



MALARIA PREVENTION

SHAPING NEXT-GEN MEDICAL INTERVENTIONS

iTPP1 OUTCOMES REPORT

NEXT-GENERATION SEASONAL INTERVENTIONS

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EXTENDED EXECUTIVE SUMMARY

This report presents the first round of quantitative modelling evidence to support criteria recommendations for the Bill and Melinda Gates Foundation (the Foundation) interventional Target Product Profiles for next-generation seasonal interventions (iTTPP1). The primary focus of this report is to evaluate the public health impact of anti-infective monoclonal antibody (mAb) interventions for seasonal use and secondary considerations for anti-infective long-acting injectable (LAI) drugs for seasonal use.

By combining stakeholder engagement and analytic approaches using detailed models of malaria transmission and intervention dynamics, we present initial evidence-informed recommendations for updating iTTPP1's product development criteria. These recommendations are based on a breadth of analyses from a range of modelling scenarios, examining and linking key performance characteristics of mAbs and LAIs to the public health impact expected from these products. The model-generated scenarios serve to address priority questions by stakeholders that include: a range of seasonality profiles and malaria prevalence levels, varying levels of access to treatment, various deployment strategies in terms of coverage and timing of deployment, and breadth of intervention and product properties including efficacy and duration of protection.

The use case for mAbs in this initial modelling round focuses on children aged three to 59 months receiving a single round of the intervention ahead of peak transmission in seasonal and perennial settings. This initial priority use case, which targets the most vulnerable children, was established following discussions with stakeholders from a broad range of expertise during the June 2021 convening. Rankings by target age group were then further refined by the scientific committee as part of the World Health Organization (WHO) mAb Preferred Product Characteristics (PPC) meeting held in November 2021 in consultation with the Foundation. Children aged three to 59 months were ranked as a top priority use case for modelling followed by expansion to children up to 119 months in a future second round of modelling.

Additional evidence from clinical trials [1] and modelling evidence from previous publications from the Swiss TPH modelling group [2, 3] are presented where necessary.

The full report provides suggested edits to the iTTPP criteria covering the key recommendations and key results below.

KEY RECOMMENDATIONS FOR iTTPP1

RECOMMENDATION ONE: Generate early evidence of key pharmacological characteristics of mAb and LAI drugs. Modelling shows the duration of protection and its decay over time is the most critical characteristic which priority candidates are most likely to increase public health impact. Given the limited availability of clinical evidence, we present model predicted health target ranges for duration of protection from malaria infection for different types of decay. Modelling shows that co-administration of mAbs or LAI drugs with blood stage clearance drugs is essential to expanding the range of achievable health goals. Secondly, we recommend the iTTPP1 base case criteria of at least 150 days of protection against infection with a single round of mAbs or LAI drugs, towards ensuring that an acceptable range of potential health targets can be achieved.

The added value of mAbs or LAIs over current seasonal interventions is likely to be realized if mAbs can sustain a sigmoidal decay pattern of protection. Therefore, pharmacokinetic (PK) studies combined with early pharmacodynamics (PD) studies are crucial to understanding the duration and decay dynamics of intervention efficacy. Unlike vaccines where immune correlates of protection are uncertain, when using clinical PK/PD data for mAbs decay dynamics can be extrapolated. If mAbs can demonstrate sufficient PD against infection versus plasma concentrations, both the decay and duration of protection can be determined. Data can be generated from 1) human challenge studies and 2) clinical trial phase 2b monitoring of PK and all infections in small cohorts during early stages to confirm the human challenge studies. Narrowing down possible decay and protection dynamics of seasonal interventions will allow minimum key performance criteria to be better informed by the modelling.

RECOMMENDATION TWO: Generate evidence for likely achievable coverage for mAbs or LAI drugs. Modelling shows the critical importance of mAb and LAI coverage in reducing the occurrence of clinical or severe malaria, highlighting the need to look beyond an intervention's clinical performance to evaluate its likely downstream effectiveness. Community access and acceptance should also be addressed through community engagement as they will be key to coverage. Product characteristics likely to impact an intervention's coverage, such as the injectable formulation and safety profile in combination with blood stage clearance drugs, should be considered in parallel to the intervention's clinical efficacy and duration of protection. For a single deployment, higher coverage will be

required in perennial settings than in seasonal settings to achieve similar reductions. Modelling evidence to support the benefits of a second deployment round in perennial settings is needed as well as surveys to evaluate community acceptability for such a strategy.

RECOMMENDATION THREE: Clearly specify intervention efficacy target criteria and priority use-cases in the iTPP, alongside comparator standard of care where appropriate. 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 iTPP's base case and upside criteria. The evaluation period and measure of efficacy or burden reduction should be specified, and clear guidance given regarding the phase of product development in which this evidence should be generated. We have recommended minimum key performance criteria to achieve at least 50% reduction in clinical incidence in the target age group 6-months post-deployment during the 5th year of rollout. As noted by our stakeholders, comparator standard of care, where available, should be stated alongside current clinical reduction (e.g. SP-AQ with or without resistance).

RECOMMENDATION FOUR: Define next use-cases and support generation of evidence for and future development of blood stage combination mAb. Current modelling evidence supports co-administration of an effective non-specific blood stage drug with an anti-infective mAb or LAI drug, to increase public health benefit. Furthermore, for use-cases targeting extended age groups or a large proportion of the population, drug administration together with an anti-infective mAb or LAI will have increased indirect effects on population-level transmission leading to larger prevalence reductions. This may require reconsidering the value proposition and the evidence required to evaluate the benefit of other mAb parasite targets and combination mAbs, including how to assess breakthrough infections. Further modelling will require prioritization of other use-cases or product characteristics.

KEY FINDINGS FOR iTPP1

Product

Current clinical trial evidence indicates that a single injection of mAbs with circumsporozoite protein-binding activity has the potential to provide four to 36 weeks of protection from *Plasmodium falciparum* infection [1] **[clinical evidence]**. Increased public health impact through co-administration with a blood stage drug is supported by our previous modelling study [3] **[modelling evidence]**. Clinical trial investigators will co-administer artemether-lumefantrine (AL) in upcoming phase 2 trials of the first human malaria mAb CIS43LS generating additional evidence over the next 12 months **[expert opinion]**.

Target Population

The priority age group for a mAb intervention is children aged three to 59 months as supported by **[expert opinion]**. All results in this report are given for this age group exclusively. Following stakeholder feedback on our findings, the next phase of this project will evaluate whether similar results on trade-offs and minimum key performance criteria should be generated for an expanded group of children aged three to 119 months old.

Indication

Initial efficacy against infection and duration

LAI drugs and mAbs potentially cover a large range of protective efficacy decay properties (Figure A). Our modelling indicates that the potential public health impact of LAI drugs and mAbs will depend on the efficacy decay profiles of novel candidates. The efficacy decay profile is our model-specific individual level probability of protection against infection function of the intervention described by the initial efficacy, efficacy decay shape over time, and the half-life duration of protective efficacy. For mAb and LAI this is the PKPD relationship over time.

We found that the **duration of protection** of LAI drugs and mAbs against infection is an **important determinant of public health impact** and will be influenced by other interventional properties, including deployment timing. In a four-month seasonal setting with >80% deployment coverage and >80% initial efficacy, **durations of protection 30-90 days long can achieve a median 40% clinical incidence reduction** as compared to **150-210 days achieving a median ~70% reduction** (Figure B). Our results along with previous modelling work [2] demonstrate the need for the duration of protection to cover the length of the high transmission period to reach sufficient burden reduction targets. For delayed deployment closer to the peak of high transmission or if seasonal transmission is shorter, shorter duration of protection will be sufficient.

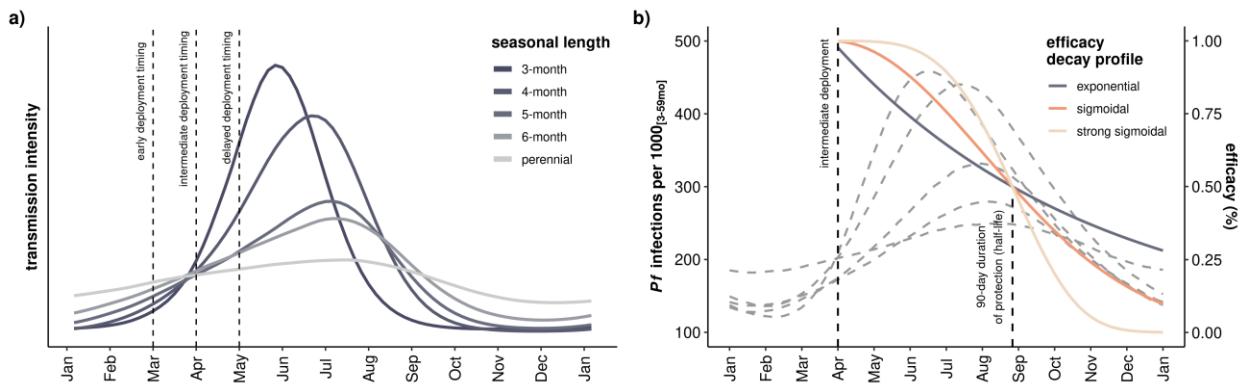


Figure A. Intervention deployment and efficacy decay profiles. **a)** We investigate three deployment timing strategies for the five seasonal transmission profiles modelled for seasonal interventions. **b)** For a single seasonal deployment, we model three example seasonal medical interventions by their differential efficacy decay dynamics (%) with a duration of protection of 90 days: exponential, sigmoidal, and strong sigmoidal profiles. We show the clinical incidence in children three to 59 months (per 1000) for different transmission seasons (dashed lines) to demonstrate infection risk versus protection from the intervention.

The importance of the duration of protection will also depend on the decay profile. **Exponential decay profiles require longer durations of protection due to the rapid decay of efficacy after administration (i.e. at least 150 days of protection to achieve >60% clinical incidence reduction (Figure B)). Sigmoidal profiles require maintaining high levels of efficacy for the duration of the high transmission season before the rapid decay in efficacy when the duration of protection period ends. Longer durations of protection greater than 90 days for mAb or LAI drug candidates with sigmoidal decay profiles are required for >60% clinical incidence reduction [modelling evidence].** The efficacy decay profile and duration of protection against infection of LAI drugs and mAb candidates should be investigated by clinical testing as early as possible to evaluate the range of achievable health targets.

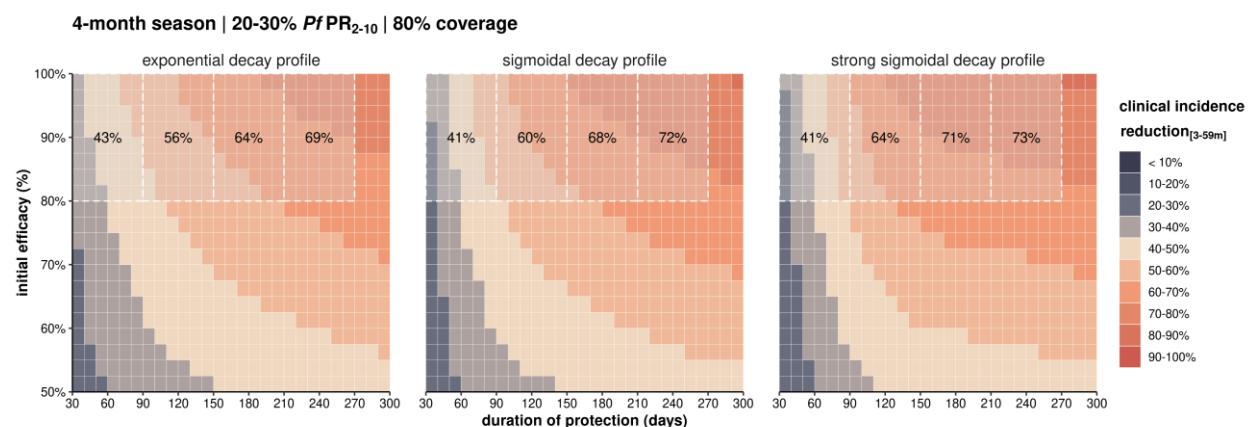


Figure B. Minimum intervention performance criteria to achieve clinical incidence reduction targets. In a 4-month seasonal setting with a baseline prevalence of 20-30% $PfPR_{2-10}$ and 80% deployment coverage for different decay profiles (exponential, sigmoidal, strong sigmoidal), we show model predicted initial efficacy (%) and duration of protection (days) required to achieve clinical incidence reduction in children three to 59 months old during a 6-month follow-up period during the 5th year. Values show the average clinical incidence reduction in the highlighted parameter space. Similar trends are observed for seasonal settings 3-6 months long and perennial settings.

Given the importance of duration of protection in increasing public health impact and the different requirements for optimization by decay profile, **early PK and PD through human challenge studies and early Phase 2b studies that closely monitor all infections are needed to refine minimum criteria and support candidate selection.**

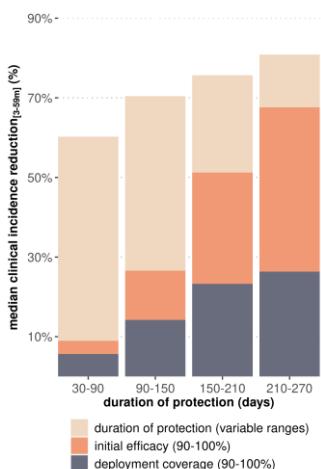


Figure C. Sensitivity analyses quantifying the relative importance of intervention properties. Median reductions on y-axis shown for clinical incidence children three to 59 months for ranges of duration of protection, >90% initial efficacy and >90% coverage. Example shown for a 4-month seasonal setting with a baseline 20-30% $PfPR_{2-10}$. Similar trends for severe disease and mortality.

Clinical Reduction

In **clinical trial settings** (i.e. coverage levels above 90% and high access to first-line malaria treatment) the initial efficacy is an important determinant of impact **if LAI drug and mAb candidates can achieve 150 days of protection** (Figure C) and efforts should focus on increasing initial efficacy and coverage to achieve greater public health impact. Candidate LAI drugs and mAbs than can achieve more than 150 days of protection are predicted to achieve over 70% burden reduction in clinical trial settings. Regardless of whether this duration can be achieved, increasing duration as much as

possible should be prioritized, especially for sigmoidal profiles that demonstrate high ranges of achievable health goals as compared to exponential profiles. With low initial efficacy against infection ranging from 50% to 60%, protection 150-210 days long can reduces 40-50% of clinical cases (six-month follow-up) in trial settings. In contrast, **an initial efficacy above 90%** (for a similar duration) **can reduce 70-80% of clinical cases**. **To achieve at least 75% clinical incidence reduction with a single deployment round candidates with sigmoidal and strong sigmoidal decay profiles with initial efficacy of at least 90% should be prioritized.**

Deployment Coverage

For a single deployment within a season, an intervention's coverage is the most important determinant of public health impact in **implementation settings**, particularly for mortality. Deployment coverage will play a more important role in further expanding burden reduction targets as durations of protection increase and for stronger sigmoidal profiles. High levels of deployment coverage are required to achieve desirable burden reduction targets in the intervention age group. In most settings and across decay profiles and durations, candidates with 80% initial efficacy require a **minimum deployment coverage of 70% to achieve 50% burden reduction of clinical incidence, severe disease and mortality over a 6-month follow-up period**. Coverage is even more crucial to increasing impact in settings with low access to first-line treatment and lower transmissions settings. If high coverage is achieved, the role of initial efficacy becomes increasingly important for further increasing burden reduction targets (Figure C).

Target Settings

Low transmission settings and settings with low access to first-line treatment will benefit most from seasonal interventions. Sufficient burden reduction (**at least 50% clinical incidence reduction** over 6-months follow-up) with LAI drugs or mAbs **requires maintaining high efficacy with limited decay for at least three months** (with a minimum initial efficacy >80% and coverage >60%). Achieving durations of protection longer than the duration of the transmission season will be a major driver of further increasing this public health impact, particularly for sigmoidal and strong sigmoidal decay profiles. Extending the duration of protection of LAI drug and mAb candidates beyond 150 days will not have important implications for public health impact in seasonal settings with annual transmission less than five months long. However, extending the duration of protection beyond 150 days will be moderately important in longer transmission seasons and perennial settings.

Public Health Impact

The target age group (children aged three to 59 months) will benefit the most from seasonal interventions with the level of impact depending on the underlying age patterns of burden of disease. Clinical incidence reduction is a good proxy for measuring the burden reduction of seasonal interventions. Currently, SMC achieves 61.4% incidence reductions six weeks post-treatment with 90% coverage [4]. **Seasonal interventions can reach similar targets with at least 75% efficacy and 90-120 days of protection for strong sigmoidal profiles, 120-150 days for sigmoidal profiles, and 150-180 for exponential profiles.** Several factors will influence the achievable public health targets needed to further refine the minimum intervention key performance criteria above. These include the deployment strategy, the transmission setting, the population of interest, and the evaluation period. Modelling evidence will be generated for expanding the target population age range to children up to 119 months old in a second round of analyses, although preliminary analysis indicates results will be similar **[modelling evidence needed]**.

INTRODUCTION

This report presents the first round of quantitative modelling evidence for the Bill and Melinda Gates Foundation (the Foundation) interventional Target Product Profiles criteria for next-generation seasonal interventions (iTTPP1). This draft report covers the first round of suggested updates to the current iTTPP1 criteria from Version 1.0-25Jul2019. We assume a seasonal intervention is a medical malaria prevention intervention that is deployed at the beginning of each transmission season in seasonal settings. The intervention may also be deployed in other settings to achieve protection for the duration of the season with a single or multiple deployments, provided that it achieves at least three months of protection from new malaria infections. The primary focus of this report is **to evaluate the public health impact of anti-infective monoclonal antibody (mAb) interventions for seasonal use with secondary considerations for the impact of anti-infective, long-acting injectable (LAI) drugs.**

Currently, very little clinical evidence is available to inform the properties of mAbs and LAI drugs and their potential impact on public health. However, by combining stakeholder engagement and analytic approaches using detailed models of malaria transmission and intervention dynamics, we can provide evidence-informed recommendations for updating the Foundation's iTTPP1 product development criteria. In order to better understand the minimum key performance criteria of mAb or LAI drugs for seasonal interventions, an initial round of modelling was conducted to generate evidence for a broad range of intervention characteristics across a broad range of scenarios and settings. **This initial round of evidence will serve to identify the importance of different drivers of public health impact and to guide the generation of clinical and modelling evidence to address current knowledge gaps and further refine the required performance criteria. In this report we highlight key recommendations and key results.**

As per the existing iTTPP1, this initial modelling round focuses on the current use case for mAbs: children aged three to 59 months receiving a single round of the intervention before the onset of peak transmission in seasonal and perennial settings. This initial priority use case was established following discussions with stakeholders during the Swiss TPH's and the Foundation's convening in June 2021. Rankings by age group were then further refined by the scientific committee for the World Health Organization (WHO) mAb Preferred Product Characteristics (PPC) in November 2021 in consultation with the Foundation. Children aged three to 59 months were ranked as a first priority followed by expanding to children up to 119 months, which will be explored in a second round of modelling.

BACKGROUND

Before this first round of detailed modelling, seasonal interventions were only informed by two previous modelling studies. Golumbeanu and Yang et al. [3] established the analytical approaches for our TPP modelling and provided generalized results for various interventions targeting all age groups. Regarding seasonal interventions with anti-infective mAbs, they found that when coupling mAbs **with an effective short-acting blood stage parasite treatment, there was a strong effect on expanding the range of achievable health goals** and on reducing the minimum key performance criteria required. They also demonstrated the **strong impact of deployment coverage** on public health outcomes.

A second study by our team Burgert et al. [2] was conducted predicting the impact of LAIs from late-stage clinical trials through to implementation stages in children aged three months to 59 months old for seasonal settings (Senegal- and Mali-like settings) with varying coverage and transmissions intensities. The authors found that establishing non-inferiority of LAIs to SMC was difficult in clinical trial stages with high deployment coverage; however, in implementation settings, where the achievable SMC coverage was much lower, **LAIs were found to be a suitable replacement to SMC if the duration of protection of LAIs covered the duration of the transmission season.** Furthermore, the differential impact of exponential and sigmoidal decay profiles of LAIs highlighted the importance of investigating the protective efficacy decay as early as possible during clinical development to ensure a well-informed candidate selection process.

Current clinical evidence of the first human mAb CIS43LS [1] suggests that there is potential for anti-infective mAbs to demonstrate high initial efficacy and to prevent malaria infection with extended duration of protection. However, more clinical evidence is needed to better refine candidate selection criteria. Modelling has suggested the importance of the protective efficacy and duration of anti-infective mAbs to public health impact and, thus, **pharmacokinetic (PK) studies combined with early pharmacodynamic (PD) studies are crucial to understanding the duration and decay of efficacy.** Unlike vaccines, where immune correlates of protection are uncertain, by using clinical PKPD data of mAbs, these decay dynamics can be extrapolated. If mAbs can demonstrate sufficient PD against infection versus plasma concentrations, both the decay and duration of protection can be determined. This data can be generated from: 1) human

challenge studies and 2) phase 2b monitoring of PK and all infections in small cohorts very early to confirm the human challenges studies. Narrowing down the possible decay and protection dynamics of seasonal interventions will better inform minimum key performance criteria.

There are several knowledge gaps that can be addressed by modelling to inform the minimum key performance criteria of seasonal interventions:

- First, consultation with stakeholders on the most appropriate use cases. While children in highly seasonal setting is the top priority, there may be benefits of seasonal interventions for pregnant women or high risk workers in other settings. There is little known about the benefits of mAbs or LAI drugs in perennial settings and the different minimum key performance criteria for these settings. Modelling can explore transmission profiles from seasonal to perennial to identify the differences in minimum requirements and potential benefits to public health.
- Second, since considerations for expanding SMC to children three to 119 months are ongoing, seasonal interventions expanded to this age group may also be considered and could potentially provide an advantage to SMC. Modelling is needed to demonstrate the potential public health impact of expanding to this target age group.
- Third, stakeholders do not have a solid consensus on the most appropriate standard of care comparator for season interventions. In seasonal settings, SMC has been suggested. Non-inferiority analyses have demonstrated that a single injection of LAI drugs requires a duration of protection that covers an entire season [3]. Whether clinical trials can demonstrate this remains to be seen, as it will be challenging to achieve non-inferiority for areas with high SMC coverage.
- Finally, the first human mAb CIS43LS has demonstrated protection from infection lasting four to 36 weeks and, as a result, there is potential for mAbs to have significant public health impact. Should more clinical data suggest an extended duration of protection, CIS43LS may offer a replacement for SMC. As mentioned previously, the efficacy decay and duration of seasonal interventions is a major driver of public health impact, yet current clinical data is lacking.

Modelling can address these gaps by evaluating the impact of mAbs and LAIs in several different transmission settings, target age groups, standard of care comparators, and a broad range of efficacy decay profiles, durations of protection, and deployment strategies. In this initial modelling round, we provide a large breadth of scenarios to highlight the importance of different drivers of impact and to provide a foundation for stakeholder discussions.

OBJECTIVES

While modelling and clinical evidence has suggested the potential public health value of seasonal interventions, **this modelling round is required to better identify the minimum key performance criteria**. Three main priorities for seasonal interventions were identified during the June 2021 convening with stakeholders. These priorities, along with outcomes from the WHO mAb PPC meeting held in November 2021, shape the required modelling analyses for seasonal interventions:

PRIORITY 1: Understanding impactful ranges and minimum intervention properties for different health targets to understand: a) the relationship and **trade-offs** between properties; b) the relationship between intervention impact and **administration time**, and; c) in which population and transmission setting the highest impact can be expected.

PRIORITY 2: Optimizing clinical trial design to **translate efficacy from clinical trials to implementation**, considering that intervention requirements may differ between transmission settings.

PRIORITY 3: Understanding how the impact of new interventions for seasonal malaria prevention may differ in placebo-controlled trials compared with standard of care, and what the **standard of care comparators** may be in the future.

After these expert consultations, it was determined that the priority use case of next-generation seasonal interventions is to prevent infections and severe disease in children, specifically in children aged three to 59 months. For this first round of modelling, **trade-offs analyses along with sensitivity analyses were conducted to explore the relationship between intervention properties and implementation factors** to identify the minimum key performance criteria. While seasonal settings with moderate to high transmission are considered to be priority settings for implementation, the potential impact benefit of these interventions in perennial settings is unknown and was therefore explored in this first round. As well, a single round of intervention deployment was considered for different timings before the seasonal peak.

DEFINITIONS TABLE

Term	Definition	Example
Clinical incidence reduction _[3-59m]	A primary outcome , the percentage reduction in malaria clinical incidence measured in comparison with the counterfactual of no intervention, where clinical incidence is defined as the number of new cases of uncomplicated malaria in children 3-59 months old in the six-month follow-up period in the fifth year of rollout.	<i>In a population of 1000 children monitored over a six-month intervention period in the fifth year after first deployment, the mAb intervention led to a reduction in the number of new cases of uncomplicated malaria from 400 to 200, i.e. uncomplicated clinical incidence reduction of 50%.</i>
Decay profile	The decrease in protective efficacy over time, resulted in the decay or reduction of the intervention's initial efficacy. This decay curve can have multiple shapes: a strong decrease shortly after administration (exponential decay, modelled as a Weibull function where $k = 1$), or a longer-lasting high efficacy after administration with a sharp decrease (sigmoidal decay modelled as a Weibull function where $k = 2$ or strong sigmoidal where $k = 4$). The decay curve can also display different levels of initial efficacy half-life or what is defined as the duration of protection.	<i>LAI drugs may likely display exponential decay profiles with rapid decay in initial efficacy shortly after administration followed by steady duration of lower level efficacy.</i> <i>Monoclonal antibodies may display sigmoidal or strong sigmoidal decay profiles with long-lasting high efficacy after administration with a sharp decrease when the initial efficacy half-life is reached.</i>
Deployment coverage	A key performance criteria. Defined as the operational coverage of the seasonal intervention's deployment in a given target population for a single round.	<i>A mAb intervention is available to a population of children between three and 59 months of age with 80% deployment coverage.</i>
Duration of protection	A key performance criteria. Defined as the number of days until the intervention's initial protective efficacy half-life against liver stage infection is reached i.e. the duration of time the initial efficacy against infection reaches 50% of its original value	<i>An individual receives an intervention with an initial efficacy of 90% and a 100-day duration of protection. 100 days after the intervention was given, the individual is protected against 45% of liver stage infections.</i>
Initial efficacy	A key performance criteria. Defined as the average initial efficacy of the intervention or the percentage of the maximum intended efficacy against pre-erythrocytic infection in the target age group before decay, with or without inter-individual variation.	<i>An individual receives an intervention with a 90% initial efficacy and is protected from 90% of new pre-erythrocytic infections.</i>
Mortality reduction _[3-59m]	A secondary outcome. Defined as the percentage reduction in the number of direct malaria deaths compared with a no intervention counterfactual, where the number of deaths is evaluated among children 3-59 months in the six-month follow-up period in the fifth year of rollout.	<i>In a population of 1000 children monitored over a six-month intervention period in the fifth year after first deployment, the mAb intervention led to a reduction in the number of new cases of uncomplicated malaria from 10 to 5, i.e. to a mortality reduction of 50%.</i>
PfPR ₂₋₁₀	The baseline annual <i>Plasmodium falciparum</i> parasite rate in children two and ten years of age (<i>PfPR₂₋₁₀</i>) is a measure of prevalence in a given year. Given in 10% intervals.	<i>The annual PfPR₂₋₁₀ in a 4-month seasonal setting is 25%.</i>
Seasonal profile	A mathematical equation that captures the shape and length of a region's highest risk period to malaria infection, driving transmission patterns.	<i>A four-month seasonal profile has the most intense transmission of malaria during a consecutive four-month period followed by eight months of very low transmission.</i>
Severe disease reduction _[3-59m]	A primary outcome. Defined as the percentage reduction in the number of severe malaria cases measured in comparison to the counterfactual of no intervention, where severe cases of malaria are evaluated in children 3-59 months in the six-month follow-up period in the fifth year of rollout.	<i>In a population of 1000 children monitored over a six-month intervention period in the fifth year after first deployment, the mAb intervention led to a reduction in the number of new cases of uncomplicated malaria from 30 to 10, i.e. to a severe disease reduction of 67%.</i>

MODELLING ASSUMPTIONS

The development of next-generation medical interventions is guided by Target Product Profile documents, which help to prioritize candidates and ensure health targets are reached. Swiss TPH has developed an evidence generation framework that uses mathematical modelling to support the identification of minimum necessary product requirements (Figure D). 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) [5]. 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.
- **Optimization:** 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 of long acting injectables [2]. Golumbeanu and Yang at al. have also provided a detailed description of the methodology [3]. We provide guidance on interpreting the results of each component of the method in the following sections.

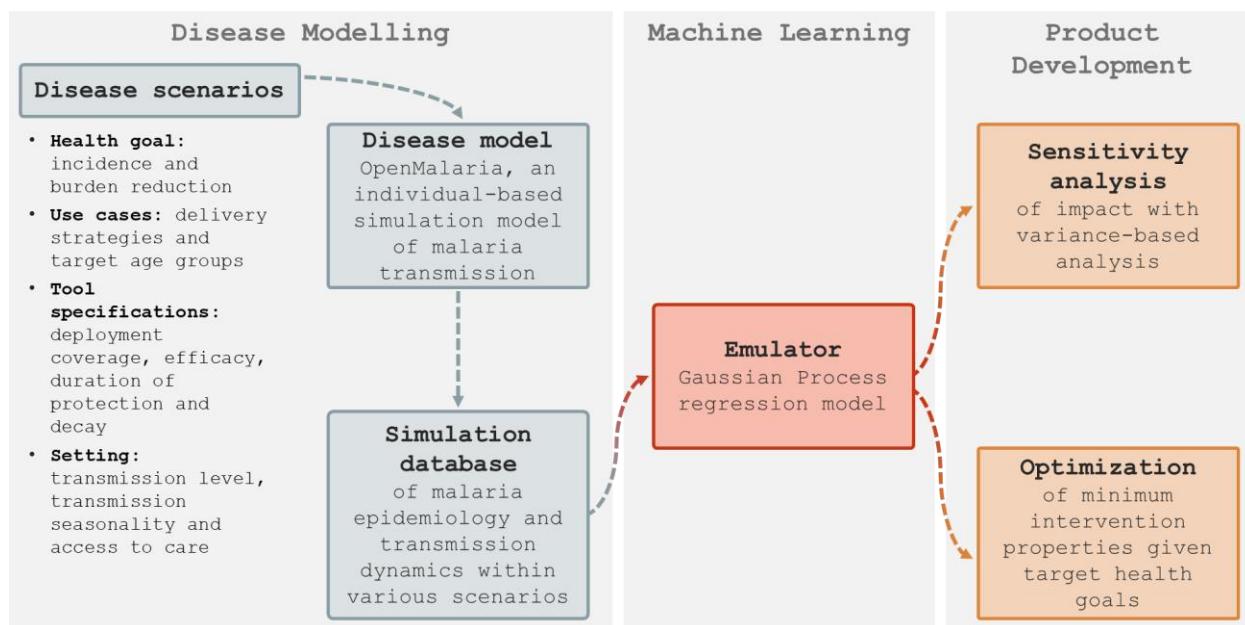


Figure D. Schematic diagram of the evidence-generation framework to support the identification of minimum necessary product characteristics.

We highlight sources of evidence to inform the results as follows:

- **[modelling evidence]** for results that are supported by quantitative modelling evidence
- **[clinical evidence]** for data that is supported by clinical trials
- **[expert opinion]** for statements supported by stakeholder discussions and meetings with experts
- Main results or conclusions are highlighted in **black bold color**
- Result recommendations for candidate selection are highlighted in **bold red color**

All modelling results are analyzed across a range of scenarios, where each scenario consists of a unique combination of the different settings summarized in Table 1. By analyzing a range of scenarios, we capture a range of dynamics across the complexity of malaria-endemic geographies and health systems.

Table 1. Seasonal intervention modelling scenario assumptions

Parameter	Parameterization
Intervention	A long-acting injectable drug or monoclonal antibody with protection from new pre-erythrocytic infections as main mode-of-action co-administered with a 100% effective blood stage clearance drug
Target population	Children 3 to 59 months old
Initial efficacy range*	50% – 100%
Duration of protection range*	30 days – 300 days
Decay profiles*	Continuous Weibull function k shape parameter values 0.25 to 7 (from bi-phasic to strong sigmoidal) and three categorical profiles: <ul style="list-style-type: none"> • Exponential, $k = 1$ • Sigmoidal, $k = 2$ • Strong sigmoidal, $k = 4$
Deployment coverage range*	30% – 100%
Deployment rounds and timing	A single round deployed at 3 different timings: early in the season, during the start of the season, later in the season all one month apart
Survey time	2030 – 2045, where intervention deployment starts in 2035
Seasonality	Five generic seasonal profiles with varying lengths: <ul style="list-style-type: none"> • 3-month seasonal • 4-month seasonal • 5-month seasonal • 6-month seasonal • 9-month perennial
Transmission	Four baseline categories of $PfPR_{2-10}$ from low, moderate to high transmission: <ul style="list-style-type: none"> • 10% – 20% • 20% – 30% • 30% – 40% • 40% – 50%
Case management	Three levels of health system coverage for uncomplicated malaria: <ul style="list-style-type: none"> • 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)
Endpoints	Relative reductions in the target populations: <ul style="list-style-type: none"> • Incidence of symptomatic cases • Incidence of expected severe cases • Incidence of expected deaths
Evaluation period	Endpoints will compare the average 5-year level before the intervention and the 6- and 12-months following the intervention after the 5 th year of seasonal deployment
Demography	Constant population size (10,000 individuals) and demography profile based on population estimates for Ifakara, Tanzania
Diagnostic	Rapid diagnostic test with a parasite detection limit of 50% and 94.2% specificity
Experimental properties	Simulations will be run with 5 or 10 random seeds and 1000 replicates of all continuous parameters (initial efficacy, half-life, coverage and k shape parameter) for all seasonal profiles, transmission levels and levels of access to case management

* Continuous parameter sampling

KEY RESULTS Q&A

A summary ranking the most important questions and answers informed by modelling for seasonal interventions:

Criteria	Key Results	Priority ranking of questions to inform iTPP1 criteria
Intervention	Mode-of-action and co-administration Priority question 1a: what type of seasonal intervention? Long-acting injectable (LAI) drugs and monoclonal antibodies (mAb) for seasonal interventions are in early clinical testing and have shown promising results protecting against infection with a single administration. Co-administration with blood-stage drugs is necessary to clear previous infections and extend the range of achievable health goals.	
	Target population Priority question 1b: what is the expected impact of these interventions? Children 3-59 months are a top priority target age group for LAIs and mAbs. These will observe direct impact on clinical incidence, severe disease, and mortality reduction. At least 70% clinical incidence reduction can be achieved for the following minimum key performance criteria: protection >120 days, initial efficacy >95%, coverage >70% for a single round of LAI drugs or mAbs.	
Protective efficacy dynamics	Initial efficacy Priority question 2a: what type of efficacy decay profile and duration of protection are required? For seasonal intervention with single deployment, the decay profile that determines the level of efficacy over time is a very important driver of impact. In seasonal setting, maintaining a high level of efficacy for the duration of the high transmission season is required. Across seasonal lengths and efficacy decay profiles, at least 150 days protection is required to achieve 60% clinical incidence reduction with 80% initial efficacy and 80% coverage. For delayed deployment closer to the peak of high transmission or shorter transmission seasons, shorter duration of protection will be sufficient.	
	Efficacy decay Priority question 2b: what should be the minimum protective efficacy criteria? Candidates with strong sigmoidal profiles will demonstrate the highest clinical reduction for similar scenarios i.e. achieving at least 60% clinical incidence reduction with 90% coverage like SMC requires 75% initial efficacy and 90-120 days of protection for strong sigmoidal profiles, 120-150 days for sigmoidal profiles, and 150-180 for exponential profiles. With low initial efficacy against infection ranging from 50-80%, protection 150-210 days long can reduces 40-50% of clinical cases (six-month follow-up) in trial settings (90% coverage and high access to first-line treatment). In contrast, an initial efficacy above 90% (for a similar duration) can reduce 70-80% of clinical cases.	
	Efficacy half-life Priority question 3a: what is the role of deployment coverage? For a single deployment, coverage is the most important determinant of public health impact in implementation settings. Deployment coverage will play a more important role in further expanding burden reduction targets as durations of protection increase and for stronger sigmoidal profiles. High levels of deployment coverage are required to achieve desirable burden reduction targets in the intervention age group. In most settings and across decay profiles, a minimum deployment coverage between 50% and 70% is required to achieve 50% burden reduction across clinical incidence, severe disease and mortality.	
Deployment	Coverage Priority question 3b: how does deployment timing impact the minimum criteria? The range of achievable health goals is higher when timing of deployment is delayed towards peak high transmission in the season, in particular for seasonal settings for all decay profiles. Timing of the intervention will impact the required duration of protection in shorter seasonal settings or for delayed timing as shorter duration of protection can achieve similar target health goals e.g. in a 4-month season, early deployment requires 150 days protection versus 120 days for delayed deployment to achieve 60% clinical incidence reduction.	
	Rounds Priority question 4a: how does seasonal length influence the minimum duration of protection? The duration of protection is most important for sigmoidal and strong sigmoidal profiles especially in seasonal settings. The minimum duration of protection needs to be greater than the length of the season and longer for earlier deployment timings. Extending the duration of protection > 150 days in seasonal settings will be less important than further extending protection in perennial settings. Perennial settings require longer minimum durations of protection. Additional modelling evidence is needed to assess the impact of a second round on minimum key performance criteria, particularly for perennial settings.	
	Timing Priority question 4b: what transmission settings will benefit the most from seasonal interventions? Transmission settings with low baseline prevalence and low levels of access to first-line malaria treatment are predicted to benefit the most from seasonal interventions. Deployment coverage is a very important driver of impact for low transmission settings i.e. for similar scenarios, 50-70% coverage can achieve a median 60% clinical incidence reduction in settings with $PfPR_{2-10} < 30\%$ and a median of 50% for settings with $> 30\% PfPR_{2-10}$. Very low prevalence settings are subject to higher levels of stochastic model uncertainty and elimination is predicted with modelled scenarios.	
Transmission setting	Seasonal length Priority question 5a: what is the most important endpoint for mAbs? Clinical incidence reduction in the intervention group is an important endpoint for seasonal interventions, followed by severe disease and mortality which follow the same downstream implications of clinical disease. The best measure of effectiveness of seasonal interventions is the rate of patent and sub-patent malaria infections in the target age group; however, in trial settings this is difficult to observe. Therefore, clinical incidence serves as a good proxy for translating protective effectiveness of mAbs and LAI drugs. We observe the same relationships of intervention characteristics for severe disease and mortality. The most important driver of mortality reduction is deployment coverage.	
	Baseline $PfPR_{2-10}$ prevalence Priority question 5b: how does the evaluation period influence the estimated public health impact? Evaluating outcomes for shorter follow-up periods shows higher rates of reductions compared to longer periods of follow-up due to seasonality and decay of protective efficacy. Seasonal deployment will result in higher reductions in the target age group over time until model equilibrium is reached. We chose to report outcome reductions based on a 6-month follow-up evaluation period after intervention deployment during the 5th year of rollout.	
	Access to 1st line treatment Priority question 5c: what are the ranges of achievable health targets? Depending on the scenario of intervention properties a large range of outcomes reductions are predicted. Aggregated scenarios predict a median clinical incidence reduction in children three to 59 months old between 30% to 80%. Only scenarios with 100% deployment coverage can achieve >80% clinical incidence reduction. Further refinement of the intervention properties and deployment strategies is required to better evaluate the range of achievable health targets which in return will inform the minimum key performance criteria for seasonal interventions.	
Public health impact	Endpoint Evaluation period Evaluation year Health target	

Figure E. Seasonal interventions key results Q&A

1. PRODUCT (MODE-OF-ACTION)

1.1 CURRENT CRITERIA

Table 1.1. Current criteria for iTPP1 product

Base Case	Upside Case	Annotations
Combination no more than two active components that prevent infection (i.e., targeting CSP or other sporozoite antigens) or kill the blood stage of dominant circulating <i>Plasmodium falciparum</i> strains.	One active component that prevents infection (i.e., targeting CSP or other sporozoite antigens) or kills the blood stage of dominant circulating <i>Plasmodium falciparum</i> by targeting a conserved domain in Pf strains.	Transmission-blocking targets or activity are not in scope for this interventional TPP. MAbs epitopes: If targeting a single epitope in a conserved domain is not sufficient, two mAbs or a single bivalent mAb may be used. If the product contains two components, the efficacy of each component may have to be demonstrated separately.

1.2 SUGGESTED UPDATES

Current [**clinical evidence**] indicates that a single injection of mAbs with CSP-binding activity has the potential to provide four to 36 weeks of protection from new *Plasmodium falciparum* infections [1]. Increased public health impact through co-administration with a blood stage drug is supported by our previous modelling study [3] [**modelling evidence**]. Further clinical evidence with the use of artemether-lumefantrine (AL) in upcoming phase-2 clinical trials of the first human malaria mAb CIS43LS will be generated [**expert opinion**]. Blood stage mAbs or LAI drugs will be considered in 2nd round of updates if deemed necessary after discussions.

Table 1.2. Updated criteria for iTPP1 product

Base Case	Upside Case	Annotations
Combination no more than two active components that prevent infection (i.e., targeting CSP or other sporozoite antigens) or kill the blood stage of dominant circulating <i>Plasmodium falciparum</i> strains.	One active component that prevents infection (i.e., targeting CSP or other sporozoite antigens) or kills the blood stage of dominant circulating <i>Plasmodium falciparum</i> by targeting a conserved domain in Pf strains.	Transmission-blocking targets or activity are not in scope for this interventional TPP. MAbs epitopes: If targeting a single epitope in a conserved domain is not sufficient, two mAbs or a single bivalent mAb may be used. If the product contains two components, the efficacy of each component may have to be demonstrated separately. An anti-infective LAI drug or mAb is currently prioritized without combination with other antigen mAbs. Modelling confirms, co-administering with a blood stage clearance drug is recommended to achieve desirable public health impact targets.

1.3 KEY RESULTS

1.3.1 Combining an anti-infective mAb with a short duration blood stage drug significantly increases the range of achievable health goals (Figure 1A).

1.3.1.1 Combining a mAb with a blood stage drug is more impactful than increasing the deployment frequency of a mAb alone when targeting all ages ([3] Fig. 5, Fig. S6.2). [**modelling evidence**]

1.3.2 Combining an anti-infective mAb with a short duration blood stage drug decreases the required intervention characteristics to achieve health goals (Figure 1B).

1.3.2.1 The minimum coverage, initial efficacy, and duration of protection (half-life) required to reach desired health outcomes decreased considerably when a mAb was co-administered with a blood

stage drug for both single and two deployment frequencies for all ages ([3] Fig. 5B, S6.1-S6.2, S7.1). [modelling evidence]

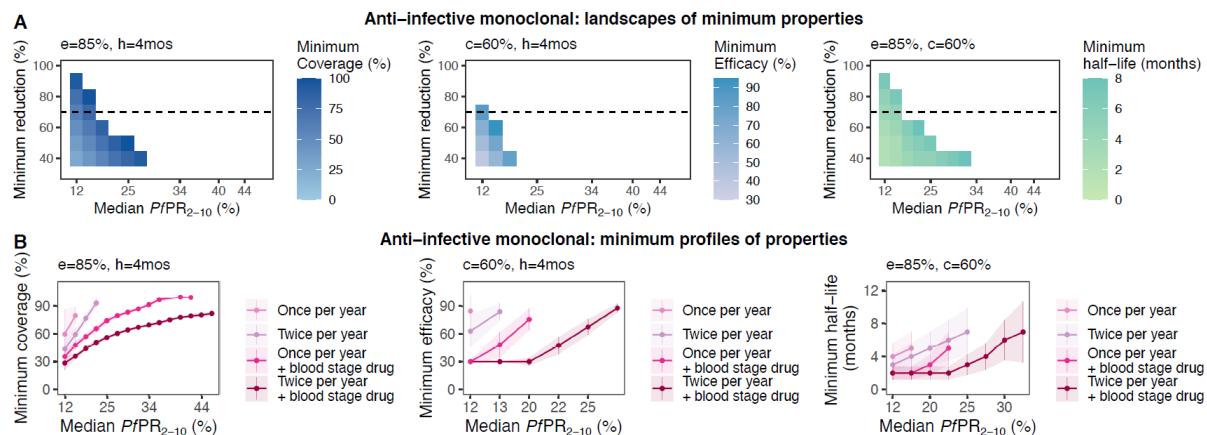


Figure 1. Modelling results of minimum profile properties for an anti-infective mAb from Fig. 5 Golumbeanu, Yang, et al. [2] Panel A shows the landscape of minimum required characteristics to achieve various target $PfPR_{0-99}$ reductions across different transmission settings for different scenarios. Panel B shows how for these same scenarios, the minimum profile changes with transmission intensity.

1.3.3 Combining anti-infective mAb is not a current priority (Appendix 1). Combining anti-infective and blood stage mAbs remains debatable in the malaria community [expert opinion].

2. TARGET POPULATION

2.1 CURRENT CRITERIA

Table 2.1 Current criteria for iTPP1 target population

Base Case	Upside case	Annotations
Children 3- to 119-months of age	<p>Minimum target population plus all adults at risk of <i>Plasmodium falciparum</i> infection:</p> <ul style="list-style-type: none"> • Adults in endemic regions, in addition to ACT course, if determined to be infected by RDT or blood smear • Women of childbearing age and pregnant women in antenatal care <p>Non-infected adults and children traveling to endemic regions.</p>	<p>WHO policy recommendation for SMC currently only covers children 3- to 59-months of age in eligible countries (West Africa). Age-extension to 119-months is currently being studied in Senegal.</p> <p>The majority of the burden is in children. Therefore this group was prioritized in the base case.</p> <p>Applies to all children who are not in case management (SME question: is it safe to administer to febrile children?)</p>

2.2 SUGGESTED UPDATES

Based on [expert opinion] and consultation with BMGF, children three to 59 months old will be the initial priority target population for seasonal interventions followed by extending the intervention to children three to 119 months old. The importance of drivers of public health impact and the trade-offs between intervention key performance criteria are not expected to change when expanding the age group to older children. However, higher reduction targets may be achieved due to indirect reduction in population-level prevalence and infection risk. In a second phase, modelling will be conducted for children three months to 119 months old. **All public health impact results shown in this first round are for children three to 59 months old.**

Table 2.2 Updated criteria for iTPP1 target population

Base case	Upside case	Annotations
<p>Children 3- to 119-months of age</p> <p>1st priority: children 3- to 59-months of age</p> <p>2nd priority: children 3- to 119-months of age</p>	<p>Minimum target population plus all adults at risk of <i>Plasmodium falciparum</i> infection:</p> <ul style="list-style-type: none"> • Adults in endemic regions, in addition to ACT course, if determined to be infected by RDT or blood smear • Women of childbearing age and pregnant women in antenatal care <p>Non-infected adults and children traveling to endemic regions.</p>	<p>WHO policy recommendation for SMC currently only covers children 3- to 59-months of age in eligible countries (in West Africa). Age-extension to 119-months of age is currently being studied in Senegal.</p> <p>The majority of the burden is in children. Therefore this group was prioritized in the base case.</p> <p>Applies to all children who are not in case management (SME question: is it safe to administer to febrile children?)</p> <p>Modelling suggests that irrespective of the target population we expect similar trade-offs results on priority efficacy and duration ranges for candidate selection [2]. However, with expanded targeted ages, higher burden reduction targets can be achieved, and indirect benefits realized. Indirect benefits are more likely, if high efficacy blood stage drugs are delivered at the same time as an anti-infective LAI drug or mAb. A dual deployment reduces prevalence alongside individual anti-infective protection.</p>

3. INDICATION (DURATION OF PROTECTION)

3.1 CURRENT CRITERIA

Table 3.1 Current criteria for iTPP1 indication

Base case	Upside case	Annotations
Prevent infection by <i>Plasmodium falciparum (Pf)</i> for at least three (four?) months post-administration.	Prevent infection by <i>Plasmodium falciparum (Pf)</i> for at least six months post-administration.	This interventional TPP describes a first-generation product with minimum criteria for malaria burden control in seasonal transmission settings. First administration to occur before the onset of the high-transmission season. A second administration may be required during the transmission season. The main differences between the base and upside cases are the duration of prevention and the possibility to use the product for extended prophylaxis Minimum duration of protection of six months may be required to differentiate biologics-based prevention from chemoprevention.

3.2 SUGGESTED UPDATES

Assuming a single deployment across seasonal and perennial settings with low to high baseline prevalence, we explored the impact for 30 to 300 days of protection (with varying types of decay) against infection from malaria in children three to 59 months old for seasonal intervention properties of next-generation LAI drugs and monoclonal antibodies. We defined **duration of protection as the protective efficacy half-life against infection** which corresponds to the duration of time the initial efficacy against infection reaches 50% of its original value. The same definition was used for all efficacy **decay shapes ranging from exponential to strong sigmoidal decays** (see Figure 2.1 for illustration of the different decays). As results from a recent clinical trial [1] demonstrate protection between four to 36 weeks, we justified expanding the range of half-life values modelled up to 300 days beyond the current upside case.

Recommendations on the definition of the base and upside case for the indication of a seasonal intervention are shown in Table 3.2. Overall, deployment timing in regards to the transmission peak will influence the required duration of protection due to the relationship between individual protection and population-level transmission risk. **Individuals should be protected for the initial duration of the season for at least 90 to 120 days.** Maintaining a high level of LAI drug or mAb efficacy greater than 90% against infection during this duration is essential across all settings and will be a major determinant of public health impact. If a high level of individual protection can be maintained for at least 150 days, increasing the initial efficacy of the LAI drug or mAb along with deployment coverage will become more important to further increasing public health impact.

Table 3.2 Updated criteria for iTPP1 indication

Base case	Upside case	Annotations
Prevent infection by <i>Plasmodium falciparum (Pf)</i> for at least three (four?) months post-administration. For seasonal interventions to reach at least 60% clinical incidence reduction for 6-month follow-up with 90% coverage as observed for SMC, they require at least 75% efficacy and 90-120 days of protection for strong sigmoidal profiles, 120-150 days for sigmoidal profiles, and 150-180 for exponential profiles.	Prevent infection by <i>Plasmodium falciparum (Pf)</i> for at least six months post-administration. Modelling shows that individual protection from infection (for initial efficacy >80% and coverage >80%) between 180-210 days will achieve 60-65% clinical incidence reduction for exponential profiles, 70-75% reduction for sigmoidal profiles and 70-75% reduction for strong sigmoidal profiles. If prolonged durations of protection can be	This interventional TPP describes a first-generation product with minimum criteria for malaria burden control in seasonal transmission settings. First administration to occur before the onset of the high-transmission season. A second administration may be required during the transmission season. The main differences between the base and upside case are the duration of prevention and the possibility to use the product for extended prophylaxis without need for a second administration in a year. Minimum duration of protection of six months may be required to differentiate biological-based prevention from chemoprevention. Candidates that maintain high efficacy for longer durations (sigmoidal and strong sigmoidal efficacy decay profiles) have the potential to achieve higher levels of burden reduction. Thus, as duration of protection and how protection decays over time is the most critical characteristic to understand and to support selection of priority candidates likely to increase public health impact PK studies combined with early PD studies are crucial

<p>For initial efficacy >80% and coverage >80% and all profiles in general, durations of protection 30-90 days long can achieve a median 40% clinical incidence reduction as compared to 150-210 days achieving a median ~70% reduction.</p>	<p>achieved, the initial efficacy of the intervention and deployment coverage will play a more important role in maximizing the burden reduction.</p>	<p>Delayed deployments closer to peak of high transmission can also reduce the required duration of protection for individuals. Modelling is required to demonstrate the impact of a second deployment round on the required duration of protection from infection.</p>
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3.3 KEY RESULTS

- 3.3.1 The public health impact of LAI drugs and mAbs will vary depending on the efficacy decay profiles of novel candidates to provide individuals with protection against malaria infection. The decay profile is described by the initial efficacy, shape of the decay over time and the efficacy half-life duration of protection.**
- 3.3.1.1 Modelling a range of decay profiles with Weibull shape parameter k ranging from 0.25 to 7, we observe that the k shape parameter will have important implications on public health impact (Figure 2.1). The k shape parameter range includes bi-phasic decay shapes ($k < 1$), exponential decay shape ($k = 1$), sigmoidal decay shapes ($k > 1$ and $k < 2$), and strong sigmoidal decay shapes ($k > 2$). The cut-off between sigmoidal and strong sigmoidal shapes was based on modelling outputs where differences in public health impact emerged.
- 3.3.1.2 While LAI drugs are more likely to display exponential decay shapes, **mAbs may encompass a large range from exponential to strong sigmoidal decay shapes**, unfortunately evidence is missing to be certain. These three categories of efficacy decay shapes along with variable durations of protection and initial efficacy will have varying implications for public health impact (Figure 2.1). **We recommend that PK and early PD/efficacy studies should use traditional PKPD modelling approaches to extrapolate and estimate the decay over time of protection against infection. And thus, candidates can be compared and categorized into exponential-like protection or more sustained protection (sigmoidal-like decay profiles).**
- 3.3.1.3 Decay profiles of LAI drugs and mAbs are not well described. There is some evidence to suggest they may have a range from 30 to 300 days of protection from malaria infection [**clinical evidence**] which we explored with modelling. For durations of protection longer than 120 days, sigmoidal and strong sigmoidal decays ($k > 2$) are expected to achieve higher levels of burden reduction as compared to exponential decay profiles [**modelling evidence**]. An example is shown for a fixed initial efficacy of 100% and four levels of coverage (100%, 80%, 60% and 40%) in a seasonal setting (Figure 2.1C). **The decay profile and duration of protection against infection of LAI drugs and mAb candidates should be investigated by clinical testing as early as possible in the development process.**

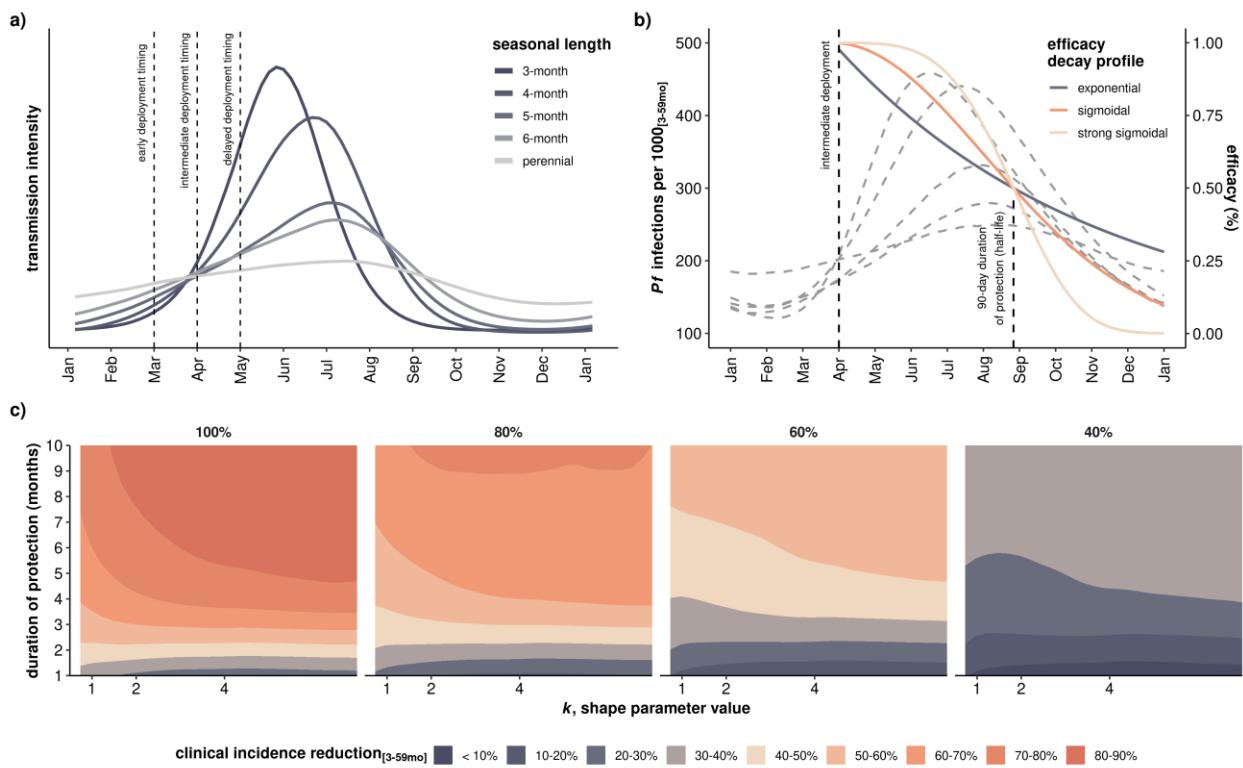


Figure 2.1. Seasonal and efficacy decay profiles for seasonal interventions with blood stage clearance drug.
a) Single deployment at the start of the transmission season in 5 seasonal profiles. **b)** Example decay profiles with a 100% initial efficacy and 90-day half-life duration of protection for varying efficacy Weibull decay over time (exponential $k = 1$, sigmoidal $k = 2$, and strong sigmoidal $k = 4$). Incidence of all infections in the intervention age group (children 3 to 59 months of age) for each seasonal profile are shown by dashed lines. **c)** Model predictions of clinical incidence reduction in the intervention group for continuous Weibull k shape parameter and duration of protection for scenarios with an initial efficacy of 100% and 100%, 80%, 60%, and 40% deployment coverage.

3.3.2 The duration of protection (described as half-life irrespective of decay profiles) of a seasonal intervention against malaria infection is an important determinant of public health impact. Impact will also vary based on the initial efficacy decay shape or how efficacy wanes over the course of the transmission season.

- 3.3.2.1 Across a range of transmission settings and levels of access to first-line malaria treatment, the decay profile (exponential, sigmoidal, strong sigmoidal) will be an important determinant of public health impact [modelling evidence] (Figure 2.2, Appendix 2).
- 3.3.2.2 Longer durations of protection against infection will increase the median clinical incidence reduction in the intervention age group across all transmission settings and decay profiles (Figure 2.2). Similar trends were observed for reduction of clinical infections, severe disease and direct deaths in the intervention age group (Appendix 2). Wider ranges for direct death reductions were observed due to higher levels of uncertainty in model predictions (Appendix 2).
- 3.3.2.3 Sigmoidal and strong sigmoidal profiles will most be influenced by the duration of protection as compared to exponential decay profiles due the decay of initial efficacy (Figure 2.1B, Figure 2.2). For durations of protection longer than 90 days, sigmoidal profiles will have significantly more impact than exponential decay profiles in seasonal settings (Figure 2.2B). **Longer durations of protection (greater than 90 days) for mAb or LAI drug candidates with sigmoidal decay profiles should be prioritized for higher public health impact [modelling evidence].**

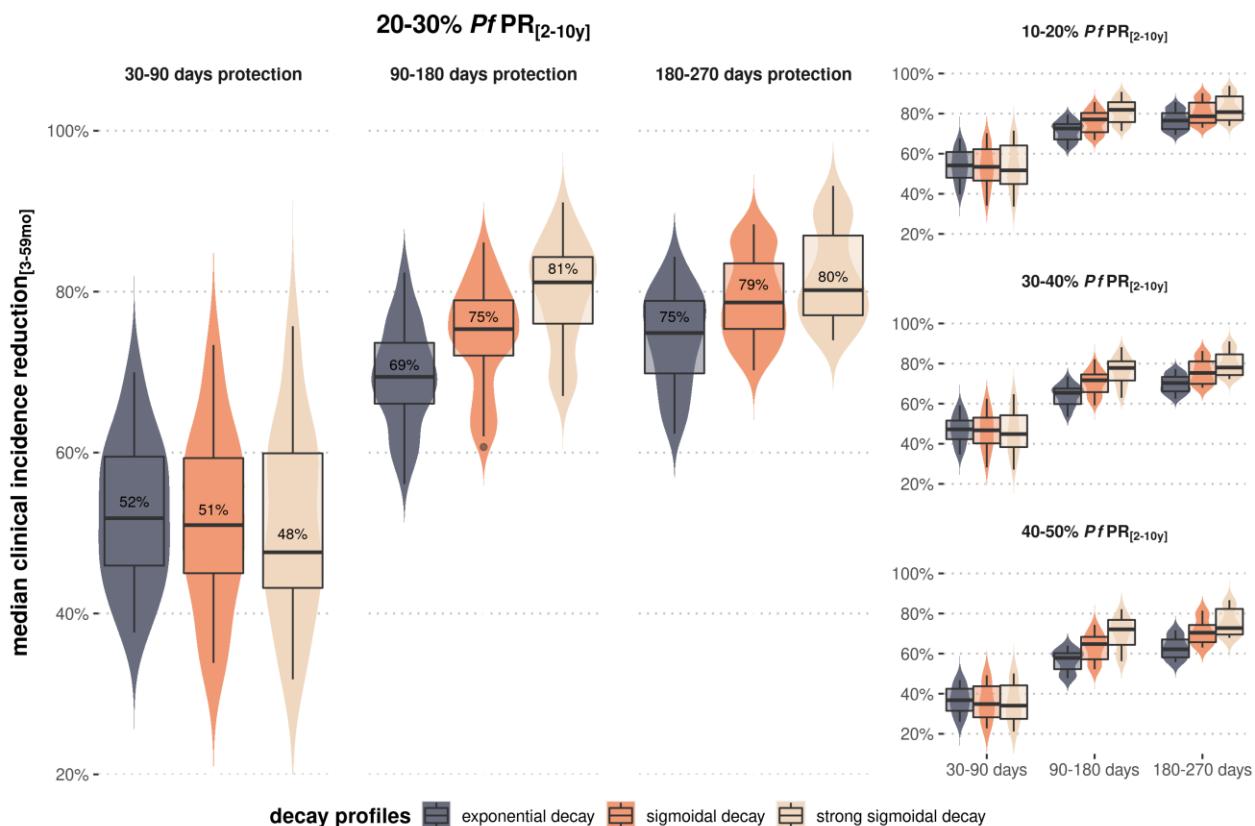


Figure 2.2. Median clinical incidence reduction for different mAb or LAI decay profiles (delivered with blood stage clearance drug) across transmission settings and intervention durations of protection in ideal settings example (>90% initial efficacy, >80% coverage) (noting these medians are over a large range of parameter uncertainty of duration and relatively lag for coverage). The median and distribution of clinical incidence reduction are shown using violin and box plots. These values were estimated from model outputs during a 6-month period following the single round of seasonal interventions during the 5th year of deployment in children three to 59 months old. This example represents a setting with a 4-month seasonal period with intermediate deployment timing and 25% (moderate) access to first-line malaria treatment over a 14-day period for initial efficacy 90-100% and deployment coverage 80-100%. Results are shown across a range of baseline $PfPR_{2-10}$ and durations of protection ranges from 30-90, 90-180, and 180-270 days.

3.3.3 The duration of protection against infection is an important driver of public health impact with varying levels of importance depending on the decay profile, outcome of interest, deployment timing, and transmission settings [modelling evidence]. In order to demonstrate these variations, we consider the importance of the key intervention properties with the following ranges: initial efficacy >90%, deployment coverage >90% and four ranges of duration of protection (30-90, 90-150, 150-210, and 210-270 days) (Figure 2.3). These sensitivity analyses demonstrate the relative importance of these three intervention properties in contributing to changes in public health outcome measures.

3.3.3.1 In ideal scenarios where both the initial efficacy and deployment coverage are above 90%, we observe that the duration of protection is the most important determinant of public health impact in the intervention age groups for shorter durations of protection of less than 150 days (Figure 2.3). Once this duration is reached, increasing the duration of protection becomes less important than increasing the initial efficacy or coverage. **If LAI drug and mAb candidates can achieve 150 days of protection or more, efforts should focus on increasing initial efficacy and coverage to maximize the public health impact. If 150 days duration cannot be achieved, increasing the duration of protection as much as possible should be prioritized.**

3.3.3.2 Extending the duration of protection will increase different public health impact outcomes **[modelling evidence]** (Figure 2.3, Appendix 2). For clinical incidence, severe disease, and direct death reduction in the intervention age group, for short durations between 30 and 90 days, the duration of protection plays a very important role for all three decay profiles in predicting all outcomes measures. For longer durations of protection, from 90 to 150 days, the durations of protection plays a more important role in determining clinical incidence reduction compared with severe disease and direct deaths due to malaria as these outcomes are more driven by initial

efficacy and deployment coverage (Figure 2.3, Appendix 2). For durations of protection greater than 150 days, variations between 90-100% initial efficacy and coverage, respectively, play a more important role for these health outcomes (Appendix 2). We also observe that the variation of the duration of protection has relatively more importance for sigmoidal and strong sigmoidal decay profiles. **Predicted levels of public health impact for LAI drugs or mAb candidates with shorter duration of protection (<150 days) will be largely influenced by this duration of protection for all relevant outcomes. The public health impact of LAI drugs or mAbs with longer durations of protection against infection (>150 days) will be more influenced most by the initial efficacy and deployment coverage. Overall, clinical incidence reduction serves as a good proxy for severe disease and direct deaths for relative importance of intervention properties.**

- 3.3.3.3 The importance of the duration of protection across all decay profiles is more important with earlier deployment timings but will have more impact as deployment timing is delayed towards the peak of transmission (Figure 2.3, Appendix 2).
- 3.3.3.4 The importance of the duration of protection in determining public health impact is similar across different baseline prevalence settings (Figure 2.3) with moderately more significance for sigmoidal and strong sigmoidal decay profiles. The impact of seasonal interventions is highest in lower baseline transmission settings.
- 3.3.3.5 For shorter durations of protection of less than 90 days, the duration of protection plays the most important role for all seasonal profiles in determining public health impact (Appendix 2). With increasing durations of protection ranging from 150 days and longer, the duration of protection plays a less important role in seasonal settings and a slightly more important role in longer seasonal settings (Appendix 2). **Extending the duration of protection of LAI drug and mAb candidates beyond 150 days will not have important implications for public health impact in seasonal settings with transmission less than 5 months long. Extending the duration of protection beyond 150 days will be moderately more important in longer transmission seasons and perennial settings.**

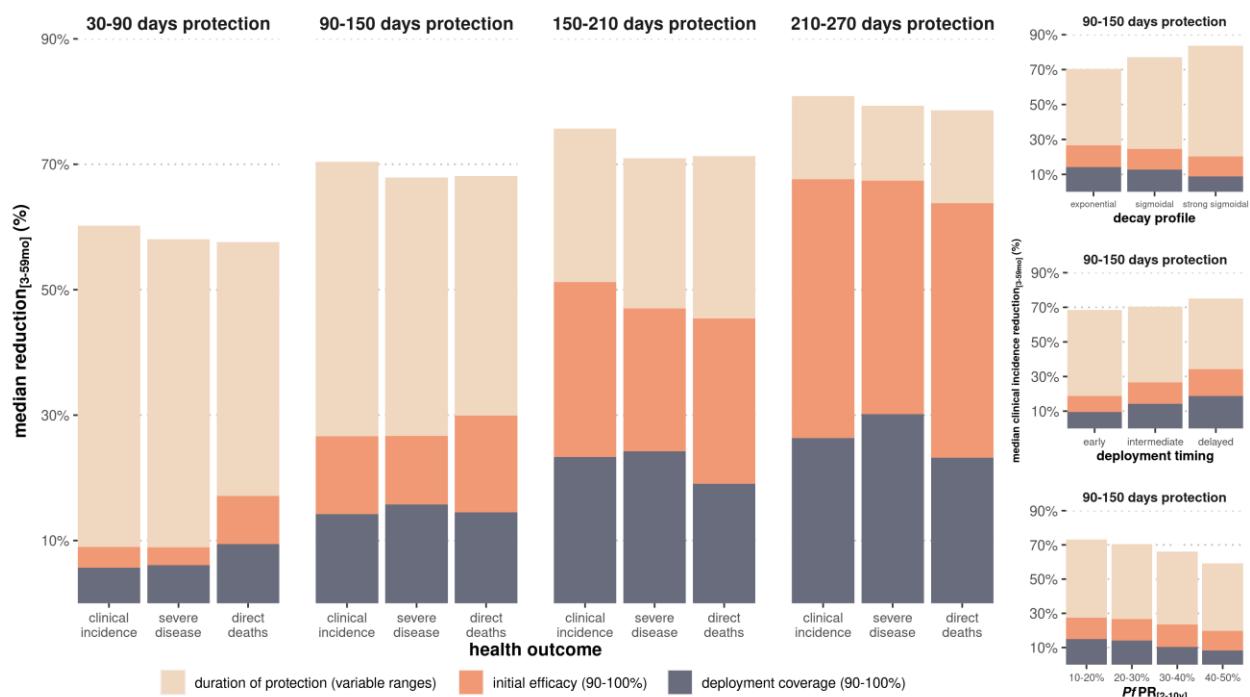


Figure 2.3. Trade-offs between key characteristics: variance-based importance of intervention characteristics to determining health outcome reductions in intervention age group in ideal settings (>90% initial efficacy, >90% coverage). Bar heights represent the median health outcome reduction and the proportion is the relative importance of intervention properties based on the Sobol method for global sensitivity analysis. For this example, we explore the importance for different ranges of duration of protection, 90-100% initial efficacy ranges, and 90%-100% deployment coverage. Unless otherwise noted, results are shown for exponential decay profiles for a 4-month seasonal setting with moderate first-line access, with 20-30% PfPR_[2-10y] and intermediate deployment timing.

3.3.4 The minimal duration of protection to achieve target burden reductions will vary by decay profile, deployment timing, seasonal length, baseline prevalence, initial efficacy and deployment coverage.

3.3.4.1 Extending the duration of protection is required to achieve the same burden reduction target in increasingly higher transmission settings for all decay profiles (Figure 2.4, Appendix 2). For the same target burden reduction and transmission level, strong sigmoidal decay profiles require shorter durations of protection as compared with sigmoidal and exponential profiles.

3.3.4.2 Longer seasonal lengths require longer durations of protection to achieve the same health targets as shorter seasonal settings, particularly for sigmoidal and strong sigmoidal decay profiles (Figure 2.4, Appendix 2).

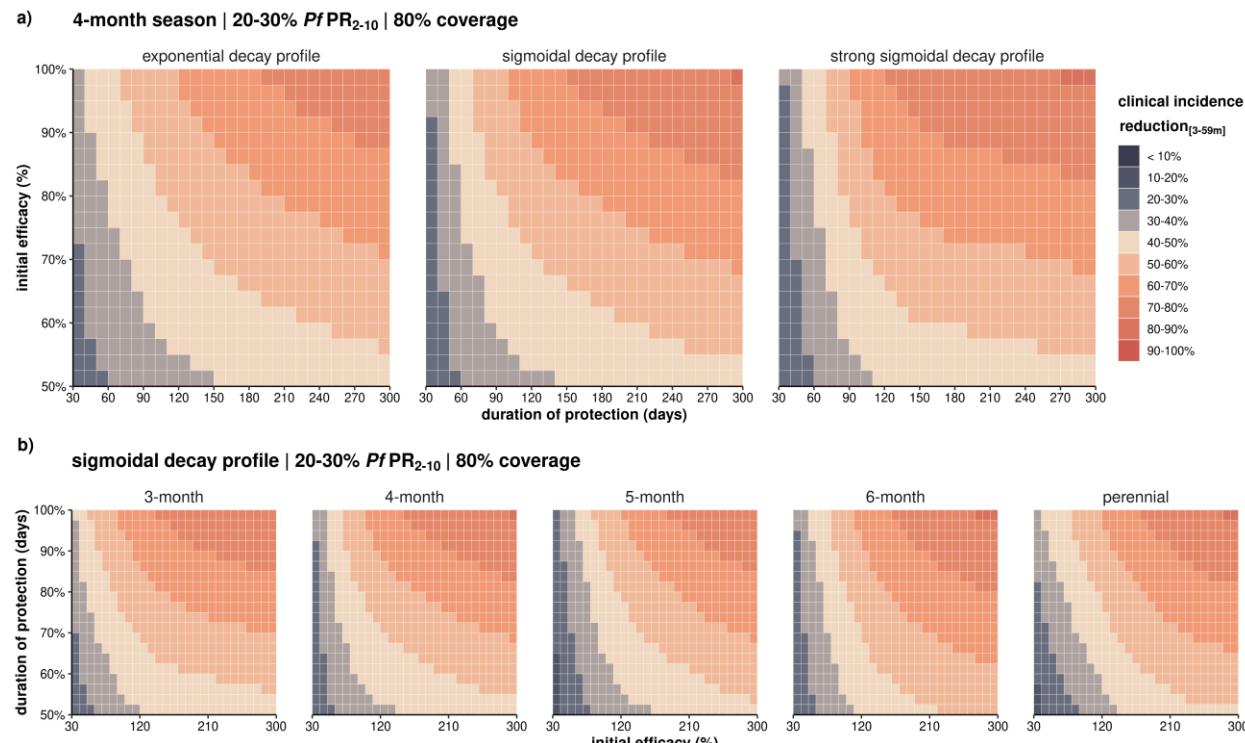


Figure 2.4. Minimum intervention performance criteria to achieve clinical incidence reduction targets. a) In a 4-month seasonal setting with a baseline prevalence of 20-30% $PfPR_{2-10}$ and 80% deployment coverage of a single round, for different decay profiles (exponential, sigmoidal, strong sigmoidal), we show model predicted initial efficacy (%) and duration of protection (days) required to achieve clinical incidence reduction in children three to 59 months old during a 6-month follow-up period during the 5th year of rollout. We investigate three deployment timing strategies for the five seasonal transmission profiles modelled for seasonal interventions. Values show the average clinical incidence reduction in the highlighted parameter space. b) For the same baseline prevalence and deployment coverage, we show results for sigmoidal decay profiles across different seasonal transmission settings.

3.3.4.3 As deployment is delayed and approaches the transmission peak, the minimum required duration of protection against infection to reach target health reductions decreases (Figure 2.5, Appendix 2).

3.3.4.4 The preferred duration of protection will vary depending on the initial efficacy and deployment coverage (Figure 2.5, Appendix 2). Trade-offs between higher initial efficacy and coverage will lower the required duration of protection against infection. Deployment coverage of at least 70% requires durations of at least 90-120 days if initial efficacy is high (>90%) towards achieving at least 50% incidence reduction. If deployment coverage is high (>90%, similar to clinical trial settings), an initial efficacy of 90% and duration of protection of 90-120 days can achieve at least 60% clinical incidence reduction. The variation in deployment coverage will play an important role in the required duration of protection to meet health targets. **Modelling predicts that seasonal intervention candidates with a duration of protection of 90-120 days can achieve at least 50% incidence reduction if initial efficacy is >70% and deployment coverage is >60%.**

3.3.4.5 Achieving similar reduction targets in severe disease requires an additional 30 days of protection as compared to clinical incidence reduction across decay profiles and transmission settings (Appendix 2).

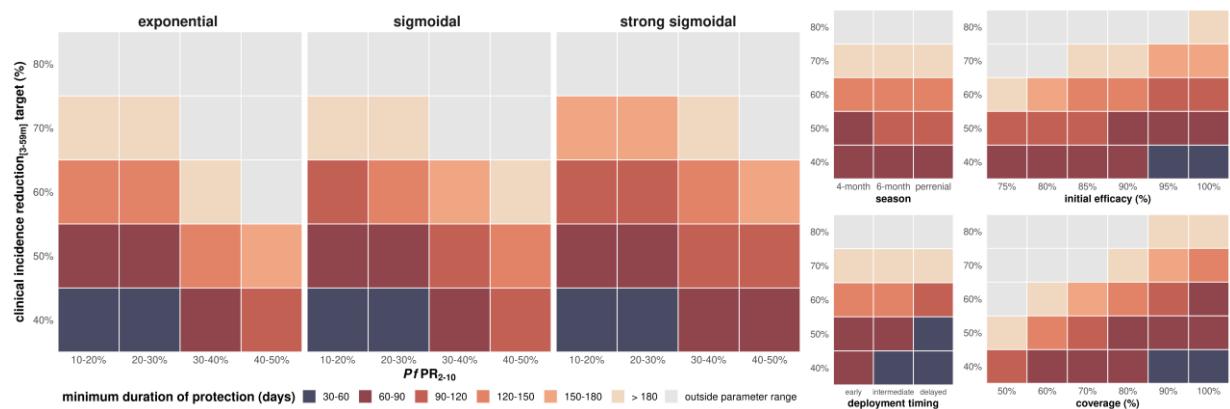


Figure 2.5. Minimal duration of protection for clinical incidence reduction targets. All results shown are for scenarios with at least 90% initial efficacy, 90% deployment coverage, a baseline $PfPR_{2-10}$ of 20%-30% and moderate first-line access in a 4-month season with intermediate deployment and sigmoidal decay profiles unless otherwise shown.

4. CLINICAL EFFICACY

4.1 CURRENT CRITERIA

Table 3.1. Current criteria for iTPP1 clinical efficacy

Base Case	Upside Case	Annotations
Preventive efficacy: 80% to achieve non-inferiority to SMC.	Preventive efficacy: 98% to achieve non-inferiority to Malarone (atovaquone/proguanil).	Target reduction goals are preliminary; modeling necessary to ensure targets meet elimination goals (herd protection).

4.2 SUGGESTED UPDATES

In order to assess the importance of clinical efficacy/clinical reduction, we evaluated the importance and minimal initial efficacy properties of a seasonal intervention in a clinical trial-like setting. In these clinical trial settings, we assume high access to first-line treatment (50% over a 14-day period) and > 90% coverage of the intervention in children three to 59 months old.

Strong sigmoidal profiles with long durations of protection > 180 days will have achieve moderate to high clinical efficacy for a large range of clinical efficacy (> 60%). For all decay profiles across most transmission settings for higher burden reduction targets, candidates with initial efficacy of at least 80% should be prioritized.

Table 3.2. Updated criteria for iTPP1 clinical efficacy

Base Case	Upside Case	Annotations
Preventive efficacy: 80% to achieve non-inferiority to SMC. A single deployment to achieve non-inferiority to SMC may require strong sigmoidal profiles with protection >120 days and initial efficacy >75%.	Preventive efficacy: 98% to achieve non-inferiority to Malarone (atovaquone/proguanil).	Target reduction goals are preliminary; modeling necessary to ensure targets meet elimination goals (herd protection) Further modelling evidence of non-inferiority is required when new evidence of SP-AQ or current SMC drug efficacy and PK-PD information is obtained (with and without SP resistance)

4.3 KEY RESULTS

4.3.1 In clinical trial settings with high access to first-line treatment and high deployment coverage > 90%, the duration of protection and initial efficacy will impact the range of achievable health goals [modelling evidence].

4.3.1.1 Higher ranges of initial efficacy will increase the range of clinical efficacy across all health outcomes (Figure 3.1). Low durations of protection < 180 days will achieve lower clinical efficacy. Candidate LAI drugs and mAbs than can achieve > 180 days of protection are predicted to achieve ~50% clinical efficacy with low initial efficacy against infection ranging from 50-60% and > 80% clinical efficacy for initial efficacy > 90%.

4.3.1.2 For direct death mortality, deployment coverage will play the most important role in burden reduction (Figure 3.1).

4.3.1.3 Initial efficacy will play a more important role in clinical efficacy in lower transmission settings and shorter seasonal settings compared with perennial settings (Figure 3.1).

4.3.1.4 The initial efficacy will be a more important factor for clinical efficacy for strong sigmoidal decay profiles compared with exponential profiles, in particular for high durations of protection (Figure 3.1).

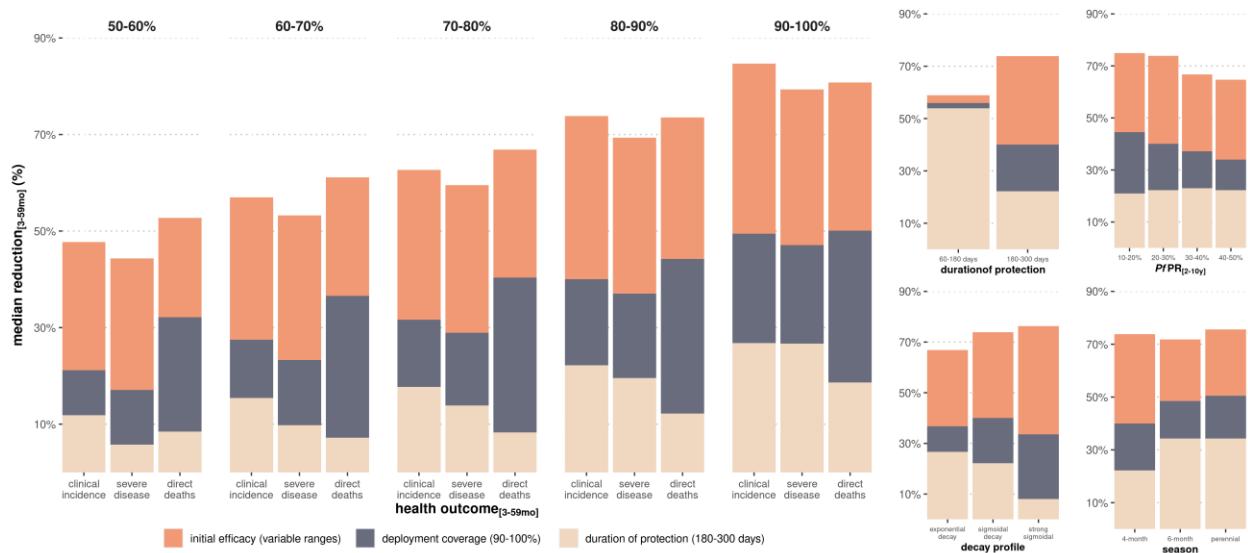


Figure 3.1. Variance-based importance of intervention characteristics to clinical efficacy in intervention age group in clinical settings (coverage > 90%, high access). The heights of the bars represent the median health outcome reduction and the proportion is the relative importance of intervention properties based on the Sobol method for global sensitivity analysis. For this example we explore the importance for different ranges of initial efficacy and two ranges of duration of protection (< 180 days and > 180 days). Unless shown otherwise, results are shown for sigmoidal decay profiles with protection > 180 days for a 4-month seasonal setting with high first-line access, 20%-30% PfPR₂₋₁₀ and intermediate deployment timing.

4.3.2 In clinical trial settings with high access to care and high coverage, initial efficacies >80% will achieve 60% clinical efficacy for all decay profiles (Figure 3.2, Figure 3.3).

4.3.2.1 Increasing the initial efficacy and duration of protection increases the range of achieve health outcome targets in clinical settings. Sigmoidal and strong sigmoidal decay profiles with lower clinical efficacy can achieve the same health targets as exponential decay profiles (Figure 3.2, Figure 3.3). **Candidates with strong sigmoidal profiles are predicted to demonstrate the highest clinical efficacy for initial efficacies >60%.**

4.3.2.2 The same target reduction can be achieved for severe disease and mortality compared with clinical incidence if the initial efficacy increases by 10% (Figure 3.2). **Candidates with 50% to 70% initial efficacy are predicted to achieve moderate (50-60%) burden reductions across most settings and for all decay profiles. For higher burden reduction targets (>60%), candidates with initial efficacy of at least 80% should be prioritized.**

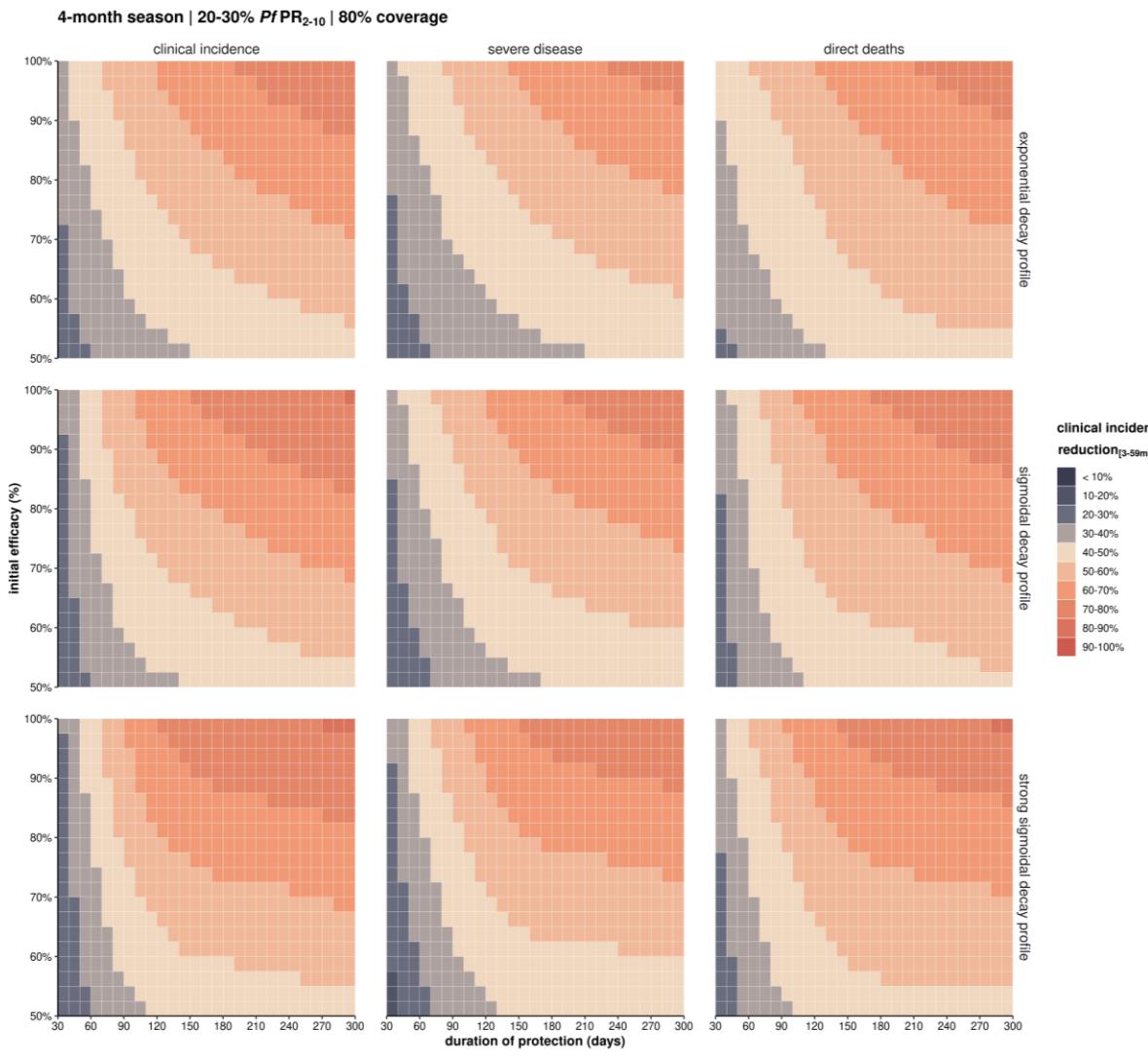


Figure 3.2. Minimum intervention performance criteria to achieve clinical incidence reduction targets in clinical trial settings. In a 4-month seasonal setting with a baseline prevalence of 20-30% $PfPR_{2-10}$, 90% deployment coverage of a single round at intermediate deployment timing and high access to first-line treatment example. For different decay profiles (exponential, sigmoidal, strong sigmoidal), we show model predicted initial efficacy (%) and duration of protection (days) required to achieve clinical incidence, severe disease, and direct death reduction in children three to 59 months old during a 6-month follow-up period during the 5th year of rollout.

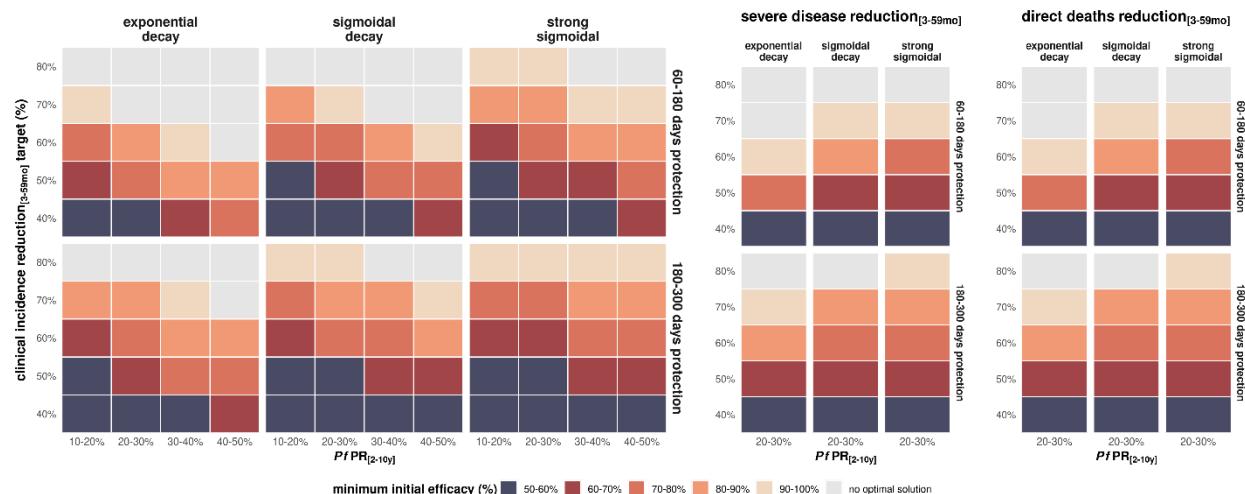


Figure 3.3. Minimal initial efficacy (%) for health outcomes reduction targets in clinical trial settings. Results are shown for a seasonal 4-month setting with high (50%) access to first line treatment, 90% deployment coverage in with intermediate deployment for different health outcomes and a baseline $PfPR_{2-10}$.

5. COVERAGE REQUIREMENT

5.1 CURRENT CRITERIA

Table 4.1. Current criteria for iTPP1 coverage requirement

Base Case	Upside Case	Annotations
To be determined	To be determined	To achieve community effect compatible with achieving herd immunity consistent with interruption of transmission during the protection window (in the absence of SMC). Based on modeling studies.

5.2 SUGGESTED UPDATES

Assuming implementation scenarios where deployment coverage is suboptimal, <80%, and access to first-line treatment is low to moderate, we explore the trade-offs between deployment coverage, where initial efficacy is >80% for both high and low durations of protection. We evaluated the role of coverage and the minimum requirement to achieve burden reduction for LAI drugs and mAb in children three to 59 months old.

Table 4.2. Updated criteria for iTPP1 coverage requirement

Base Case	Upside Case	Annotations
To be determined For seasonal or perennial settings, targeting children 3-59 months old, at least 50%-70% of population needs to be covered to achieve minimum burden reduction targets for single deployment.	To be determined At least 70% to achieve minimum burden reduction targets for single deployment to achieve 50% clinical incidence, severe disease, and mortality reductions in children 3-59 months	Modelling results indicate coverage for use in children when deployed with a blood stage clearing drug. Higher coverage targets required if mAb or LAI drug delivered alone. To achieve community effect compatible with achieving herd immunity consistent with interruption of transmission during the protection window (in the absence of SMC), both coverage and duration of protection will be crucial . Based on modeling studies. [note for the Foundation's reference and to be deleted later – herd immunity is not the correct term, rather consistent with interruption]

5.3 KEY RESULTS

5.3.1 Coverage is the most important determinants of public health impact in implementation settings.

5.3.1.1 Deployment coverage is the important determinant of burden reduction in implementation settings (Figure 4.1). As deployment coverage increases, the importance of initial efficacy becomes increasingly important for burden reduction.

5.3.1.2 Deployment coverage is a more important determinants of burden reduction when access to first line treatment is low, the duration of protection is higher, for strong sigmoidal decay profiles, and in low transmission settings (Figure 4.1).

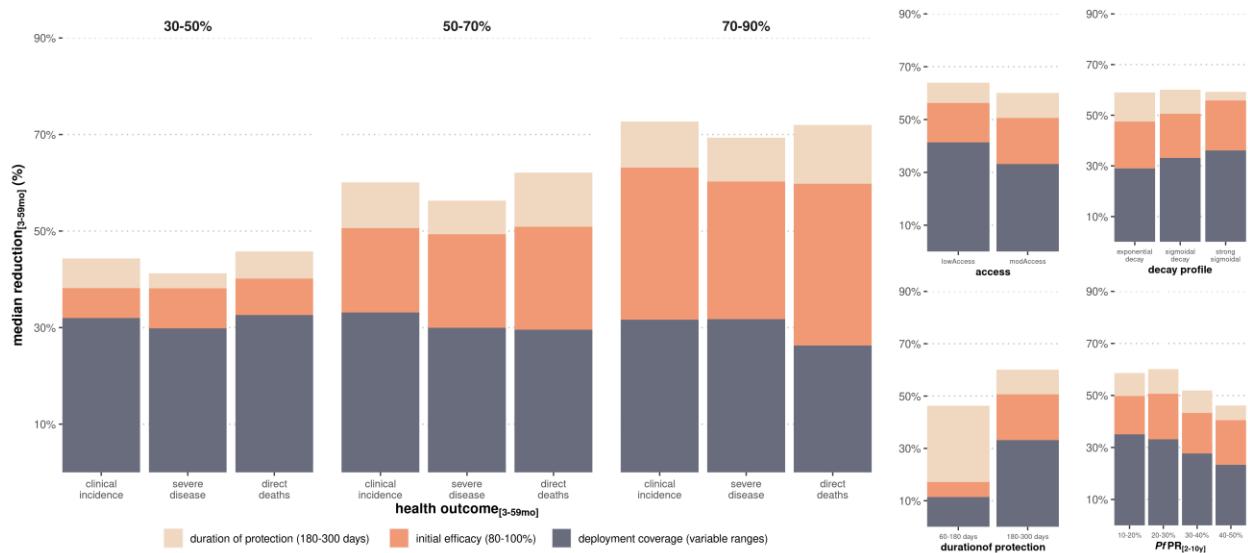


Figure 4.1. Variance-based importance of intervention characteristics in implementation settings (initial efficacy >80%, low to moderate access). Bar heights represent the median health outcome reduction and the proportion is the relative importance of intervention properties based on the Sobol method for global sensitivity analysis. For this example we explore the importance for different ranges of coverage and two ranges of duration of protection (<180 days and >180 days). Unless shown otherwise, results are shown for sigmoidal decay profiles with protection >180 days for a 4-month seasonal setting with moderate first-line treatment access, 20-30% $PfPR_{2-10}$ and intermediate deployment timing.

5.3.2 High levels of deployment coverage are required to achieve desirable burden reduction targets in the intervention age group.

- 5.3.2.1 In most settings and across decay profiles, a minimum deployment coverage of 60% for durations at least 120 days long is required to achieve 50% burden reduction across outcomes (Figure 4.2, Figure 4.3). Higher minimum intervention criteria are required for moderate access settings (Appendix 2, Appendix 3).
- 5.3.2.2 In settings with <30% $PfPR_{2-10}$, implementation settings requires at least 70% deployment coverage for all decay profiles with at least 180 days of protection to achieve at least 70% burden reduction (Figure 4.3). **Candidate LAI drugs or mAbs that can achieve at least 80% initial efficacy and 180 days of protection require at least 70 deployment coverage of a single round to achieve 70% burden reduction. Therefore, to further increase public health impact, community acceptability of these interventions in the target population is essential. A single round of deployment will heavily rely on deployment coverage.**

4-month season | 20-30% $PfPR_{2-10}$ | 80% initial efficacy | low access

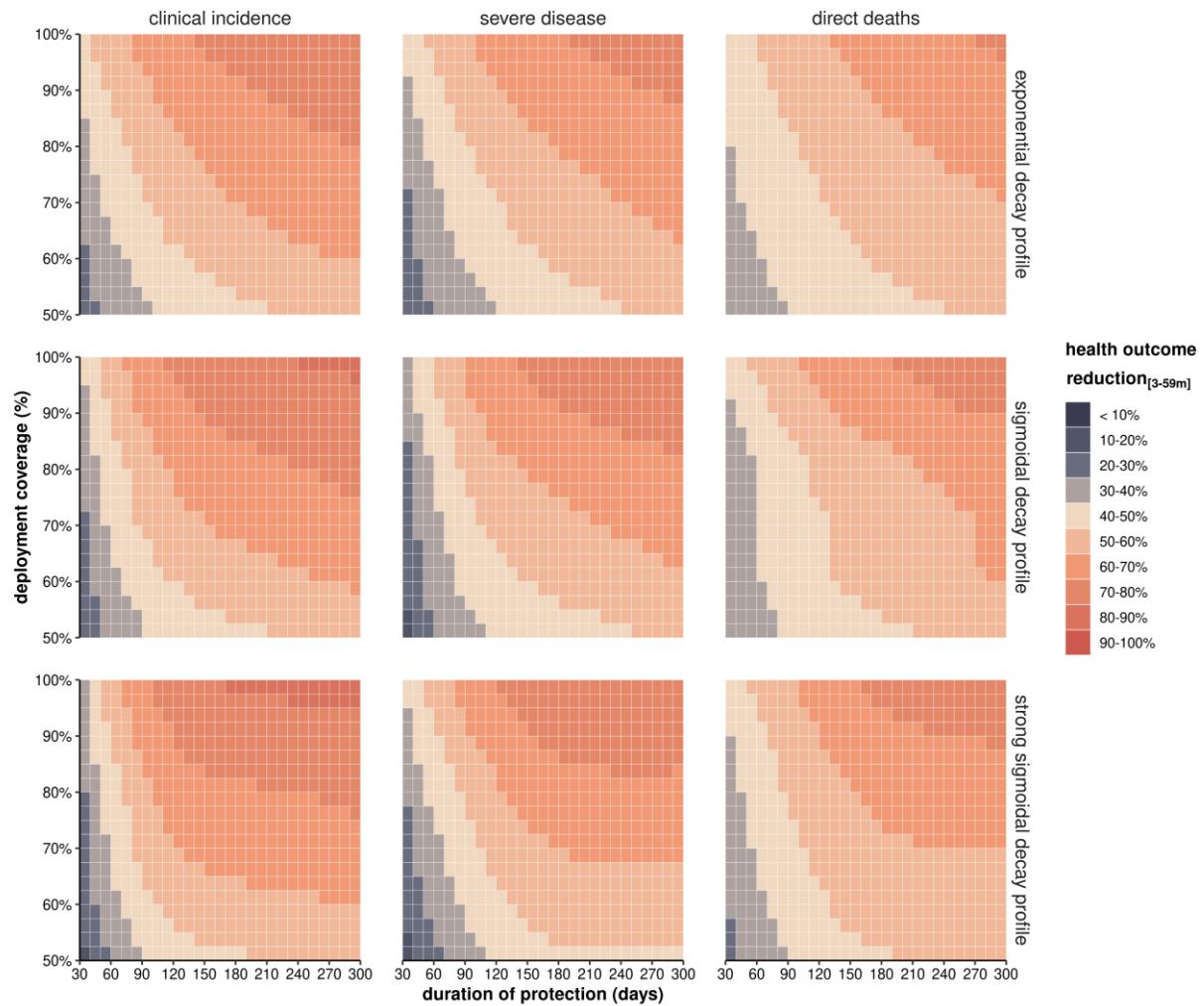


Figure 4.2. Minimum intervention performance criteria to achieve clinical incidence reduction targets in implementation settings with low access. In a 4-month seasonal setting with a baseline prevalence of 20-30% $PfPR_{2-10}$, 80% initial efficacy of a single round at intermediate deployment timing example. For different decay profiles (exponential, sigmoidal, strong sigmoidal), we show model predicted deployment coverage (%) and duration of protection (days) required to achieve clinical incidence, severe disease, and direct death reduction in children three to 59 months old during a 6-month follow-up period during the 5th year of rollout.

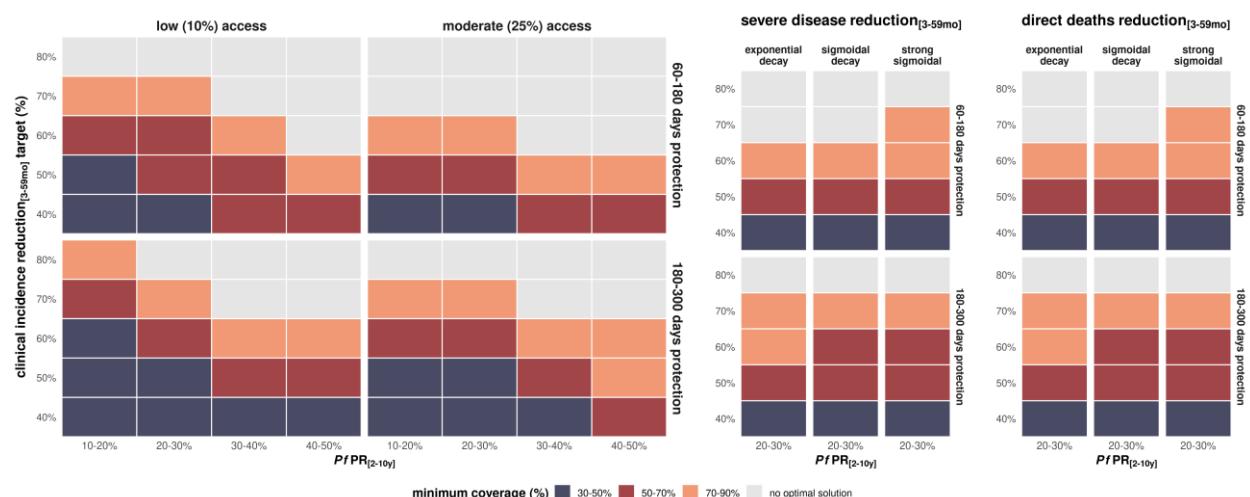


Figure 4.3. Minimal deployment coverage (%) of a single round for health outcomes reduction targets in implementation settings (initial efficacy >80%, low and moderate access). Results are shown for a seasonal 4-month setting with intermediate deployment for different health outcomes and a baseline $PfPR_{2-10}$.

6. TARGET SETTINGS

6.1 CURRENT CRITERIA

Table 5.1. Current criteria for iTPP1 target settings

Base Case	Upside Case	Annotations
(SMC eligible) Geographies with moderate to high transmission in eligible endemic countries experiencing seasonal malaria transmission patterns (West, East and South Africa) (Chemoprophylaxis) for travel to endemic countries, mainly seasonal malaria in Eastern, Western, and Southern Africa. (Outbreak) Any country experiencing a malaria outbreak or where large populations of displaced individuals are at risk for contracting malaria	All seasonal settings and travelers from countries aiming for elimination as well as non-endemic countries.	"Geographical archetypes" will inform the final language here. Get updates from Bruno.

6.2 SUGGESTED UPDATES

In this first round of updates we explore a range of seasonal length from short seasonal settings to perennial settings and from low to high prevalence settings. We also consider low, moderate, and high access to first-line treatment.

Table 5.2. Updated criteria for iTPP1 target settings

Base Case	Upside Case	Annotations
(SMC eligible) Geographies with moderate to high transmission in eligible endemic countries experiencing seasonal malaria transmission patterns (West, East and South Africa). Including non-eligible geographies with current SP resistance (PMC eligible) Geographies experiencing low to high perennial transmission. (Chemoprophylaxis) for travel to endemic countries, mainly seasonal malaria in Eastern, Western, and Southern Africa. (Outbreak) Any country experiencing a malaria outbreak or where large populations of displaced individuals are at risk for contracting malaria.	All seasonal settings and travelers from countries aiming for elimination as well as non-endemic countries.	"Geographical archetypes" will inform the final language here. Get updates from Bruno. Convening stakeholder indicated for all target settings compactor (or lack of) standard of care should be indicated. For seasonal and perennial chemoprevention settings current chemoprevention efficacy target ranges should be indicated

6.3 KEY RESULTS

6.3.1 Seasonal settings will highly rely on the duration of protection and decay profile to achieve health goals.

- 6.3.1.1 We found that the duration of protection of LAI drugs and mAbs against infection is an important determinant of public health impact and will be influenced by other interventional properties, including deployment timing (see Indication section).
- 6.3.1.2 For non-inferiority to SMC, our results along with previous modelling work [2] demonstrate the **need for the duration of protection to cover the length of the high transmission period to reach sufficient burden reduction targets.**
- 6.3.1.3 SMC achieves 61.4% [47.4–71.8%] incidence reductions three to six weeks post-treatment with 90% coverage [4]. **For candidates LAI drugs and mAbs to achieve similar reductions to SMC, they require at least 75% efficacy and 90-120 days of protection for strong sigmoidal**

profiles, 120-150 days for sigmoidal profiles, and 150-180 for exponential profiles (Figure 6.1).

6.3.1.4 Since sigmoidal and strong sigmoidal profiles heavily rely on the duration of protection, durations of at least 90-120 days are required in seasonal settings with an initial efficacy >70% to achieve at least 50% clinical incidence reduction in the target age group. **Extending the duration of protection beyond 180 days is most beneficial for burden reduction in perennial settings since higher minimum intervention criteria are required for these settings.**

6.3.1.5 Low prevalence settings are expected to benefit most from seasonal interventions (Figure 6.1).

6.3.1.6 Settings with low access to first-line treatment will benefit most from LAI drug and mAb interventions (Figure 6.1).

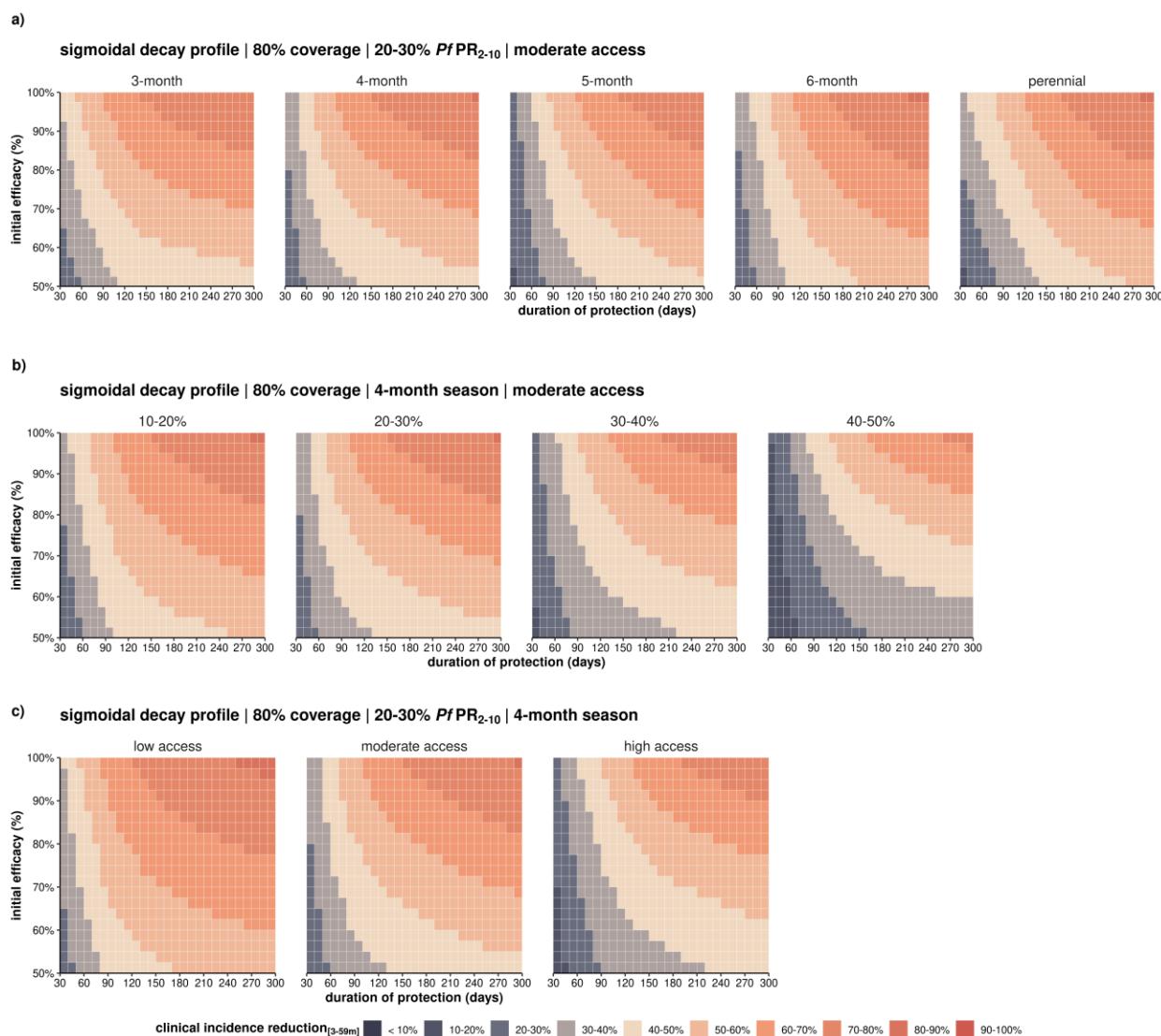


Figure 6.1. Minimum intervention performance criteria to achieve clinical incidence reduction targets with 80% deployment coverage across a range of settings for sigmoidal decay profiles. a) An example with baseline prevalence of 20-30% $PfPR_{2-10}$ and moderate access show criteria by seasonal length b) An example 4-month season with moderate accessing showing criteria for different baseline prevalence settings c) An example 4-month season with baseline prevalence of 20-30% $PfPR_{2-10}$ for different levels for access to first line malaria treatment.

7. IMPACT ON PARASITE PREVALENCE (PFPR)

7.1 CURRENT CRITERIA

Table 6.1. Current criteria for iTPP1 impact

Base Case	Upside Case	Annotations
To be determined	To be determined	Pending on modeling studies and policy standards discussion with WHO to determine what community benefit would be necessary for a recommendation on the product.

7.2 SUGGESTED UPDATES

Seasonal interventions will have several endpoints and evaluation periods to consider. Public health impact will vary by: transmission setting, timing of deployment, and population of interest. Further refinement of target health outcome are required to tune minimum intervention criteria.

Table 6.2. Updated criteria for iTPP1 impact

Base Case	Upside Case	Annotations
To be determined	To be determined	<p>Pending on modeling studies and policy standards discussion with WHO to determine what community benefit would be necessary for a recommendation on the product.</p> <p>Modelling indicates that the evaluation period of clinical or burden reduction will influence targets. Shorter follow-up will demonstrate higher achievable health targets before rebound.</p> <p>Clinical incidence reduction is a good proxy for measuring the burden reduction of seasonal interventions. Severe disease and mortality outcomes follow similar trade-offs for intervention criteria.</p> <p>Several outcomes are possible with a range of combination of criteria to achieve different levels of clinical incidence reduction: e.g. In a four-month seasonal setting with >80% deployment coverage and >80% initial efficacy, durations of protection 30-90 days long can achieve a median 40% clinical incidence reduction as compared to 150-210 days achieving a median ~70% reduction. e.g. Longer durations of protection greater than 90 days for mAb or LAI drug candidates with sigmoidal decay profiles are required for >60% clinical incidence reduction [modelling evidence]. e.g. In most settings and across decay profiles and durations, candidates with 80% initial efficacy require a minimum deployment coverage of 70% to achieve 50% burden reduction of clinical incidence, severe disease and mortality over a 6-month follow-up period. e.g. Sufficient burden reduction (at least 50% clinical incidence reduction over 6-months follow-up) with LAI drugs or mAbs requires maintaining high efficacy with limited decay for at least three months (with a minimum initial efficacy >80% and coverage >60%).</p>

7.3 KEY RESULTS

7.3.1 The most significant public health impact of seasonal interventions will be in the target age group.

- 7.3.1.1 Very low levels of population-level prevalence reduction are expected with seasonal interventions targeting only children three to 59 month olds ranging from 10-30% with a maximum of 40% reduction achieved only with very high minimal intervention criteria (Figure 7.1, Figure 7.2). Since children aged three to 59 months old are the target age groups and the most vulnerable group to severe disease and mortality outcomes, we observe higher ranges of reductions for these outcomes when assessing the entire population-level impact. **Expanding the target population**

to children under 10 will have more impact on population-level prevalence but modelling evidence is required to demonstrate this [modelling evidence needed].

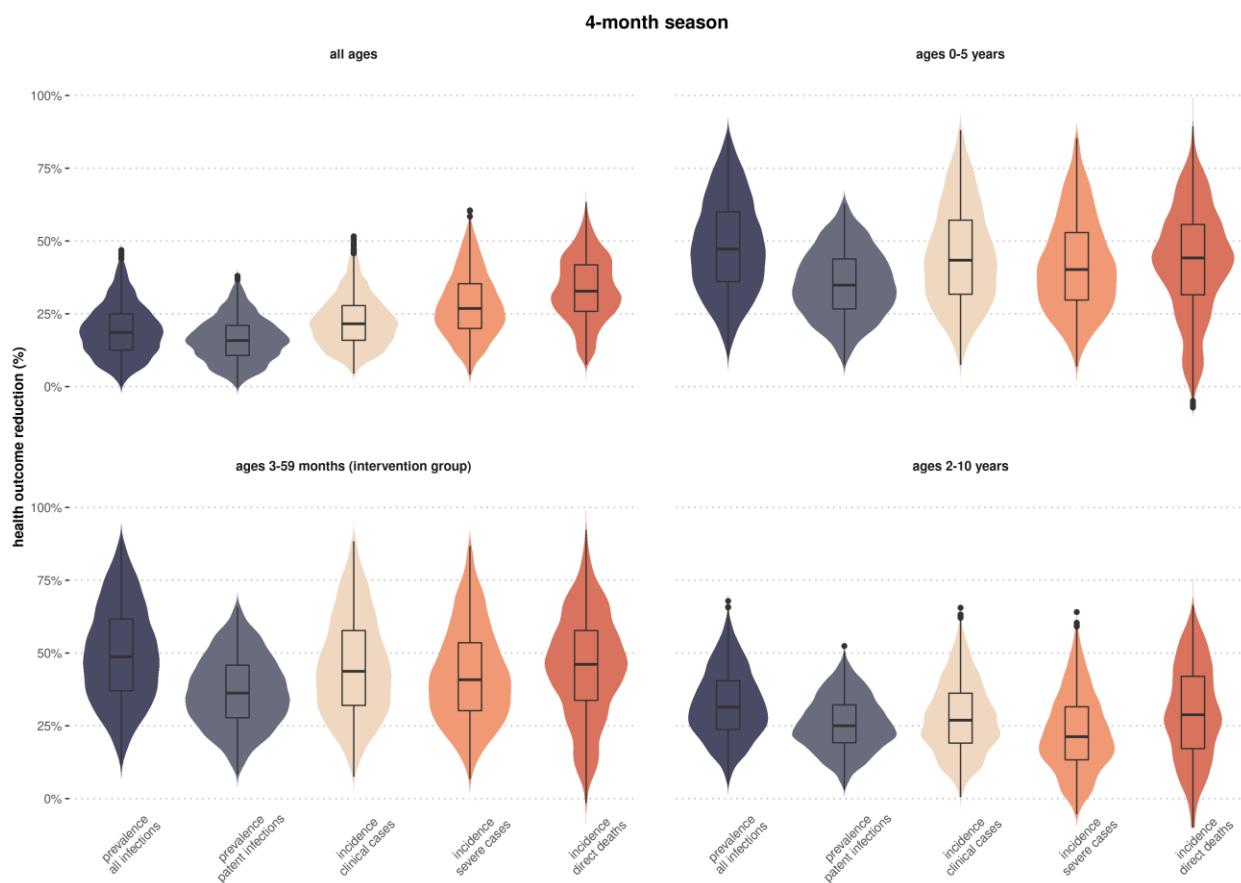


Figure 7.1. Median health outcome reduction for sigmoidal mAb or LAI decay profile (delivered with blood stage clearance drug) across all scenarios for different age groups. The median and distribution of clinical incidence reduction are shown using violin and box plots for all scenarios (aggregated duration 30-300 days, initial efficacy 50-100%, deployment coverage 30-100%). These values were estimated from model outputs during a 6-month period following the single round of seasonal interventions during the 5th year of deployment in children three to 59 months old. This example represents a setting with a 4-month seasonal period with intermediate deployment timing and 25% (moderate) access to first-line malaria treatment over a 14-day period and 20-30% baseline $PfPR_{2-10}$.

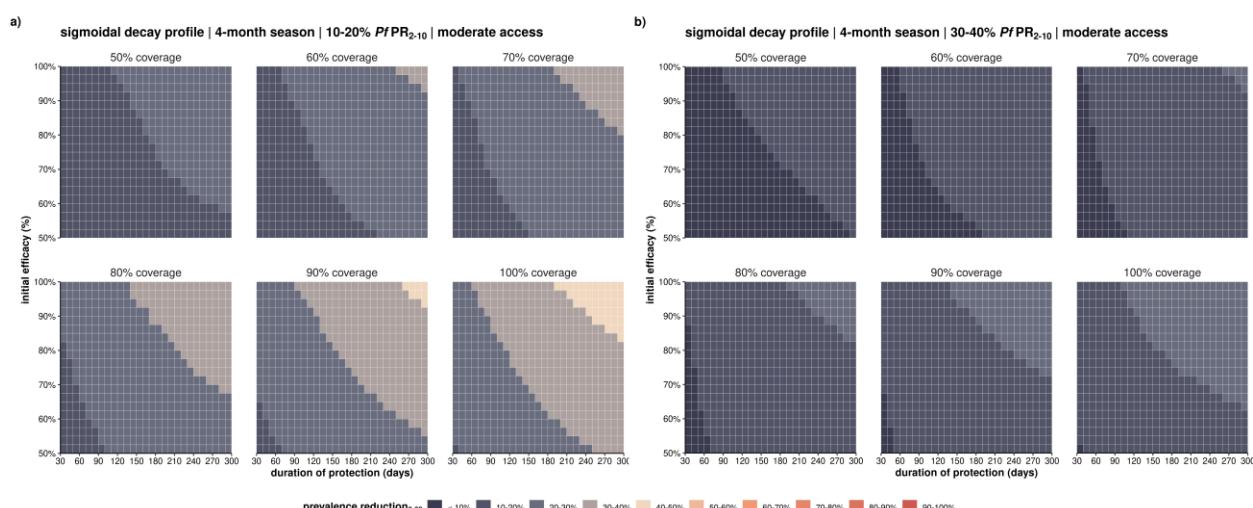


Figure 7.2. Minimum intervention performance criteria to achieve prevalence reductions in all ages. In a 4-month seasonal setting with a baseline prevalence of a) 10-20% $PfPR_{2-10}$ and a) 30-40% $PfPR_{2-10}$ for a single round of seasonal interventions in children three to 59 months old at intermediate deployment timing and moderate access to first-line treatment example. For sigmoidal decay profile prevalence reduction in all ages was measured in during a 6-month follow-up period during the 5th year of rollout.

7.3.2 Several general conclusions can be made about the impact of transmission settings and evaluations periods that impact health outcome reductions.

- 7.3.2.1 Clinical incidence reduction is a good proxy for measuring the burden reduction of seasonal interventions (Appendix 2, Appendix 4).
- 7.3.2.2 Clinical incidence reduction will be higher in low transmission settings with low access to first-line malaria treatment (Appendix 2, Appendix 4).
- 7.3.2.3 Clinical incidence reduction will be higher when deployment is delayed towards the seasonal peak (Appendix 2).
- 7.3.2.4 Clinical incidence reduction will be higher when evaluating transmission over 6-months versus 12-months follow-up (Appendix 4).
- 7.3.2.5 Clinical incidence reduction will be higher when evaluating transmission during the 10th year versus 5th year of deployment (Appendix 4).

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1. Gaudinski, M.R., et al., *A Monoclonal Antibody for Malaria Prevention*. N Engl J Med, 2021. **385**(9): p. 803-814.
2. Burgert, L., et al., *Model-informed target product profiles of long acting-injectables for use as seasonal malaria prevention*. medRxiv, 2021: p. 2021.07.05.21250483.
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4. Moroso, D., et al., *Effectiveness of seasonal malaria chemoprevention at scale in west and central Africa: an observational study*. Lancet, 2020. **396**(10265): p. 1829-1840.
5. Smith, T., et al., *An epidemiologic model of the incidence of acute illness in Plasmodium falciparum malaria*. American Journal of Tropical Medicine and Hygiene, 2006. **75**(2): p. 56-62.

APPENDIX

A.1 Expert opinion

The following summarizes the most relevant points during the November 2021 WHO mAb PPC Meeting

- Blood stage mAb such in combination with an anti-infective CSP-binding mAb may help prevent breakthrough infections.
- Sufficient levels of potency of a combined blood stage (e.g. RH5) and anti-infective mAb combination with little immune interference is expected. Blood stage mAb may demonstrate improved efficacy when combined with an anti-infective since lower levels of blood stage parasites will occur. Proof-of-concept is still needed.
- Combination mAb may be considered when there will be a better understanding of the delivery requirements needed for a single-component mAb to a target population. Combination mAbs will need to meet sufficient potency, volume and delivery costs in order to be considered.
- The added value of combining mAb with an LAI with either blood- or liver-stage compounds will depend on the potency of the mAb. The drug would need to remain active beyond two or three months when mAb activity wanes. Modelling this combination is not an immediate priority.

A.2 Indication supplementary figures

Severe disease reduction in all scenarios

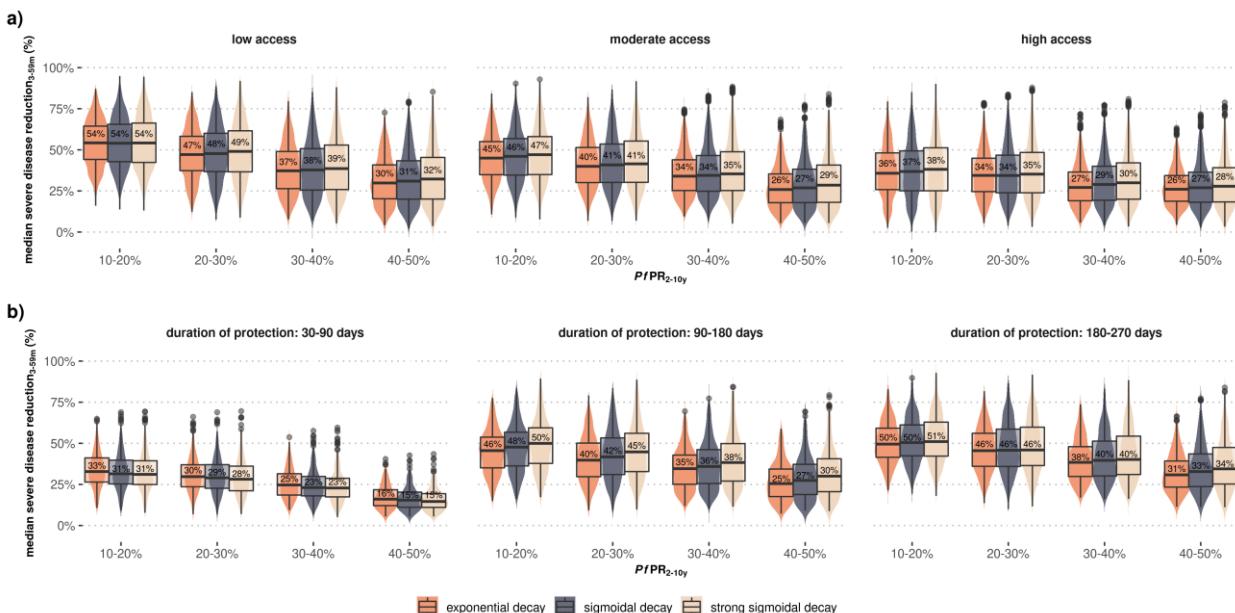


Figure A.2.1. Median severe disease reduction across transmission settings and intervention durations of protection (noting these medians are over a large range of parameter uncertainty of efficacy, duration and coverage). For a range of initial efficacy 50-100%, deployment coverage 30-100%, durations of protection from 30-300 days, and intermediate deployment timing in a 4-month seasonal setting, the median and distribution of clinical incidence reduction in the intervention age group is show for violin and box plots **a)** across a range of baseline $PfPR_{2-10}$ and 10% (low), 25% (moderate), and 50% (high) access to first-line malaria treatment over a 14-day period and **b)** across a range of baseline $PfPR_{2-10}$ and 10% in moderate access levels stratified by durations of protection: 30-90 days, 90-180 days, and 180-270 days.

Direct death reduction in all scenarios

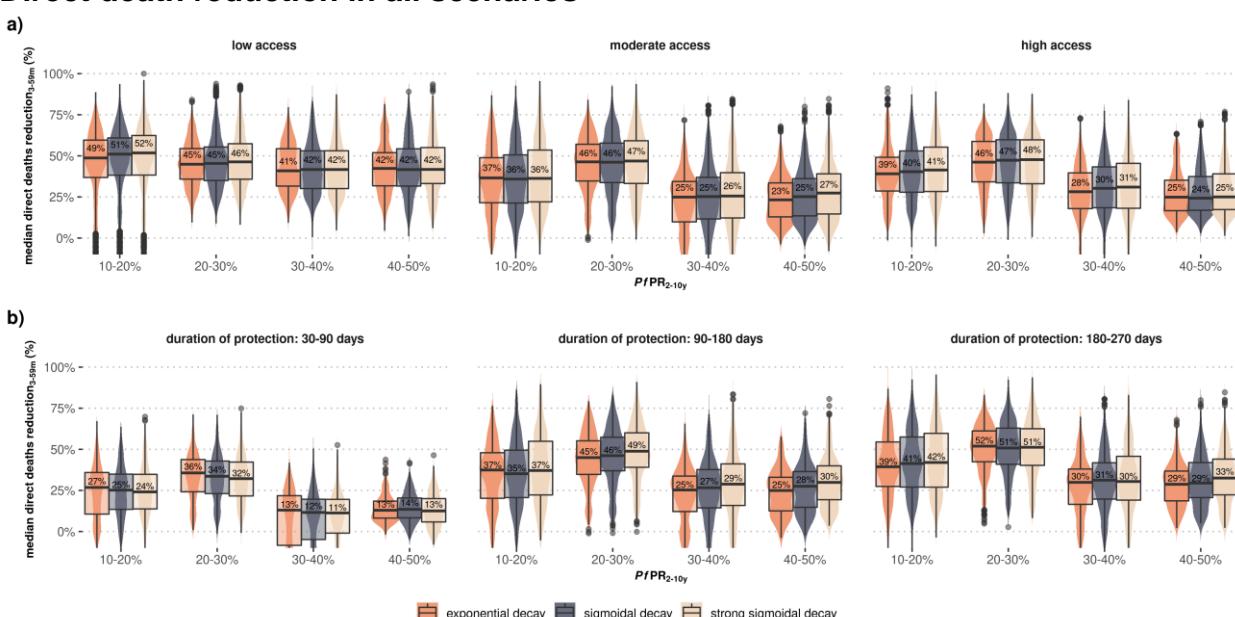


Figure A.2.2. Median direct death reduction across transmission settings and intervention durations of protection (noting these medians are over a large range of parameter uncertainty of efficacy, duration and coverage). For a range of initial efficacy 50%-100%, deployment coverage 30%-100%, durations of protection from 30 to 300 days, and intermediate deployment timing in a 4-month seasonal setting, the median and distribution of clinical incidence reduction in the intervention age group is shown using violin and box plots, **a)** across a range of baseline $PfPR_{2-10}$ and 10% (low), 25% (moderate), and 50% (high) access to first-line malaria treatment over a 14-day period and **b)** across a range of baseline $PfPR_{2-10}$ and 10% in moderate access levels stratified by durations of protection: 30-90 days, 90-180 days, and 180-270 days.

Importance of intervention properties on public health outcomes

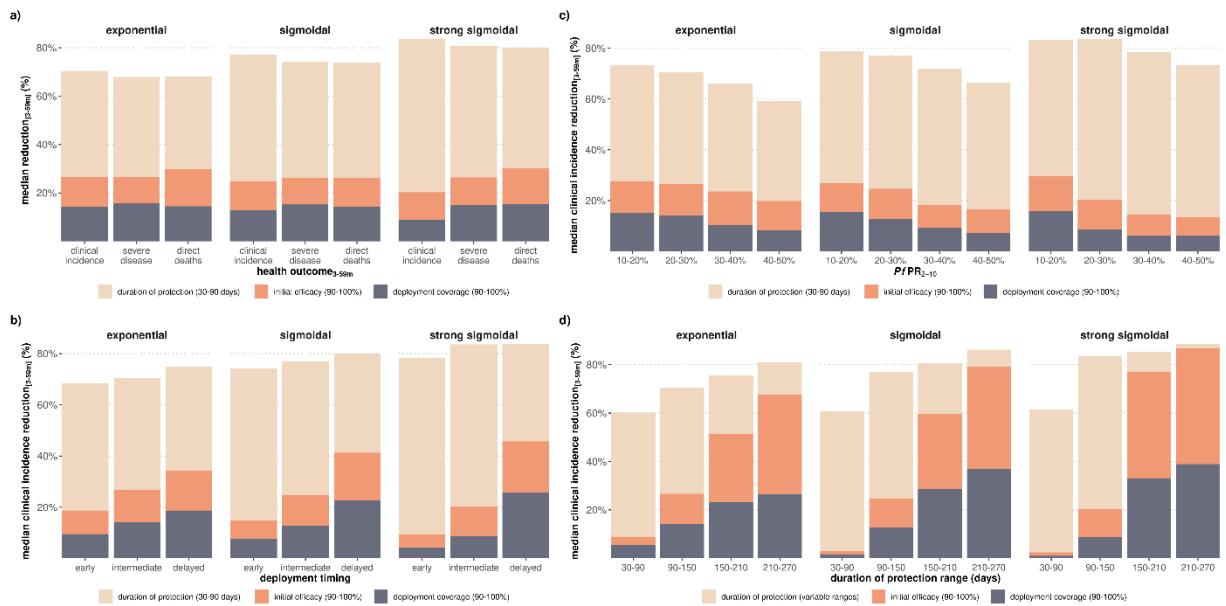


Figure A.2.3. Variance-based importance of intervention characteristics to determining health outcomes in children three to 59 months. The proportion of the bar charts represents the importance or the variance in the outcome measure explained by intervention key performance criteria: the range of initial efficacy, deployment coverage, and different ranges of duration of protection of the intervention. The relative importance is based on the Sobol method for global sensitivity analysis which was calculated for various ranges of duration of protection, 90%-100% initial efficacy ranges, and 90%-100% deployment coverage ranges in a 4-month seasonal setting with moderate access to first-line treatment and 20%-30% $PfPR_{2-10}$ unless shown otherwise. The median health outcome reduction is measured in the intervention age group 6-months post-deployment during the 5th year. The importance of intervention properties for exponential, sigmoidal, and strong sigmoidal decay profiles are shown in a-c) for duration of protection from 90-150 days, a), b), and d) for a moderate transmission settings with 20%-30% $PfPR_{2-10}$, b-d) for moderate deployment timing and clinical incidence reduction. a) For 3 outcomes: clinical incidence reduction, severe disease reduction, and direct death reduction. b) For 3 deployment timings: early, intermediate, and delayed. c) For varying baseline $PfPR_{2-10}$ prevalence in settings with 25% probability of receiving first-line treatment over a 14-day period. d) For 4 ranges of duration of protection: 30-90 days, 90-150 days, 150-210 days, 210-270 days.

Importance of intervention properties by season

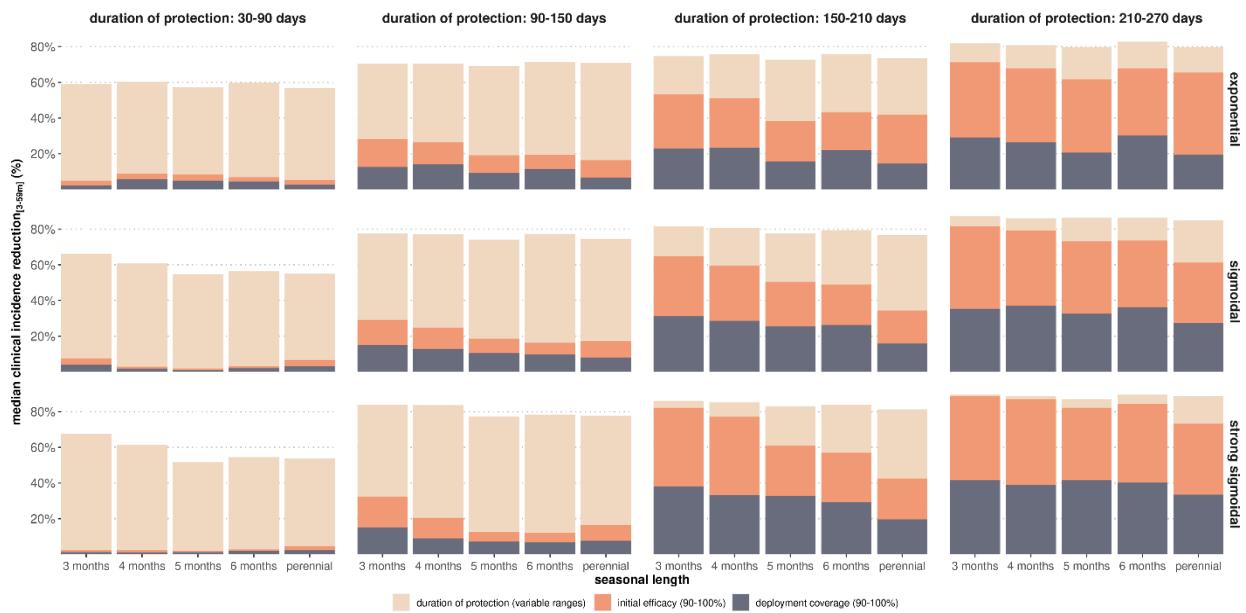


Figure A.2.4. Variance-based importance of intervention characteristics to determining clinical incidence in children three to 59 months across seasonal profiles. The proportion of the bar charts represents the importance or the variance in the outcome measure explained by intervention key performance criteria: the range of initial efficacy, deployment coverage, and different ranges of duration of protection of the intervention. The relative importance is based on the Sobol method for global sensitivity analysis was calculated for various ranges of duration of protection, 90%-100% initial efficacy ranges, and 90-100% deployment coverage ranges. The median health outcome reduction is measured in the intervention age group 6-months post-deployment during the 5th year. The importance of intervention properties for exponential, sigmoidal, and strong sigmoidal decay profiles are shown for a moderate transmission settings with 20-30% $PfPR_{2-10}$, and intermediate deployment timing for the following durations of protection: 30-90 days, 90-150 days, 150-210 days, 210-270 days.

90-150 days, 150-210 days, 210-270 days; and 5 seasonal settings: 3-month, 4-month, 5-month, 6-month and 9-month perennial setting.

Importance of intervention properties by deployment timing

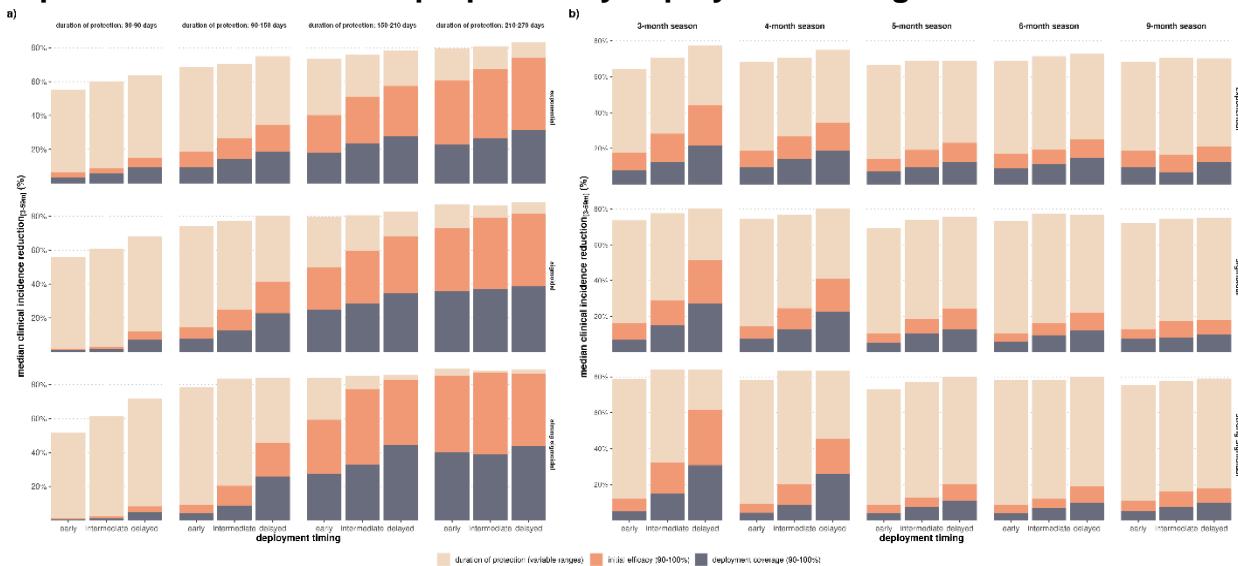


Figure A.2.5. Variance-based importance of intervention characteristics to determining clinical incidence in children three to 59 months old across different deployment timings and seasonal profiles. The proportion of the bar charts represents the importance or the variance in the outcome measure explained by intervention key performance criteria: the range of initial efficacy, deployment coverage, and different ranges of duration of protection of the intervention. The relative importance is based on the Sobol method for global sensitivity analysis was calculated for various ranges of duration of protection, 90%-100% initial efficacy ranges, and 90-100% deployment coverage ranges. The median health outcome reduction is measured in the intervention age group 6-months post-deployment during the 5th year. The importance of intervention properties for exponential, sigmoidal, and strong sigmoidal decay profiles are shown for a moderate transmission settings with 20%-30% *PfPR*₂₋₁₀ for early, intermediate and delayed deployment for the following durations of protection: 30-90 days, 90-150 days, 150-210 days, 210-270 days; and 4 seasonal settings: 3-month, 4-month, 5-month, 6-month and perennial setting for 30-90 days of protective duration.

Minimum initial efficacy and duration of protection by season and decay profile

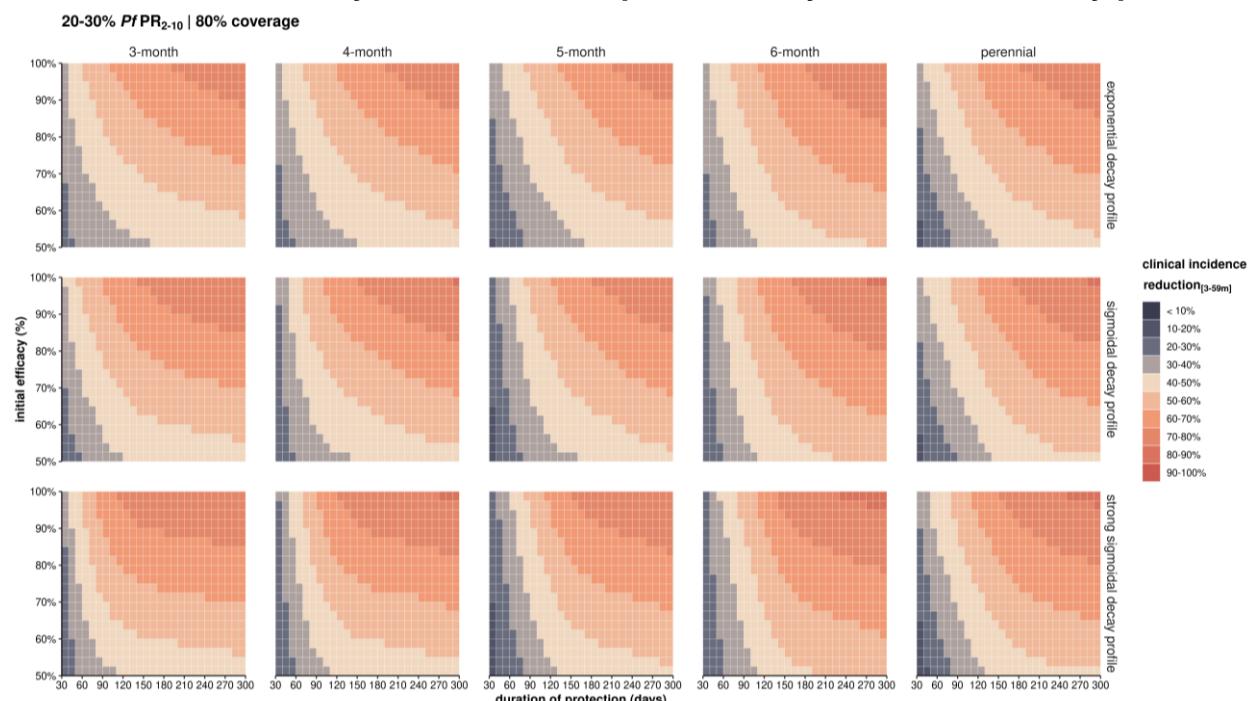


Figure A.2.6. Minimum intervention performance criteria to achieve clinical incidence reduction targets across seasons. In a setting with a baseline prevalence of 20-30% *PfPR*₂₋₁₀ and 80% deployment coverage for different decay profiles (exponential, sigmoidal, strong sigmoidal), we show model predicted initial efficacy (%) and duration of

protection (days) required to achieve clinical incidence reduction in children three to 59 months old during a 6-month follow-up period during the 5th year for different seasonal settings.

Minimum initial efficacy and duration of protection by coverage and decay profile

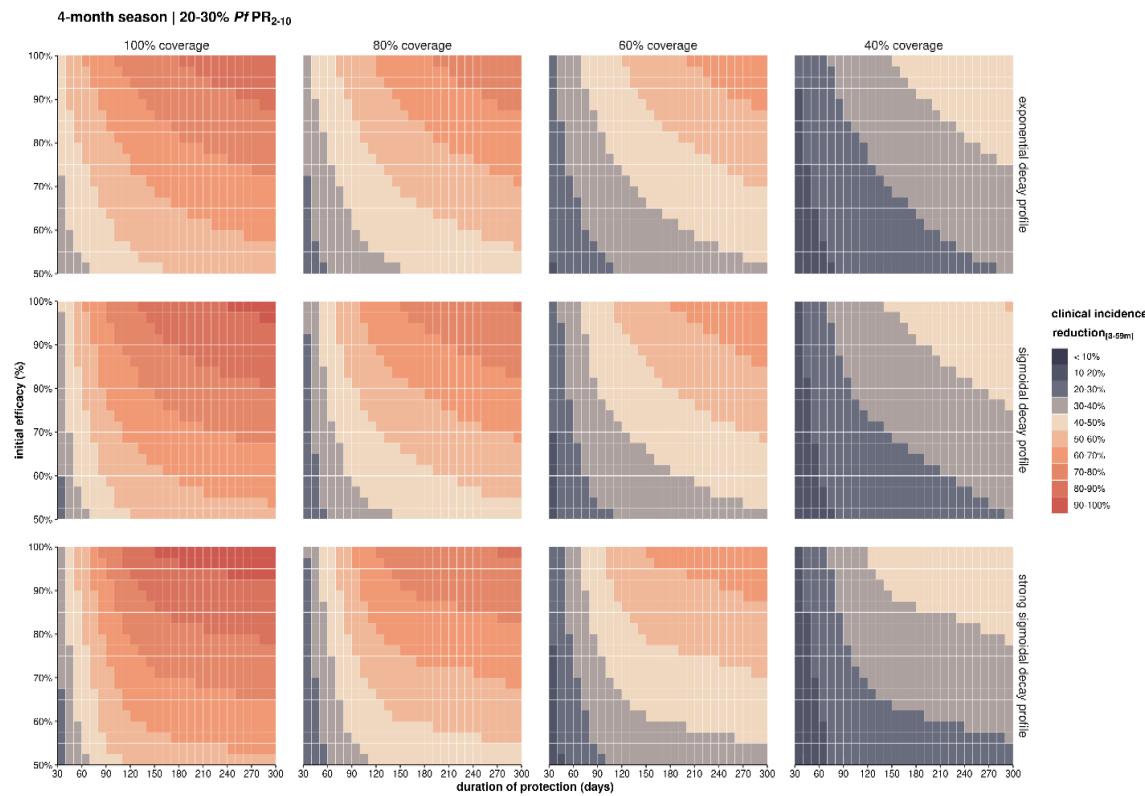


Figure A.2.7. Minimum intervention performance criteria to achieve clinical incidence reduction targets across deployment coverage levels. In a 4-month seasonal setting with a baseline prevalence of 20-30% $PfPR_{2-10}$ for different decay profiles (exponential, sigmoidal, strong sigmoidal), we show model predicted initial efficacy (%) and duration of protection (days) required to achieve clinical incidence reduction in children three to 59 months old during a 6-month follow-up period during the 5th year for different seasonal settings for four deployment coverage levels: 100%, 80%, 60%, 40%.

Minimum initial efficacy and duration of protection by prevalence and decay profile

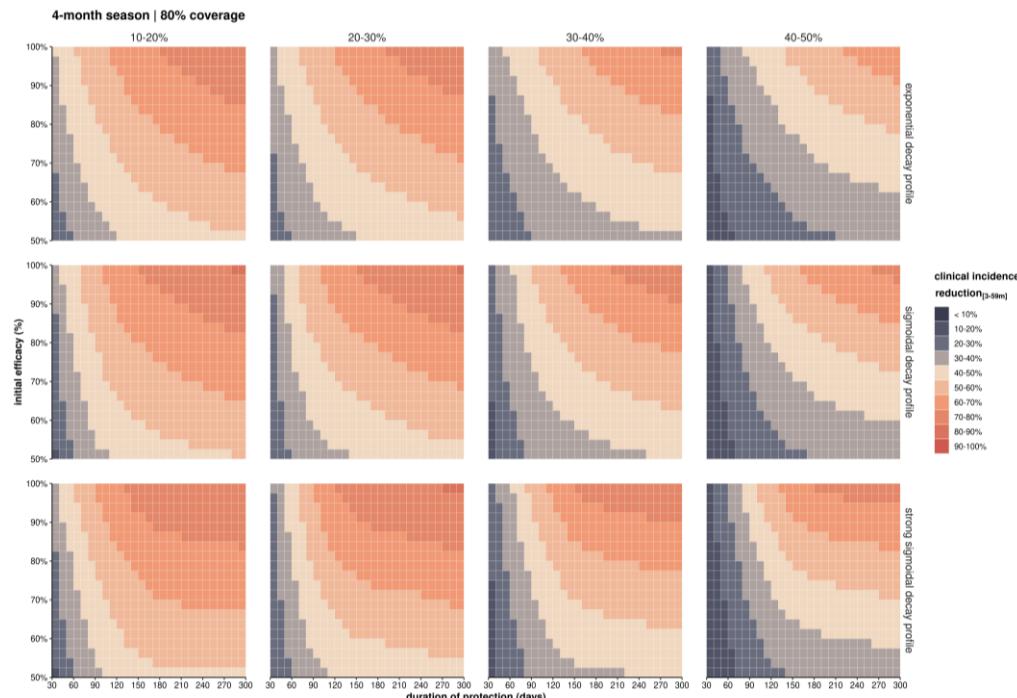


Figure A.2.8. Minimum intervention performance criteria to achieve clinical incidence reduction targets across $PfPR_{2-10}$ prevalence levels. In a 4-month seasonal setting and 80% deployment coverage for different decay profiles (exponential, sigmoidal, strong sigmoidal), we show model predicted initial efficacy (%) and duration of protection (days)

required to achieve clinical incidence reduction in children three to 59 months old during a 6-month follow-up period during the 5th year for different baseline prevalence $PfPR_{2-10}$: 10-20%, 20-30%, 30-40%, 40-50%.

Minimum initial efficacy and duration of protection by prevalence and decay profile

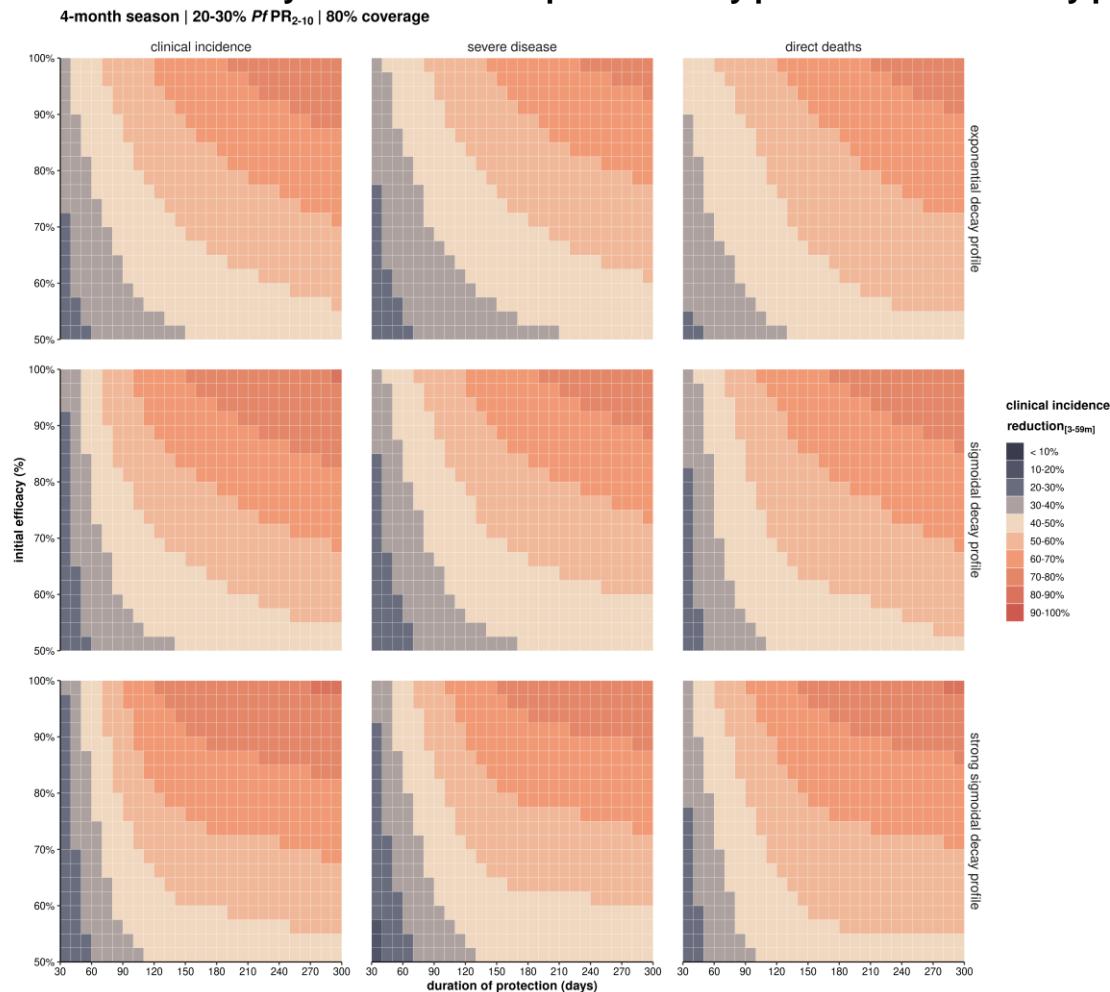


Figure A.2.9. Minimum intervention performance criteria to achieve different health outcome reduction targets.

In a 4-month seasonal setting with 20-30% $PfPR_{2-10}$ and 80% deployment coverage for different decay profiles (exponential, sigmoidal, strong sigmoidal), we show model predicted initial efficacy (%) and duration of protection (days) required to achieve different health outcome reductions in children three to 59 months old during a 6-month follow-up period during the 5th year for: clinical incidence, severe disease, and direct death mortality.

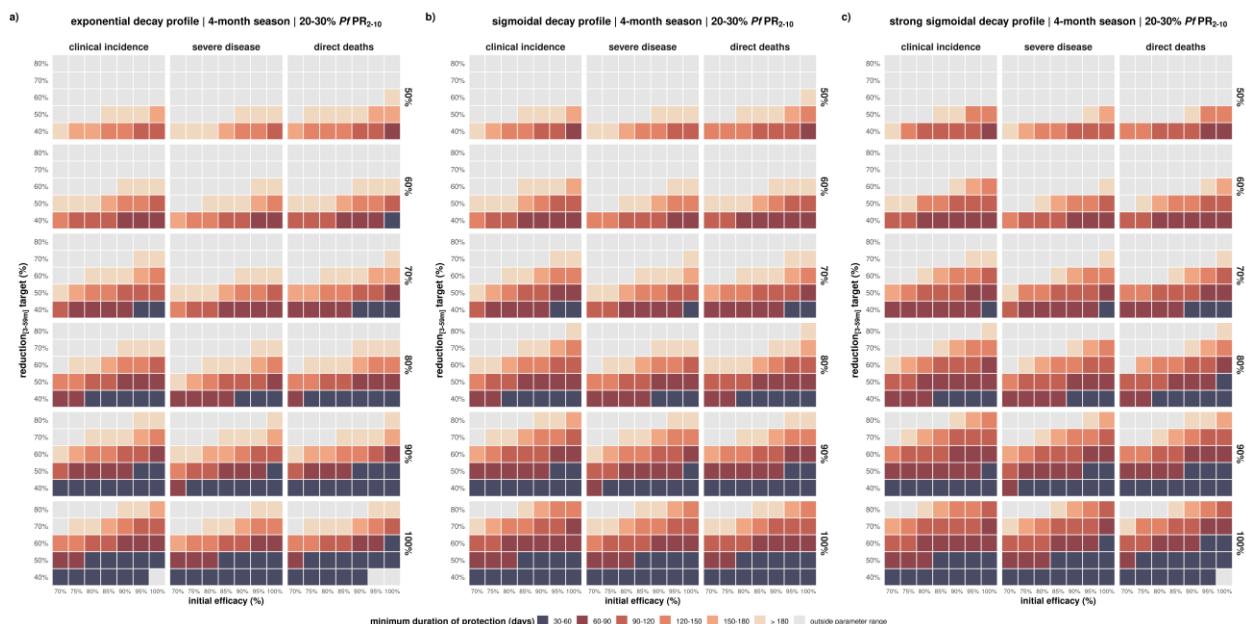


Figure A.2.10. Minimum duration of protection by initial efficacy and deployment coverage for health outcome reduction targets in children three to 59 months old in seasonal settings. All results shown are for seasonal

intervention exponential, sigmoidal and strong sigmoidal decay profiles deployed in scenarios with a baseline $PfPR_{[2-10]}$ of 20-30% with moderate (25%) first-line access for intermediate in a 4-month season by deployment coverage (rows) for **a**) clinical incidence **b)** severe disease and **c)** direct deaths.

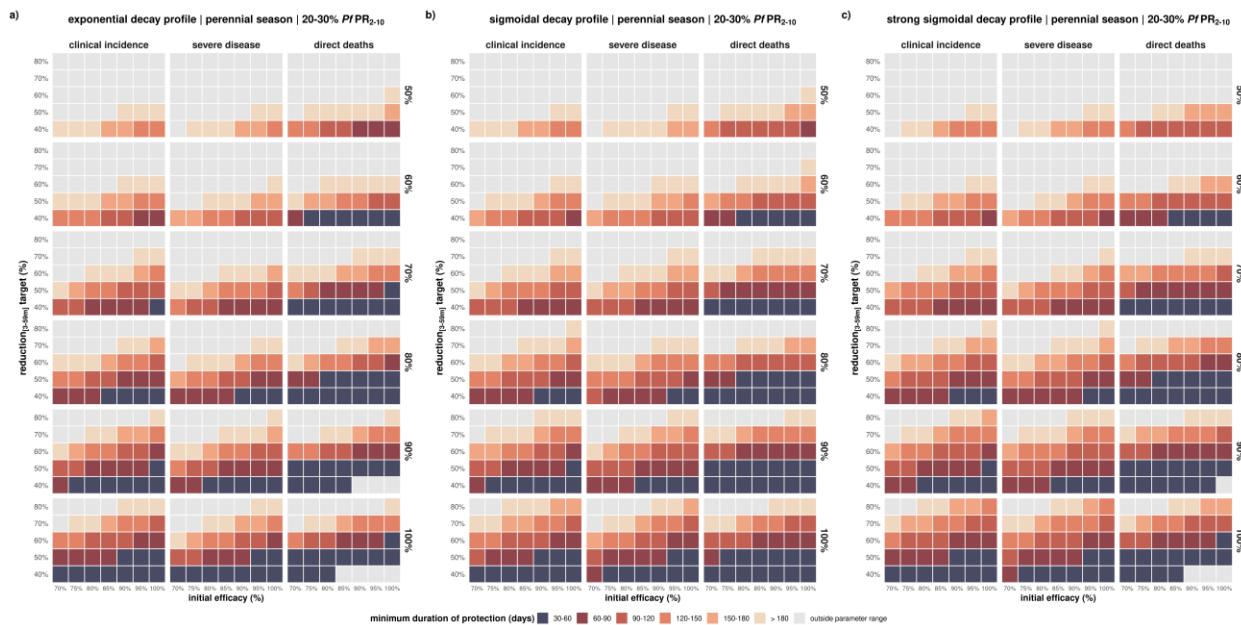


Figure A.2.11. Minimum duration of protection by initial efficacy and deployment coverage for health outcome reduction targets in children three to 59 months old in perennial settings. All results show are for seasonal intervention exponential, sigmoidal and strong sigmoidal decay profiles deployed in scenarios with a baseline $PfPR_{[2-10]}$ of 20-30% with moderate (25%) first-line access for intermediate in a perennial season by deployment coverage (rows) for **a**) clinical incidence **b)** severe disease and **c)** direct deaths.

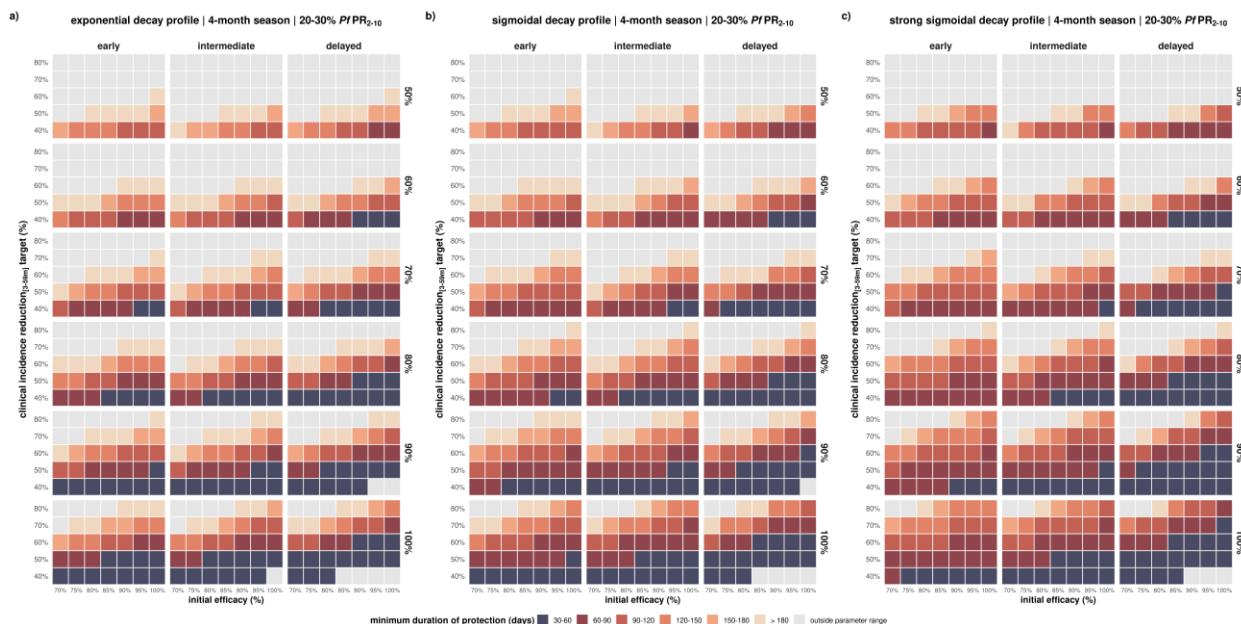


Figure A.2.12. Minimum duration of protection by initial efficacy and deployment coverage for clinical incidence reduction targets in children three to 59 months old in seasonal settings by deployment timing. All results show are for seasonal intervention exponential, sigmoidal and strong sigmoidal decay profiles deployed in scenarios with a 4-month seasonal setting and a baseline $PfPR_{[2-10]}$ of 20-30% with moderate (25%) first-line access by deployment coverage (rows) for **a)** early deployment **b)** intermediate deployment and **c)** delayed deployment timing in relation to the start of the transmission season and high transmission peak.

A.3 Coverage supplementary figures

Minimum deployment coverage and duration of protection by decay profile

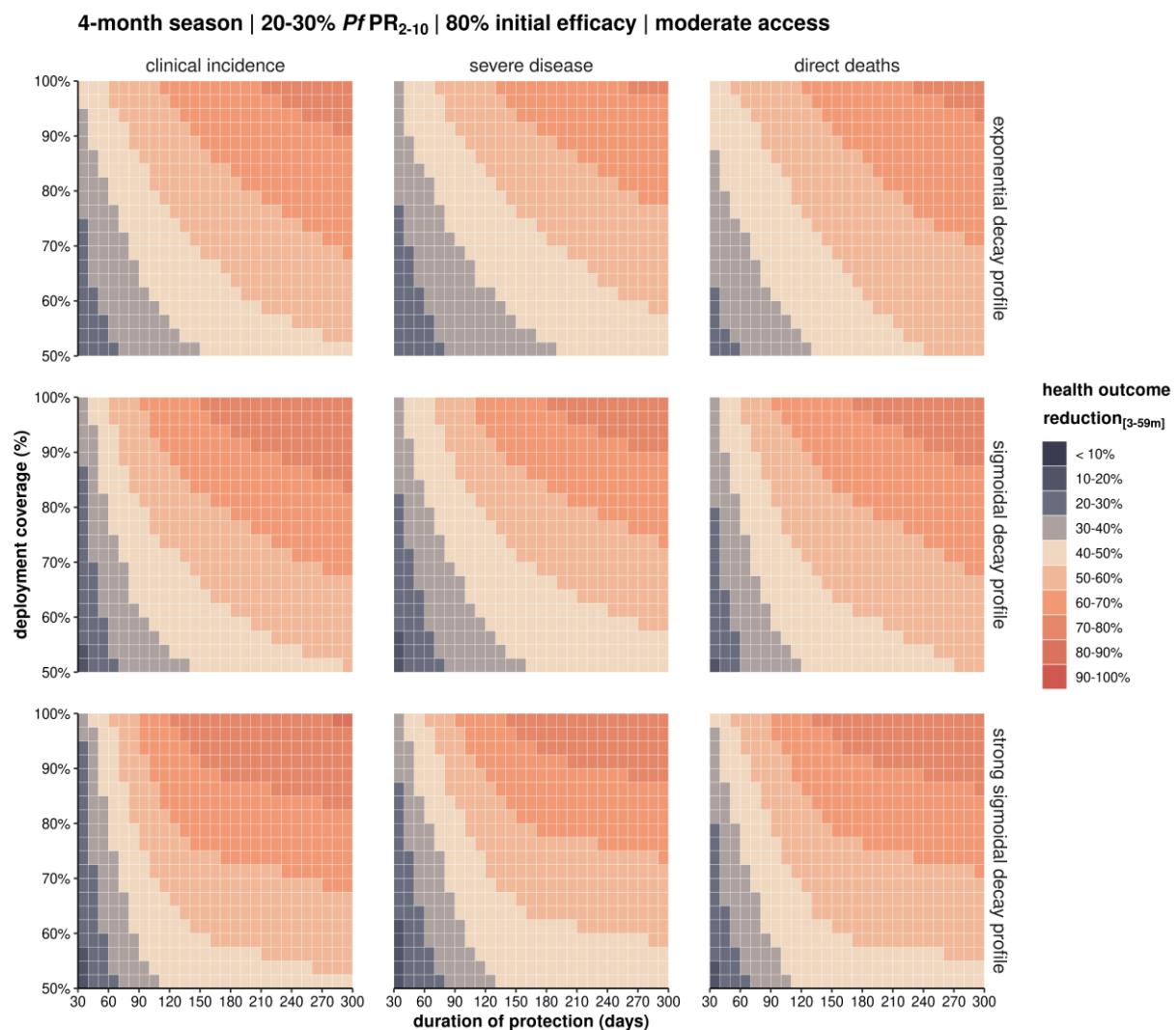


Figure A.3.1. Minimum intervention performance criteria to achieve clinical incidence reduction targets in implementation settings with moderate access. In a 4-month seasonal setting with a baseline prevalence of 20-30% $PfPR_{2-10}$, 80% initial efficacy of a single round at intermediate deployment timing example. For different decay profiles (exponential, sigmoidal, strong sigmoidal), we show model predicted deployment coverage (%) and duration of protection (days) required to achieve clinical incidence, severe disease, and direct death reduction in children three to 59 months old during a 6-month follow-up period during the 5th year of rollout.

A.4 Public health impact supplementary figures

Median health outcome reductions for all scenarios by seasonal length

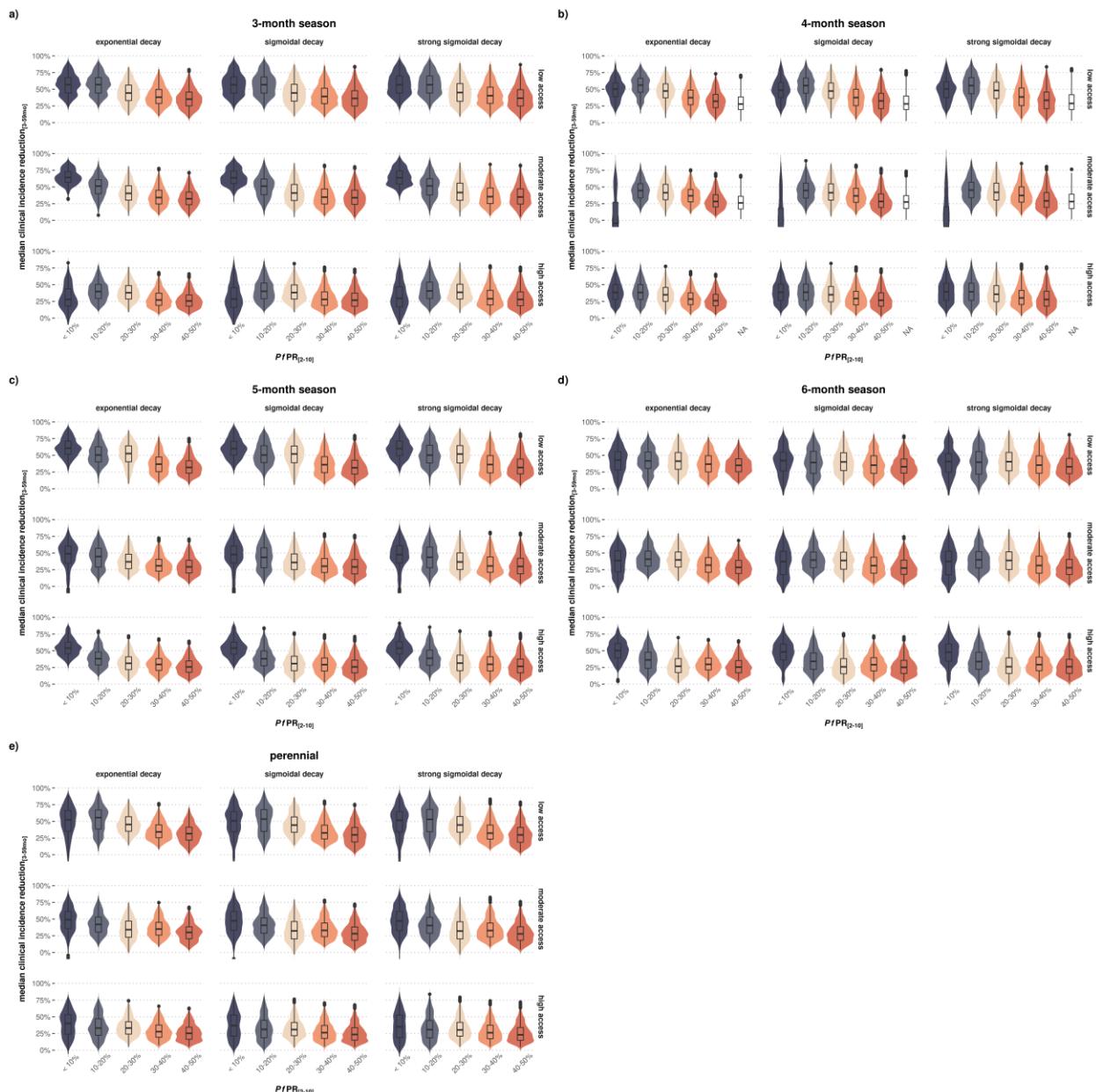


Figure A.4.1. Median clinical incidence reduction in children three to 59 months across all scenarios by seasonal setting. The median and distribution of clinical incidence reduction are shown using violin and box plots for all scenarios (aggregated duration 30-300 days, initial efficacy 50-100%, deployment coverage 30-100%). These values were estimated from model outputs during a 6-month period following the single round of seasonal interventions during the 5th year of deployment in children three to 59 months old. This example represents a setting with intermediate deployment timing and 25% (moderate) access to first-line malaria treatment over a 14-day period for different baseline $PfPR_{2-10}$ and seasonal lengths: 3-month, 4-month, 5-month, 6-month, and perennial.

Median health outcome reductions for all scenarios by rollout year

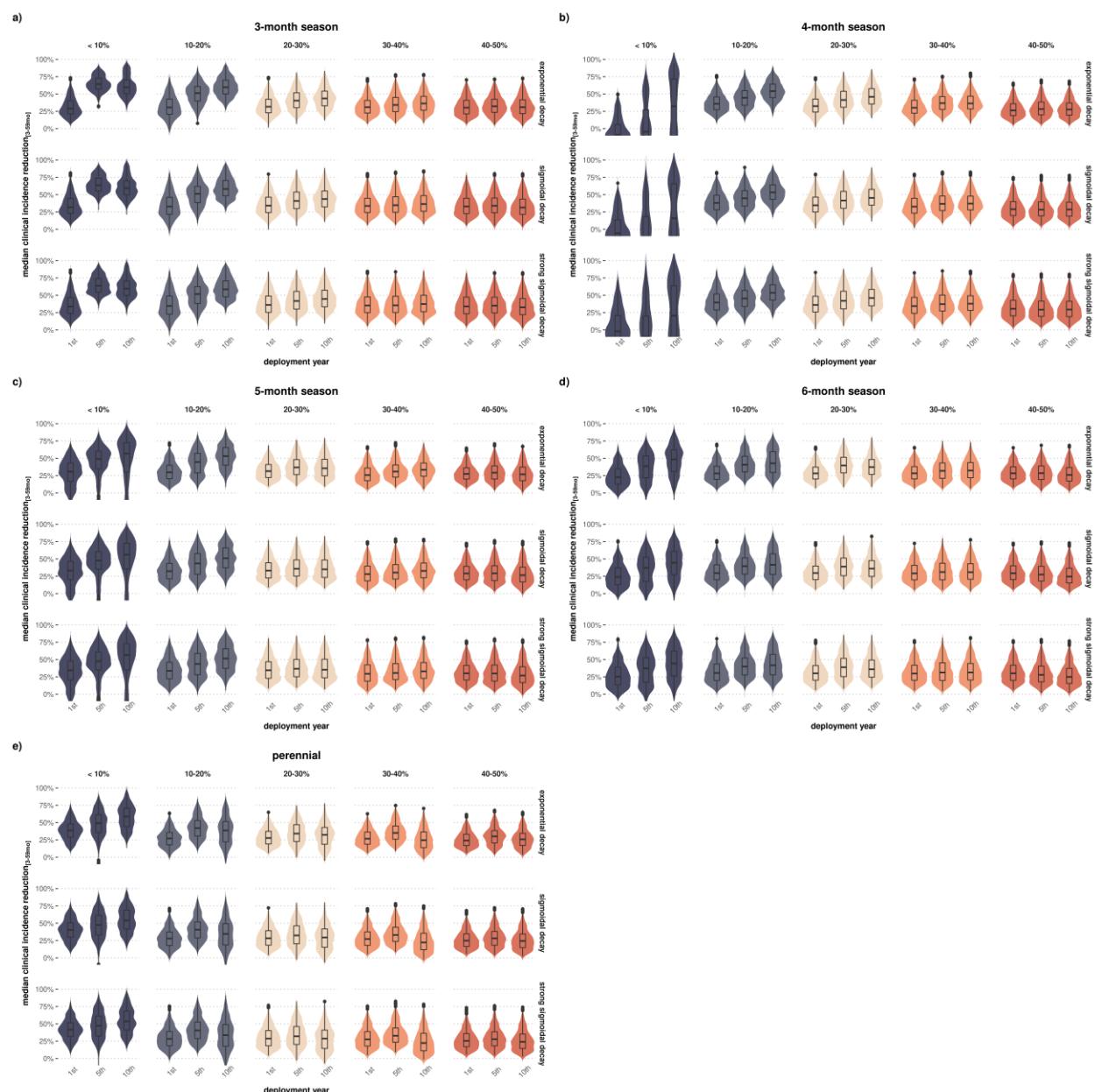


Figure A.4.2. Median clinical incidence reduction in children three to 59 months across all scenarios by seasonal setting for 1st, 5th and 10th year of rollout. The median and distribution of clinical incidence reduction are shown using violin and box plots for all scenarios (aggregated duration 30-300 days, initial efficacy 50-100%, deployment coverage 30-100%). These values were estimated from model outputs during a 6-month period following the single round of seasonal interventions during the 1st, 5th or 10th year of deployment in children three to 59 months old. This example represents a setting with intermediate deployment timing and 25% (moderate) access to first-line malaria treatment over a 14-day period for different baseline *PfPR*₂₋₁₀ and seasonal lengths: 3-month, 4-month, 5-month, 6-month, and perennial.

Median health outcome reductions for all scenarios by follow-up period

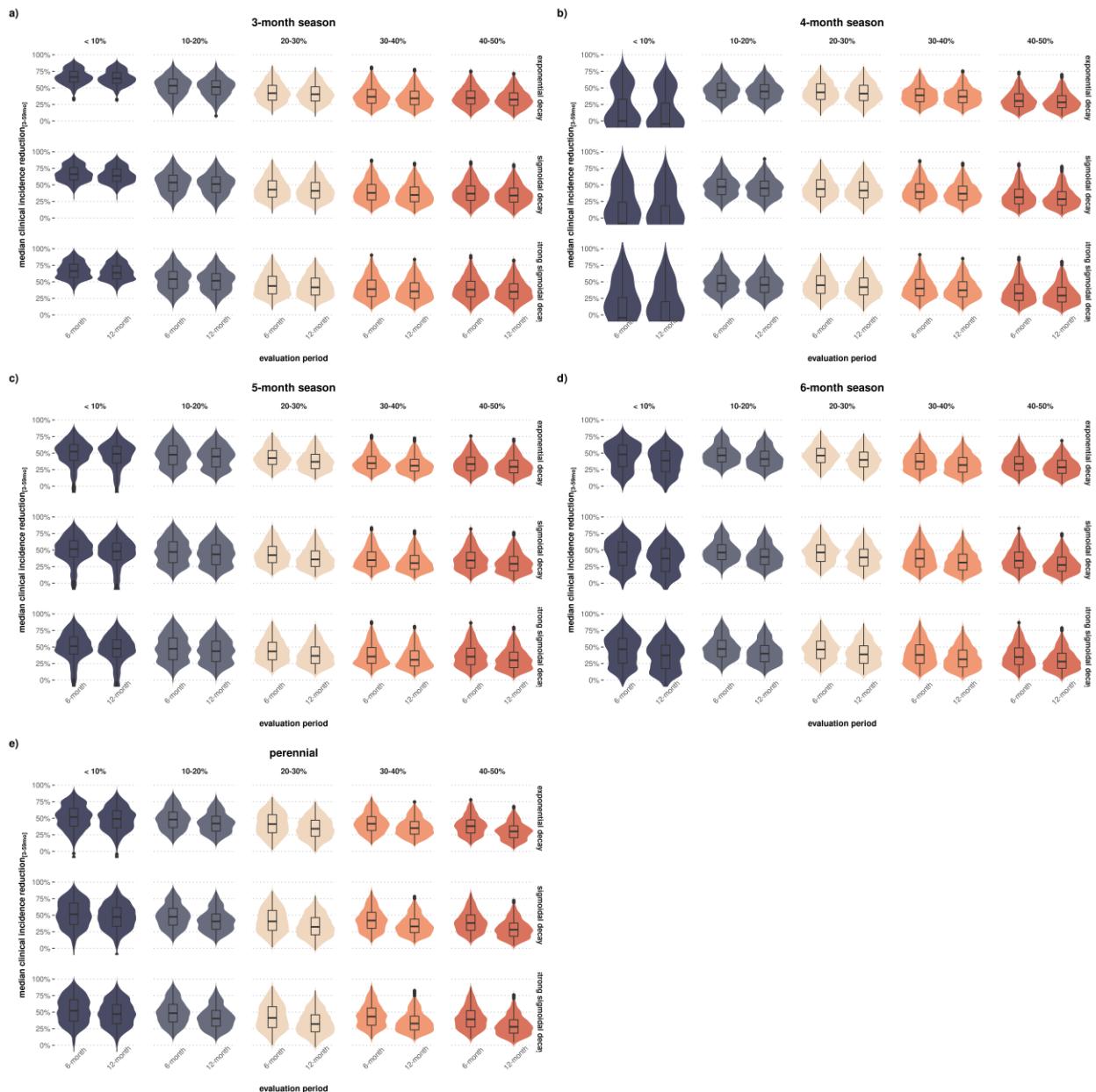


Figure A.4.3. Median clinical incidence reduction in children three to 59 months across all scenarios by seasonal setting 6 and 12-month follow-up period. The median and distribution of clinical incidence reduction are shown using violin and box plots for all scenarios (aggregated duration 30-300 days, initial efficacy 50-100%, deployment coverage 30-100%). These values were estimated from model outputs during a 6-month or 12-month period following the single round of seasonal interventions during the 5th year of deployment in children three to 59 months old. This example represents a setting with intermediate deployment timing and 25% (moderate) access to first-line malaria treatment over a 14-day period for different baseline *PfPR*₂₋₁₀ and seasonal lengths: 3-month, 4-month, 5-month, 6-month, and perennial.

Median health outcome reductions for all scenarios by age group

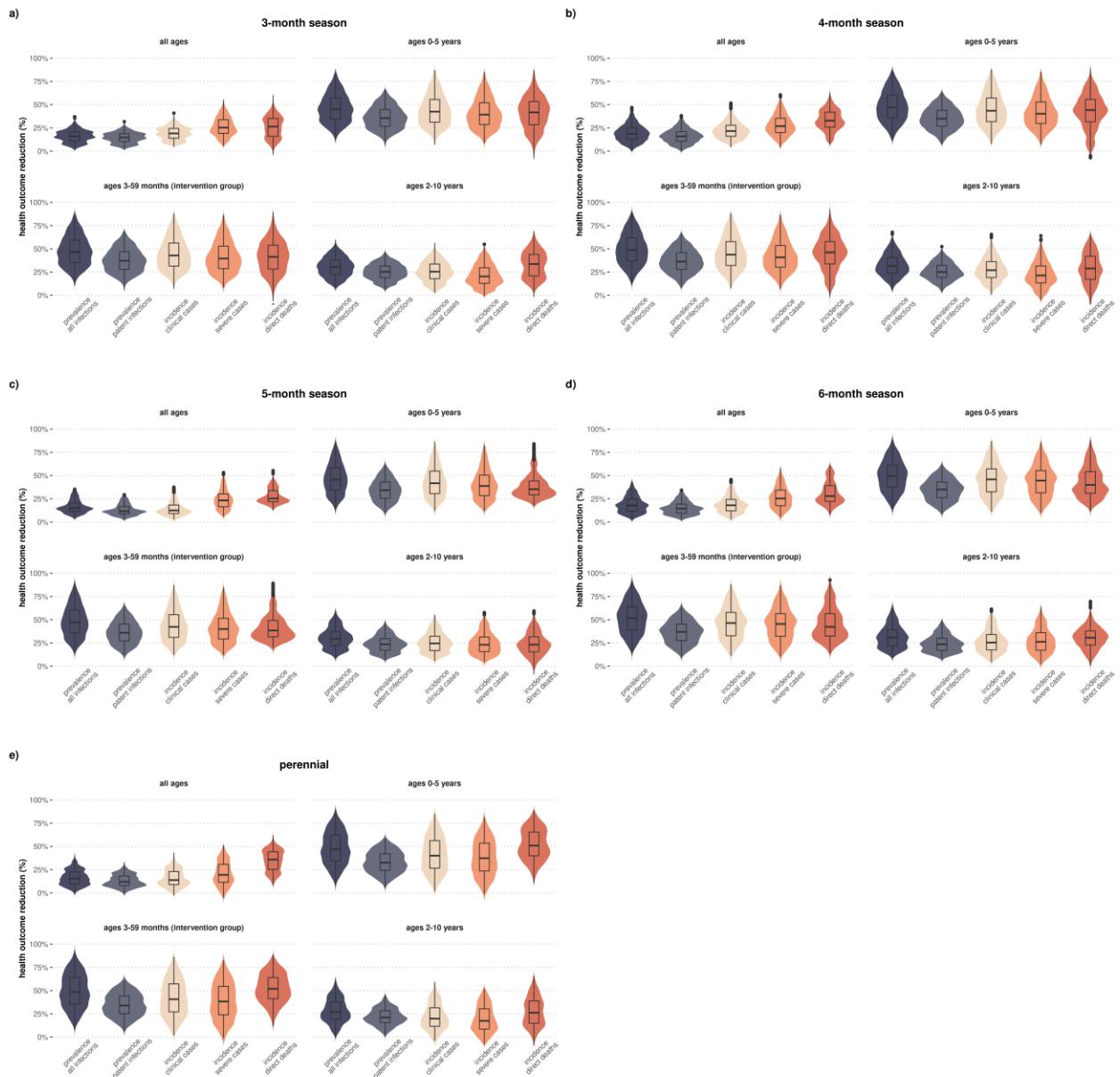


Figure A.4.4. Median health outcome reduction for sigmoidal mAb or LAI decay profile (delivered with blood stage clearance drug) across all scenarios for different age groups. The median and distribution of prevalence of all infections, prevalence of patent infections, clinical incidence, severe disease and direct deaths reduction are shown using violin and box plots for all scenarios (aggregated duration 30-300 days, initial efficacy 50-100%, deployment coverage 30-100%). These values were estimated from model outputs during a 6-month period following the single round of seasonal interventions during the 5th year of deployment in children three to 59 months old. This example represents a setting with intermediate deployment timing and 25% (moderate) access to first-line malaria treatment over a 14-day period for different baseline $PfPR_{2-10}$ and seasonal lengths: 3-month, 4-month, 5-month, 6-month, and perennial.