**A systematic review of the incremental costs of implementing a new vaccine in the Expanded Program of Immunization in sub-Saharan Africa.**

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**Introduction**

When contemplating introduction of a new healthcare intervention for the first time, an accurate estimation of its full costs based on real world data will usually not be available. But, it is increasingly widely recognized that rational decision making on the allocation of healthcare resources requires comprehensive assessments of the outcomes and benefits as well as the costs of interventions, so it may be necessary to base decisions on provisional, approximate data. One approach to resolve this dilemma may be to examine the costs of interventions that are similar to the one under consideration and which have already been implemented in the jurisdiction of interest or elsewhere.

A case in point is the newly developed RTS,S vaccine against malaria, which is considered for introduction in several sub-Saharan countries in Africa, where the disease burden of malaria is still heavy. Despite sustained progress in the fight against malaria with an estimated decrease in malaria deaths worldwide of 60% since 2000, data from the World Health Organization (WHO) indicate that around 438,000 individuals died of malaria in 2015 [WHO, 2016]. More than 90% of these deaths occurred in sub-Saharan Africa and most of them were children under the age of five years.

The RTS,S vaccine received a positive evaluation of the European regulatory authorities and WHO has recommended pilot implementation of the vaccine in several sub-Saharan countries with moderate to high malaria transmission intensity [WHO, 2016]. To inform the consideration about including RTS,S as part of the Expanded Program on Immunization (EPI) of these countries, estimates of the anticipated incremental costs of doing so are highly relevant and important [Galactionova, 2015].

The purpose of this study was to derive an estimate of the anticipated costs of introducing RTS,S vaccine in sub-Saharan countries by performing a systematic review of the literature in search of studies of the costs of recent vaccine introductions in these countries. Ideally, such studies should be using micro-costing principles with itemized costs and separate reporting of quantities of resources and their unit prices. However, relatively few studies based on these principles have been published until now, although the importance of using this approach is increasingly recognized guidelines for their performance, reporting and appraisal are under preparation [Xu, 2014; Ruger, 2016]. We therefore applied less strict criteria for inclusion of studies but as a minimum studies should report itemized costs to be selected. Further inclusion criteria are detailed in the next section.

**Methods**

PubMed was searched for relevant articles published between 2000 and June 2016 using the following search string:

“((vaccine) OR (vaccination) OR (immunization) AND (cost) AND (Africa)”

The criteria for selection of articles were: 1) costing study performed in a sub-Saharan African country (or more); 2) study performed between 2000 and 2016; 3) costing performed for a human vaccine; 4) costs should be itemized and quantified; itemized costs could be reported in monetary terms or as percentages of an overall cost figure reported in monetary terms.

From the selected articles the itemized costs of immunization (excluding the acquisition cost of the vaccine itself) were extracted and categorized into one of seven categories:

* Equipment: Materials and supplies such as syringes, needle disposal boxes, bandages, paper, etc.
* Human resources: All human labor costs, including salaries and wages.
* Sensitization: All public awareness campaigns, advertising and other mobilization and opinion-influencing activities.
* Training: Education and training for program personnel other than what they would already have received independently of the existence of the vaccination program.
* Transportation: All costs associated with moving vaccine and/or supplies and/or personnel for the vaccination program; cold storage was included in this category.
* Wastage: Any non-productive costs.
* Administration: All non-vaccine, non-material and non-vaccine costs not already covered by one of the afore-mentioned categories related to the actual delivery of the vaccine either at a health facility or another site of vaccination.

Distinctions between economic and financial costs were ignored, because their use was infrequent and inconsistent across studies. In the same vein, distinctions between cost types such as fixed and variable, start-up and recurrent were not retained, because they were used inconsistently across studies, sometimes overlapping, sometimes incompatible.

We distinguished between ‘trial’ studies (related to non-routine vaccination campaigns) and studies costing the regular, routine implementation of vaccination. We also distinguished between studies pertaining to the introduction of a vaccine in an area for the first time and costing studies of vaccines that were already included in the EPI of the country concerned.

All cost data were converted to 2016 US$ costs by using the foreign exchange rates found in Quandl [Quandl, 2016]. Subsequently, we converted the costs in US$ to international dollars (Int$) by means of the purchasing power parities (PPPs) estimated by the World Bank to account for the fact that the nominal exchange rates do not reflect differences between countries in the costs of living [World Bank, 2015].

The item-specific costs were standardized and expressed per dose of vaccine administered. The item-specific standardized cost per dose were averaged across studies and reported with a minimum-maximum range. The overall average cost per dose was subsequently estimated as the sum of the averages of the item-specific costs. The observed distributions are presented for each item-specific cost and for the total cost per dose.

**Results**

The initial search returned 985 articles. Upon reading the abstracts of all, 135 were retained and 850 were eliminated for one of the following reasons: 1) did not include cost assessment for a sub-Saharan African country; 2) was conducted before the time period selected; 3) did not estimate the costs of a human vaccine; or 4) did not report quantitative cost information. The retained 135 articles were all read in full and a further 94 eliminated because they did not present cost information clearly, the costs were not itemized or the items or categories used were not compatible with those used by the majority of the studies. The process of article selection is summarized in Figure 1.

The systematic review and analysis thus included the 41 articles retained after screening. Some of these reported itemized costs for all seven categories but most reported itemized costs for only some of these. The number of studies reporting itemized costs ranged from five for equipment costs to 27 for administration.

Table 1 presents the estimated average costs per dose (in Int$) for each item and in total. In addition, the minimum-maximum range for each item is included and the proportion of the average total costs accounted for by each item. The costs data based on market exchange rates and expressed in US$ are presented in Table 2. Average total costs per dose amounted to Int$ 5.94 per dose with human resources and wastage combined accounting for more than half with 28.7% and 27.1%, respectively. Based on a Monte Carlo simulation with 10,000 resamplings, the distribution of the estimated total costs per dose is shown in Figure 2 with a range from 0.08 to 34.83 Int$ and a substantial right skew. The mode corresponded to approximately half the mean.

The distributions of all the itemized costs are presented in Figure 3. All the distributions are heavily right skewed with modal values considerably below the mean in each case and with outliers more than 10 times higher than the mode.

In an attempt to explain the huge variation in the estimated costs, the effect of the type of vaccination campaign was investigated. Surprisingly, it was found that routine vaccination campaigns had higher reported costs than trials campaigns even though some trial campaigns had very high human resources costs. We hypothesize that this finding might be explained by a tendency for costing studies of routine vaccination programs to be thorough and comprehensive whereas costing of trial introduction programs might likely focus only on those costs that differed from routine programs.

**Discussion**

This review and summary analysis of vaccination costing studies performed in sub-Saharan African countries showed that the estimated cost per dose (excluding vaccine procurement costs) varied very substantially across studies, by more than a factor 10 even excluding the most extreme high-cost outliers. The studies lack standardization with respect to which cost items are reported and how these are reported, so their findings are not easily comparable. We suspect that a large part of the variance in the estimated costs reflect differences in what is reported under each cost category rather than actual cost differences.

Using PPPs instead of market exchange rates for currency conversion reduced the averages of all cost items by about half and also diminished the range of costs considerably, most for human resources, transportation and training and least for equipment. It may be useful to present results using both currency conversion approaches. When cost collection, categorization and presentation have been standardized, expressing the costs by means of market exchange rates may be helpful for donors’ and financing bodies’ assessment of the relative financing requirements for implementation of vaccination in various settings. On the other hand, converting the costs by means of PPPs may be helpful in comparing the vaccination implementation costs across countries when local resources are used partially or completely, which is the case for preventive vaccinations (excluding the vaccine acquisition costs) [Mogasale, 2016].

With cost distributions as skew as observed here, using the mode and not the mean would be more useful for policy considerations about implementation. Using the mode of the costs estimated from the studies included in this analysis would indicate the total costs per dose to be around 3 Int$ per dose, which is very high compared to what was found in certain commendable studies. As just one example, Hutton & Tediosi, performed an exemplary analysis for Tanzania using a very transparent and clear approach and estimated the total costs per dose as 0.48 US$ in 2003 prices [Hutton, 2006]. No mention of PPPs was made in the article so it may be supposed that they just used market exchange rates. Using market exchange rates, the mode in the present study was about total costs of US$8 per dose. Even considering that 2016 unit prices must be somewhat higher than 2003 prices, the gap between their estimate and the estimate resulting from the present review is extreme and needs to be investigated further to be understood……….

One limitation of this study is that even after screening articles for inclusion based on their quantification of itemized costs, several of the studies included in the analysis organized the costs using their own methods and categories merging cost items in non-compatible ways that could not be de-merged and reclassified for consistency with the majority of the studies [References]. The articles’ unclear and insufficient information about cost item classification may have resulted in our classification of cost categories. This review clearly underlines the need for developing standardized methods for micro-costing exercises to improve transparency, consistency and comparability across studies [Xu, 2014; Ruger, 2016].