevant for all stakeholders involved to know the costs of this essential medical intervention to support economic valuations of each immunization programme.

Thirty-nine contributions containing quantitative economic data have been selected. In order to elaborate a complete cost accountability, nine cost categories were identified. Our analysis takes into account also those costs that accompany and follow the actual administration of the vaccine, such as the costs borne by household to get the vaccination. To the best of our knowledge, this is the first review on this topic to take such a broad perspective and include all these categories.

Our contribution points out that quantitative data are lacking and more research on quantitative studies is highly needed. Some cost categories are characterized by an unclear cost estimation: for instance, for the category of research and development most studies report the total figure without distinguishing among the different phases and components (Serdobova and Kieny, 2006; Phelps *et al.*, 2017; Pronker *et al.*, 2013). Moreover, most studies deal with delivery, administration and procurement costs, while a lower number of publications were found on the cost of the good sold and the costs borne by households to get and benefit from the vaccination, although they should be included in order to provide a complete cost accountability for new vaccines in developing countries. Precisely, these costs are less vaccine-specific and, thus, they could be even more helpful in supporting cost evaluations of immunization programmes. Similarly, the costs referred to AEFI are generally overlooked and not included in cost computations: actually, we found no quantitative estimation for this category referred to sub-Saharan countries.

Moreover, broadly speaking, a clearer definition of the costs estimated should be provided, in order to enhance the comparability among different settings. Finally, policy makers and international agencies could definitely benefit from more data on cost subcategories.

Although the number of relevant contributions of this review could have been larger, our study provides relevant points of reference for scholars and decision makers when assessing costs associated to the introduction of a new vaccine in poor countries. It aims at rationalizing the different cost estimation found in the literature, by providing quantitative cost identification, including categories that are usually overlooked. Thus, it paves the way for extensive future research and the elaboration of sustainability plans that are highly needed when evaluating the opportunity of introducing vaccines in developing countries, providing sound and reliable estimations for cost-effectiveness analysis.

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Supplementary File

Supplementary data related to this article can be found online.

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