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REVIEW

Plasmodium vivax in Children: Hidden Burden and Conspicuous Challenges, a Narrative Review

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ABSTRACT

There has been progress towards decreasing malaria prevalence globally; however, *Plasmodium vivax* has been less responsive to elimination efforts compared with *Plasmodium falciparum*. *P. vivax* malaria remains a serious public health concern in regions where it is the dominant species (South and South-East Asia, the Eastern Mediterranean region, and South America) and is increasingly recognized for its contribution to overall morbidity and mortality worldwide. The incidence of *P. vivax* decreases with increasing age owing to rapidly acquired clinical immunity and there is a disproportionate burden of *P. vivax* in infants and children, who remain highly vulnerable to severe disease, recurrence, and anemia with associated developmental impacts. Diagnosis is sometimes difficult owing to the sensitivity of diagnostic tests to detect low levels of parasitemia. Additionally, the propensity of *P. vivax* to relapse following reactivation of dormant hypnozoites in the liver contributes to disease recurrence in infants and children, and potentiates morbidity and transmission. The 8-aminoquinolines, primaquine and tafenoquine, provide radical cure (relapse prevention). However, the risk of hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency necessitates testing prior to administration of 8-aminoquinolines, which has limited their uptake. Additional challenges include lack of availability of pediatric dose formulations and problems with adherence to primaquine owing to the length of treatment recommended. A paucity of data and studies specific to pediatric *P. vivax* malaria impacts the ability to deliver targeted interventions. It is imperative that *P. vivax* in infants and children be the focus of future research, control initiatives, and anti-malarial drug development.

PLAIN LANGUAGE SUMMARY

Plasmodium vivax malaria is the most common type of malaria in South and South-East Asia, the Eastern Mediterranean region, and South America. Following a mosquito bite, the *P. vivax* parasite enters the blood and travels to the liver. It may cause malaria immediately or lie dormant and reactivate to cause relapses, weeks, months, or even years later. In *P. vivax* endemic

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regions, population immunity develops over time with repeated exposure to the parasite. Children bear the burden of disease since they have not acquired clinical immunity. Repeated relapses can cause anemia and affect growth and development. Radical cure refers to treatment of parasites in the blood and dormant parasites in the liver to prevent relapse. Until recently, primaquine was the only medicine approved for radical cure. When a primaquine regimen (7–14 days, depending on dose) is not completed, it is less effective. Additionally, there is no pediatric formulation currently available. Recently, tafenoquine, prescribed as a single dose, was approved for radical cure in children. Before radical cure, testing patients for deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD) is necessary since patients with this deficiency may have rupturing or destruction of red blood cells. However, access to G6PD deficiency testing is limited, creating barriers to treatment. Eradication of *P. vivax* is challenging due to its ability to relapse, and the treatment challenges described above. It is imperative that future elimination efforts focus on improving access to curative treatments for infants and children who bear the burden of disease.

Keywords: *Plasmodium vivax*; Primaquine; Tafenoquine; Malaria; Children; Epidemiology

Key Summary Points

Malaria elimination initiatives have been more successful at decreasing *Plasmodium falciparum* than *Plasmodium vivax* incidence.

Infants and children in endemic areas have not yet acquired clinical immunity to *P. vivax* through repeated exposure. They bear the burden of *P. vivax* malaria since they remain vulnerable to severe disease, recurrence, and anemia associated with developmental impacts.

The propensity for *P. vivax* to relapse from dormant forms and lower levels of parasitemia compared with *P. falciparum* have posed diagnostic and treatment challenges, adding complexity to eradication efforts.

Limited access to point-of-care G6PD testing, lack of availability of pediatric formulations of 8-aminoquinolines for radical cure, and challenges with adherence to primaquine have also hampered elimination efforts.

Availability of pediatric formulations of 8-aminoquinolines, testing for G6PD deficiency, and adherence to treatment must be the emphasis of future public health initiatives.

INTRODUCTION

Plasmodium vivax has the broadest geographic distribution of human malaria species [1, 2] and is second in prevalence to *Plasmodium falciparum*. More than one-third of the world's population is at risk for *P. vivax* infection, with the greatest endemicity in South and South-East Asia, the Eastern Mediterranean region, and South America [3, 4]. In areas of moderate-to-low transmission, where population immunity has not been acquired, all age groups are at risk of *P. vivax* infection. In areas of high and mixed endemicity (where both *P. falciparum* and *P. vivax* are prevalent), population immunity develops over time with repeated exposure. Infants and children without repeated exposure have not yet acquired clinical immunity and are at the greatest risk of infection and severe and recurrent disease; therefore, children and adolescents account for a significant global burden of infection [5–10].

The propensity of *P. vivax* to relapse following reactivation from the dormant liver stage of the parasite increases transmission potential, and contributes to clinical caseloads and to the disproportionate burden of *P. vivax* in infants and children. Standard malarial control

methods used for *P. falciparum*,, which are targeted at children, are not effective for *P. vivax* owing to biological differences between the two species and challenges related to the treatments to prevent relapse [11]. Available diagnostic testing is not always sensitive enough to detect non-*P. falciparum* species, and artemisinin-based combination therapies (ACTs) do not prevent relapses characteristic of *P. vivax* [12].

While emphasis placed on *P. falciparum* in childhood is appropriate owing to its high morbidity and mortality, *P. vivax* should also be recognized as an important cause of pediatric morbidity owing to severe and recurrent disease, and associated impact on children's development [13–15]. This review highlights the biological features and diagnostic and treatment challenges of *P. vivax* that adversely affect malaria control campaigns, and the resulting disproportionate burden of morbidity and mortality that *P. vivax* poses to infants and children.

METHODS

Search Strategy and Selection Criteria

References for this targeted literature review were identified through searches of PubMed, Embase, and Google Scholar. Search terms included (*malaria*, *Plasmodium vivax*) OR (*malaria*, *vivax*) OR (*msp1*, *P vivax*) OR (*P vivax msp1*) OR (*Plasmodium vivax*) AND (*children*) OR (*adult children*) OR (*adolescent*) OR (*infants*) OR (*infants*, *newborn*) OR (*neonate*) OR (*neonates*) OR (*paediatrics*) OR (*hospital*, *pediatric*). Articles published from January 2000 to November 2021 were screened for relevance by title and abstract. Relevant references cited in those articles were also reviewed. One hundred forty-six articles published in English and Spanish were ultimately included. In addition to the reference list, Supplementary Table 1, entitled "References in Alphabetical Order by Section", is provided.

This review manuscript is based on a literature search of previously published studies and does not include any new studies with human participants or animals and therefore does not require ethics approval.

RESULTS/DISCUSSION

Epidemiology of *Plasmodium vivax* in Children

Age Distribution

Surveillance data and epidemiological modeling approaches have been used to estimate *P. vivax* cases, but the actual global number of cases in children is not known [6].

In nonendemic regions such as Europe and North America, and low transmission settings such as Thailand, the Solomon Islands, and sub-Saharan and central Africa, the burden of *P. vivax* malaria spans all age groups, since clinical immunity has not been attained during childhood [7]. Conversely, while migrant work and proximity to forested areas confer some risk in endemic areas with high *P. vivax* prevalence (large portions of South and South-East Asia, the Eastern Mediterranean region, and South America), children and adolescents bear the greatest burden of *P. vivax* disease, with the parasite rate in children aged 2–6 years approximately four times that in adults, and the incidence of clinical infection decreases significantly with increasing age [8, 16–20]. A prospective cohort study in Papua New Guinea determined that *P. vivax* monoinfections as well as mixed *Plasmodium* infections were associated with severe malaria, with most cases occurring in children less than 5 years old [13]. *P. vivax* morbidity in a study in Vanuatu peaked in children aged 0–2 years and declined after the age of 6 years [21]. In Brazil, a study demonstrated that the risk of infection and disease decreased significantly with increasing age [22]. Continued efforts to accurately quantify the burden of disease by age group will help to improve targeted interventions.

Acquired Clinical Immunity

Over time, acquired immunity achieved through repeated exposure to the parasite reduces clinical symptoms and the risk of a severe outcome [23]. The host mechanisms for

development of acquired clinical immunity are better understood for *P. falciparum* than for *P. vivax* [23–26]. In areas of high endemicity, clinical immunity patterns follow distribution of disease prevalence by age group owing to the rapid acquisition of immunity following repeated parasitemia [7, 8, 23, 27–31]. A study conducted in Papua New Guinea demonstrated that the incidence of clinical *P. vivax* episodes decreased with age in children aged 1–4 years, and that the acquisition of clinical immunity to *P. vivax* was significantly faster than for *P. falciparum* [30]. Similarly, in a study conducted on the western border of Thailand, there was a decline of *P. vivax* malaria incidence with increasing age, whereas the incidence of *P. falciparum* increased with age [32]. *P. vivax* was also more prevalent in younger age groups (1–4 and 5–9 years of age) than *P. falciparum* in another study in Thailand [31]. The reasons for faster acquisition of protective immunity with *P. vivax* compared with *P. falciparum* are unclear [25, 33, 34]. High transmissibility due to the production of gametocytes concurrent with a blood stage infection, regular relapses from reactivated hypnozoites, and biological differences in parasite interactions with host hematopoietic cells may contribute [30, 33, 35]. The rapid relapse rate of the Chesson strain of Papua, Indonesia, Papua New Guinea, and the South Pacific contributes to the number of acute *P. vivax* episodes in this region, with relapse occurring approximately 3 weeks from the time of the primary infection and continuing for more than 18 months [35, 36]. A rapid relapse rate may contribute to faster acquisition of clinical immunity.

Repeated *P. vivax* infections at a young age may also contribute to earlier acquisition of immunity. Infants (< 6 months of age) are thought to benefit from innate or maternal protection from *P. falciparum* infection, but less is known about *P. vivax* and maternal protection in infancy. Studies in Papua, Indonesia, a mixed endemicity setting, have shown that a higher proportion of malaria cases in infants is due to *P. vivax* [37, 38].

More research is needed to clarify whether the effectiveness and durability of acquired clinical immunity to *P. vivax* is age dependent. The development of an adaptive B- and T-cell immune response appears to be dependent on continuous antigenic exposure and the durability of acquired immunity in the absence of concurrent infection has been variable across studies [23, 39]. In addition to patient age, durability may depend on antigenic variation, the level of transmission, or the number of previous malarial infections [23]. This has implications for resurgent infection risk in children born in an area in which disease has previously been eradicated and where there is limited antigen diversity [40].

Risk Factors

In addition to lack of acquired clinical immunity (associated with younger age in endemic settings), household proximity to vector breeding site is associated with increased risk for acquiring *P. vivax* in pediatric populations (Fig. 1) [41, 42]. A variety of socioeconomic factors, including maternal education level and travel to or residence in a rural area, have also been linked with a greater burden of disease, although these associations have varied across studies [43–48]. The risk of infection increases during rainy seasons in tropical agricultural communities, greatly affecting productivity and impacting families [7]. Additionally, the geographic distribution of malaria largely affects lower income countries where socioeconomic factors are more pronounced, limiting access to preventative measures [43, 49].

Pathogenesis

Plasmodium vivax *Lifecycle*

Following inoculation and initial clinical symptoms during the blood stage of *P. vivax* infection, sporozoites may enter a dormant, nonreplicating, hypnozoite stage in the liver, from which they can reactivate weeks to years later following the initial infection to cause a relapse of infection (Fig. 1) [50]. Overall, the pathophysiology of *P. vivax* is similar in children versus adults; however, infants with congenital *P. vivax* infection are not known to experience relapse, presumably as sporozoites

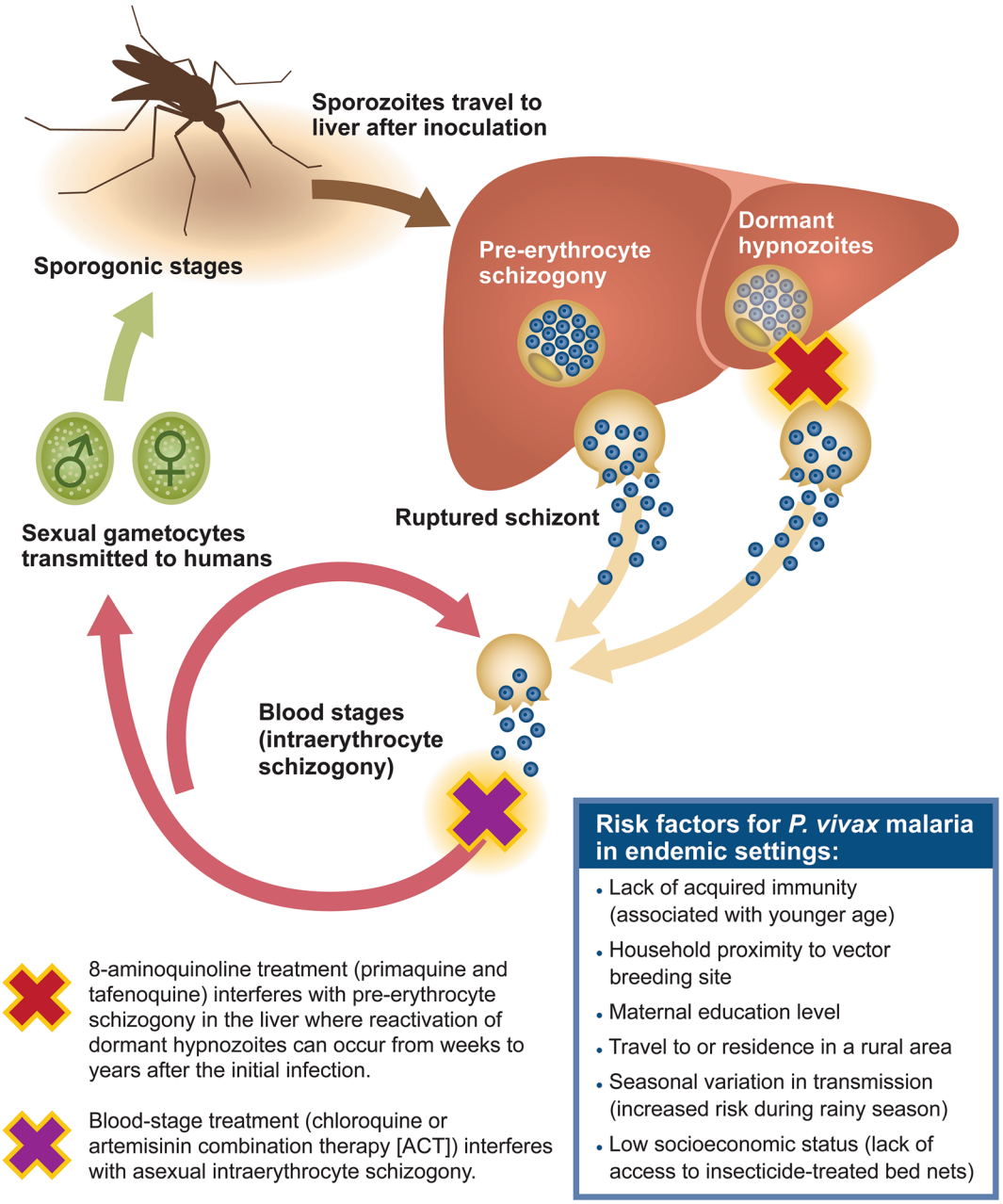

Fig. 1 *P. vivax* lifecycle

do not enter the fetal circulation to form liver hypnozoites [51].

Clinical Features

Uncomplicated Plasmodium vivax *Malaria*

Uncomplicated acute *P. vivax* malaria episodes present similarly in children as in adults, ranging from asymptomatic to an undifferentiated febrile illness. Asymptomatic illness is less likely in children < 1 year of age [37]. After a short period of irregularity, fever paroxysms coincide with schizogony and occur approximately every 24–48 h depending on the *Plasmodia* strain, previous exposure, and host immunity [52, 53]. In both *P. vivax* and

P. falciparum, similar nonspecific symptoms may accompany fever, including headache, malaise, myalgia, chills, anemia, nausea, vomiting, abdominal discomfort, and/or diarrhea [53, 54]. Respiratory symptoms are common, despite earlier misconceptions that pulmonary complications were associated with *P. falciparum* infection but not with *P. vivax* [55]. Intermittent fever, where *P. vivax* is the predominant species, as well as combinations of symptoms have been investigated for use as diagnostic criteria. However, no symptom alone or in combination has been shown to be sensitive or specific enough to diagnose or discriminate between malarial species [56–59]. Laboratory findings common in *P. vivax* malaria, including thrombocytopenia and increased bilirubin, also lack diagnostic and discriminant value [58, 60, 61].

Few studies have directly compared the clinical presentation of *P. vivax* between children and adults. A Colombian study reported vomiting more frequently in children (50% versus 35%). A study from India (where both *P. falciparum* and *P. vivax* are prevalent) suggested that headache, body pain, and chills are more common in adults than children [57, 58]. Splenomegaly and hepatomegaly may be more frequent in children than in adults [58].

Complicated Plasmodium vivax *Malaria*

The risks of severe disease and case fatality rates vary and have not been firmly established in the pediatric population, which suggests a need for more detailed studies to fully understand the risks of severe disease across age groups. A study of complicated *P. vivax* malaria in Colombia found a greater proportion of complicated cases in individuals aged > 15 years (76.2%) versus ≤ 15 years (23.8%) [62]. Other studies have indicated that morbidity and mortality are higher for children aged < 5 years [63, 64]. The risk for severe *P. vivax* malaria in patients < 2 years of age in Papua New Guinea is reportedly similar to that for *P. falciparum* in this age group (14% versus 18%, respectively) with risk decreasing similarly with increasing age for both species [13]. Earlier studies in Papua, Indonesia showed that *P. vivax* species predominated over *P. falciparum* in infant hospital admissions, with *P. vivax* accounting for 56% of malaria infections in young infants (0–3 months of age) versus 30% due to *P. falciparum* [65]. *P. vivax* accounted for nearly 20% of all-cause hospital admissions, with severe disease risk in young infants similar to that of older infants.

Among patients with severe *P. vivax* infection, anemia, thrombocytopenia, jaundice, and acute respiratory distress syndrome (ARDS) are common manifestations [10, 66–68]. Severe anemia (defined as hemoglobin < 50 g/L) is considered the most common manifestation of severe *P. vivax* in children [15, 52]. Rates of severe anemia are higher in *P. vivax* than *P. falciparum* malaria, with infants and children < 5 years of age at greatest risk. In areas of high endemicity such as Papua, Indonesia, up to one third of infants admitted to the hospital with *P. vivax* have severe anemia [65, 69], and in other geographical regions, including India, Ethiopia, and Colombia, it is common in children with severe malaria [70–73].

Severe anemia associated with *P. vivax* is likely a consequence of relapsing disease prior to the development of clinical immunity [74, 75]. In acute disease, hemolytic anemia develops rapidly owing to both the destruction of parasitized red blood cells and a high proportion of nonparasitized cells [75, 76]. A shift towards erythropoiesis (over hemolysis) typically occurs within 4–6 weeks after an acute episode; however, in areas where high transmission rates result in repeated or recurrent infections, malarial anemia is a significant contributor to morbidity and mortality in children (see recurrence) [5, 69, 75, 77].

Other hematological and respiratory complications of severe *P. vivax* infection have been reported at a similar rate between children and adults [60, 68]. Although rare, splenomegaly leading to splenic rupture may be more common for *P. vivax* than other Plasmodium species [78–80]. In children with severe malaria, the proportion who experience respiratory distress may differ between species. Compared with severe *P. falciparum*, young children (< 5 years of age) in Papua New Guinea with severe *P. vivax* malaria presented more often with respiratory distress (61% versus 41%, $P = 0.002$) [13].

Mortality rates in patients with *P. vivax* infections who develop respiratory complications resemble those of *P. falciparum* [68].

Recurrence

Among recurrent cases, it is not possible to distinguish between *P. vivax* reinfections (new inoculation of sporozoite), relapses (activation of latent hypnozoites), and recrudescence (the resurgence of erythrocytic parasites), because molecular markers have not yet been fully validated [81–83]. However, by analyzing seasonal patterns of malaria, it is possible to estimate the proportion of cases due to relapse versus reinfection [84]. Modeling to simulate the impact of treatment to clear liver stages of disease in *P. vivax* has also been used to estimate relapse rates [85].

Relapse patterns vary by region and the level of malaria endemicity. The proportion of *P. vivax* infections that relapse, the time to relapse, the interval between subsequent relapses, and the total number of relapses also varies by strain [35, 86]. Time to relapse ranges from approximately 3 weeks following initial infection in the Chesson strain, to long latency for temperate and subtropical forms of *P. vivax*, where there may be approximately 8 months between the first symptomatic infection and first relapse [35]. Studies have reported relapse rates in children and across age groups ranging from approximately 20% to > 80%, dependent upon ethnicity, immunity, the sporozoite inoculum, co-endemicity with *P. falciparum*, and seasonal variations in infection rates [81, 83–87].

Although there are few studies of baseline relapse rates of *P. vivax* malaria in children, it has been suggested that both the proportion of infections that relapse and the number of symptomatic relapses decline with age owing to the acquisition of clinical immunity [17, 87]. One study conducted in Papua, Indonesia estimated that the cumulative risk of representation (relapse, reinfection, and recrudescence) with clinical *P. vivax* infection within 1 year in children aged 1 to < 5 years was 49.6% versus 31.2% in those aged 5 to < 15 years [88].

Overall, the dormant liver stage of the *P. vivax* parasite contributes to the clinical case load, increases the transmission potential, and complicates control measures, given this potential source of reintroduction of the parasite into the vector population [85, 89]. Children who have not yet acquired clinical immunity are disproportionately affected since they often experience multiple relapses, as well as recurrence, owing to reinfection or recrudescence [17, 81]. Studies in children in Papua New Guinea demonstrated that radical cure with primaquine reduced the risk of *P. vivax* episodes, and relapses were considered accountable for the higher prevalence, multiplicity, and incidence of *P. vivax* infection and disease in early childhood [81]. In addition, *P. vivax* was no longer a source of morbidity in children of school age largely owing to the acquisition of immunity [8]. In a study from Papua, Indonesia, children younger than 5 years old with *P. vivax* malaria were at significant risk of multiple representations with malaria and of dying within 1 year of their initial presentation. Children that died were generally younger than those who survived, and the authors suggested that this was likely owing to a lack of effective immunity, resulting in a greater number of clinical malaria episodes leading up to death compared with those who survived [63].

Recurrence not only has physical impacts with illness, sometimes requiring repeat hospitalization, but also affects growth, development, and educational progress [90, 91]. School performance may be impacted by malaria-induced anemia. In a randomized trial in Sri Lanka (where both *P. vivax* and *P. falciparum* are prevalent), children aged 6–12 years treated with chloroquine had higher hemoglobin levels than the placebo group, and mathematics and language scores on end-of-term examinations were significantly inversely related to the number of malarial attacks and absenteeism from school [90]. Another study in Peru found that children aged 0–72 months had significantly less weight gain over 2-, 4-, and 6-month intervals following an episode of uncomplicated *P. vivax* [92].

Diagnostics

There is little data on diagnostic test performance in children. While patient age does not appear to impact testing accuracy per se, the sensitivity of rapid diagnostic tests (RDTs) is decreased at low levels of parasitemia. In non-immune populations (i.e., children in regions endemic for *P. vivax*), symptomatic disease can occur with low levels of parasitemia and go undetected by standard RDTs [93]. Newer hemozoin-based testing is more sensitive for the detection of low levels of parasitemia, however, field deployment is limited [94]. Microscopy is still commonly used in endemic areas and is considered the gold standard. However, test sensitivity is dependent upon the experience of the laboratory, and underdiagnosis of *P. vivax* may occur in mixed infection owing to the low density of the parasitemia [93]. While the risks of false negative tests must be balanced with concerns about overtreatment (in the absence of test availability), a decision tree model for children with *P. falciparum* suggested that universal access to sensitive and specific rapid diagnostic tests could have a significant effect on malaria morbidity and mortality in children aged < 5 years [95].

G6PD Deficiency

Reliable diagnosis of glucose-6-phosphate dehydrogenase (G6PD) deficiency is clinically relevant because the only available treatments for radical cure (relapse prevention) targeting the dormant liver *P. vivax* parasite are the 8-aminoquinoline compounds (primaquine and tafenoquine) [96, 97], which can cause hemolysis in individuals with G6PD deficiency [98, 99]. The prevalence of G6PD deficiency is high in many *P. vivax* endemic areas, with a heterogeneous allele frequency that typically ranges from below 5% to 15%, but can be as high as 35% [99–101].

The method used to diagnose G6PD deficiency in the pediatric population is identical to that in adults. Testing may be genotypic or phenotypic, with the latter being qualitative or quantitative. For the purposes of malaria case management, point-of-care quantitative tests offer advantages over qualitative tests by precise classification of cases with particular utility in screening G6PD deficiency in hemizygous males and homozygous females with two mutant alleles associated with G6PD deficiency [102]. While accurate G6PD testing is available, there are practical limitations to G6PD testing that are barriers to 8-aminoquinoline uptake, including access to quantitative point-of-care testing and subjectivity in applying results for females with a heterozygote genotype [99, 103]. Additionally, G6PD is an age-dependent enzyme that does not reach maturity until 6–12 months of age, and a relatively high reticulocyte count in infants, overestimating G6PD activity, may contribute to the misinterpretation of test results [104–106]. As there is a paucity of safety data in females with intermediate activity, and severe hemolytic reactions carry a high risk of mortality in children, primaquine treatment without an accurate assessment of G6PD status is advisable only with careful monitoring, and tafenoquine cannot be administered without prior quantitative G6PD testing [98, 105, 107, 108]. To realize the potential of 8-aminoquinolines to minimize the impact of relapsing disease in children, the implementation of a reliable quantitative G6PD point-of-care test capable of accurately differentiating deficient, intermediate, and normal G6PD activity levels (where normal is > 70% of the population median) is needed [105]. One such test, capable of detecting intermediate enzymatic activity in females that is registered in several endemic countries, was recently approved by the Australian Therapeutic Goods Administration (TGA) [109]. Other quantitative point-of-care tests are in development or have been submitted for FDA approval [110, 111], representing an important step towards delivering better tolerated relapse prevention.

Current Treatments

For both adults and children, the World Health Organization (WHO) recommends treatment of acute uncomplicated *P. vivax* malaria infections with ACTs (a short-acting artemisinin derivative

and a longer-acting partner drug) or chloroquine (CQ), depending on the prevalence of resistance to CQ [112].

In areas without CQ resistance, studies across age groups (including children) and a pooled analysis have shown that CQ and ACTs are equally effective for preventing recurrent parasitemia in the short term; however, treatment with ACTs has been shown to have more rapid fever reduction and parasite clearance compared with CQ for blood stage treatment [113–115]. In high-transmission settings, dihydroartemisinin–piperaquine (DP) is superior to other ACTs [artesunate–amodiaquine (AS–AQ), artesunate–mefloquine (AS–MQ), and artemether–lumefantrine (AL)] for the treatment of *P. vivax* in comparative trials, both with and without primaquine. Owing to the longer half life of piperaquine versus other partner drugs, DP provides an improved post-treatment protective effect that may delay relapse, allowing for hematological recovery between clinical infections. As frequent recurrences in children are associated with repeated insults to growth and development, this modest benefit should be considered in areas with high transmission of both *P. vivax* and *P. falciparum*, or where limited diagnostics preclude species-specific treatment [115, 116]. Pyronaridine–artesunate, a combination treatment that provides broad antimalarial activity, can also be considered and has been endorsed by the European Medicines Agency for uncomplicated *P. falciparum* and *P. vivax* malaria [115, 117].

Underdosing is a concern with both CQ and ACTs, potentially leading to inadequate clinical and parasitic responses [113, 118]. The total recommended dose of chloroquine in children is 25 mg/kg over 3 days; however, owing to the unavailability of scales to weigh patients in many endemic regions, chloroquine is sometimes dispensed based on age, a practice which may lead to suboptimal dosing [115, 119]. Additionally, to achieve clinical cure, prevent relapse, and limit transmission, dormant hypnozoites must be treated [81, 120].

Primaquine and tafenoquine are the only therapeutic options available for radical cure. Present recommendations are to treat children and adults with primaquine on a mg/kg basis [121, 122]. Primaquine is recommended for children $\geq$ 6 months of age [112]. Although a registered formulation to facilitate appropriate dosing in children is in development [123], currently, primaquine tablets must be cut or crushed to dose by weight [or a minimum effective dose of 3.5 base (0.5 mg/kg/day) to 7 mg base (0.5 mg/kg/day), depending on plasmodia strain] and administered over 14 days [5, 97, 112, 124]. Crushing, cutting, or grinding of tablets may affect the pharmacokinetic (PK) properties of a drug, as has been reported for other anti-infectives [125], which may in turn affect drug efficacy (underdosing allowing for possible recurrence of *P. vivax* malaria) or safety (overdosing, possibly resulting in hemolysis or methemoglobinemia) and underscores the need for pediatric dosing formulations. This limits the benefit derived by patients from primaquine and has important public health consequences.

The effectiveness of primaquine following CQ or ACTs for radical cure of *P. vivax* malaria has previously been reviewed [113, 115]. In studies that included children, supervised treatment with primaquine significantly reduced the risk of recurrent *P. vivax* at 42 days, and reduced the incidence rate of malaria episodes at 1 year [113, 126].

The TGA approved tafenoquine co-administered with CQ for pediatric patients 2 years or older with *P. vivax* malaria in March 2022, and the pediatric dossier is being submitted and reviewed for approval in endemic countries. In the Tafenoquine Exposure Assessment in Children with *Plasmodium vivax* malaria trial (TEACH), children (aged $\geq$ 2 to $<$ 16 years) weighing $\geq$ 5 kg, with G6PD activity $>$ 70%, who were diagnosed with *P. vivax* in Vietnam and Colombia, received open-label single-dose tafenoquine on a weight-based dosing schedule following their initial CQ dose [127]. The initial pediatric dosing regimen was selected using a base population pharmacokinetic model that included data from patients aged 16 years or older, incorporating allometric scaling for body weight. Recurrence-free efficacy at 4 months was 94.7%, and adverse events were of mild-to-moderate severity. Post-dose vomiting, which occurred in seven patients who received a 50 mg dispersed tablet, was successfully

mitigated by clarifying food and drink delivery, administering the tablet undispersed, or by substituting with a 150-mg tafenoquine tablet in subjects > 35 kg in the study. Of note, a recently completed study in adults in Indonesia showed no clinically meaningful benefit of tafenoquine in combination with DP, and efficacy of tafenoquine with other ACTs has not yet been established [128].

In addition to dosing concerns stemming from lack of pediatric drug formulations, there are additional challenges with 8-aminoquinoline treatment, including limited access to point-of-care G6PD testing and problems with adherence (see adherence). In both children and adults, G6PD status should guide treatment for liver stage disease. However, owing in part to the practical limitations and uncertainties around G6PD testing discussed above, tafenoquine is not approved for children < 2 years of age or for women breastfeeding a child < 2 years, primaquine is not recommended for infants < 6 months or for women breastfeeding an infant < 6 months, and neither tafenoquine nor primaquine is recommended for pregnant women or for women breastfeeding older infants with unknown G6PD status [35, 96, 97, 129]. Additional studies of 8-aminoquinolines in breastfeeding women are warranted since 8-aminoquinolines are contraindicated in pregnancy and in lactation where the G6PD status of the infant is unknown. The exclusion of many women from receiving hypnozoitocidal treatment over years of childbearing potential eliminates the opportunity for radical cure and impacts efforts to curb malaria transmission [129, 130]. A study in lactating women showed very low concentrations of primaquine in breast milk, which would be unlikely to cause adverse events in the breastfeeding infant, even with G6PD deficiency [129].

Alternate primaquine regimens have been used with close monitoring in nonpregnant females with intermediate G6PD activity (> 30%), and studies are ongoing in which alternative dosing has been used in patients with < 30% activity [98, 131]. Self-limited decreases in hematocrit with clinically mild signs and symptoms were observed in male and female G6PD deficient patients in Thailand treated with primaquine 15 mg daily for 14 days [132]. As the degree of G6PD deficiency varies within and across regions, caution must be exercised in both children and adults prior to using either primaquine or tafenoquine when G6PD deficiency has been determined, or when G6PD status is unknown [98, 112, 133].

There has also been concern that cytochrome P450 2D6 (CYP2D6) genetic polymorphisms could affect radical cure efficacy for *P. vivax* [134, 135]. Age, body weight, and CYP2D6 genotype appear to influence primaquine and carboxy-primaquine (the predominant measurable primaquine metabolite) plasma levels. Patients with CYP2D6 genetic polymorphisms may not generate sufficient levels of the active metabolite for efficacy, resulting in relapses despite full adherence to primaquine [134, 136]. In one study of primaquine pharmacokinetics in African children, toddlers categorized as intermediate metabolizers had low plasma levels of primaquine versus older children with poor metabolizer status, suggesting that in addition to the weight of the child, CYP2D6 metabolizer status should be considered [137]. For tafenoquine, one study in patients at least 16 years of age suggested that CYP2D6 phenotype does not have a significant effect on efficacy; however, in this study it was not possible to distinguish between relapses and new infections [138]. Further studies are needed to assess differing population efficacies for radical cure and the threat posed to elimination campaigns.

Adherence

In addition to dose and plasmodium strain, the modest efficacy of primaquine for preventing *P. vivax* recurrences observed in real-world settings versus clinical trials may be due to poor adherence to treatment [88]. Adherence varies across studies, suggesting that adherence is dependent on context, age, tolerability, and education [88, 103, 139]. Although data are limited for children alone, several studies evaluated adherence across age groups. In separate studies in Ethiopia and at the

Thailand–Myanmar border, the risk of recurrence was significantly higher with unsupervised primaquine versus semi-supervised or supervised therapy [126, 139]. Children aged 8–13 years were more likely than other age groups to report nonadherence, although differences did not reach statistical significance [139]. Parental supervision may improve adherence in younger children [88], and educating patients on the importance of adherence to treatment even after symptoms have subsided is critical.

To improve adherence, higher primaquine doses for a shorter period of time (e.g., 3.5, 5, or 7 days) are sometimes utilized. Recent evidence suggests a 7-day primaquine course (1.0 mg/kg/day) is noninferior to a 14-day course (0.5 mg/kg/day) [124, 140]. Since tafenoquine is given as a single dose, nonadherence is expected to be alleviated, resulting in improved public health outcomes [141].

Elimination Efforts

In many mixed endemicity settings (e.g., Southeast Asian, Eastern Mediterranean, and Western Pacific regions), control campaigns have led to a decrease in the incidence of *P. falciparum* infections, but the proportion of *P. vivax* cases has trended upwards [3, 7, 142–145]. In sub-Saharan Africa, where *P. falciparum* is the dominant species, overall malaria prevalence has decreased in response to elimination efforts, while the proportion of *P. vivax* cases has increased [12]. Where overall malaria incidence is the lowest in these areas of Africa, the proportion of *P. vivax* cases tends to be the highest (up to 25%). These trends are likely attributable to the aforementioned biological differences between the two parasites and the difference in predisposition to interventions.

Interventions such as insecticide-treated bed nets and the wider availability of RDTs and effective treatments have led to decreases in *P. falciparum* cases [146]. However, a focus on the treatment of both blood and liver stages of *P. vivax* malaria are necessary to achieve clinical cure, limit transmission, and achieve malaria elimination [115]. A recent update to the WHO treatment guidelines also recommends mass drug administration to prevent transmission; however, efforts should be followed with an effective elimination program to avoid resurgence after 1–3 months [112].

Despite improved diagnostics, the low parasitemia of *P. vivax* continues to pose challenges in areas of co-endemicity with *P. falciparum*, with *P. vivax* often going undetected and untreated, adding complexity to elimination efforts [12]. In response to the elusiveness of the *P. vivax* reservoir to current public health initiatives, more sensitive diagnostics, with a focus on radical cure including wider availability and use of point-of-care G6PD testing, adherence to current treatments, and improved availability of pediatric formulations of 8-aminoquinolines, must be the focus of future public health initiatives.

CONCLUSIONS

A paucity of data and studies specific to pediatric *P. vivax* malaria impacts the ability to deliver targeted interventions. Although progress has been made towards malaria elimination, there remains a substantial burden of *P. vivax* disease globally. Children who have not previously acquired clinical immunity in endemic areas are at greatest risk of infection with *P. vivax* and carry the greatest burden of infection. The higher relapse frequency of *P. vivax* in children has a serious impact on growth and development. In many countries, malaria elimination efforts are hampered by the capacity of *P. vivax* to relapse. New tools to improve compliance and to provide a better tolerated radical cure (relapse prevention) are urgently needed.

The single-dose regimen of tafenoquine may have positive effects on adherence; however, limitations exist for both primaquine and tafenoquine related to the access and implementation of point-of-care G6PD testing, CYP2D6 metabolizer status, and the costs of testing and treatment in areas with limited resources. Since primaquine and tafenoquine are both contraindicated in pregnancy and in young infants, this poses additional challenges related to radical cure.

Progress has been slow on reducing the childhood impacts of *P. vivax* [120]. Studies have highlighted the enduring consequences of early deficits on growth and development, and therefore it is imperative that the disproportionate burden of *P. vivax* in infants and children be the focus of future control initiatives.

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