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Maximizing Impact: Can Interventions to Prevent Clinical Malaria Reduce Parasite Transmission?

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Abstract

Malaria interventions may reduce the burden of clinical malaria disease, the transmission of malaria parasites, or both. As malaria interventions are developed and evaluated, including those interventions primarily targeted at reducing disease, they may also impact parasite transmission. Achieving global malaria eradication will require optimizing the transmission-reducing potential of all available interventions. Herein, we discuss the relationship between malaria parasite transmission and disease, including mechanisms by which disease-targeting interventions might also impact parasite transmission. We then focus on three malaria interventions with strong evidence for reducing the burden of clinical malaria disease and examine their potential for also reducing malaria parasite transmission.

Keywords

Plasmodium falciparum; Seasonal malaria chemoprevention; School-based preventive treatment; RTS,S/AS01 vaccine

The Relationship Between Malaria Parasite Transmission and Disease

The incidence of malaria decreased dramatically between 2000 and 2014 [1]. During this same period, there was a shift in global policy to move beyond malaria **control** (see Glossary) and aim for regional **elimination** followed by global **eradication** [2]. More recently, progress has stalled, and the global burden of malaria remains high with an estimated 228 million cases of malaria occurring in 2018 [1]. For many regions with high malaria parasite **transmission** intensity, coordinated implementation of multiple malaria interventions will be required to incrementally reduce transmission and move toward elimination [3,4]. Malaria interventions are typically evaluated primarily on their impact on

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clinical malaria disease and mortality. However, the impact of interventions on parasite transmission may be the key component in determining how to overcome the current barriers in our effort to decrease the burden of malaria in the hardest hit areas.

The presence of blood-stage parasites in the human host is classified as malaria **infection**. In some, but not all cases, the malaria infection causes illness in the host, resulting in clinical malaria disease. The factors that contribute to infection causing disease are complex and beyond the scope of this review, but include host immunity, parasite density and parasite surface protein diversity. The proportion of infections that cause disease, versus those that remain asymptomatic, varies according to host and parasite factors [5]; in settings with moderate to high transmission intensity, this proportion generally decreases with age as immunity to the parasite builds up over time with repeated exposure [6]. In all settings, it has become clear that asymptomatic infections are more common than previously thought, as revealed by molecular diagnostic tools, which are more sensitive than light microscopy for parasite detection [7].

Quantifying the extent to which infections contribute to the **infectious reservoir** depends on several factors that modulate successful transmission [8]. Malaria infections are only transmissible from humans to mosquitoes when mature **gametocytes** are present [9]. *Plasmodium falciparum* takes about 8 to 10 days to complete five stages of gametocyte development, and only the mature stage V gametocytes are present in blood circulation [9,10]. The density of female *P. falciparum* gametocytes in the infected human is a key factor in determining the likelihood of successful transmission for any one mosquito bite [11], although male gametocytes are also obligatory for zygote formation in the mosquito midgut. Importantly, gametocytes may not be homogeneously distributed among infected hosts. For example, in settings with high transmission intensity, children are more likely than adults to carry gametocytes during asymptomatic *P. falciparum* infections [12,13]. The relationship between symptoms and gametocytemia in *P. falciparum* infections is complex and depends in part on the time since the initial infection, because *P. falciparum* gametocytes take about 8–10 days to reach maturity [9,14]. While individuals with fever are less likely to have microscopically detectable *P. falciparum* gametocytes than those without fever at the time of sampling [15], the majority of both symptomatic and asymptomatic infections likely include mature gametocytes that are detectable by, at least, molecular diagnostic methods [16]. Additionally, the duration of time that gametocytes are present is essential for quantifying transmission potential because a longer duration increases the opportunities for mosquito bites [5]. The duration of an asymptomatic infection remains difficult to quantify, but likely ranges from a few weeks [17] to many months [18,19] and depends on factors such as the level of host immunity. Symptomatic infections are truncated by effective treatment, although the extent to which this occurs depends on the likelihood of treatment-seeking behavior, access to effective drugs, and the effect of the drugs on gametocytes. Finally, the number of competent vector mosquitoes that bite an infectious person is critical for quantifying their contribution to parasite transmission [20], while transmission to another human host depends on factors such as parasite development to the **sporozoite** stage, the number of sporozoites produced, mosquito survival, and the mosquito biting another human host [21,22].

Measuring Malaria Parasite Transmission

Due to the high burden of malaria remaining in many countries, interventions that can reduce the incidence of disease are still a fundamental component of the fight against malaria. However, the potential for these interventions to impact parasite transmission should not be overlooked, because any reduction of transmission would be an additional public health benefit in the form of reduced infection (and potentially disease) in individuals not covered by the intervention directly. Insecticide-treated bed nets provide one example of such a case: originally targeted for children under five years of age and pregnant women to prevent infections (and therefore prevent disease) in these vulnerable groups, policy later shifted to target universal coverage because of the clear impact of insecticide-treated bed nets on parasite transmission [23,24]. Therefore, it is important to measure the potential impact of disease-targeting malaria interventions on transmission.

The extent to which a disease-targeting malaria intervention reduces transmission will depend on the contribution of the targeted population to the infectious reservoir (Figure 1). A number of studies over the last decade have shed light on the relative contribution of different age groups to the infectious reservoir, based on the prevalence of infection in the population, the relative infectiousness and duration of those infections, and the frequency of bites by malaria vectors [13,19,20,25,26]. Interventions targeted at reducing clinical malaria disease in high-burden age groups may also reduce parasite transmission by decreasing the number of infections that develop gametocytes, decreasing the density or duration of gametocytemia, or reducing exposure to mosquito bites. Nevertheless, evaluations of recently developed disease-targeting interventions have placed limited emphasis on measuring potential changes in parasite transmission.

Outcomes for estimating malaria transmission or transmission potential include the **entomological inoculation rate**, the incidence of new infections in people, and measuring the prevalence of gametocytes in people [27]. Changes in these outcomes can indicate the degree to which an intervention impacts malaria parasite transmission. Alternatively, when assessing an intervention targeted to a particular group, a reduction in infections (either symptomatic or asymptomatic) in a non-target group following implementation of the intervention provides a strong indication of transmission reduction. In the field, a number of challenges exist for the accurate and precise measurement of outcomes related to transmission: e.g. selection bias and measurement error may affect the accuracy of the outcomes; larger sample sizes are generally required to maintain the same precision as transmission intensity decreases; and the most appropriate outcome likely depends on the intervention being evaluated [27]. Below, we highlight three malaria interventions with strong evidence for reducing the burden of clinical malaria disease and examine their potential for also reducing malaria parasite transmission.

Seasonal Malaria Chemoprevention

Across the Sahel region of Africa, most morbidity and mortality from malaria occurs during the relatively short rainy season [28]. Seasonal malaria chemoprevention (SMC), the monthly administration of antimalarial drugs during the rainy season, reduces illness and

death from malaria in infants and young children [29]. The current SMC regimen recommended by the World Health Organization is sulfadoxine-pyrimethamine plus amodiaquine given at monthly intervals to children aged 3–59 months, beginning at the start of the transmission season up to a maximum of four doses during the transmission season [29].

Several randomized clinical trials of SMC conducted in areas of West Africa with highly seasonal transmission of *P. falciparum* showed substantial impact on the burden of disease in children under six years of age [30], with further supportive evidence reported by studies evaluating SMC implemented through the routine health system [31,32]. A systematic review of randomized trials found that SMC prevented approximately three quarters of all clinical malaria disease episodes and three quarters of **severe malaria** episodes in children under six years of age during the transmission season [30]. In addition to the clear impact on disease, SMC also reduced the prevalence of infection by about two thirds in children under six years of age [30]. In recent years, countries in the Sahel have experimented with expanding SMC to ten years of age and shown similar reductions in the incidence of malaria cases and severe malaria as well as the prevalence of infection, in both clinical trials and implementation studies [31–34]. Other modifications that have been tested include the use of an additional, fifth dose [34].

The ability of SMC to decrease *P. falciparum* infection raises the question of whether SMC also has an impact on parasite transmission in the overall community. The age group that currently receives SMC, i.e. children under five years of age, is less likely to carry gametocytes and more likely to develop symptoms than older age groups, and thus SMC in children under five years of age seems unlikely to have a significant impact on transmission. However, expanding SMC to older children may have a greater impact on the infectious reservoir because children ages 6–10 are less likely to become symptomatic and seek treatment while still having among the highest rates of gametocytemia among all age groups [8]. Only one study has empirically estimated the indirect effects of SMC: Cisse *et al.* [33] measured the incidence of clinical malaria disease in age groups that were not treated during a cluster-randomized trial. When SMC was administered to children up to ten years of age at 82–96% coverage, the incidence of clinical malaria disease in individuals over ten years of age was reduced by 26%, suggesting an impact on parasite transmission in this setting [33]. Following this study, Senegal has expanded SMC to include children up to 10 years old [35]. The only modeling study to consider the effect of SMC on parasite transmission assumed very high transmission intensity, no vector control interventions, and 50% coverage of SMC with dihydroartemisinin-piperaquine in children up to ten years of age [36]. The results indicated that SMC prevented relatively few cases of clinical malaria disease in age groups not treated by SMC under the assumed conditions [36]. Thus, additional studies are needed to quantify variation in the effect of SMC on parasite transmission according to site-specific factors such as the coverage of other malaria interventions and the pre-SMC transmission intensity. Further refinement of SMC design, including age of intervention group, choice of drug, frequency and coverage targets may maximize the impact of the program on parasite transmission.

School-Based Preventive Treatment

While malaria-related mortality rates are highest in children under five years of age, malaria still causes significant morbidity in school-age children [37]. In many settings the prevalence of *P. falciparum* infection is higher in school-age children than both younger children and adults. School-based preventive treatment may be a feasible intervention to ameliorate the burden of malaria in this age group. Multiple clinical trials have evaluated school-based preventive treatment, in which all participants were treated regardless of their infection status [38–47]. The drug used for treatment and the frequency of the intervention differed among trials, but the target population was generally children aged 6–15 years old. Among the five trials that measured clinical malaria disease as an outcome, a recent meta-analysis revealed a 50% reduction in disease following school-based preventive treatment [48]. These findings suggest the potential for school-based preventive treatment to reduce disease burden if added to the existing set of malaria control tools.

A meta-analysis including all eleven trials cited above showed a 54% reduction in subsequent *P. falciparum* prevalence [48]. As with SMC, predicting how this reduction in infection may translate to reduction in transmission remains complicated and depends on the transmission setting. In many transmission settings, school-age children likely contribute disproportionately to malaria transmission because this age group has developed disease-reducing immunity, but are not yet able to control parasite density [8]. Compared to younger children, they experience less overt clinical malaria disease and thus have infections that go untreated. Compared to adults, they have higher density infections including higher densities of gametocytes. Additionally, in many settings school-age children are less likely to use malaria prevention methods like insecticide-treated bed nets [49,50], leaving them more likely to be bitten by malaria vectors and thus perpetuating transmission.

Though limited, the available data support the hypothesis that treatment interventions targeting school-age children may reduce parasite transmission in the overall community. In a cluster randomized controlled trial in Uganda, school-based preventive treatment reduced *P. falciparum* infection in other age groups and decreased entomological inoculation rates in the communities surrounding intervention schools [47]. This is further supported by two studies showing that school-based preventive treatment reduced gametocyte prevalence in school-age children [40,44].

No modeling studies have assessed the effect of school-based preventive treatment on parasite transmission. One modeling study [51] has assessed the impact of a similar intervention on transmission: screening school children for infection using rapid diagnostic tests and then treating those with infection (screen-and-treat). According to the results of that study, this intervention was estimated to reduce the prevalence of infection in the overall population by 22% in western Kenya when delivered twice per school-term with 80% coverage [51]. The impact of adding this more limited school-based intervention to the current coverage of insecticide-treated bed nets (56%) and indoor residual spraying (70%) was similar to increasing the coverage of insecticide-treated bed nets and indoor residual spraying to 80% and 90%, respectively [51]. School-based preventive treatment may be more effective than a screen-and-treat approach because infections below the limit of

detection of currently available rapid diagnostic tests contribute to transmission. In addition, the cost of the screening test in settings where many tests are positive may decrease the cost-effectiveness.

Future modeling studies and clinical trials are needed to further determine and optimize the impact of school-based preventive treatment on transmission. Specifically, implementation of school-based preventive treatment as a pilot program in multiple transmission settings will facilitate measuring the impact on transmission in real world settings and aid in determining where the intervention is most suitable. Adding drugs with high efficacy against mature *P. falciparum* gametocytes, e.g. primaquine [52], to enhance the transmission reduction of school-based preventive treatment should also be considered.

The RTS,S/AS01 Vaccine

The RTS,S/AS01 vaccine is another tool for reducing the burden of malaria in young children. In a multi-country, randomized controlled trial of RTS,S, children aged 5–17 months at their first vaccination had 36% fewer cases of clinical malaria disease and 32% fewer cases of severe malaria in the four-dose RTS,S arm over 48 months of follow-up [53]. Although efficacy against both outcomes declined over time [53], this still represented an important reduction in burden. Pilot RTS,S vaccine implementation programs began in Malawi, Ghana and Kenya in 2019 to evaluate the public health impact of RTS,S in the context of routine use and inform policy on broader deployment of the vaccine [54]. In the pilot implementation programs, the vaccination schedule includes four total doses: three prior to the first birthday and one booster around the second birthday.

The most likely mechanism of RTS,S protection against clinical malaria disease is that RTS,S vaccination builds pre-erythrocytic immunity, which lowers the likelihood of an infectious bite progressing to blood-stage infection [55,56]. This could indirectly affect transmission in several ways. In principle, for any infectious bite that is completely blocked from progressing to blood-stage infection, the parasite life cycle ends. Early trials of RTS,S using a different adjuvant (AS02) found an increased time to first *P. falciparum* infection in adults [57] and children [58] vaccinated with RTS,S/AS02, suggesting that sterilizing immunity may occur, at least in the first weeks following vaccination. However, in individuals vaccinated with RTS,S, some proportion of infectious bites will progress to blood-stage infection, with increasing likelihood over time. Whether these breakthrough infections contribute to transmission differently than unvaccinated individuals is unknown due to insufficient data. The early trials with RTS,S/AS02 found similar parasite densities in the first infections of participants in the RTS,S and control arms [57,58], but these studies relied on microscopy for parasite detection and therefore may have missed infections with sub-microscopic densities. Further studies using more sensitive molecular techniques to determine infection status and parasite density are needed to determine whether these breakthrough infections have lower densities of parasites and/or are less likely to lead to clinical malaria disease. Lower overall parasite densities may be associated with lower gametocyte densities [59], which would lower an individual's contribution to transmission [11]. On the other hand, infections that do not progress to disease contribute to transmission for a longer

period than if they were truncated by treatment, so that the total contribution over time may be correspondingly higher [5].

No studies have assessed the impact of the RTS,S vaccine on any indicators of transmission, such as gametocyte densities, infection in non-vaccinated age groups, or the entomological inoculation rate. One modeling study used data from the multi-country randomized controlled trial [53] to parameterize four mathematical models and then estimate impacts of the RTS,S vaccine in a range of transmission settings, but only two of the four models allowed for possible indirect effects on transmission [60]. Of these two, one model predicted an indirect effect only in settings with low malaria transmission (i.e. *P. falciparum* prevalence < 5% in children aged two to ten years). However, these models assumed that the impact of RTS,S was restricted to reducing the probability of an infectious bite leading to blood-stage parasites. Whether the vaccine impacts the probability of an infection leading to clinical symptoms, the rate of asexual parasites converting to gametocytes, or gametocyte survival rates could determine the effect of the vaccine on transmission.

Concluding Remarks

SMC, school-based preventive treatment, and the RTS,S vaccine serve as three examples of interventions with compelling evidence for reducing the burden of clinical malaria disease in a specific, targeted population but which also have some potential to impact parasite transmission. One clearly important factor for determining the impact on transmission is the age group being targeted for the intervention. School-based preventive treatment is the most likely of the three to reduce transmission because of the disproportionate contribution of school-age children to transmission in high transmission settings, although further studies of all three interventions are needed to better predict their transmission reducing potential under a range of conditions, including local environmental factors, transmission intensities and intervention coverage. Using highly efficacious drugs or vaccines and optimizing implementation strategies to increase coverage will increase the effectiveness of these interventions against disease and proportionally decrease parasite transmission. In contrast, the addition of drugs or vaccines that target gametocytes will likely have little impact on disease in the targeted population but may maximize the impact of interventions on transmission. The benefits, cost-effectiveness and ethics of each of these approaches require further evaluation (see Outstanding Questions).

The studies reviewed here have taken a number of different approaches to measuring malaria parasite transmission, as precisely quantifying transmission – and the effect of interventions on transmission – remains challenging. The sensitivity of existing transmission metrics varies across epidemiological settings, and the applicability of a metric for evaluating an intervention may depend on the number of steps in the parasite transmission cycle between the metric and the intervention target [27]. Defining and validating a standardized approach for measuring parasite transmission in a cost effective, feasible manner will improve our ability to predict the impact of interventions on parasite transmission in different settings and monitor progress towards elimination [61].

Malaria interventions that reduce the incidence of clinical malaria disease play a critical role in improving public health. Many of these disease-targeting interventions may also impact malaria parasite transmission. Applying these interventions to maximize their impact on transmission could accelerate the path to malaria elimination in settings where the current interventions have not been sufficient to move beyond malaria control. Therefore, intervention trials and implementation evaluations should measure outcomes that estimate intervention impacts on transmission. Additional modeling studies that evaluate indirect effects of interventions on transmission, combined with studies that measure the complex interactions among hosts, parasites and vectors to accurately parameterize the models, are also needed. While great strides have been made to implement currently available interventions and develop new interventions to further reduce morbidity and mortality due to malaria, achieving global malaria eradication will require prioritization of understanding and optimizing the transmission-reducing potential of all available interventions.

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Glossary

Control

Reducing the burden of clinical malaria disease below a locally acceptable level

Clinical malaria disease

Infection with malaria parasites associated with symptoms of disease, including fever, headache, and chills

Elimination

Interrupting local transmission of malaria parasites within a defined geographical area

Entomological inoculation rate

The number of infectious bites by a vector, expressed per person per unit time

Eradication

Permanently reducing the worldwide incidence of malaria parasite infection to zero

Gametocyte

The first sexual stage of malaria parasite development, and the only malaria parasite stage in humans able to continue development in the mosquito. When both female and male forms are ingested by a mosquito, the respective gametes join in the mosquito midgut to form a zygote

Infection

In the context of human malaria, the invasion and establishment of a *Plasmodium* parasite in the body of a host, with or without disease/symptoms

Infectious reservoir

The collective group of individuals infected with a parasite serving as the source from which other individuals can become infected

Severe malaria

An extreme category of malaria disease characterized by signs of organ dysfunction and/or a severe anemia

Sporozoite

The malaria parasite developmental stage that is transmitted from a mosquito to a human through the mosquito bite

Transmission

the spread of a pathogen/parasite from one host to another; for vector-borne parasites like *P. falciparum*, this includes the transfer of the parasite from the vertebrate host (i.e. humans for *P. falciparum*) to the vector/invertebrate host (i.e. *Anopheles* mosquitoes for *P. falciparum*) and *vice versa*

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Outstanding Questions Box

- Is it possible to monitor transmission in a more cost effective, easily deployable way?
- Can serological markers be developed for quantifying changes in mosquito or parasite exposure over short time scales?
- Can more effective methods be developed for sampling mosquitoes outdoors – or at low densities indoors – for measuring transmission?
- How does the level of intervention coverage affect any impact on parasite transmission?
- Will successful interventions in young children alter their immunological response to malaria, leading to changes in the infectious reservoir?
- What is the impact of RTS,S vaccination (and other pre-erythrocytic vaccines) on gametocyte presence and density?
- How can adjunctive transmission reducing drugs, e.g. primaquine, be best utilized in the context of disease control interventions?
- What is the role of transmission-blocking vaccines within the context of currently available malaria interventions?

Highlights

- Malaria parasite transmission and disease are related, but have different patterns.
- Malaria interventions aimed at reducing disease may also reduce parasite transmission if they decrease infections that develop gametocytes, decrease the density or duration of gametocytemia, or reduce exposure to malaria vectors.
- The available data suggest that seasonal malaria chemoprevention and school-based preventative treatment contribute to reducing parasite transmission, but further studies are needed to quantify and optimize this indirect effect.
- Modeling suggests the RTS,S vaccine may affect parasite transmission under specific circumstances; there are currently no empirical data to support this.
- Optimizing disease control interventions to also decrease parasite transmission can enhance the contribution of these interventions to malaria elimination.

Figure 1. Potential intervention effect on *Plasmodium falciparum* transmission in relation to age.

(A) In moderate- to high-transmission settings, the prevalence of *P. falciparum* infections changes with age [62]. The proportion of those infections that lead to clinical malaria disease (dark gray), as opposed to remaining sub-clinical or asymptomatic (light gray), decreases with age [63,64]. Both types of infection contribute to transmission (diagonal lines), which also varies with age due to changes in the relative infectiousness and duration of the infections and the frequency of bites by malaria vectors [5,8]. The proportions shown here are hypothetical, and the exact proportions will vary across geographic locations according to epidemiological, environmental and ecological factors [8,62–64]. (B) In this setting, an intervention that prevents *P. falciparum* infection in children from five to ten years of age (blue) will prevent more human-to-mosquito transmission of *P. falciparum* than an intervention that prevents infection in children under five years of age (orange).