Comparison of the cost effectiveness of LLINs, SMC, the RTS,S vaccine and RTS,S plus IPTi in African settings.

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This document summarises the outcomes from a modelling exercise to compare the cost-effectiveness of LLINs, SMC, IPTi and the RTS,S vaccine in African settings. The report is based on the results provided to the WHO Joint Technical Expert Group in June 2015 and the Malaria Policy Advisory Committee in September 2015.

These results are not for citation or further distribution.

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AIMS

As recommended by WHO[1, 2], a detailed exercise has been undertaken to estimate the public health impact and cost-effectiveness of the RTS,S/AS01 candidate vaccine if introduced in African settings from 2017[3]. This included comparison of harmonised modelling outputs from four independent groups (STPH, Imperial, GSK and IDM). In that exercise we assumed that the transmission levels remained constant throughout, with recommendations on impact and cost-effectiveness based on parasite prevalence (PfPR). Applying these results to the most recent estimates of parasite prevalence across Africa would therefore give an indication of impact in the presence of current levels of other interventions. It is also worth noting that the models all utilise the Phase III data to estimate vaccine efficacy and hence represent impact in the presence of high coverage of long-lasting insecticide treated nets (LLIN). However, given the different structures of the four models, it was not possible to undertake a wider comparison of the potential additional value of the vaccine compared to investing resources in other WHO-recommended interventions.

To fill this gap, we therefore undertook an additional exercise using one of the four models (Imperial College[4-8]). Our aim was to compare the value of investing in RTS,S/AS01 in the 6-9 month schedule (both 3- and 4-dose) to the following WHO-recommended interventions – LLINs, seasonal malaria chemoprevention (SMC) and a proposed package combining RTS,S with intermittent preventive treatment in infants (IPTi) – with the aim of reducing malaria burden in children under 5 years. To do this, we calculated the most efficient (in terms of minimal cost for maximum impact) pathway to introduce interventions across a range of transmission settings. In all of the scenarios we assumed that investment in diagnostic testing and first-line treatment would continue alongside investment in interventions and hence this was not considered in our ordering of intervention choice.

METHODS

(A) Transmission Strata and Intervention Combinations

We first stratified transmission across Africa according to three characteristics:

(1) **Baseline endemicity:** PfPR (parasite prevalence in all age groups) in the range 1% to 80% in 5% increments (17 strata);
(2) **Seasonality**: Four seasonal profiles based on malaria transmission patterns commonly observed in sub-Saharan Africa: single-peaked highly seasonal (~3 months), single-peaked but longer season (4-6 months), two malaria seasons (short and long) and perennial.
(3) **Vector species**: Four profiles were used to represent different mixes of the three main species and their bionomics, from purely *Anopheles gambiae*/*An. funestus* to purely *An. arabiensis*.

This generates a total of 17 x 4 x 4 = 272 transmission strata.

We considered four possible interventions:

(A) **Increasing LLIN coverage**: LLIN usage levels of 0%, 15%, 30%, 50%, 55%, 60%, 65%, 70%, and 75% were included. We assumed that nets would be distributed every 3 years at these levels (i.e. proportion of the population sleeping under a net). Usage levels are assumed to decline over time with a mean retention time of 23 months. Decay in insecticide efficacy and wear-and-tear over time is also included[5, 10]. For costing purposes, we assumed that a net would cover 1.8 people (consistent with the approach taken in the World Malaria Report[9]).

(B) **Increasing SMC coverage (seasonal areas only)**: Coverage levels were: 0%, 25%, 50%, 75% and 90%. SMC was administered following WHO-recommendations to children between 6 months and 5 years of age, with 3 monthly doses of SP-amodiaquine[11].

(C) **RTS,S vaccine**: Coverage levels were 0%, 25%, 50%, 75% and 90%. Consistent with the wider modelling comparison exercise, we assumed children would be vaccinated with 3 doses at 6, 7.5 and 9 months. The results presented here include a fourth dose 18 months post dose 3 (i.e. at 27 months). Vaccine efficacy and waning parameters were as reported in the wider model comparison exercise based on the Phase III trial data[3].

(D) **RTS,S vaccine plus IPTi**: As proposed by WHO as a comparison, we additionally included a schedule with RTS,S combined with IPTi. Here we assumed three doses of SP (assuming it was fully effective) at 6, 10 and 14 weeks, followed by three RTS,S doses at 5, 6 and 7 months, and a final further dose of SP at 9 months Coverage levels were 0%, 25%, 50%, 75% and 90%.

Combinations of interventions were distributed either randomly or with high correlation between recipients (i.e. for a given coverage level the same individuals receive all interventions and the remainder receive none) to represent two possible extremes in distribution. Throughout we assumed that 60% of those with clinical disease received prompt and effective first-line treatment. Whilst this may differ between settings[12], modifying this assumption only affects the level of impact that can be achieved and not the ordering of cost-effectiveness of the other interventions. In total, applying each possible combination of coverage of each intervention to the 272 transmission strata resulted in just under 500,000 simulations.

(B) Calculation of the most efficient investment order

Since the aim of the vaccine is to reduce the burden of malaria in young children, we calculated the most efficient (i.e. least costly) order in which to scale-up interventions to reduce the cumulative number of malaria cases in children aged 6 months to 5 years olds over a period of 10 years. The costing of each intervention package was based on an average unit cost for treatment of uncomplicated malaria and each of the interventions, undertaken from a public health provider perspective. We did not include the additional costs of severe disease management, programme costs or surveillance as these are not expected to vary between the scenarios being considered. The unit costs are summarised in Table 1. Where applicable these are the same as used in the wider modelling comparison exercise. All unit costs are also similar to those derived as part of the detailed Global Technical Strategy costing exercise (Table 1). In general they reflect a situation in which intervention distribution has already achieved economies of scale.

Table 1 | Unit costs (US$, 2013) for interventions and treatments.

Intervention	Unit Cost ($)	GTS Unit Cost ($)	Reference/Notes
LLINs	7.03 per LLIN delivered	6.87 per LLIN delivered	White *et al,* 2011[13] for 2009 – more recent estimates give a very similar figure and so these were not inflated.
SMC	1.75 per child per round	1.24 per child per round	CHAI/MSF estimates[14, 15]
Vaccine	24.99 per fully vaccinated child	-	Under the assumption of $5/dose[3]
Vaccine + Booster	39.25 per fully vaccinated child	-	Under the assumption of $5/dose[3]
IPTi	0.16 per dose	-	White *et al,* 2011[13] (inflated to US$, 2013)
Treatment	3.51 per person treated	4.31 per treatment including testing and for median OPD visit costs	K. Galactionova, Swiss TPH[3]

From an economics perspective, the relationship between the unit cost of an intervention and coverage can be summarised by the health production function. This is generally assumed to be linear at low levels of coverage (assuming economies of scale have been reached) but becomes non-linear at high levels of coverage since it becomes increasingly difficult (and hence costly) to access the hardest-to-reach populations.

To capture these effects we used empirical relationships for the health production function for LLINs and RTS,S (Figure 1). The LLIN production function was based on the work undertaken by Bhatt et al.[16] as reported in the 2014 World Malaria Report[9]. Here we used the "business as normal" function (Figure 1A), which is an estimate of the production function between net allocation and use obtained from a comparison of distribution data and DHS/MIS usage reports. For the vaccine, we collated data from WHO reports and DHS surveys on the relationship between DTP3 coverage and spending data from GAVI and country-specific DTP3 (Figure 1B). An empirical relationship was fitted to these data. This relationship was used for RTS,S alone and for the combination of IPTi/RTS,S since they would both occur through health centre visits similar to DTP3. For SMC no relevant data were available and hence we assumed a linear relationship.

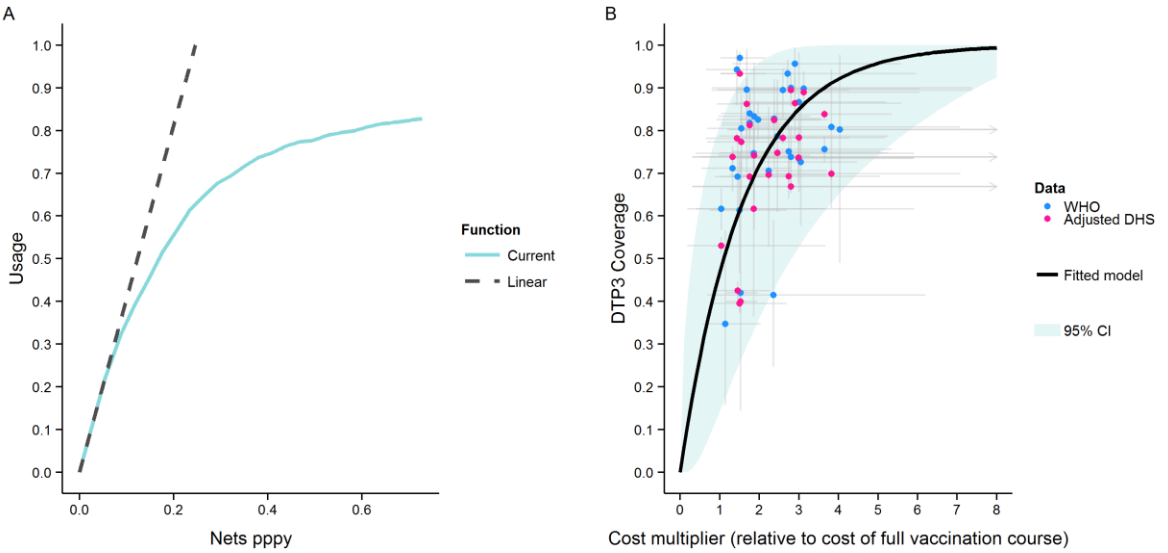

Figure 1 | Production functions for A) LLIN usage[9], the linear function is included for comparison and B) vaccine coverage. The function in B is empirically derived from WHO/DHS reported DTP3 coverage and GAVI/country-specific DTP3 spending data.

The most efficient ordering of interventions was then calculated using the incremental cost-effectiveness ratio (ICER) at each step:

$$ICER = \frac{Cost_{current} - Cost_{next\ step}}{Incidence_{current} - Incidence_{next\ step}}$$

RESULTS

Figure 2 summarises the order of scale-up of each intervention for non-seasonal (panel A) and seasonal (panel B) settings. Here each row is a different transmission strata (PfPR) and within each of these bands the different vector species, seasonality pattern strata and intervention clustering (random versus correlated) are included. The colours show the order in which the different interventions are most efficiently introduced. Note that we did not directly compare RTS,S with 4-doses and RTS,S+IPTi and so these are shown as separate lines (turquoise and dark blue respectively). As interventions are introduced in different orders for each scenario, the x-axis represents increasing coverage but is not on a single scale. The level of intervention coverage is therefore shown by the shade of colouring, as given in the scale legend.

The most efficient scale-up of interventions showed very consistent patterns regardless of differences in seasonality, vector dynamics, vaccination regime or correlation between interventions. In all settings we found that scaling up LLINs to high usage was more cost-efficient than introducing the other interventions. This is due to LLINs being predicted to provide both direct protection and a wider indirect protection at the community level[5]. In non-seasonal settings, the vaccine was introduced only once LLINs had reached very high coverage (in most cases 75% usage, the maximum level achievable under the business as usual model[16]) with our assumptions regarding decay in adherence over time (Table 2).

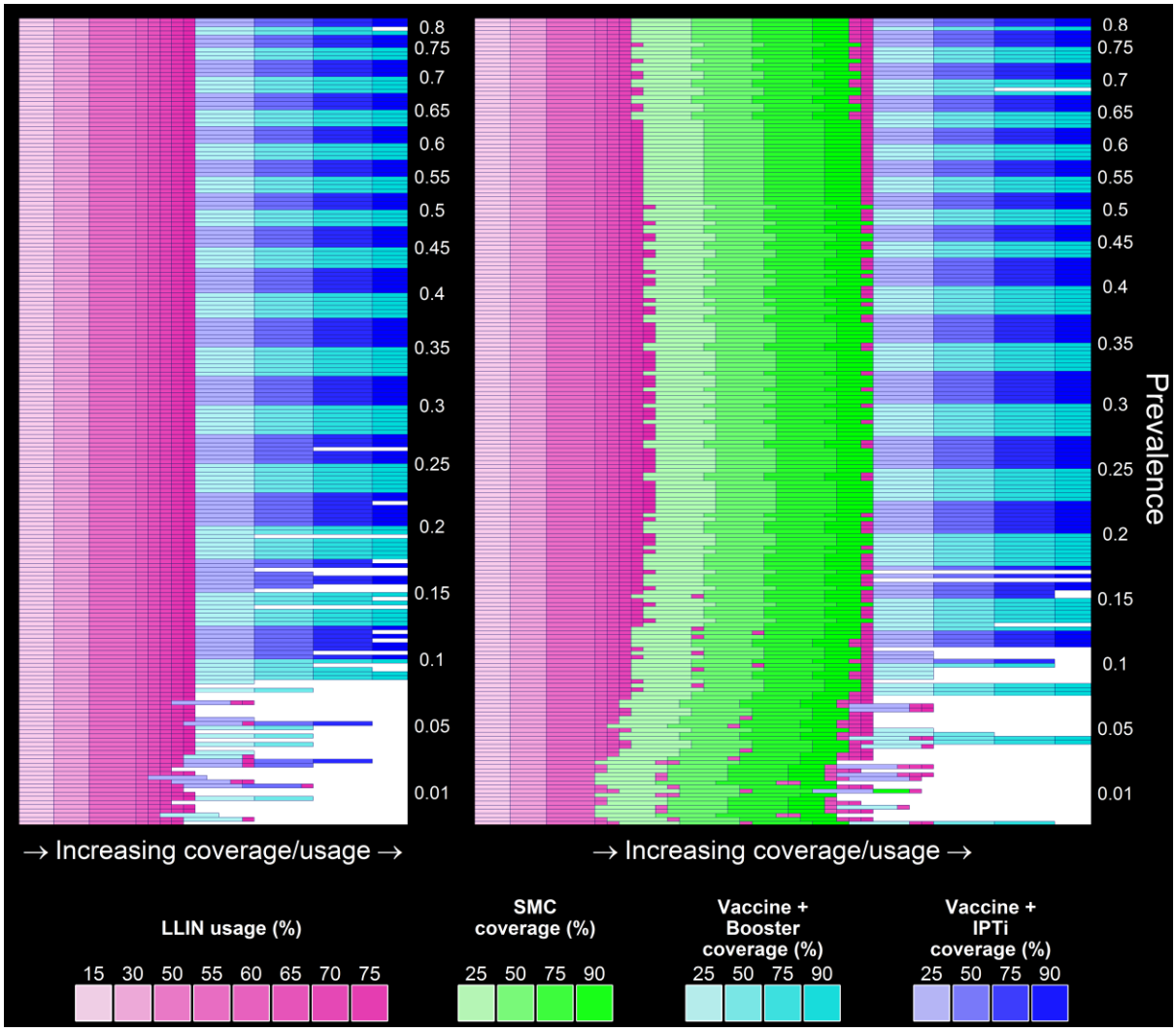

Figure 2 | Order of scale up for A) non-seasonal and B) seasonal sites, stratified by baseline prevalence. Scale up of LLINs to high usage was consistently the first option before switching to SMC in seasonal and vaccination in non-seasonal settings. The colour intensity represents coverage (LLIN usage: light pink = 15%, dark pink = 75%. SMC coverage: light green = 25%, dark green = 90%. Vaccine + booster: light navy = 25% , dark navy = 90% coverage. Vaccine + IPTi: light sky blue = 25%, dark sky blue = 90% coverage).

Table 2 | The frequency (% of simulations) of LLIN usage at which a switch to SMC or RTS,S first occurred for seasonal and non-seasonal settings.

	LLIN Usage					
	30%	50%	60%	65%	70%	75%
Seasonal settings	2.5%	2%	5.5%	15%	27%	48%
Non-seasonal settings	1%	1%	1%	1%	4%	92%

In seasonal settings, the most efficient ordering of interventions varied more between the strata. In general, LLINs remain the most efficient intervention, but SMC is introduced as a second intervention in some settings prior to maximising LLIN coverage. Thus, depending on

the vector species (which is predicted to affect the efficacy of LLINs) and the degree of seasonality (which is predicted to affect the efficacy of SMC), it can be more efficient to introduce SMC at LLIN usage levels of 65-70% rather than waiting to first maximise LLIN usage. To put this in context of current levels, the reported bed net usage in children under five is summarised in Figure 3 based on recent DHS/MIS survey data. Whilst reported usage is >60% in some settings, there remain many settings where this level has not yet been achieved.

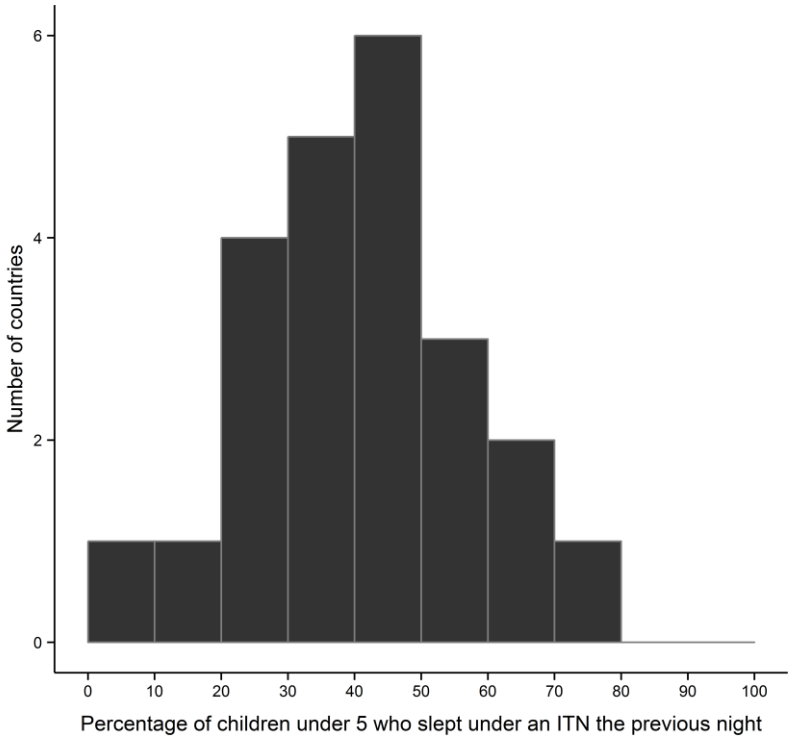

Figure 3 | The frequency distribution of ITN usage in children under 5 for sub-Saharan African settings (Data source: most recent DHS and MIS surveys, 2011, 2012 and 2013).

In both seasonal and non-seasonal settings the vaccine was included in the intervention package only after LLIN and SMC coverage had already been maximised. This is primarily due to the overall higher predicted cost of the vaccine in preventing a single episode of malaria. At the lower simulated cost per dose of $2, this pattern remained, with the RTS,S vaccine introduced only in very high transmission settings when LLIN coverage reached 60-70%.

We found very little difference in the optimal ordering of intervention scale-up between the three vaccine regimes considered (3 doses of vaccine, 4 doses of vaccine and 3 doses of vaccine plus IPTi), consistent with the wider predictions of the cost-effectiveness of the first two regimens in the model comparison exercise[3]. The addition of IPTi to an existing RTS,S vaccine schedule provided little additional benefit in our simulations. This is likely due to our model incorporating maternal immunity which is predicted to provide some protection up to 6 months of age, hence resulting in little predicted impact of the early IPTi doses. In addition, the vaccine is predicted to provide a high level of protection following dose 3, with this

protection remaining at high levels at the time that the final IPTi dose is scheduled (2 months after dose 3). Hence we predict relatively little additional benefit of this IPTi dose.

Despite the vaccine being less resource efficient at reducing burden in children under 5 years than either LLINs or SMC, we found that it would still be a useful addition to settings where the baseline PfPR prior to intervention scale-up was greater than 15%-20% if the ultimate aim is to reduce incidence to pre-elimination levels since at these levels of baseline transmission LLINs and SMC alone are unlikely to achieve this aim. At levels lower than this, we predict that LLINs plus SMC alone could achieve low incidence in this age group as well as across a wider age range. However, decisions around geographical limits for introducing the vaccine are better informed by the wider public health impact and cost-effectiveness estimates in the four-group model comparison[3] as these are related to current rather than historical levels of endemicity.

CONCLUSIONS

Our results confirm that LLINs are the most cost-efficient intervention (i.e. the first most cost-effective intervention to include to reduce burden in children under 5 years) across the full range of different transmission strata found in Africa. In seasonal areas where SMC is recommended, it is predicted to be the second most cost-efficient intervention. In settings in which low incidence could not be achieved with the first two interventions alone, the RTS,S vaccine – administered either as 3 doses in 6-9 month age group or as 3 doses in the 6-9 month age group plus a fourth dose 18 months post dose 3, could be considered once the use of the other two interventions had been optimised. Introduction at this stage should be based on the cost-effectiveness estimates presented in the model comparison report[3].

It should be noted that throughout we did not consider improving diagnostic testing and case management as an alternative intervention and assumed a fixed effective coverage of 60% of clinical cases receiving appropriate ACT treatment. In addition, we assumed here that there was a linear relationship between SMC investment and coverage due to a lack of data – this could be amended in further analyses.

We also did not consider impact on other metrics such as all-age incidence and parasite prevalence, for which vector control (LLINs and IRS) is likely to be more efficient than SMC or the RTS,S vaccine due to its substantial transmission impact[17] and applicability to all age groups. In addition, we did not take into account operational barriers to achieving high uptake and adherence to the individual interventions, nor the potential for drug or insecticide resistance to reduce impact. Variation in these factors could substantially alter these conclusions.

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