MALARIA PREVENTION

SHAPING NEXT-GENERATION MEDICAL INTERVENTIONS

iTPP2 OUTCOMES REPORT

MULTI-SEASONAL INTERVENTIONS

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CONTEXT AND OVERVIEW OF ANALYSIS

This report presents the initial round of modelling evidence generated to inform the Bill and Melinda Gates Foundation (the Foundation) interventional Target Product Profile criteria for multi-seasonal interventions (iTPP2). The iTPP document guides the development of second-generation malaria vaccine products to meet the need for an extended duration medical protection, to cover multiple seasons or years for all populations at risk in malaria endemic settings.

Through a combination of stakeholder engagement and analytic approaches integrating clinical data with detailed malaria transmission models of intervention dynamics (Figure 1), **we present initial, evidence-informed recommendations for updating the Foundation's iTPP2 development criteria and for informing further modelling research.**

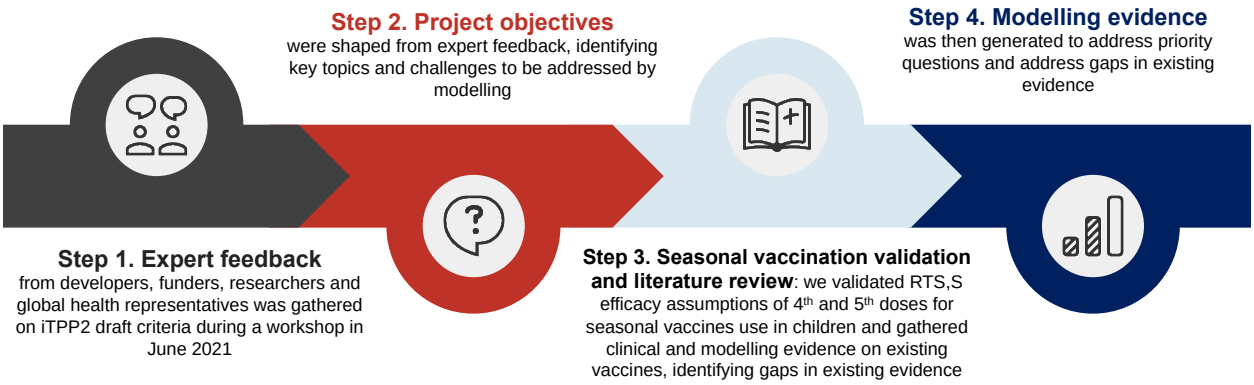

Figure 1. Summary of sources of evidence. The modelling evidence is generated using Swiss TPH's individual-based model of malaria transmission, epidemiology and intervention dynamics [1].

Iterative evidence generation from first- to second-generation malaria vaccines

During our **June 2021 convening "Malaria Prevention: Shaping Next-Gen Medical Interventions",** stakeholders, including researchers, implementation partners, global health experts, product developers and funders, identified the challenges and knowledge gaps involved in the development and implementation of next-generation vaccines. These priorities include:

- Understanding trade-offs and relationships between vaccine properties (initial efficacy, duration of protection) and health system factors (intervention coverage, access to treatment) across a range of transmission settings for multi-seasonal intervention candidates.
- Translating from clinical efficacy to effectiveness under various implementation settings for seasonal vaccine use.
- Understanding trade-offs between potential intervention impact and time to development of new interventions in comparison to the impact of incrementally improved first-generation vaccines.

In October 2021, the World Health Organization's (WHO) gave a positive recommendation for RTS,S/AS01 for pediatric use and seasonal vaccination in children (following the publication of the efficacy and clinical evidence for seasonal use of RTS,S[2]). Given this recommendation and the important considerations identified for a vaccine's evidence generation process during the June convening, modelling evidence generation only began in November 202, awaiting the positive recommendation. Modelling objectives were as agreed with the Foundation.

In this first modelling report, we focus on understanding the **implementation tradeoffs for *improved* first-generation vaccines** and their related public health impact for the **seasonal use case in children**, with the expectation that **insights will guide a better understanding of the standard of care and of the potential increased public health benefits of next-generation anti-infective malaria vaccines**. We do not suggest definitive updates to the Foundation's iTPP2 document for multi-seasonal vaccines. Rather, we suggest some annotations and investigate the trade-offs between key intervention characteristics and

health system factors for first-generation vaccines, which will inform the discussion of performance characteristics for novel next-generation products. Our analysis has thus centered on understanding:

1. The public health impact of an anti-infective vaccine deployed with or without drugs as a seasonal prevention intervention for children.
2. Trade-offs between performance characteristics of anti-infective vaccines – initial efficacy and duration of protection – for impact in clinical trial settings and implementation settings, over a range of epidemiological outcomes. This includes exploring trade-offs between efficacy and reduced vaccine doses to improve coverage.
3. The public health impact of improved first-generation vaccines over multiple seasons for burden reduction in children.

In 2022 and beyond, modelling will guide priority use-cases through analysis beyond children and first-generation vaccines, including analysis of multi-antigen vaccines. We will update our findings with further results for use-cases and combination vaccines guided by the Foundation, with health targets beyond burden reduction to potentially include elimination.

Understanding the impact of improved first-generation and second-generation vaccines

We base our initial recommendations on a breadth of analyses over a range of modelled scenarios of improved first-generation vaccines, examining and linking key intervention performance characteristics with expected related public health impact. The initial modelling scenarios and questions are informed by stakeholder discussions, literature reviews, previous modelling evidence, and by a recent validation exercise on clinical trials for seasonal vaccine use (see supplement). The modelled scenarios include: a range of seasonality profiles and malaria prevalence levels, a range of levels of intervention coverage and access to first-line treatment, various deployment strategies in terms of co-administration with or without drugs, and a broad range of efficacy and duration properties for anti-infective vaccines (see Table 1).

We modelled improved, first-generation anti-infective vaccines deployed prior to the peak malaria transmission season, either alone or co-administered with a highly efficacious blood stage antimalarial drug that clears parasites with a five-day effective duration. Vaccines as primary series consists of three initial doses given in monthly intervals to children aged between five and 17 months at recruitment. This primary series is followed by annual booster doses given prior to the peak malaria season until the child reaches five years of age. The timing of deployment is approximately two months before the highest peak in the malaria transmission seasonal profile. We assume that the vaccine's maximal initial efficacy is achieved after the third dose in the primary series, as indicated in Figure 2. Annual booster doses are assumed to restore waning vaccine efficacy to the initial level (see validation below).

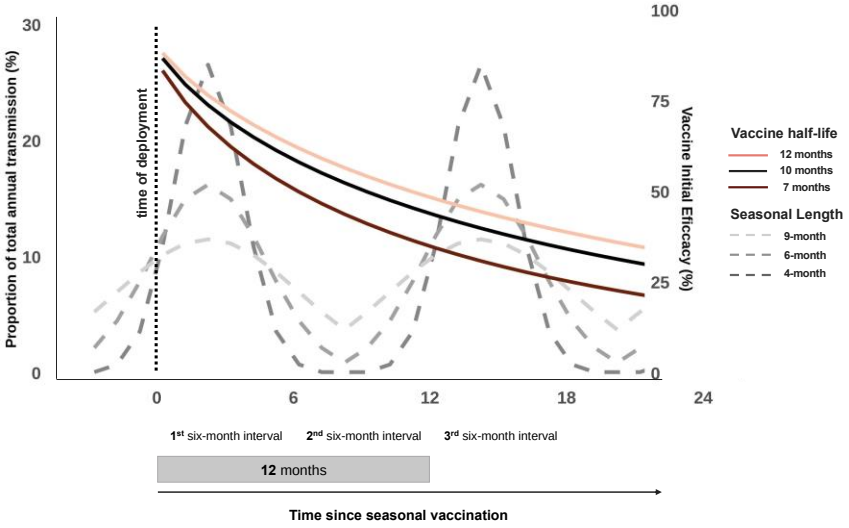

Figure 2. Schematic diagram of the modelled seasonal profiles in relation to vaccine efficacy against infection decay profile over two years for a first-generation anti-infective vaccine with variable half-life. In this scenario, the intervention is deployed prior to peak malaria season (month zero; black dashed vertical line). We explore three seasonal length profiles (dashed grey lines): short (four-month), moderate (six-month) and long (nine-month), for three illustrative vaccine half-life values, seven, ten and twelve months (red, black, and brown curves respectively). The 12-month and 1st, 2nd and 3rd six-month intervals illustrate the vaccine evaluation periods in our analysis. The 3rd six-month period estimates the impact in the second malaria season (shaded region).

We chose to evaluate the impact of the vaccine over several different periods: **in the initial six and 12 months after seasonal vaccination, as well as in the 12 to 18 months following a single non-boosted vaccination to estimate the extended protection provided into the next season** (Figure 2). We also evaluated vaccine impact on several epidemiological outcomes: prevalence reduction in children under five years old, reduction of clinical malaria, reduction of severe malaria, and reduction of mortality.

Validation with trial data: efficacy of four, five and six doses of an anti-infective vaccine

We used the results of a clinical trial of seasonal vaccination with RTS,S/AS01 [2] to validate the vaccine properties of RTS,S against the original Phase Three trial data, informing assumptions of the efficacy of a vaccine booster given 12 months after a primary series (rather than at 18 months as in the original RTS,S trial). Previously, for children aged between five and 17 months at recruitment, RTS,S/AS01 was estimated to have high initial vaccine efficacy (over 90%) waning under a biphasic decay profile, with a half-life of 7.32 months [95%CI 6–10 months], estimated over 32 months following the four-dose primary series [3]. Our validation analysis (not shown here) indicated that the efficacy, decay, and half-life of the primary three doses calibrated to the Phase 3 data was consistent with the seasonal trial observed clinical incidence. However, unlike previous trials, where the efficacy of a fourth dose was estimated to be less than 60%, the **validation analyses suggested that a fourth dose 12 months after the primary series is likely to return vaccine efficacy close to the initial 90% efficacy**. This result is consistent with Imperial College's independent analysis of vaccine efficacy, presented at the joint MPAG/SAGE decision on RTS,S/AS01 in October 2021. Thus, for the purpose of our iTPP2 analysis, we assume that four-, five- and six-dose vaccination returns protection to the efficacy achieved by the primary series.

KEY RECOMMENDATIONS FOR iTPP2

Given the implications of our initial vaccine modeling results reported below, we provide key recommendations for anti-infective vaccines. **Potential annotations to the iTPP2 document tables follow the key results**. These are potential only and should be discussed

RECOMMENDATION ONE: To achieve multi-seasonal protection for next-generation vaccines, iTPP2 must set minimum requirements for both a vaccine primary-series' duration of protection and initial efficacy. Our modelling analysis to date suggests that a duration of protection (defined as half-life for biphasic vaccine efficacy decay) greater than ten months and an initial efficacy greater than 90% are useful, initial base-case requirements for iTTP2 criteria to achieve minimal multi-seasonal burden reduction.

As described in the summary of results below, we found that initial efficacy and duration of protection characteristics are critical for identifying which priority vaccine candidates are most likely to increase public health impact (in implementation settings and clinical studies), as well as to achieving greater impact than current first-generation vaccines. Vaccine initial efficacy and duration of anti-infective protection are of similar importance in achieving high levels of burden reduction in the first year or season following vaccination. However, multi-seasonal vaccine impact (i.e., impact beyond the first year after vaccination) is determined by the duration of antibody protection, requiring at least ten to 12 months of half-life protection to achieve a burden reduction of half the preceding year's level. **If initial efficacy against infection of a new vaccine candidate is greater than 90% then development should concentrate on half-life extension.** As expected, we found coverage to be an additional major driver of impact in implementation settings.

Even longer half-life requirements, of greater than 12 months, are likely to be needed to achieve higher impact targets (greater than 40–50% burden reduction) in the year following vaccination. This range lies beyond our initial assessment and will require further modelling.

RECOMMENDATION TWO: Support Research and Development (R&D) to identify efficient immune correlates of anti-infective protection, essential for identifying promising second-generation vaccine candidates. The implementation of Recommendation One requires improved metrics for evaluating the efficacy and impact of second-generation vaccine candidates; clinical evaluation will need to focus on anti-infective efficacy and half-life duration in the second and third year after the primary vaccine series. R&D should therefore focus on novel evaluation methods that enable early evaluation of pharmacodynamics and likely long-term protection of candidate immune correlates. Validated immune

correlates in early clinical phases will support the evaluation of dosing regimens prior to large clinical trials. Despite the risk and difficulty of identifying immune correlates and other assays, investment in R&D will result in huge gains if successful. And these gains will translate to benefits for R&D beyond malaria vaccines. Furthermore, future clinical trials will require evaluating 'any' infection endpoints (with sensitive diagnostics or appropriate serological monitoring), especially if vaccines are considered for elimination targets. Monitoring the incidence of any malaria infection in a sub-cohort of a clinical trial will confirm a vaccine's underlying efficacy against infection associated with immune correlates of protection and will enable better translation between transmission settings.

Our initial modelling analysis assumed a biphasic-like decay in protection, as observed clinically with RTS,S/AS01. This decay results in a slower, longer decay of protection following the half-life period, which supports multi-seasonal protection. Onboarding newer clinical data or knowledge of a new vaccine candidate's decay in protection will be essential for the models to assess the multi-seasonal protectivity of a candidate and, thus, to assess a vaccine candidate's public heath impact.

RECOMMENDATION THREE: Clearly specify priority use-cases for next generation vaccine candidates alongside clinical efficacy target criteria and standard of care comparator (where appropriate) in the iTPP2 document. In particular, the preventative efficacy (clinical efficacy, or clinical reduction criteria or targets) and prevention of infection (indication criteria) must be clearly defined and specified for the iTPP2's base case and upside criteria alongside potential standard of care. The evaluation periods and measure of efficacy or burden reduction should also be specified, focusing on 12 and 24 months.

Modelling shows that co-administrating anti-infective vaccines with blood stage clearance drugs greatly improves the burden reduction health impact on children and should be considered essential (base case criteria) for expanding the range of achievable health reduction levels when protecting children. Results will be similar for many use-cases; the impact of clearing infections in a larger proportion of the population will lead to higher prevalence reduction, support larger indirect effects of next-generation longer acting vaccines, and support use-cases aiming for interruption or elimination. Thus, the base case iTPP2 criteria should specify that anti-infective vaccines need to be deployed with antimalarial treatments. Similar criteria are likely to be required for other antigen or multi-antigen next-generation malaria vaccine candidates and further modelling is needed.

RECOMMENDATION FOUR: Generate evidence for likely achievable coverages for vaccines in different use-cases, particularly concerning acceptable number of vaccine doses. Modelling shows the critical importance of vaccination coverage in reducing the occurrence of clinical or severe malaria in vaccine implementation. Product characteristics likely to impact an intervention's coverage, such as an injectable formulation, cold storage requirements, the number of doses, and a favorable safety profile in combination with blood stage clearance drugs, should be considered in parallel to the intervention's clinical efficacy and duration of protection. Community access and acceptance for the Foundation's use-cases in iTPP2 should be addressed through community engagement, which will be key to achieving high coverage. In particular, higher coverage will be required in perennial settings to achieve similar reductions to those predicted in seasonal settings, evidencing the need for further evidence to support the benefits of a second deployment round in perennial settings, as well as for the evaluation of community acceptability for such a strategy.

Our trade-off analysis, which examines the likely public health impact for a range of efficacy and coverage levels, indicates that reducing the number of vaccine doses to improve intervention coverage, at the cost of reducing vaccine efficacy, may not necessarily lead to greater public health impact. We found that for a vaccine candidate with initial efficacy less than 90% (i.e., less than R21 or RTS,S/AS01), requiring fewer doses that RTS,S/AS01, but with very high coverage (more than 80%), the total burden reduction is in any case lower than if the initial efficacy were more than 90%. Since both initial efficacy and duration of protection are critical determinants of vaccine health impact, accepting lower efficacy (i.e., allowing fewer doses) has negative implications for impact during the first- and second-years following vaccination, even if coverage can be increased. However, this finding may not necessarily hold for the co-administration of vaccines in combination therapies.

RECOMMENDATION FIVE: Re-evaluate the use-cases of improved first-generation anti-infective vaccines and of next-generation vaccines. A priority ordering of use-cases for multi-seasonal vaccines should be constructed with stakeholders, considering what impact can be achieved with improved first-generation vaccines with half-life protection of 12 months or more. Our initial modelling results for iTPP2 imply that even extending the half-life of antibody longevity by three to five months over that of RTS,S/AS01 may result in sustained impact into a second year following vaccination. Such a vaccine, combined with antimalarial treatment or other interventions, may reduce severe disease burden or be useful for interrupting transmission.

As a next step, we recommend the prioritization of use-cases and other important considerations for multi-seasonal interventions. The Foundation and modellers should consider (in no particular order):

1. Prioritizing combination vaccine use-cases, such as combining a blood stage antigen with existing CSP antigen vaccines to achieve burden reduction or to prevent hospitalisation.
2. For use cases where combination with treatment is essential, the choice of appropriate partner drugs should be carefully considered:
    a. What is the impact of using current first line antimalarials, particularly with respect to resistance?
    b. Can older antimalarials be repurposed for combined use with a vaccine?
    c. Have the safety profiles of the drugs been demonstrated separately, and have possible vaccine-drug interactions investigated?
3. Targeting vaccine use-cases towards areas with age patterns with the highest risk of severe disease and with low access to treatment.
4. Evaluating the efficacy of vaccine booster doses and the potential impact of timing on boosting efficacy.
5. Evaluation and considering vaccine use-cases combined with interventions that will interrupt transmission and maintain interruption, such as reactive case detection and treatment.
6. Evaluating schedules of biennial (once every two years) vaccination campaigns with longer durations than first-generation vaccines, possibly combined with a single chemoprevention round each year.
7. Performing economic analysis of future vaccine use-cases. Although larger relative impact is predicted in lower transmission sites, the total burden averted as cases or hospitalizations will be lower, which has the potential to distort a standard cost-effectiveness analysis. We suggest that these considerations should be accounted for when considering elimination targets, combination antigen vaccines, or combination interventions.
8. Modelling intermediate use-cases of current or slightly improved first-generation vaccines. With a long-tailed antibody protection extended into a second year, the value of first-generation vaccines as a combination intervention may have not been fully realised.

Following the prioritization of use-cases, we will adapt our modelling approaches to explore elimination or transmission interruption targets, as well as modeling combination vaccines.

KEY RESULTS FOR iTPP2

Public health impact on *Plasmodium falciparum* parasite prevalence and other epidemiological outcomes

Modelling results confirmed that an anti-infective vaccine's highest impact is likely to be on reduced parasite prevalence in the intervened children. Other key outcomes, listed in order of relative reduction, were reductions in clinical incidence, severe disease, and mortality (Figures 3 and 4). For example, we found a range of approximately 45% to 76% reduction in infections and a 35% to 70% reduction in clinical incidence in the initial 12 months after seasonal vaccination for a clinical trial setting.

The intervention impact (as a proportional reduction in burden in the first and second year) was found to be higher in low transmission settings, particularly when the seasonal length was shorter and access to treatment was high (Figure S1). Impact was lower in the 12 to 18 month period post intervention compared to the previous 6 month intervals (Figure 4a). The 12to 18 month period post intervention is a measure of potential impact for multi-seasonal vaccines. Vaccines with efficacy half-life greater than ten

months were able to sustain >30% reduction in clinical incidence in the 12 to 18 month period post intervention (Figure 4 and recommendation two).

Modelling confirms that co-administering an anti-infective vaccine product with a blood stage parasite clearing drug with a five-day duration provides substantially stronger burden reduction when compared to vaccination alone, in both seasonal and perennial settings (Figure 4c, 4d).

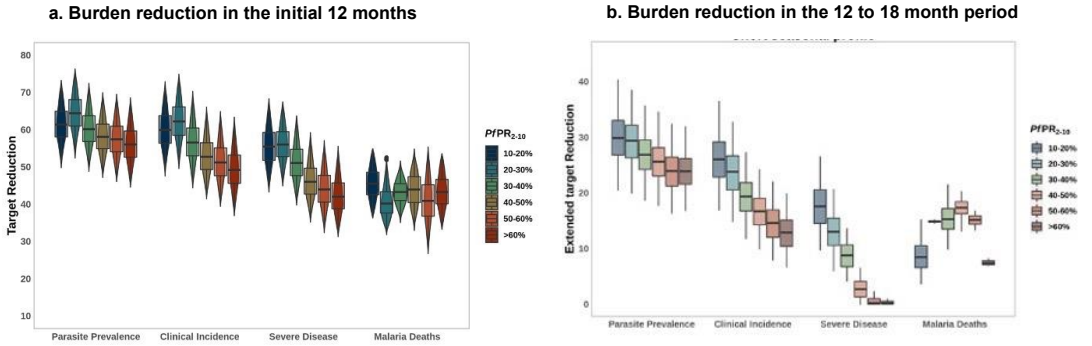

Figure 3. Predicted relative reduction (% y-axis) in parasite prevalence, clinical incidence, severe disease and malaria deaths after a seasonal vaccination program in children aged 5 to 17 months at recruitment to age 5 years compared with a no intervention counterfactual in a clinical trial setting. a) in the initial 12 months of evaluation, and b) in the 12 to 18 month period representing the second season. Results are shown for different levels of the baseline *Pf*PR$_{2-10}$ for a setting with high intervention coverage (>95%), high access to treatment (50%) for a four-month seasonal profile and a range of initial efficacy (80% to 100%) and duration of protection as half-life (6 to 12 months)**.**

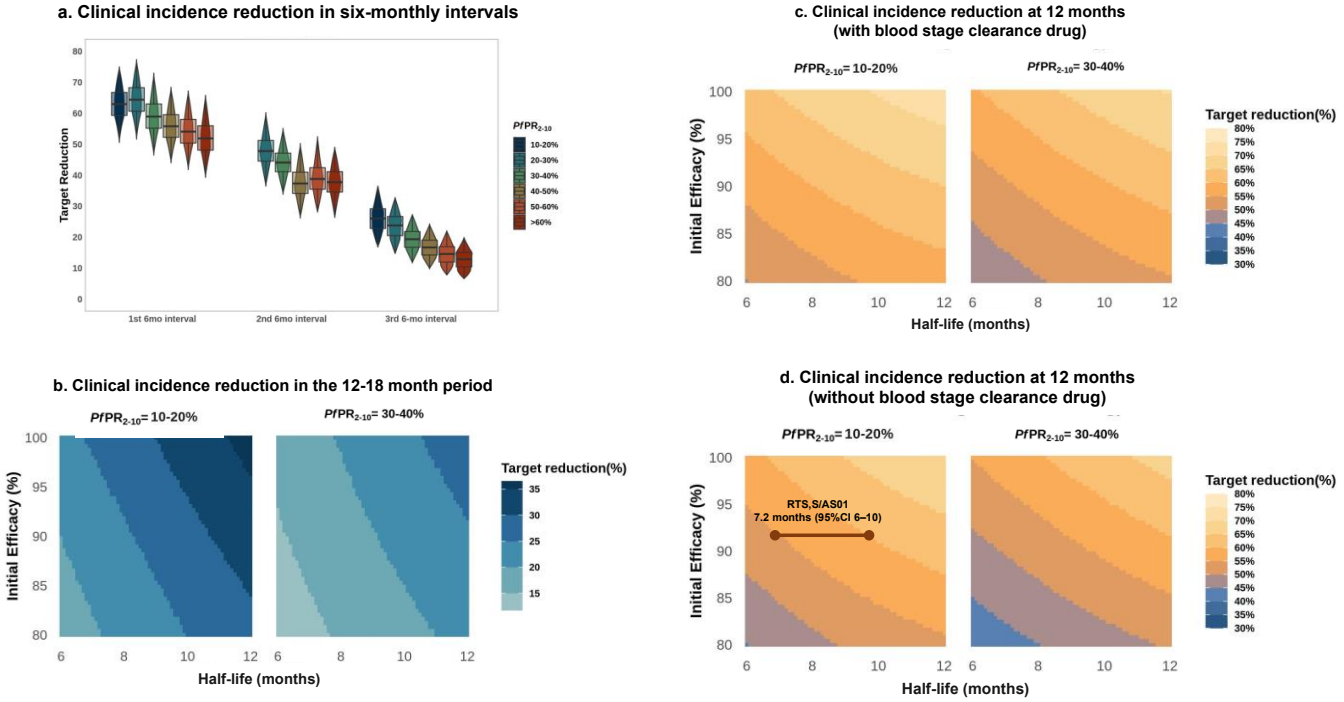

Figure 4. Predicted relative reduction in clinical incidence after a seasonal vaccination program in children aged 5 to 17 months at recruitment to age 5 years compared with a no intervention counterfactual in a clinical trial setting. a) for the first three six-monthly intervals, b) for the 12 to 18 month period representing the second season (3rd 6-month interval), c) for the initial 12 months of evaluation with a blood stage clearance drug with a five-day duration, and d) for the initial 12 months of evaluation without a blood stage clearance annotated with the RTS,S/AS01 estimated half-life duration only for low transmission (<20%). Results are shown for different levels of the baseline *Pf*PR$_{2-10}$ for a setting with high intervention coverage (>95%), high access to treatment (50%) for a four-month seasonal profile and a range of initial efficacy (80% to 100%) and half-life (6 to 12 months)**.**

Several factors will influence the achievable public health targets needed to refine the minimum intervention key performance criteria above. These include the deployment strategy, the transmission setting, the population of interest, and the evaluation period. We will generate modelling evidence for expanded use cases or target population age groups in a second round of analysis. Note that, to date, evidence suggests that initial vaccine efficacy of circumsporozoite (CSP) vaccines is likely to be lower in adults, which will influence the multi-seasonal impact and minimum performance criteria of anti-infective vaccines for expanded ages.

Product characteristics

In all settings, both the **initial efficacy against infection and duration of protection (as half-life) were critical drivers of burden reduction in both clinical trial settings and implementation settings**. Coverage was consistently a critical determinant of burden reduction in implementation settings (Figures 5 and 6).

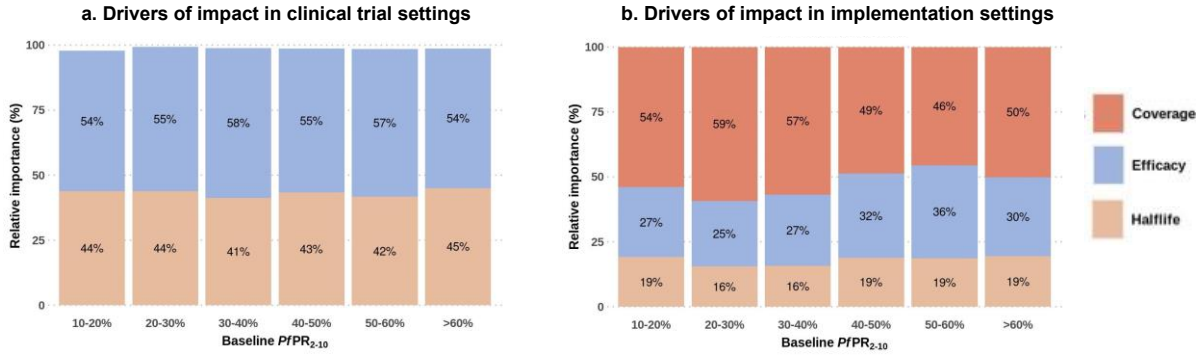

Figure 5. Drivers of impact on predicted clinical incidence reduction after seasonal vaccination in children under 5 years of age in a) a clinical trial setting, b) implementation setting, compared to a no-intervention counterfactual. Bars indicate the Sobol total effect indices (explaining the variance in relative reduction predictions) **for an intervention modelled as an anti-infective vaccine** (co-administered with a blood stage clearance drug with a five-day duration). These indices can be interpreted as the proportion of variation in the outcome attributable to a change in each variable. Results are shown across different baseline *Pf*PR2-10 for a four-month seasonal profile. In the clinical trial setting, the intervention coverage (>95%) and access to treatment (50%) are high. In the implementation setting, the intervention coverage ranges from 60 – 100% for a moderate access to treatment (25%).

The proportion contributed by each of these vaccine properties to overall impact depended on the clinical endpoint of interest, the timing of evaluation, and the length of the evaluation period (Figure S4, S6). For a second-generation vaccine product, these results suggest that the clinical efficacy profile should be well demonstrated.

Initial efficacy against infection

Our modelling evidence shows that **high initial efficacy against infection (achieved after a primary series of vaccination) is crucial to achieving high burden reduction in seasonal and perennial settings, in both clinical trial and implementation settings**. In clinical trial settings, initial efficacy was the most important driver of impact in the 12-month period following deployment of a seasonal vaccination. Initial efficacy was, however, consistently the second most important driver in implementation settings regardless of the clinical endpoint or the seasonal period length; vaccination coverage was the main driver of impact in implementation settings. Furthermore, initial efficacy was a low priority driver for extended burden reduction during the subsequent year (12 to 18 months following deployment). Yet, a vaccine product would still need to have a high initial efficacy to achieve adequate burden reduction; aiming for a >70% reduction of clinical incidence in the first 12 months requires > 10 months half-life and > 90% initial vaccine efficacy if coverage is 80%. This impact would vary for settings by seasonal length.

In this preliminary analysis, we assumed that booster doses 12 months apart 'reset' a vaccine's efficacy and efficacy decay to that shown after the primary series (see validation). Clinical evidence from first- and next-generation vaccines will be required to validate these assumptions. If required, we will consider alternative assumptions in future modelling.

Indication (duration of protection as half-life)

In both clinical trial and implementation settings, a first-generation vaccine product with a half-life of less than one year provided extended protection beyond the first year following deployment, to cover part of the following season. We found that half-life of protection was an important driver of impact in the first 12 months, with importance closely following initial efficacy in clinical trial settings (Figure 5) and following both vaccine coverage and initial efficacy in implementation settings (Figure 5 and 6).

In contrast, we found that **duration of protection, rather than coverage or initial efficacy, was the most important intervention characteristic for burden reduction in the 12 to 18 months following deployment in both clinical trial and implementation settings**. This was because vaccines with long half-lives (here only up to 12 months) provided extended protection to cover the initial months of the second malaria season after intervention.

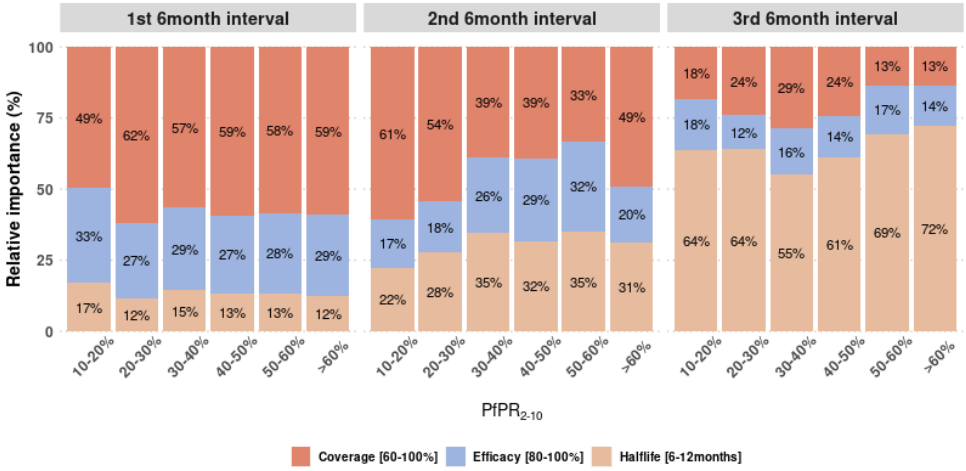

Figure 6. Drivers of impact on predicted clinical incidence reduction after seasonal vaccination in children under 5 years of age in an implementation setting, compared to a no-intervention counterfactual for six-monthly interval evaluation periods including the 12 to 18 month period. Bars indicate the Sobol total effect indices (explaining the variance in relative reduction predictions) **for an intervention modelled as an anti-infective vaccine** (co-administered with a blood stage clearance drug with a five-day duration). These indices can be interpreted as the proportion of variation in the outcome attributable to a change in each variable. Results are shown across different baseline *Pf*PR$_{2-10}$ for a four-month seasonal profile. The intervention coverage ranges from 60 – 100% for a moderate access to treatment (25%).

Substantial burden reduction was predicted when a first-generation product with a longer half-life of at least 10 months was deployed (Figure 4). When the duration of protection was longer, the vaccine's protection could extend to cover the entire second season following deployment (although at reduced efficacy). This was particularly apparent in settings with longer transmission seasons (more than six months), leading to a potential product that could be classed as a multi-seasonal vaccine in the iTPP2, as long as initial efficacy is high. **The minimum half-life requirement for sustained impact in the second season was also higher for highly seasonal (4-month) than for perennial (9-month) settings. In contrast, the half-life requirement was higher for perennial settings in the initial 12 months of evaluation (Figure S7).**

As a result, **there is need to investigate the possibility of long-lived protection against *Plasmodium falciparum* infection for the various, existing vaccine products by generating evidence for each vaccine's duration of protection**. If a vaccine's duration of protection can be optimized to provide extended protection over multiple seasons, then the feasibility of increasing the intervals between doses for seasonal vaccination programs should be evaluated. As indicated in the recommendations above, evaluating and selecting appropriate next candidates will rely on reliable immune correlates. Evaluating 'any' infection endpoints (with sensitive diagnostics or appropriate serological monitoring) and not just clinical efficacy will be required in future clinical trials, especially if vaccines will be considered for elimination targets. As a next step, we will discuss generating modelling evidence for a vaccine product with an efficacy half-life longer than 12 months with the Foundation. We may also investigate the potential for multi-

component modelling, where vaccines targeting a range of antigens or stages in the *Plasmodium falciparum* life cycle can be combined to enhance protection against malaria.

Coverage requirements

As a health system factor, intervention coverage is one of the most important determinants of an intervention's impact in implementation settings. Regardless of the vaccine protective efficacy profile or duration of protection, the impact will be limited if intervention coverage is inadequate. Intervention coverage should be optimized in settings where access to treatment is low, even when the intervention is highly efficacious and provides long-duration protection against infections (Figure 7). These results suggest that, while optimizing key performance properties such as initial efficacy and duration of protection are important, we should also prioritize product attributes that influence intervention coverage, such as a product's dosing regimen; safety profile; and acceptance for different use cases.

Yet, our trade-offs analysis indicates that reducing the number of vaccine doses to improve intervention coverage, at the cost of reducing vaccine efficacy, may not lead to the greatest public health impact. For example, we found that for a vaccine candidate with initial efficacy of 70% to 80% (less than RTS,S and R21) and half-life greater than nine months (more optimistic than first-generation vaccines) the total burden reduction that can be achieved with a very high coverage of >80% is less than if the initial efficacy were greater than 90% (Figure 7).

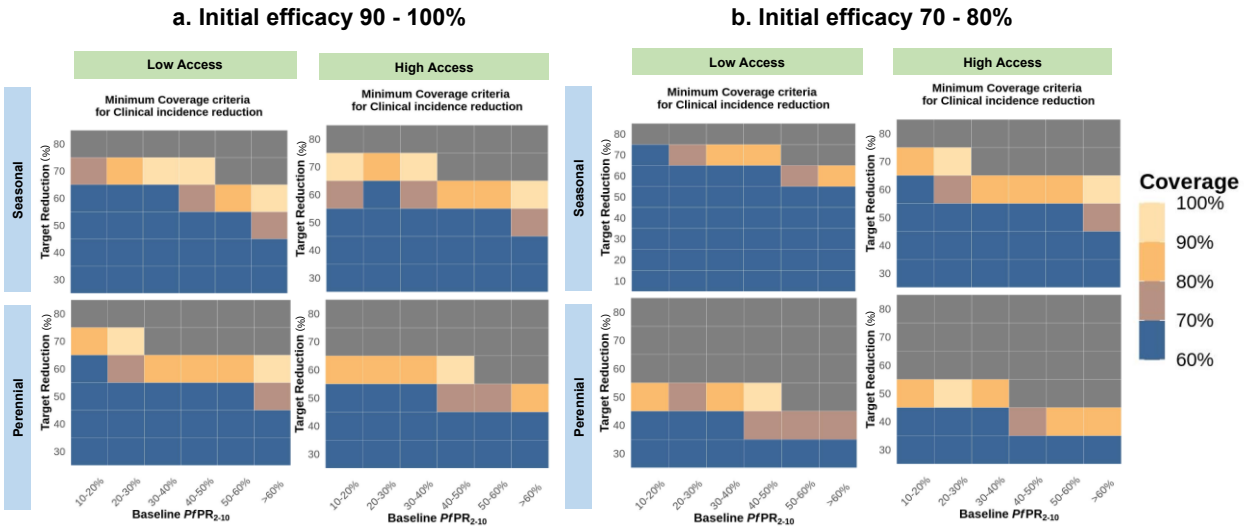

Figure 7. Summary of the predicted minimum indication criteria for the intervention coverage of an improved first-generation vaccine product in clinical incidence reduction measured in implementation settings, compared with a no intervention counterfactual in the initial 12 months of evaluation. The vaccine is co-administered with a blood stage clearance drug with a five-day duration. The results show the estimated minimum half-life required to *achieve a given target reduction (y-axis) in clinical incidence impact, with grey indicating that the target is outside of the parameter range.* Results are shown for two initial efficacy conditions, a) initial efficacy 80-100% and b) initial efficacy 70-80%, two seasonal profiles, 4-month - highly seasonal profile and 9-month – perennial setting, for both low (10%) and high (50%) access to treatment. The half-life duration ranges from 9 to 12 months

Target population

The priority age group for initial modelling analysis of seasonal vaccination was informed by the Foundation and by our stakeholders. **This priority age group was comprised of children aged between five and 17 months at recruitment**, who received the three-dose primary series followed by annual booster doses until the age of five years. This target age group corresponded to the clinical trials for RTS,S/AS01 and matches the current WHO recommendation. Evaluation of additional target age populations will be guided by the Foundation in balance with ongoing evidence of new vaccines and public health goals for burden reduction and/or elimination with combination interventions.

Target endpoints and settings

We investigated a range of seasonal and perennial transmission settings and, although absolute burden reduction varied between these settings, our key results around relative importance of duration and initial efficacy remain the same. Care will be needed to define appropriate target evaluation periods to assess new vaccines, as well as primary epidemiological outcomes. Our modelling shows that, over and above clinical incidence reduction, efficacy, or reduction of all infection in at least a subset of the clinical trial cohort is a preferable endpoint to evaluate intervention impact. Evaluating impact on any infection, rather than clinical incidence reduction alone, will lead to greater ability to:

1. Confirm and assess a vaccine's underlying efficacy against infection and associated immune correlates of protection, and;
2. Enable better translation between transmission settings.

Although larger relative impact was seen in lower transmission sites, the total burden averted as cases or hospitalizations will be lower, with the possibility of distorting a standard cost-effectiveness analysis. We suggest, as per recommendation five, that these considerations should be accounted for when considering elimination targets, combination antigen vaccines and combination interventions.

POTENTIAL INPUT ANNOTATIONS FOR iTPP2 CRITERIA

Inputs are noted in red are preliminary inputs only for discussion.

1. Product

Variable	Base Case	Upside Case	Annotations
Product	Combination **no more than two active components** that prevent infection by (i.e., targeting CSP or other sporozoite antigens) or kill the blood stage of dominant circulating *Plasmodium falciparum* strains.	**One active component*** that prevents infection by (i.e., targeting CSP or other sporozoite antigens) or kills the blood stage of dominant circulating *Plasmodium falciparum* by targeting a conserved domain in *Pf* strains.	Vaccine products that rely solely on transmission-blocking targets or activity are not in scope for this interventional TPP. We believe that personal protection during travel as malaria transmission becomes more heterogenous is a critical parameter. If the product contains two components, the efficacy of each component may have to be demonstrated separately.

* Modelling has shown that a combination vaccine could support both prevalence and clinical/severe disease reduction. For non-elimination, multi-seasonal use-cases targeting children, combinations could be included in the upside case if actions are synergistic and lead to greater protection against severe disease in children.

2. Co-Administration

Variable	Base Case	Upside Case	Annotations
Co-administration	It can be safely co-administered with antimalarial drugs (see above) or other routine interventions, including concomitant vaccines.	Same as minimum	Antimalarial drugs could include case management regimens, including primaquine, MDA, and SMC regimens. Modelling confirms that co-administering an anti-infective vaccine product with a blood stage parasite clearing drug provides higher burden reduction than vaccination alone in seasonal and perennial settings. Vaccines combined with mass drug administration (MDA) in the final stages of an elimination program may enhance the success of interrupting transmission and maintaining elimination. Vaccines may also supplement the use of multiple MDA rounds during emergencies and health system disruptions.

3. Impact on *Plasmodium falciparum* Parasite Prevalence (*Pf*PR) and other epidemiological outcomes

Variable	Base Case	Upside Case	Annotations
Impact on Parasite Prevalence (PfPR), clinical cases and severe disease	To be determined[2]	To be determined[2]	[2]Pending on modeling studies and policy standards discussion with WHO to determine what community benefit would be necessary for a recommendation on the product. For elimination programs, $PfPR_{2-10}$ is not the right measurement. May be total clinical cases and outbreaks Modelling indicates that anti-infective vaccine impact on parasite prevalence will be greater than on clinical disease. Furthermore, evaluating infection endpoints in clinical trials and not just clinical efficacy will be required in future trials (or in a sub-cohort). Parasite endpoints will confirm a vaccine's underlying efficacy against infection associated with immune correlates of protection and will enable better translation between transmission settings.

4. Indication

Variable	Base Case	Upside Case	Annotations
Indication	Prevent infection by *Plasmodium falciparum* (Pf) for at least **two years** post-administration.	Prevent infection by *Plasmodium falciparum* (Pf) for up to **five years** post-administration.	This interventional TPP describes a second-generation product with minimum criteria for infection prevention. The main differences between the base and upside cases are the duration of prevention. Seasonal interventions with duration of protection less than 2-years are not in scope Should the intervention be a vaccine, 'administration' means the primary immunization regimen. Booster immunizations are used to extend protection. Modelling evidence indicates use-cases capitalizing on the value of improved longevity first-generation vaccines should be considered, with implications on defining base-case efficacy endpoints at the beginning of second year (rather than "at least two years")

5. Clinical Efficacy

Variable	Base Case	Upside Case	Annotations
Clinical Efficacy[1]	**Preventive efficacy:** ≥ 80%, measured by prevention of infection with *Plasmodium falciparum* using a suitable clinical endpoint, at the end of the protection period (2 years)	**Preventive efficacy:** ≥ 90%, measured by prevention of infection with *Plasmodium falciparum* using a suitable clinical endpoint, at the end of the protection period (5 years).	[1]Target reduction goals are preliminary; modeling necessary to ensure targets meet elimination goals (herd protection when coupled with best available village-based vector control) Modelling indicates that protection at the beginning of second year, and the half-life of protection from the primary series, will support evaluation of the likely impact of multi-seasonal interventions into the second and third year following primary administration. Validated immune correlates of protection will be essential to reduce time periods to evaluate longer duration vaccines. Evaluating the efficacy of booster doses (and potential impact of timing on boosting efficacy) will be essential.

6. Coverage Requirement

Variable	Base Case	Upside Case	Annotations
Coverage requirement[3]	≥ 80%[4]	≥ 90%[4]	[3]To achieve community effect compatible with achieving heard immunity consistent with interruption of transmission during the protection window. [4]Based on modeling studies

7. Target Settings

Variable	Base Case	Upside Case	Annotations
Target Settings	All geographies where *Plasmodium falciparum* is endemic across the entire range of parasite prevalence.	All geographies where *Plasmodium falciparum* is endemic across the entire range of parasite prevalence.	Groups should model projected remaining transmission zones for 2035-50. Modelling should consider low transmission settings and further explore impact of model uncertainty/translation between endpoints in these settings.

SUPPLEMENTARY INFORMATION AND RESULTS

1.1 Predicted relative reduction in all endpoints in clinical trial settings and the extended burden reduction by seasonality

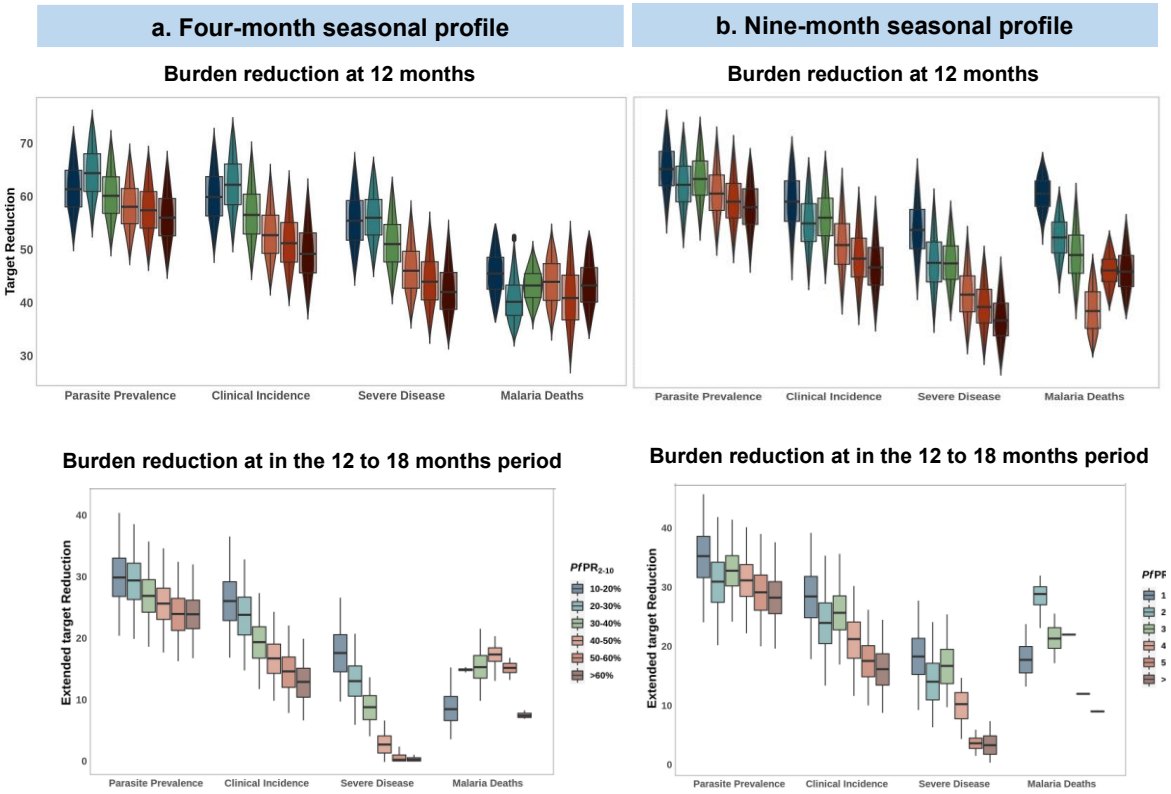

Figure S1. Predicted relative reduction in parasite prevalence, clinical incidence, severe disease and mortality after a seasonal vaccination program in children aged 5 to 17 months at recruitment to age 5 years compared with a no intervention counterfactual in a clinical trial setting. Results are shown for a) a four-monthly seasonal profile – highly seasonal setting (for both the initial 12 months and the 12 to 18 month period representing the second season) and b) a nine-monthly seasonal profile – perennial setting (for both the initial 12 months and the 12 to 18 month period representing the second season), for different levels of the baseline *Pf*PR$_{2-10}$ for a setting with high intervention coverage (>95%), high access to treatment (50%) and a range of initial efficacy (80% to 100%) and half-life (6 to 12 months)**.**

1.2 Predicted relative reduction in clinical incidence in clinical trial settings at six-monthly intervals by seasonality

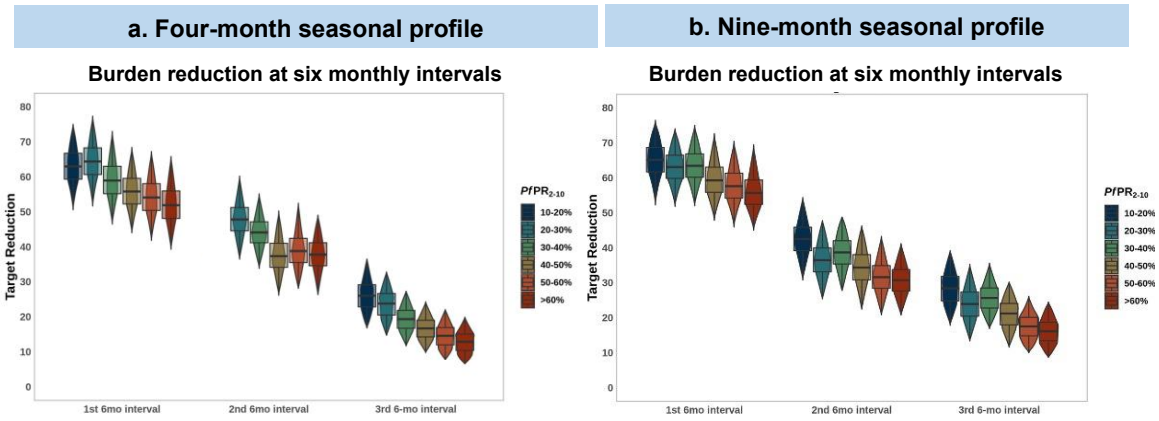

Figure S2. Predicted relative reduction in clinical incidence after a seasonal vaccination program in children aged 5 to 17 months at recruitment to age 5 years compared with a no intervention counterfactual in a clinical trial setting. Results are shown at six-monthly intervals for a) a four-monthly seasonal profile – highly seasonal setting and b) a nine-monthly seasonal profile – perennial setting for different levels of the baseline *Pf*PR_{2-10} for a setting with high intervention coverage (>95%), high access to treatment (50%) and a range of initial efficacy (80% to 100%) and half-life (6 to 12 months)**.**

1.3 Predicted relative reduction in clinical incidence in clinical trial like settings

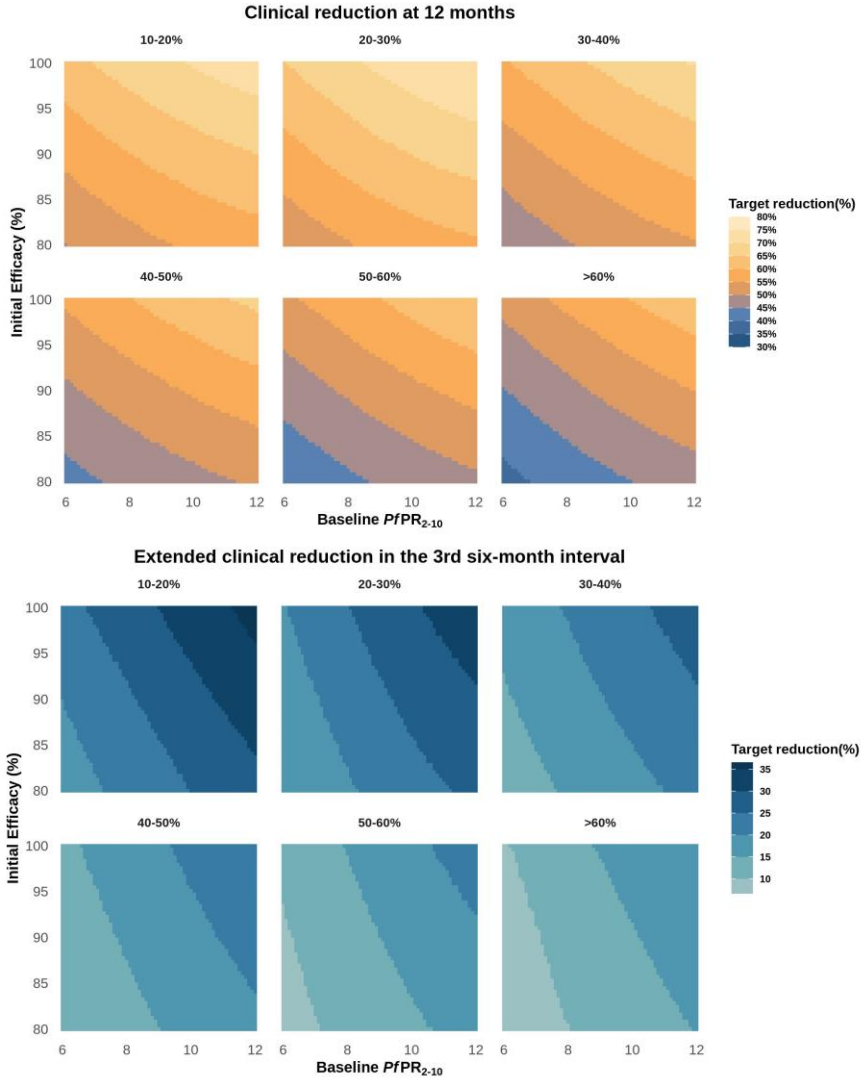

Figure S3. Predicted relative reduction in clinical incidence after a seasonal vaccination program in children aged 5 to 17 months at recruitment to age 5 years compared with a no intervention counterfactual in a clinical trial setting. Results are shown for a) initial 12 months of evaluation, b) the 12 to 18 month period representing the second season in a four-monthly seasonal profile – highly seasonal setting, for different levels of the baseline *Pf*PR_{2-10} for a setting with high intervention coverage (>95%), high access to treatment (50%) and a range of initial efficacy (80% to 100%) and half-life (6 to 12 months)**.**

1.4 Relative importance of key intervention properties in clinical trial settings

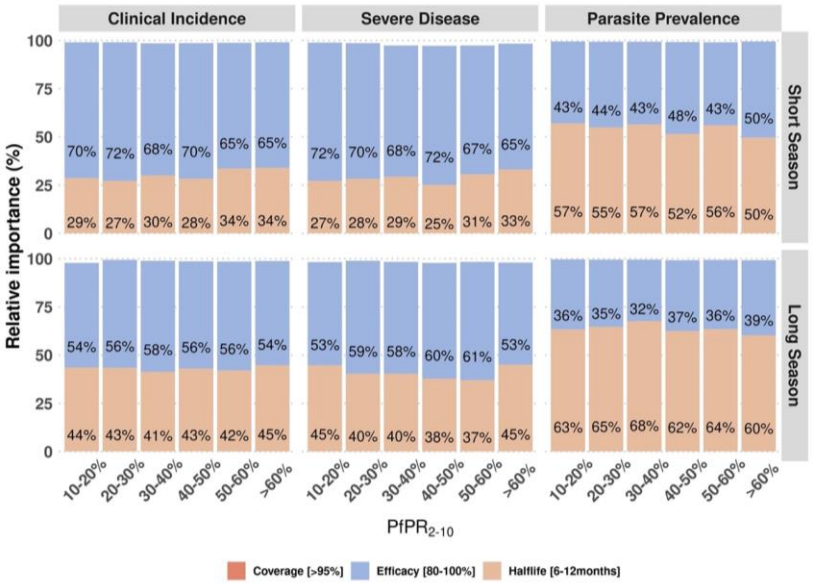

Figure S4. Drivers of impact on predicted clinical incidence reduction after seasonal vaccination in children under 5 years of age in a clinical trial setting compared to a no-intervention counterfactual. Bars indicate the Sobol total effect indices (explaining the variance in relative reduction predictions) **for an intervention modelled as an anti-infective vaccine**. These indices can be interpreted as the proportion of variation in the outcome attributable to a change in each variable. Results are shown across different baseline *Pf*PR2-10 for a four-month seasonal profile. The intervention coverage (>95%) and access to treatment (50%) are high.

1.5 Predicted minimum clinical incidence criteria for the half-life of an anti-infective vaccine in clinical trial settings

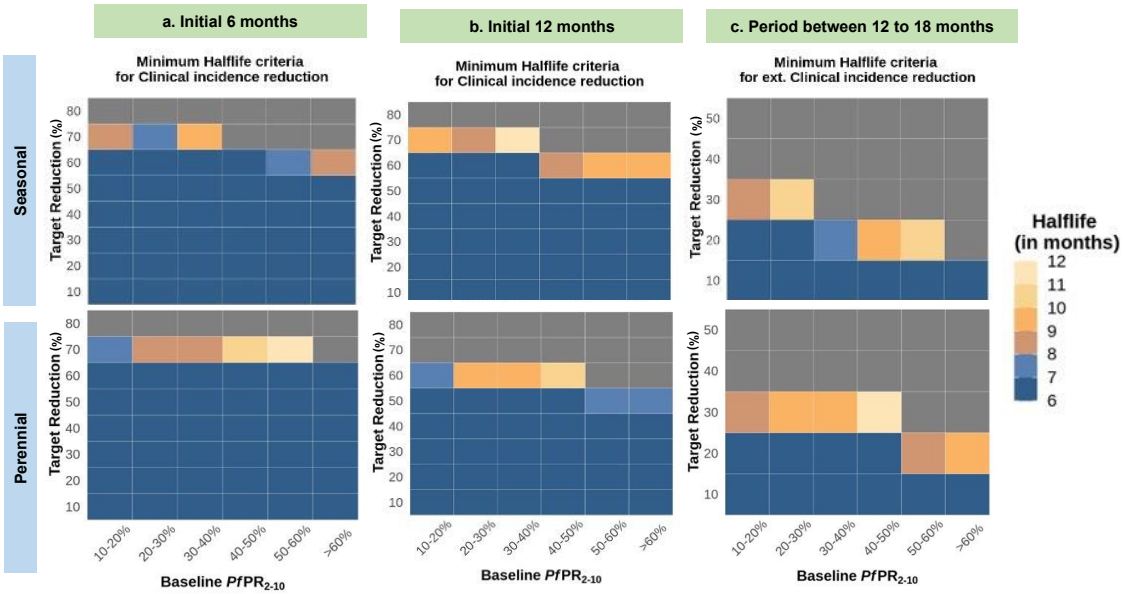

Figure S5. Summary of the predicted minimum indication criteria for the duration of protection (as half-life) of a first-generation vaccine product in clinical trial settings compared with a no intervention counterfactual. The results show the estimated minimum half-life required to *achieve a given target reduction (y-axis) in clinical incidence impact, with grey indicating that the target is outside of the parameter range.* Results are shown for three evaluation time periods, a) initial 6 months, b) initial 12 months, and c) the period between 12 to 18 months; for two seasonal profiles, 4-month - highly seasonal profile and 9-month – perennial setting; for two levels of access to treatment low (10%) and high (50%). The half-life duration ranges from 9 to 12 months.

1.6 Relative importance of key intervention properties in implementation settings

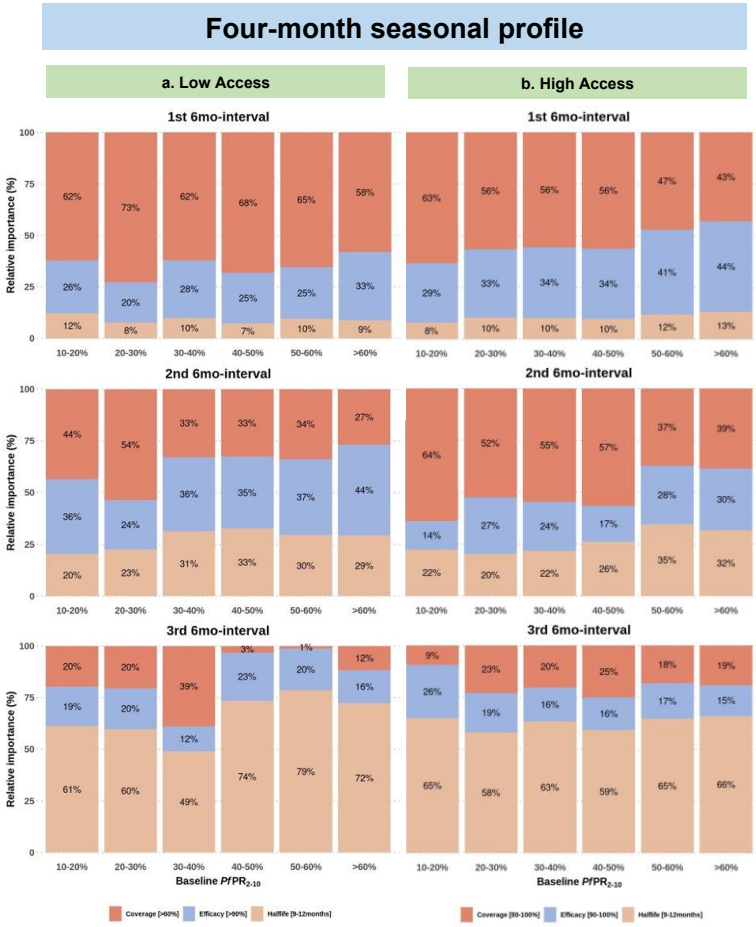

Figure S6. Drivers of impact on predicted clinical incidence reduction after seasonal vaccination in children under 5 years of age in an implementation settinsg compared to a no-intervention counterfactual for six-monthly intervals. Bars indicate the Sobol total effect indices (explaining the variance in relative reduction predictions) **for an intervention modelled as an anti-infective vaccine**. These indices can be interpreted as the proportion of variation in the outcome attributable to a change in each variable. Results are shown across different baseline *Pf*PR2-10 for a four-month seasonal profile. The intervention coverage ranges from 60% to 80%, initial efficacy 80% to 100% and the half-life between 6 to 12 months.

1.7 Predicted minimum clinical incidence criteria for the intervention coverage of an anti-infective vaccine in implementation settings

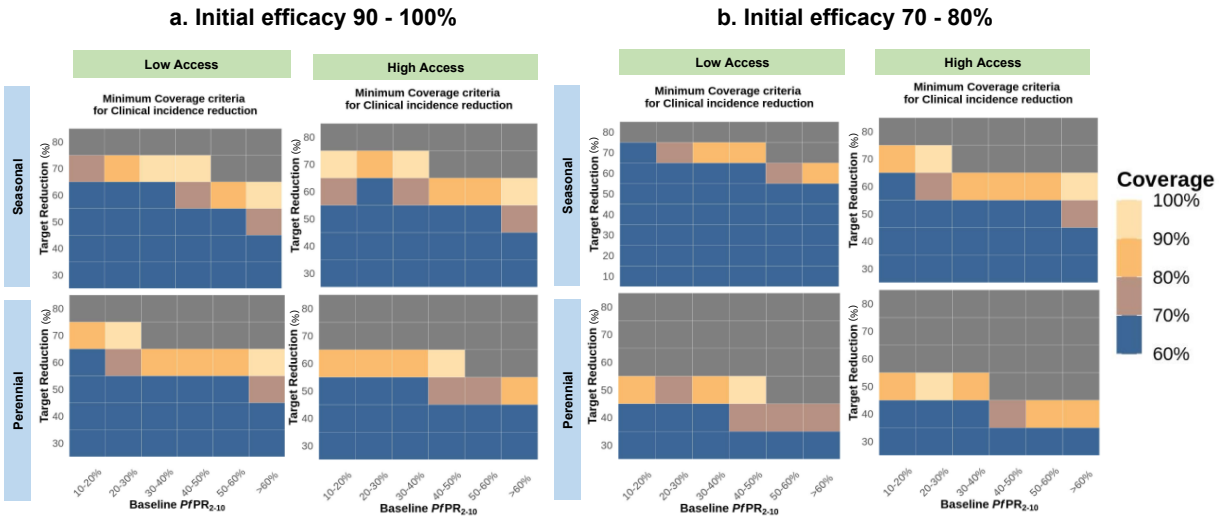

Figure S7. Summary of the predicted minimum indication criteria for the intervention coverage of a first-generation vaccine product in clinical incidence reduction measured in implementation settings compared with a no intervention counterfactual. The results show the estimated minimum half-life required to *achieve a given target reduction (y-axis) in clinical incidence impact, with grey indicating that the target is outside of the parameter range.* Results are shown for two initial efficacy conditions, a) initial efficacy 80-100% and b) initial efficacy 70-80%, two seasonal profiles, 4-month - highly seasonal profile and 9-month – perennial setting, for both low (10%) and high (50%) access to treatment. The half-life duration ranges from 9 to 12 months

SCENARIO, INTERVENTION AND OUTCOME ASSUMPTIONS

RTS,S/AS01, a first-generation vaccine against *Plasmodium falciparum* malaria has previously been modelled as a product with a pre-erythrocytic or anti-infective mode-of-action that targets the sporozoite surface antigen of the *Plasmodium falciparum* parasite. Model parameters for RTS,S have been well documented, and have been used to predict the likely public health impact and cost-effectiveness for routine implementation in African settings for a range of transmission intensities [4].

Both clinical and modelling evidence on RTS,S shows modest protective efficacy following the primary series (three initial doses given in monthly intervals) with a decay rate of approximately four years. The decay in efficacy is initially rapid in the first six to seven months followed by a slow decay (biphasic profile). An additional fourth dose (booster) given 12 to 18 months following the primary series could potentially restore waning vaccine efficacy, although it is still unclear by how much the booster doses extend protection. Model parameters were mainly estimated from simulating RTS,S use in perennial settings. Of note, favorable health outcomes have been predicted when RTS,S is used for seasonal vaccination with or without seasonal malaria chemoprevention (SMC) [2].

To inform the initial discussions surrounding the parameter ranges for the intervention properties of a multi-seasonal vaccine (initial efficacy, duration of protection and dosing regimen), we investigate the population level health impact of a anti-infective first-generation vaccine product, using an established individual-based model of malaria transmission and intervention dynamics (known as OpenMalaria), with **burden reduction as the public health goal**. The preferred performance characteristics of a second-generation vaccine are not known. Hence, we explore a range of likely values for the initial efficacy and half-life (time in months until the initial efficacy reduces by 50%) for a range of scenarios. We explore the impact for different malaria prevalence levels, seasonal profiles and health system factors including varying the intervention coverage and level of access to treatment for a single season use case. Through exploring a range of scenarios, we capture a range of epidemiological dynamics. These modelling assumptions are shown in Table 1 below and are summarized in Figure 2.

We model a seasonal vaccination program where:

- The intervention (first-generation anti-infective vaccine) is deployed prior to the peak malaria transmission season and is co-administered with a highly efficacious blood stage antimalarial drug which clears parasites with a five-day duration.
- Each year, cohorts of children aged between five and 17 months are recruited just before the malaria season and followed up over time until they are five years old. If a child is not recruited when they reach five months of age, they have a chance of being recruited into the seasonal vaccination program cohort each year until they are 17 months old.
- The primary series consists of the initial three vaccine doses given in monthly intervals to children aged between five and 17 months at recruitment, followed by annual booster doses given to the same children until they are five years of age, prior to the malaria season's peak.
- The timing of first deployment is approximately two months prior to the highest peak in the malaria transmission seasonal profile (Figure B)
- The first two doses are assumed to have zero efficacy and the initial efficacy of the vaccine is estimated after the third dose in the primary series. Annual booster doses are assumed to restore the waning vaccine efficacy to the initial level. Assumptions around decay in protective efficacy are demonstrate in (Figure 2, page 6 and Table 1, page 26)
- The intervention is deployed annually over ten years and outcomes are calculated after the tenth year for children aged between five months and five years, assumed to have received all the recommended primary and booster doses.

We evaluate outcomes in the initial six and 12 months after seasonal vaccination, and also in six-monthly intervals, **to estimate the extended protection provided after the initial 12 months.**

Modelling Assumptions

Our modelling and simulations were performed with an individual-based model of malaria transmission and intervention dynamics (OpenMalaria) [1] following the methods and workflow developed in Golumbeanu 2021 [5] and Burgert 2021 [6]. The experimental setup and assumptions are detailed in Table 1.

Parameter	Parameterization
Intervention	A first generation vaccine product with a pre-erythrocytic (anti-infective) mode-of-action e.g. RTS,S/AS01-like, co-administered with a blood-stage parasite clearing drug
Target population	Children >5 months to 17 months at time of recruitment and follow-up until 5 years
Vaccine initial efficacy range	50% – 100% (RTS,S a high estimated initial vaccine efficacy (over 90%) that wanes following a biphasic decay profile, with a half-life of 7.32 months [95%CI 6 – 10 months] estimated over 32 months after the 4-dose primary series of given monthly in the Phase III clinical trials for children aged 5 to 17 months at recruitment[3].
Initial anti-infective protective efficacy half-life range	6 – 12 months (RTS,S has half-life of 7.32 months [95%CI 6 – 10 months])
Decay profile	Weibull function *k shape* parameter is 0.69, with a biphasic decay profile (Informed by RTS,S [3])
Deployment coverage range	60% – 100%
Dosing regimen and timing	• Initial primary series consisting of three doses given in monthly intervals, deployed at the start of the peak transmission period • Yearly booster doses at the start of the peak transmission (two months before peak)
Demography	Constant population size (10,000 individuals) and demography profile based on population estimates for Ifakara, Tanzania
Seasonality	Three generic seasonal profiles with varying lengths: • 4-month seasonal (short) • 6-month seasonal (long) • 9-month ~essentially perennial
Transmission intensity	Six baseline categories of $PfPR_{2-10}$ from low, moderate to high transmission: • 10% – 20% • 20% – 30% • 30% – 40% • 40% – 50% • 50% – 60% • >60%
Case management	Three levels of health system coverage for uncomplicated malaria: • Low probability of seeking care (10% over 14 days) • Moderate probability of seeking care (25% over 14 days) • High probability of seeking care (50% over 14 days)
Diagnostic	RDT with a parasite detection limit and specificity of 50 and 94%
Health Outcomes (Endpoints)	Relative reductions in target population: • Prevalence of all infections (2-10 years of age, intervention age groups) • Incidence of clinical disease (under 5, under 10, intervention age groups) • Incidence of expected severe cases (under 5, under10, intervention age groups) • Incidence of expected deaths (under 5, under 10, intervention age groups)
Evaluation period	Endpoints compare the percentage relative reduction in malaria outcome for 6, and 12 months following the intervention (and the 6-monthly intervals). To assess multi-seasonal impact, endpoints were compared at the 6-month period from the beginning of on season with *no vaccination*, after implementation has been ongoing for at least 5-10 years. This final period evaluates the impact in the second season following vaccination. The counterfactual is the malaria burden for the same periods without intervention.
Experimental properties	Simulations were completed with 10 stochastic realizations and 1000 replicates of all continuous parameters (initial efficacy, half-life, intervention coverage), for each baseline prevalence level, seasonal profile and level of access to treatment.

Table 1. Modelling Assumptions

Table of definitions

Term	Definition	*Example*
Clinical incidence reduction	**A primary clinical trial and implementation outcome**, the percentage relative reduction in malaria clinical incidence measured compared with a no intervention counterfactual, where clinical incidence is defined as the number of new cases of uncomplicated malaria in children aged 7 months to 5 years old in the 6- or 12-months follow-up period in the 10th year of seasonal vaccination.	*In a population of 1000 children monitored over a 12-month intervention period in the tenth year after first deployment, seasonal vaccination led to a reduction in the number of new cases of uncomplicated malaria from 400 to 200, i.e., to a clinical incidence reduction of 50%.*
Decay profile	The decrease in protective efficacy over time, resulting in the decay or reduction of the intervention's initial efficacy. This decay curve can have multiple shapes. For example, a strong decrease shortly after administration (exponential decay), or a longer-lasting high efficacy after administration with a sharp decrease (sigmoidal decay).	*RTS,S/AS01 protective efficacy decays with a biphasic decay profile. We assume in our initial analysis here the antibody and corresponding protective efficacy decays the same as RTS,S and we have not varied this (Our iTPP1 report has explored the effect of varying this decay)*
Duration of protection	A **key performance characteristic**, the number of months until the intervention's initial protective efficacy against infection has decayed to half its original value.	*An individual receives an intervention with an initial efficacy of 90% and a 6-month duration of protection. 6 months after the intervention was given, the individual is protected against 45% of infections.*
Initial efficacy	A **key performance characteristic,** the average initial efficacy of the intervention as the percentage of the maximum intended efficacy against pre-erythrocytic infection in the target age group before decay, with or without inter-individual variation.	*An individual receives an intervention with a 90% initial efficacy. The individual is protected from 90% of pre-erythrocytic infections at this time.*
Intervention coverage	A **key performance characteristic,** the coverage of seasonal vaccination in a given target population.	*Seasonal vaccination is available for the target population with 80% coverage. Each child in the target age group and cohort has an 80% chance of being administered a vaccine dose.*
Mortality reduction	**A secondary clinical trial and implementation outcome**, the percentage relative reduction in the number of malaria deaths compared with a no intervention counterfactual in the intervention age group, where the number of deaths is evaluated in the 6- or 12-months follow-up period in the 10th year of seasonal vaccination.	*In a population of 1000 children monitored over a 12-month intervention period in the tenth year after first deployment, seasonal vaccination led to a reduction in the number of new cases of severe cases from 10 to 5, i.e., to a malaria deaths reduction of 67%.*
***Pf*PR$_{2\text{-}10}$**	The annual *Plasmodium falciparum* Parasite Rate in children between two and ten years old, a measure of prevalence in a given year.	*In 2021, the annual PfPR in children between two and ten years old was 25%.*
Seasonal profile	A mathematical equation that captures the shape and length of a region's highest risk period to malaria infection.	*A four-month seasonal profile has the most intense transmission of malaria during a four-month consecutive period.*
Severe disease reduction	**A primary clinical trial and implementation outcome**, the percentage relative reduction in the number of severe malaria cases measured compared with a no intervention counterfactual, where severe cases of malaria are evaluated in children aged 7 months to 5 years old in the 6- or 12-months follow-up period in the 10th year of seasonal vaccination.	*In a population of 1000 children monitored over a 12-month intervention period in the tenth year after first deployment, seasonal vaccination led to a reduction in the number of new cases of severe cases from 30 to 10, i.e., to a severe disease reduction of 67%.*

Table 2. Summary of definitions.

Methods

Modelling Criteria for Target Product Profiles

The development of next-generation medical interventions is guided by Target Product Profile documents, which help to prioritize candidates towards ensuring health targets are reached. Swiss TPH has developed an evidence-generation framework that uses mathematical modelling to support the identification of minimum product requirements. This framework, which uses established techniques from malaria disease modelling, consists of the following elements:

- **Disease and Intervention Modelling:** Simulation with a comprehensive and well-established mathematical model for the progression and transmission of malaria (OpenMalaria) [1]. This model is applied on a discrete, uniformly sampled set of input parameters that capture key intervention properties.
- **Machine Learning:** Training of a Gaussian Process regression model on a dataset constructed from the sampled set of input parameters and their corresponding, simulated outcomes. This model captures the complex dynamics of malaria transmission without large computational cost.
- **Sensitivity Analysis:** Determination of an intervention property's impact through the use of a variance-based sensitivity analysis.
- **Optimisation:** Identification of minimal intervention properties through the use of optimization techniques, which explore optimal intervention properties to achieve a target public health outcome.

The techniques employed within this framework were recently deployed in a proof-of-concept study for long acting injectables [6]. Golumbeanu at al. have also provided a detailed description of the methodology [5]. We provide guidance on interpreting results from each component of this method in the following sections.

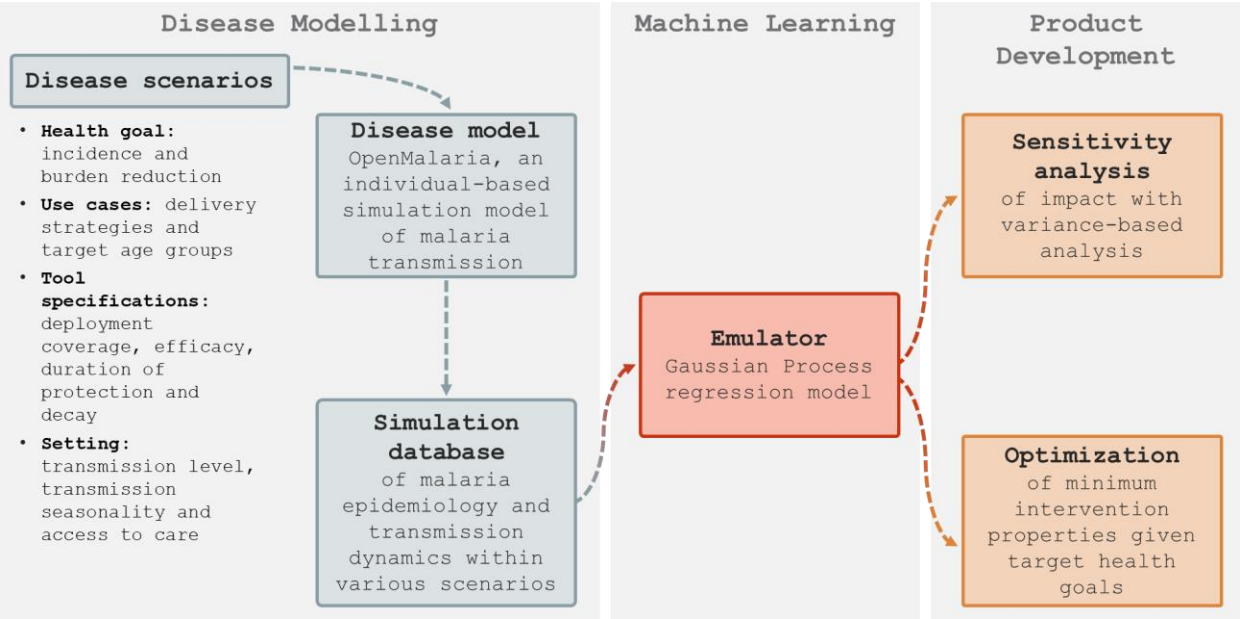

Figure S8. Schematic diagram of the evidence-generation framework to support the identification of minimum necessary key performance characteristics.

Measuring Drivers of Impact

We undertook a **global sensitivity analysis of our model results** to identify the most important drivers of impact for a new intervention. This method studies how the uncertainty in a mathematical model can be attributed to different sources of uncertainty in the model's inputs. We perform this analysis with the Sobol method, reporting the total effect indices.

In this report, we use a global sensitivity analysis to measure the extent to which a small change in an intervention's key performance properties corresponds to a change in the intervention's impact, as shown in Figure S9. For example, we may see that an increase in the initial efficacy, from say 80% to 90%, leads to a larger change in the achievable clinical incidence reduction than a small increase in the intervention's duration of protection.

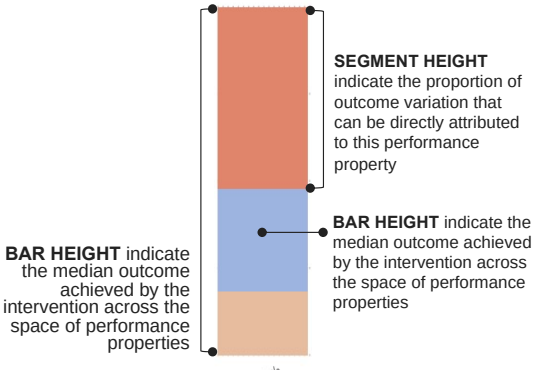

Figure S9. Understanding the measurement of drivers of impact.

Identifying Key Performance Criteria

To identify the key performance criteria for a novel intervention, we link a desired public health outcome with the required intervention properties. Following an optimization technique called a **grid search**, we use a machine learning emulator of our malaria transmission model to predict the likely public health outcome of a large combination of different values for the intervention's key performance properties.

For example, suppose that an intervention had three likely levels of duration of protection, low (six months), medium (nine months) and high (12 months). To link these properties with their likely impact, we run the malaria transmission model emulator three times, varying the level of duration of protection each time, and recording the resulting reduction in malaria clinical incidence (Figure S10).

After predicting the likely public health outcome of a large combination of different intervention property values, the results of a grid search can be used to identify optimal intervention properties. For example, given a target clinical incidence reduction, we can identify the smallest duration of protection needed for the intervention to achieve the target.

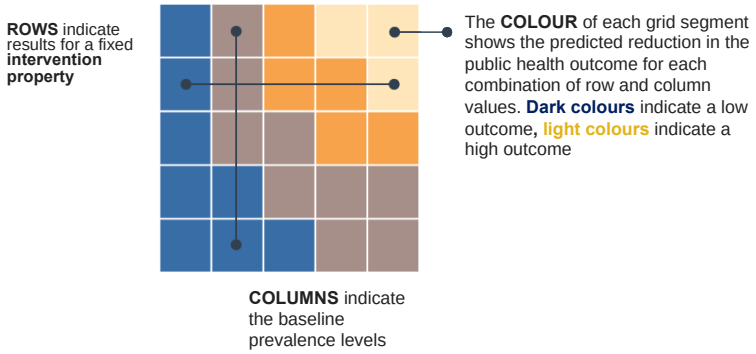

Figure S10. Understanding the identification of key performance criteria.

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