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Cost-Effectiveness of the Introduction of a Pre-Erythrocytic Malaria Vaccine into the Expanded Program on Immunization in Sub-Saharan Africa: Analysis of Uncertainties Using a Stochastic Individual-Based Simulation Model of *Plasmodium falciparum* Malaria

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A B S T R A C T

Objective: To evaluate the cost-effectiveness of introducing the RTS,S malaria vaccine into the Expanded Programme on Immunization (EPI) in Sub-Saharan Africa (SSA), the contributions of different sources of uncertainty, and the associated expected value of perfect information (EVPI). **Methods:** Vaccination was simulated in populations of 100,000 people at 10 different entomological inoculation rates (EIRs), using an existing stochastic model and a 10-year time horizon. Incremental cost-effectiveness ratios (ICERs) and EVPI were computed from weighted averages of outputs using two different assignments of the EIR distribution in 2007. Uncertainty was evaluated by resampling of epidemiological, vaccination, and health systems model parameters. **Results:** Health benefits were predicted consistently only at low transmission, and program costs always substantially exceeded case management savings. Optimal cost-effectiveness was at EIR of about 10 infectious bites per annum (ibpa). Main contributors to ICER uncertainty were uncertainty in transmission intensity, price per vaccine dose, decay rate of the vaccine effect, degree of homogeneity in host response, and some epidemiological model parameters. Other health system costs were unimportant. With a ceiling ratio of 207 international dollars per disability-adjusted life-year averted, 52.4% of parameterizations predicted cost-effectiveness in the primary analysis. **Conclusions:** Cost-effectiveness of RTS,S will be maximal in low endemicity settings (EIR 2-20 ibpa). Widespread deployment of other transmission-reducing interventions will thus improve cost-effectiveness, suggesting a selective introduction strategy. EVPI is substantial. Accrual of up-to-date information on local endemicity to guide deployment decisions would be highly efficient.

Keywords: cost-effectiveness, expected value of perfect information, malaria, probabilistic sensitivity analysis, vaccine.

Introduction

The RTS,S vaccine against *Plasmodium falciparum* malaria is currently close to licensure, having demonstrated moderate levels of efficacy in several phase II trials in Africa [1]. RTS,S is a pre-erythrocytic vaccine, meaning that it modifies the risk that a human host becomes infected when he or she is bitten by an infectious mosquito. Analysis of the initial field trial data led to an estimate that a full course of vaccination prevents 52% of new infections [2], but that no one is completely protected against infection (the vaccine is "leaky"). Even leaky malaria vaccines of moderate efficacy may be of value, given that malaria was the eighth highest contributor to the global burden of disease in 2001 (2.9% of total global disability-adjusted life-years [DALYs]) [3].

There have been several analyses of both likely effectiveness [4–6] and cost-effectiveness [7,8] of RTS,S deployment using stochastic models of malaria epidemiology, which agree that the disease burden averted and cost-effectiveness will be highly dependent on the transmission setting [4–6]. This article uses estimates of cost-effectiveness from the previously described models [7] but adds two important elements. First, it extends the analyses to consider uncertainties in the parameters of the epidemiological or case-management models, in the effects of the vaccine, or in costs. Standard techniques of probabilistic sensitivity analysis, involving randomly sampling the parameter vectors, are used to analyze the contributions of the different sources of uncertainty to the ICERs. One specific aspect of these analyses of uncertainty is quantification of the value of acquiring additional information on these parameters by computing the theoretical value of complete information about them (expected value of perfect information, [EVPI] [9]). Although EVPI has only recently been applied in health sector evaluations relevant to low- and middle-income countries [10], this analysis is highly pertinent to decisions of whether to deploy RTS,S.

The second extension is to link the cost-effectiveness to estimates of the distribution of levels of malaria transmission in the places where RTS,S might be introduced to predict overall

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ICERs for introducing RTS,S via the Expanded Programme on Immunization (EPI) across Sub-Saharan Africa (SSA). Because the distribution of malaria exposure (the entomological inoculation rate [EIR], which measures exposure to the infective stage of the parasite) across SSA is also uncertain, we present a sensitivity analysis considering two different hypothesized distributions of the EIR of African populations.

Methods

Epidemiological model

The natural history and epidemiology of *P. falciparum* were simulated using a stochastic simulation model described in detail in an open-access supplement to the *American Journal of Tropical Medicine and Hygiene* [11–16]. The simulated human populations used an age structure based on Ifakara, Tanzania [17]. At each step, new births were introduced and "removal" of simulated people was carried out to mimic deaths. Some of the deaths are malaria related, but additional "removals" were simulated to maintain a stable population size and more or less stationary age distribution [11]. A consequence of the dynamics of immunity and of the cohort effect resulting from the numbers of people immunized building up over time is that the effects (percentage of episodes averted) vary over time.

This model was fitted to field data from a variety of settings across SSA [18]. As in the original publications, the model was seasonally forced using the pattern of the vectorial capacity in Namawala, Tanzania, scaled to give 10 different values of the initial exposures ranging from an EIR of 2.1 infectious bites per person per annum (ibpa) to 420 ibpa. Pathogenesis and case management (including hospital treatment of severe cases) was also simulated, as described in the original implementation [12,13,19], but the simulated first-line treatment was changed from sulfadoxine-pyrimethamine (SP) to artemether-lumefantrine (AL) [5]. Thus, any changes in transmission intensity induced by the vaccination program (including any herd immunity effects) were simulated, but the vectorial capacity followed the same annual cycle as in the absence of vaccine.

Pre-erythrocytic vaccination was also simulated as described previously [4,5], assuming that vaccination leads to a reduction in the proportion of inoculations from the bites of infected mosquitoes that lead to blood stage infection and that the vaccine efficacy is assumed to be equal to the proportion by which this force of infection is reduced. This is substantially higher than the efficacy in preventing clinical episodes [2]. A central value of 0.6 was used for the distribution of efficacy of a full course of vaccine. This is somewhat higher than the value of 0.52 that best explained the results of initial trials using the AS02 adjuvant [2]. More recent trials with the AS01 adjuvant have reported somewhat higher efficacy values than the earlier ones. The current clinical development plan of RTS,S assumes that it will be introduced into routine immunization of infants via the EPI. In keeping with this, simulated delivery of the vaccine was at ages 1, 2, and 3 months with full vaccination coverage (three doses) of 89% and a dropout rate from the first dose to the third dose of 6% [4]. Vaccine coverage is assumed to be reached instantaneously, and vaccine efficacy is achieved immediately after vaccination.

The health outcomes simulated were uncomplicated episodes, severe episodes, and deaths, translated to DALYs [20]. Case fatality rates followed a nonmonotonic function of age based on East African data [12]. Expert opinions were elicited for the probability of neurological sequelae [7]. Consistent with Global Burden of Disease and WHO-CHOICE methodology [21], the calculation of DALYs did not include age weighting but did include 3% per annum discounting, irrespective of whether the analysis used discounting by the time of the event. The same disability weights and Ethiopian life table were used for calculating DALYs as in our previous analyses [19].

Each simulation was run with a total population of 100,000 humans and separately for the 10 different EIR values. Effectiveness results were generated by running the model for a 10-year time horizon, starting from steady-state populations and comparing status quo simulated populations with case management (as described previously), with simulations with the same initial transmission levels and case management coverage but with vaccination in addition.

Costs

A societal perspective including provider perspective costs, and out-of-pocket patient costs was used for costing, using adapting values for Tanzania from our previous study [7]. This included both vaccination and case management components. Forty percent of incremental costs are nontraded based on the breakdown of outpatient, drug, hospital care, and patient costs [7]. Nontraded costs were inflated according to a Tanzanian rate, and traded costs were inflated according to a US rate. To correct for purchasing power disparities, costs are presented as 2008 international dollars (I$) calculated as described in WHO-CHOICE [22].

Vaccination and health service use costs (Table 1) were based on those of the original analysis with these models [19], but were updated by changing the simulated first-line treatment from SP to AL [23], and adding the cost of microscopy for diagnosis (including both materials and staff time) [24]. Freight costs, wastage rates (15%), storage, and management costs of the program were also based on those used previously [19].

Population distribution of EIR

A geostatistical model developed by the Malaria Atlas Project (MAP) for prevalence of malaria [25] was used to estimate the EIR distribution for the potentially vaccinated population in Africa. This model provided georeferenced model-based estimates of prevalence, $\hat{p}$, in children aged 2 to 10 years for the year 2007, and hence the formal analyses are based on the assumption that prevalence remains similar to this. True prevalence p is substantially more variable than $\hat{p}$ because the spatially smoothed geostatistical model estimates exclude nonspatial extrabinomial variation. To avoid biased estimation of average levels of transmission and underestimation of geographic variation clearly evident in transmission maps that do not allow for this [26], the extent of this extrabinomial variation was estimated by comparing the $\hat{p}$ values to raw prevalence data.

Prevalence determinations for age 2 to 10 years from the open-access Mapping Malaria Risk in Africa database were summarized by year and location to obtain a total of 1446 year- and location-specific prevalence values, where prevalence point i corresponds to n_i parasite-positive individuals among N_i total children surveyed, for each of which a geographically matched value, $\hat{p}_i$ could be found on the MAP surface. The hierarchical model

$$n_i \sim Binomial(N_i, \tilde{p}) \tag{1}$$

$$\log\left(\frac{\tilde{p}_i}{(1-\tilde{p}_i)}\right) \sim Normal\left(\log\left(\frac{\hat{p}_i}{(1-\hat{p}_i)}\right), \sigma_1^2\right) \tag{2}$$

was used to compare the two data sets, where the SD σ_1 measures extrabinomial variation. This model was fitted using WinBUGS v1.4 software [27]. Alternative models allowing for interdatabase