Plasmodium vivax radical cure risk benefit assessment tool

A decision support framework to guide the selection of treatment regimens and delivery strategies

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The *Plasmodium vivax* radical cure risk benefit assessment tool provides decision-making guidance to support national malaria programs in the selection of *Plasmodium vivax* radical cure schemes in consideration of the effectiveness of different delivery strategies, local epidemiology of malaria, glucose-6-phosphate dehydrogenase (G6PD) deficiency, availability of G6PD testing (including point-of-care (POC) testing), and risk of recurrences with and without treatment. This narrative document is accompanied by a Shiny App program into which data inputs can be entered and outputs are generated. Findings must be interpreted in consideration of the availability and quality of data inputs, as well as programmatic objectives and resource constraints. Guidance regarding *Plasmodium vivax* treatment delivery strategies and G6PD testing can be found in World Health Organization (WHO) guidance documents.

This tool was developed by PMI Impact Malaria team members and partners: Michelle Hsiang, Sonia Herrera, Xue Wu, and Corey Rathe from the University of California, San Francisco Malaria Elimination Initiative; Leopoldo Villegas and Lawrence Barat (Population Services International (PSI); Roberto Montoya and Maria Paz Ade (Pan American Health Organization); Angela Devine and Kamala Ley-Thriemer (Menzies School for Health Research); and Paulo Manríque (Harvard University).

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Acronyms and Abbreviations

ddPQ	Double dose primaquine
ddPQ7	Double dose primaquine 7-day (7 mg/kg total dose, or 1 mg/kg/day)
ddPQ14	Double dose primaquine 14-day (7 mg/kg total dose, or 0.5 mg/kg/day)
DOT	Directly Observed Therapy
G6PD	Glucose 6 phosphate dehydrogenase
G6PDd	Glucose 6 phosphate dehydrogenase deficiency
LAC	Latin American and the Caribbean
MDA	Mass drug administration
NT	No testing
P. vivax	*Plasmodium vivax*
PMI	U.S. President's Malaria Initiative
PSI	Population Services International
PQ	Primaquine
PQ8wks	Primaquine administered over 8 weeks (6 mg/kg total dose, or 0.75 mg/kg/week)
QT	Quantitative testing
sdPQ	Standard dose primaquine
sdPQ7	Standard dose primaquine 7-day (3.5 mg/kg total dose, or 0.5 mg/kg/day)
sdPQ14	Standard dose primaquine 14-day (3.5 mg/kg total dose, or 0.25 mg/kg/day)
TQ	Tafenoquine
U.S.	United States
USAID	United States Agency for International Development
WHO	World Health Organization

Key Terms

Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency (G6PDd)	An X-linked inherited metabolic condition that results in a deficiency of the G6PD enzyme in red blood cells. Malaria patients with G6PD deficiency are at risk of hemolysis when treated with 8-aminoquinolines, such as primaquine or tafenoquine.
Hemolysis	The process of red blood cell rupture which can lead to severe anemia and death
Hemolytic risk	The level of risk for 8-aminoquinoline associated hemolysis, mainly driven by G6PD deficiency prevalence but also influenced by G6PD variants, underlying anemia, and health system capacity to prevent, detect, and manage hemolysis
Malaria	A disease caused by the *Plasmodium* parasite, which is transmitted to humans via the bites of infected mosquitoes, which then invades mainly the liver and red blood cells, where it replicates, leading to fever, anemia, jaundice, and potentially a life-threatening systemic illness
Plasmodium vivax (P. vivax)	*P. vivax* is one of five human malaria parasites. *P. vivax* infections establish latency in hepatocytes and other tissues, leading to relapse. This hypnozoite phase is a major challenge for malaria control and elimination.
Radical cure	Radical cure refers to the treatment of hypnozoites to prevent relapses. At present, 8-aminoquinolines are the only drug class available for radical cure.
Radical cure treatment regimen	Radical cure treatment options include primaquine (PQ) and tafenoquine (TQ). TQ is administered at 300 mg in a single dose for adults. PQ can be administered as a standard dose (3.5 milligrams per kilogram (mg/kg) total dose) or as double dose (seven mg/kg total dose). Standard dose PQ (sdPQ) can be administered over seven or 14 days (sdPQ7 or sdPQ14: 0.5 mg/kg/day or 0.25 mg/kg/day, respectively). Double dose PQ (ddPQ) is approved by the World Health Organization (WHO) for administration over 14 days (ddPQ14: 0.5 mg/kg/day). In those with G6PDd, PQ administered over eight weeks at 0.75 mg/kg/week (PQ8wks is recommended by WHO).
Radical cure delivery strategy	The methods by which radical cure treatment regimens can be delivered, including provision of supervision with administration, and the use of G6PD testing prior to treatment
Radical cure scheme	For the purposes of this tool, radical cure scheme refers to the different combinations of radical cure treatment regimens and radical cure delivery strategies.
Radical cure scenario	For the purposes of this tool, radical cure scenario refers to a situation for a particular site or population that takes into consideration hemolytic risk and a particular radical cure delivery strategy. The tool can accommodate up to two different scenarios for a particular site or population.
Supervised treatment	For the purposes of this tool, supervised treatment refers to any method by which adherence and safety of drug administration are enhanced. This includes directly observed therapy by a health professional; modified directly observed therapy whereby a health professional observes some but not all doses; and/or observation or support by a family member, community health worker, or through phone or video devices.

Background

Challenge of Latent *Plasmodium vivax*

The global burden of *P. vivax* is estimated to be approximately 14.3 million cases, with about one-third of the world's population at risk of transmission.[1,2] While *P. vivax* is endemic throughout the world, the highest burden is in the Latin America and the Caribbean (LAC) and South-East Asia regions, where *P. vivax* is the dominant malaria species.[3] In 2021, *P. vivax* accounted for 71.5% of all malaria cases in the Americas, roughly 600,000 cases.[3] Unlike *Plasmodium falciparum*, *P. vivax* has the ability to remain latent in the liver-stage (hypnozoites) and can cause relapses for weeks to years.[4,5] While there is limited data from LAC, modeling suggests that in areas where it is endemic, the majority of *P. vivax* episodes are due to relapse.[6] As such, hypnozoites are a major challenge for *P. vivax* control and elimination.[7]

Current Standard for *P. vivax* Radical Cure in LAC

In LAC countries, the first-line treatment recommended for *P. vivax* is chloroquine and the 8-aminoquinoline, primaquine (PQ). As a schizonticidal agent, chloroquine is largely efficacious as a first-line treatment for uncomplicated *P. vivax* malaria in most countries in LAC. To kill hypnozoites, the standard dose of primaquine (sdPQ) is 3.5 mg/kg total dose, administered over seven days (sdPQ7, 0.5 milligrams per kilogram per day (mg/kg/day)) or 14 days (sdPQ14, 0.25 mg/kg/day).[8] This treatment regimen has not changed for more than 60 years.[9] A major challenge of the sdPQ7or sdPQ14 regimens is adherence, which limits their effectiveness to prevent relapses.[10] Data from the LAC region is limited, with the largest such study from Peru showing 62% adherence to the seven day regimen.[10,11] Supervision of treatment through directly observed therapy (DOT) by a health professional is one way to improve adherence but not always operationally feasible. Modified DOT is a variation of DOT by which a health professional observes some but not all doses. In combination or as an alternative to DOT, other approaches to supervision may include observation or support by a family member, community health worker, or phone or video contact. In this tool, supervised treatment is defined as any of these methods by which adherence and safety of drug administration are enhanced.

G6PD Deficiency

G6PD deficiency (G6PDd) is an X-linked condition and the most common metabolic condition, affecting 400 million people worldwide, mainly of African, Asian, and Mediterranean descent.[12] In individuals with underlying G6PD deficiency, as defined as <30% (severe deficiency) or >30% and <70% (intermediate deficiency) activity, *P. vivax* treatment with 8-aminoquinolines can induce a dose-dependent and life-threatening hemolysis. With the use of sdPQ delivery strategies, testing for G6PD deficiency prior to treatment with PQ is not routinely conducted in LAC. PQ-induced hemolysis is rare at this dosage. A recently conducted systematic review and meta-analysis by Yilma *et al.* found only 160 cases reported worldwide since 1940.[13] The overall risk of severe hemolysis among malaria patients that received PQ and had normal or intermediate G6PD activity was about one in 1,000. Data from the LAC region is limited, but included a large surveillance study from one hospital in the Brazilian Amazon over a nine-year period and where prevalence of G6PD deficiency is estimated to be 5%.[14] Among 110,331 malaria patients receiving the local standard PQ regimen, sdPQ7, during this period, there were 94 cases of PQ-induced hemolysis and thus the risk of hemolysis was estimated to be 0.085% (or 0.85 episodes per 1,000 PQ

users). Blood transfusion was necessary in 46 patients (49%), dialysis in seven (7%), and one patient died (one percent). Due to under-detection and a lack of G6PD testing in primary care, these are likely under-estimates.

Until recently, G6PD testing required laboratory infrastructure that is often not available in rural and resource-limited settings.[15] Point-of-care qualitative tests were briefly available but they did not detect women with intermediate level deficiency (30 - 80% of normal activity).[16] However, point-of-care quantitative tests recently became available and the performance of one product, the SD Biosensor STANDARD™ G6PD test, to detect severe and intermediate levels of G6PD deficiency has been validated in operational settings and it has approval from the Global Fund's Expert Review Panel for Diagnostics.[17]

Supervision of treatment is a method to improve adherence, but it can also enable pharmacovigilance of hemolytic events and timely management including stopping of treatment, as well as referral for provision of transfusion, dialysis, and other supportive measures as indicated. A systematic review and meta-analysis of PQ-associated hemolysis found that for daily administration, most hemolytic events occurred within the first five days of administration, irrespective of total dose.[13] As such, supervised treatment of the seven-to-14-day course of PQ is likely to enable early detection of hemolytic events and prevention of progression to severe outcomes.[18]

Alternative Radical Cure Treatment Regimens

Double Dose Primaquine

Primaquine treatments are considered with the total dose in mind, rather than a daily dose. One currently used alternative radical cure treatment approach is double dose primaquine (ddPQ), which is given over 14 days (ddPQ14, 0.5 mg/kg/day). This increased PQ dose is recommended by the WHO in East Asia and Oceania where strains are frequently relapsing.[8,19] From the LAC region, the only evidence regarding ddPQ is from a randomized controlled trial conducted in the Brazilian Amazon, where ddPQ14 was superior in preventing relapses compared to sdPQ7.[20]

As noted above, most PQ-associated hemolysis has been found to occur in the first five days of administration. Further, that risk of hemolysis is associated with the daily dose of PQ, irrespective of total PQ dose.[13] Thus, the risk of hemolysis would be expected to be lowest for sdPQ14 (daily dose 0.25mg/kg) and similar for sdPQ7 and ddPQ14 (daily dose 0.5mg/kg). However, this review did not include controlled data regarding ddPQ in individuals with G6PDd and the available observational data may misrepresent underreporting of 8-aminoquinoline induced hemolytic events. As such, for this tool, sdPQ7 and ddPQ14 (supervised or unsupervised) are only considered in this tool when G6PD testing can be conducted , and no testing (NT) is only considered when administration is supervised.

The efficacy and safety of ddPQ administered over seven days (ddPQ7) has been evaluated in a multicenter trial. Compared to ddPQ14, ddPQ7 was non-inferior in terms of efficacy.[18] However, due to issues related

to tolerability, ddPQ7 and limited data regarding safety in individuals with G6PDd, ddPQ7 is not recommended by WHO and is not considered in this tool.

Weekly Primaquine for eight weeks

For individuals found to have G6PD intermediate or severe deficiency (defined by WHO as ≤80% activity), weekly PQ (0.75 mg/kg/week for eight weeks, or six mg/kg total dose) is a recommended treatment scheme.[8] While there are no published trials among individuals with G6PD deficiency, this regimen has been found to be highly efficacious compared to standard 14-day regimens.[21,22] More recently, as a sub-study of the IMPROV trial, this eight-week regimen was found to be similarly effective and safe in terms of effectiveness to prevent relapse in relation to sdPQ14 (Ley-Thriemer, personal communication). This regimen is used first in treatment of individuals found to have intermediate or severe G6PD deficiency, and as a potential first-line treatment in communities where there may be a high risk of 8-aminoquinoline-induced hemolysis, and G6PD testing is not available.

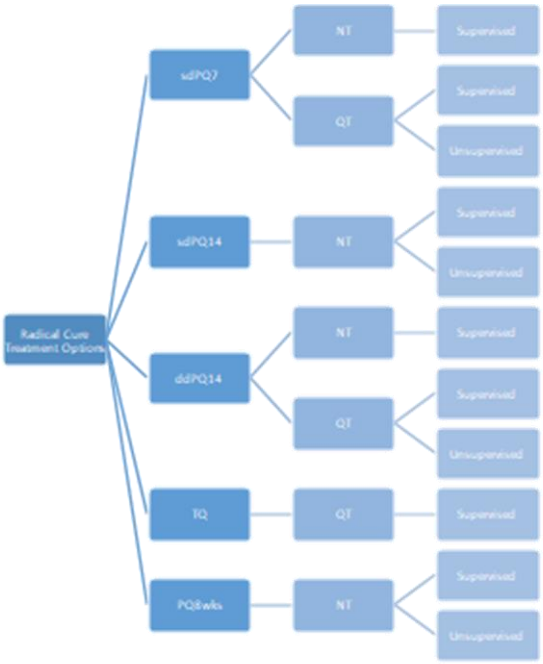


Figure 1: This tool considers 11 treatment schemes based on different treatment regimens (various dosing for PQ and TQ) and different delivery strategies whether G6PD quantitative testing (QT) is conducted or if there is NT, as well as whether administration is supervised or unsupervised).

Tafenoquine with Quantitative G6PD Testing

TQ is a newly available single-dose 8-aminoquinoline that addresses adherence challenges for PQ. A single dose is sufficient for treatment because the drug has a long half-life of 14 days, which is 50 times longer than that of PQ.[23] In multi-site trials, TQ has been shown to be non-inferior to sdPQ14 in preventing relapse.[20] However, as an 8-aminoquinoline, TQ also has a risk of hemolysis in those with G6PDd. With primaquine, if early signs of hemolysis are recognized, severe morbidity and death associated with severe hemolysis can be prevented by stopping continued administration. However, such an approach is not possible for TQ due to its single-dose administration. As such, quantitative G6PD testing is required prior to TQ administration, and severe or intermediate G6PD activity (<70%) is a contraindication for its use.

Radical Cure Delivery Strategies

Safety and effectiveness of the different radical cure treatment regimens can be improved with specific delivery strategies. For the purposes of this tool, delivery strategies are referred to as the methods by which radical cure treatment regimens can be delivered including provision of supervision with administration, and the use of G6PD testing prior to treatment. Supervision of treatment can strengthen adherence and maximize effectiveness. Supervised treatment also serves the purpose of allowing for early detection and management of adverse events, thus optimizing safety. G6PD testing prior to treatment helps to identify patients at risk for 8-aminoquinoline associated hemolytic events.

Radical Cure Treatment Schemes

For the purposes of this tool, radical cure scheme refers to the different combinations of radical cure treatment regimens and radical cure delivery strategies. For example, there are four treatment schemes associated with sdPQ14:

- with quantitative G6PD testing and supervised treatment
- with quantitative G6PD testing and unsupervised treatment
- no quantitative testing and supervised treatment
- no quantitative testing and unsupervised treatment

Risk Benefit Assessment Tool

Rationale for Tool Development

In the LAC region, sdPQ7 and sdPQ14 are currently used for radical cure. PQ8wks is an alternative regimen if G6PDd is confirmed or suspected, or no testing is available. Both ddPQ14 and TQ are being considered by policy makers, but these require G6PD testing, alongside the provision of supervision to administer to improve adherence and/or safety. See Figure 1, which shows the different treatment schemes based on drug type and dose, and different delivery strategies, i.e., whether G6PD quantitative testing (QT) is conducted or NT, and whether administration is supervised or unsupervised. Eleven different treatment schemes are considered in this tool. Note that for sdPQ7 and ddP14, unsupervised administration with no testing (NT) are not listed as options due to risk of PQ-induced hemolysis. For sdPQ14 and PQ8wks, QT were not listed as options because sdPQ7, ddPQ14, or TQ are anticipated to be more effective when QT is feasible. For TQ, NT is not an option due to manufacturer's instructions, and unsupervised administration is not an option due to feasibility of supervised administration for the single dose.

Who is the Intended User of this Tool?

This tool was developed for use by National Malaria Programs and Ministries of Health in the LAC region to support decision-making regarding safe and optimal effectiveness of radical cure treatment regimens and delivery strategies at national and subnational levels. However, other regions may find the tool useful in its current form or they can adapt it to their use. The tool is not intended to provide a specific recommendation regarding the optimal treatment regimen in a particular setting. Rather, it is intended to inform the decision-making process, which will ultimately take into consideration factors not considered in this tool (e.g., cost, health system capacity, and strength of available data as relevant to the local setting).

What is the Risk Benefit Assessment Tool?

The Risk Benefit Assessment Tool is an application that takes into consideration risk for 8-aminoquinoline associated hemolysis and compares *P. vivax* malaria radical cure benefits (prevention of recurrence) of the 11 treatment schemes. The ideal radical cure delivery strategy will maximize benefits (prevention of hemolysis and death) and minimize risks (recurrence of vivax infection).

For each of the 11 treatment schemes the tool uses a decision tree model approach to consider all possible pathways' outcomes for recurrences. Trees for the 11 possible treatment schemes are shown in Appendix A. Figure 2 shows a tree for sdPQ7 with G6PD quantitative testing and with supervised administration. The results for each branching point are guided by data inputs. The proportion of males testing deficient or normal, and proportion of females testing deficient, intermediately deficient, or normal is calculated based on G6PDd prevalence inputs and using Hardy-Weinberg assumptions regarding inheritance. Males tend to test more distinctly either deficient or normal due to being hemizygous, thus intermediate males are not included. In practice, males may have an intermediate result, however the significance of this with regards to risk for hemolysis is not clear. As more evidence is gathered, the tool can be modified as appropriate.

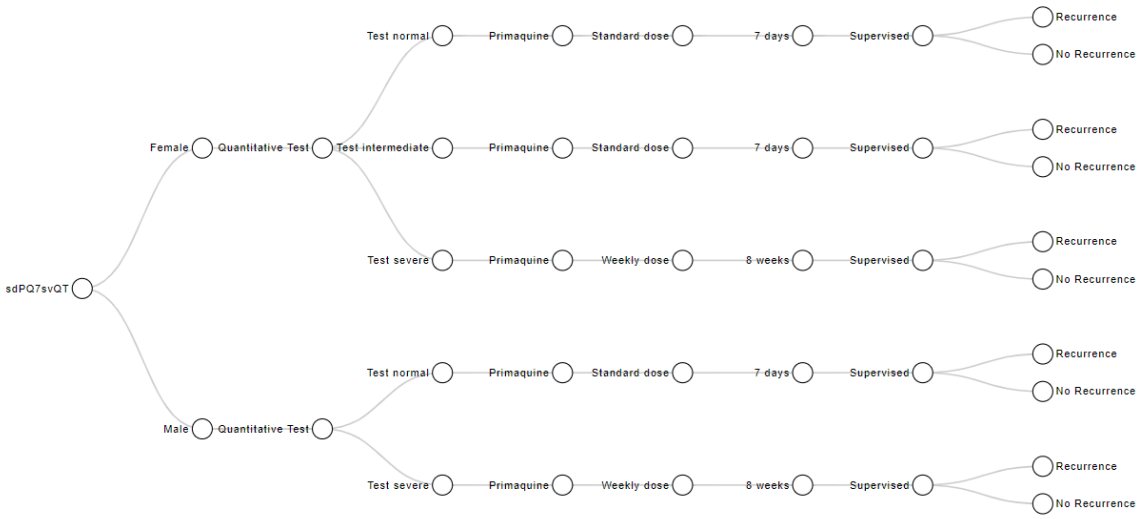


Figure 2: Possible outcomes for P. vivax female and male cases are shown here for standard dose primaquine administered over seven days supervised, and with G6PD testing

The program provides data inputs regarding epidemiology of malaria, G6PD deficiency, and designates the site of interest as low- or high-risk for hemolytic events. Regarding risk of recurrences for the different treatment regimens, supervised or unsupervised, the tool provides defaults based on available data from the LAC region through an online model built in RStudio Shiny, an R package that enables interactive websites. These inputs can be changed if other inputs better represent the site of interest.

For a given site, the tool also enables stakeholders to use two different schemes and compare the number of anticipated recurrences if the treatment schemes are used at different levels or proportions. Output data for each treatment regimen and delivery strategy are populated in a table and auto-generated graphs, allowing ease of comparison.

Guiding principles in the Tool Development

In the design process of the tool, the following considerations were made:

Evidence

IM sought to develop a tool informed by available evidence from the region regarding recurrences associated with different *P. vivax* radical cure delivery strategies, and risks of 8-aminoquinoline associated hemolysis. See Appendix B for evidence inputs on recurrences. Data regarding risk of 8-aminoquinoline associated hemolysis was limited. As such, the higher risk versus lower risk designations for the different treatment schemes and delivery strategies are guided by Pan American Health Organization expert opinion (See section "Determine radical cure scenario or scenarios" Step 2 below).

Transparency and simplicity

Decision models can be complex and opaque, making it difficult for decision-makers to understand, and therefore to trust. IM sought to develop a simple and transparent model that would be accessible to most malaria program managers with basic public health or clinical training. The decision tree approach is a deterministic model whereby the outputs resulting from inputs can be easily calculated. Further, the tool was streamlined to focus on a few key input and output values.

Cost

While costs and cost-effectiveness are key considerations for policy decisions, this tool focuses on risk of hemolysis and benefits in terms of recurrences prevented. This resulted from assertions that local economic factors and cost considerations may vary across the LAC region while those considerations of risk-benefit would remain similar. Also, it was felt that a risk and benefit analysis would precede cost considerations.

Multiple comparisons

Assessments of new treatment delivery strategies often compare one new treatment delivery strategy to the standard of care. Given the many different available delivery strategies for *P. vivax* radical cure, as well as the scheme for supervised versus unsupervised treatment, or the use of G6PD testing or not, the tool is designed to enable comparison across all possible schemes (Figure 1). This also allows for varied implementation across different levels, based on the feasibility of providing delivery strategies.

User friendly

To maximize ease of use, user uptake, and facilitate the iterative process, the tool is accessible on the internet through an open access Shiny App, and data inputs can be easily entered and changed through a simple and user-friendly interface. Outputs are provided as tables and graphs that can be downloaded and shared.

Iterative Process

The code for the Shiny App and its calculations are made available to the user. The tool is intended to allow for an iterative process whereby input values can be updated to include new treatment schemes and other new evidence regarding treatment efficacy or effectiveness. As more data become available regarding hemolytic risk of 8-aminoquinolines, the tool can be revised to enable site-specific estimates of hemolytic events or deaths associated with the different treatment schemes.

How is the Risk Benefit Assessment Tool Used?

The Risk Benefit Tool refers to this narrative document and accompanying Shiny App tool, which should always be used together. The user can first familiarize themselves with the Shiny App tool. The Tool can be accessed in English or Spanish respecetively at https://ucsf-mei.shinyapps.io/RiskBenefitTool_en/ or https://ucsf-mei.shinyapps.io/RiskBenefitTool_es/. The R code and default input data for the Shiny App can be accessed at https://github.com/XueWuUCSF/Risk-Benefit-Tool and can be reviewed or modified for the program's purposes (Appendix F). The user then gathers and inputs data, which are summarized in Figure 3. All programmatic data input fields must be completed to use the tool. Each programmatic data input requires the identification of an absolute value or range of data. If there is not a range, the same value can be entered as the minimum and maximum value. The Shiny App then generates tables and figures that enable comparisons of the different treatment schemes for different scenarios. Step-by-step instructions are detailed below.

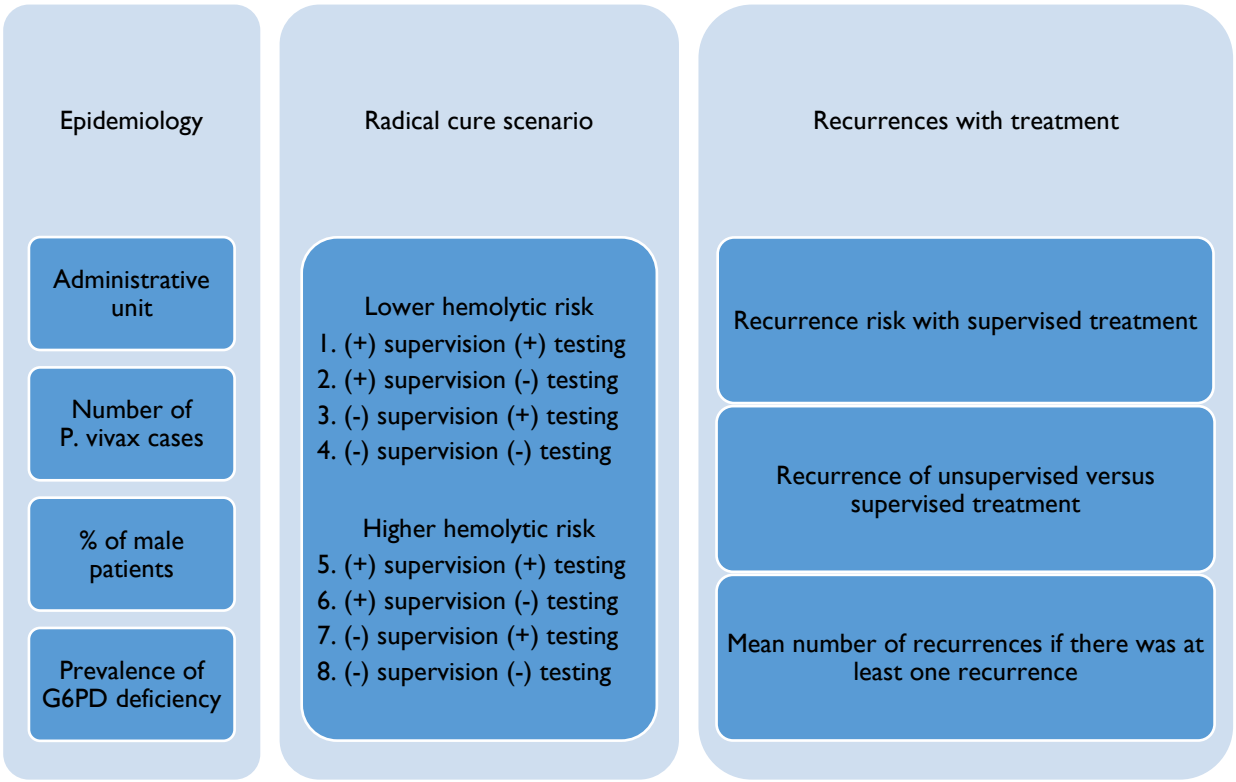


Figure 3: Programmatic data inputs by category. Testing refers to G6PD testing. Supervision refers to supervised treatment to strengthen adherence. See Appendix D for more details.

Step 1: Enter epidemiological information

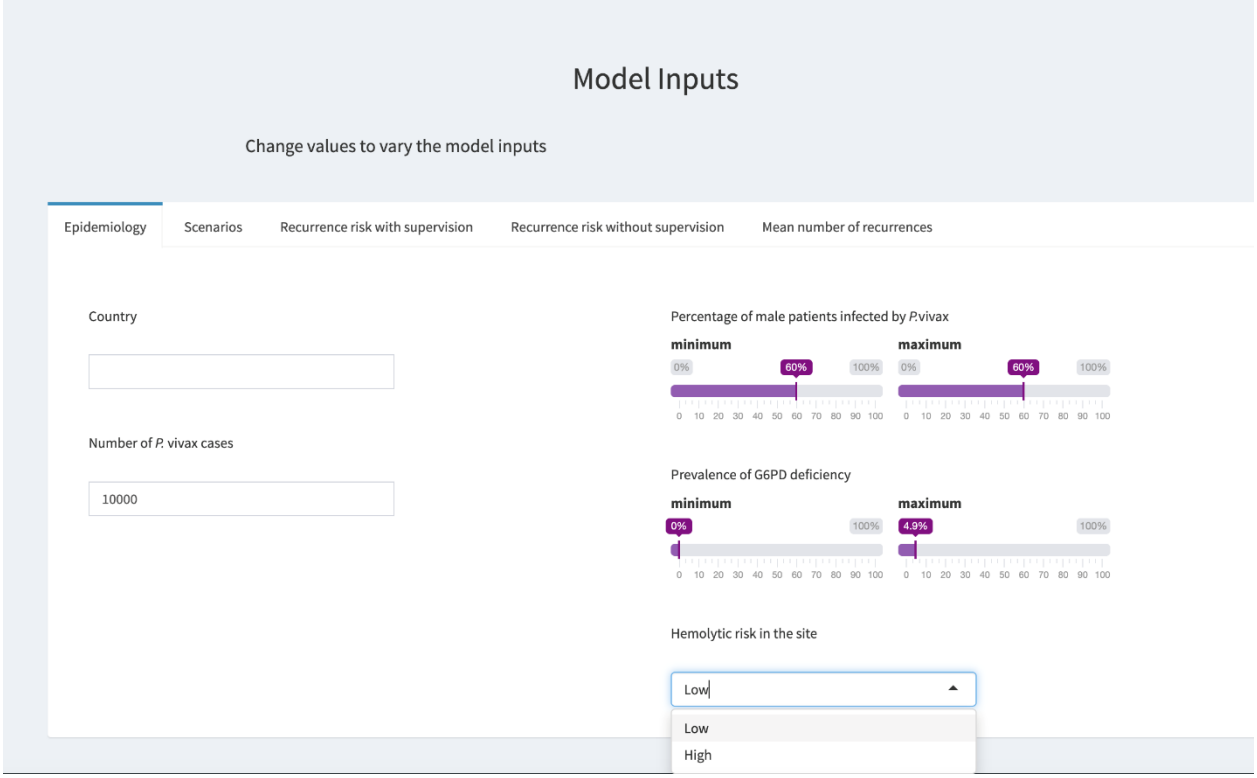


Figure 4: Shiny App model inputs, Epidemiology

See Figure 4 for the first tab of inputs for the tool, Epidemiology. The user will determine the administrative unit of interest, which may be at the national, regional, or sub-regional level. The user will gather information regarding the epidemiology of *P. vivax* malaria in this area, including the number of cases annually and the proportion of cases occurring in males. Ideally, these data are obtained from high quality surveillance data. Sex has relevance to the exercise as G6PDd is X-linked and hemizygous men have severe levels of deficiency, while homozygous women can have severe deficiency and heterozygous women have intermediate levels of deficiency.

Next, the user is also asked to provide data regarding prevalence of G6PDd in males. This input value has implications for G6PD test results, which influence treatment choice. Recognizing that quality G6PDd data may not be available, or that G6PDd prevalence can vary by geography within a country, the tool allows for inputting a minimum and maximum estimate. If estimates of G6PDd from the area of interest are not available, the user may choose to consider values from nearby geographies and in consideration of racial background, which has implications for variant type.

Finally, the user enters the hemolytic risk setting. The options are "low" versus "high" risk setting. The tool compares the number of recurrences of radical cure treatment delivery strategies between lower and higher hemolytic risk settings in the identified administrative unit of interest. The user defines the thresholds for lower and higher hemolytic risk settings based on available data from the area. Due to limited data regarding 8-aminoquinoline associated hemolysis, the tool does not specify the factors

constituting lower versus higher risk. While some experts may consider a G6PDd prevalence of five percent as a cutoff to distinguish the levels of risk, there are no data to guide this recommendation. Other factors to consider include: G6PD variant type and health system capacity to detect and manage hemolytic events.

Step 2: Determine radical cure scenario or scenario(s)

Tables 1 and 2 show the treatment regimens that can be considered for different delivery scenarios. In areas where there is neither supervised drug administration nor G6PD testing, sdPQ14 is an option irrespective of hemolytic risk (Scenarios 4 and 8). If supervised treatment is available, but G6PD testing is not, sdPQ14 and sdPQ7 are options irrespective of hemolytic risk (Scenarios 2 and 6). Between low- and high-risk areas, the only different delivery schemes, shown in bold, are in situations where G6PD testing is not available: ddPQ14 is an option in low-risk areas where supervision is conducted (Scenario 2), and PQ8weeks is an option in high-risk areas. While PQ8weeks is recommended in settings where it can be given under supervision (Scenario 6), it can be considered in settings where no supervision is available as it is potentially more effective than sdPQ14 (Scenario 8).[3] Finally, irrespective of hemolytic risk or if supervised treatment can be provided, sdPQ7, ddPQ14, and TQ are options if G6PD testing is available (Scenarios 1, 3, 5, and 7).

Table 1: Lower Hemolytic Risk Setting Delivery Strategies

	G6PD Testing	No G6PD Testing
Supervision	Scenario 1 sdPQ7, ddPQ14, TQ	Scenario 2 sdPQ7, sdPQ14, ddPQ14
No supervision	Scenario 3 sdPQ7, ddPQ14, TQ	Scenario 4 sdPQ14

Table 2: Higher Hemolytic Risk Setting Delivery Strategies

	G6PD Testing	No G6PD Testing
Supervision	Scenario 5 sdPQ7, ddPQ14, TQ	Scenario 6 sdPQ7, sdPQ14, PQ8wks
No supervision	Scenario 7 sdPQ7, ddPQ14, TQ	Scenario 8 sdPQ14, PQ8wks

The ability to provide G6PD quantitative testing prior to radical cure treatment and the provision of supervised treatment may vary within an area (e.g., a country, region, or local municipality). Rural or urban areas may use different delivery strategies due to differences in health system capacity. Different strategies could be used for individuals ≥16 years versus individuals <16 years. Different delivery strategies might be used for mobile versus resident populations due to feasibility of conducting supervised treatment and pharmacovigilance. As such, within an administrative unit of interest, where the hemolytic risk is similar throughout, the tool enables consideration of two scenarios. For example, consider a district with low hemolytic risk throughout, 4,000 vivax cases per year, and no health system capacity to conduct G6PD testing. While the current standard of care is to not conduct supervision (Scenario 4: no supervision, no G6PD testing, Table 3 and Table 4a), the district is considering scaling up supervision (Scenario 2:

supervision, no G6PD testing) (Table 3). Tables 4b through to Table 4e show situations in which 25%, 50%, 75%, or 100% of the cases could receive supervision. The tool then calculates the number of recurrences one would expect if different regimens were used.

Table 3: Lower Hemolytic Risk Setting Delivery Strategies

	G6PD Testing	No G6PD Testing
Supervision	Scenario 1 sdPQ7, ddPQ14, TQ	Scenario 2 sdPQ7, sdPQ14, ddPQ14
No supervision	Scenario 3 sdPQ7, ddPQ14, TQ	Scenario 4 sdPQ14

Table 4a: Example of low hemolytic risk area where current standard of care delivery strategy is Scenario 4, no supervision and no G6PD testing.

Number of *P. vivax* cases in a sub-area	Delivery strategy	Treatment Scheme 1	Treatment Scheme 2	Treatment Scheme 3
n=1000	Scenario 4	sdPQ14	sdPQ14	sdPQ14
n=1000				
n=1000				
n=1000				

Table 4b: Example of low hemolytic risk area where two different treatment approaches are considered: 75% still receive standard of care delivery strategy (Scenario 4) and 25% receive a Scenario 2 delivery strategy There are 3 different treatment schemes for Scenario 2.

Number of *P. vivax* cases in a sub-area	Delivery strategy	Treatment Scheme 1	Treatment Scheme 2	Treatment Scheme 3
n=1000	Scenario 2	sdPQ7	sdPQ14	ddPQ14
n=1000	Scenario 4	sdPQ14	sdPQ14	sdPQ14
n=1000				
n=1000				

Table 4c: Example of low hemolytic risk area where two different treatment approaches are considered: 50% still receive standard of care delivery strategy (Scenario 4) and 50% receive a Scenario 2 delivery strategy. There are 3 different treatment schemes for Scenario 2.

Number of *P. vivax* cases in a sub-area	Delivery strategy	Treatment Scheme 1	Treatment Scheme 2	Treatment Scheme 3
n=1000	Scenario 2	sdPQ7	sdPQ14	ddPQ14
n=1000				
n=1000	Scenario 4	sdPQ14	sdPQ14	sdPQ14
n=1000				

Table 4d: Example of low hemolytic risk area where two different treatment approaches are considered: 25% still receive standard of care delivery strategy (Scenario 4) and 75% receive a Scenario 2 delivery strategy. There are 3 different treatment schemes for Scenario 2.

Number of *P. vivax* cases in a sub-area	Delivery strategy	Treatment Scheme 1	Treatment Scheme 2	Treatment Scheme 3
n=1000	Scenario 2	sdPQ7	sdPQ14	ddPQ14
n=1000				
n=1000				
n=1000	Scenario 4	sdPQ14	sdPQ14	sdPQ14

Table 4e: Example of low hemolytic risk area where all areas receive a Scenario 2 delivery strategy of supervision but no G6PD testing.

Number of *P. vivax* cases in a sub-area	Delivery strategy	Treatment Scheme 1	Treatment Scheme 2	Treatment Scheme 3
n=1000	Scenario 2	sdPQ7	sdPQ14	ddPQ14
n=1000				
n=1000				
n=1000				

The second tab of inputs (Scenarios) for the tool enables inputs for a single scenario or two scenarios (Figures 5a-c). On the lower left of this tab, the user provides delivery strategy inputs for a single scenario. "All" or four scenarios can be selected (for a low or high-risk site), or a single scenario can be selected. On the right, the user provides delivery strategy inputs for two scenarios, and then provides the proportion of patients that will receive a treatment scheme for Scenario A, the remaining proportion, or one minus the proportion entered in Scenario A, is automatically applied to the treatment scheme for Scenario B. The proportion can be set as any value between 0% – 100%.

For a single treatment scenario, the choice of "All" produces four bar graphs for four different scenarios, and these graphs can be compared to inform decision-making. However, for two scenarios, the choice of "All" produces many outputs that can be difficult to interpret. Thus, it is recommended that for two scenarios, the analysis should be restricted to the choice of two specific scenarios (see Figure 5c and 5d, and pre-test of the two-scenario example).

The tool compares the number of recurrences of radical cure treatment delivery strategies between lower and higher hemolytic risk settings in the identified administrative unit of interest. The user defines the thresholds for lower and higher hemolytic risk settings based on available data from the area. Due to limited data regarding 8-aminoquinoline associated hemolysis, the tool does not specify the factors constituting lower versus higher risk. While some experts may consider a G6PDd prevalence of five percent as a cutoff to distinguish the levels of risk, there are no data to guide this recommendation. Other factors to consider include: G6PD variant type and health system capacity to detect and manage hemolytic events.

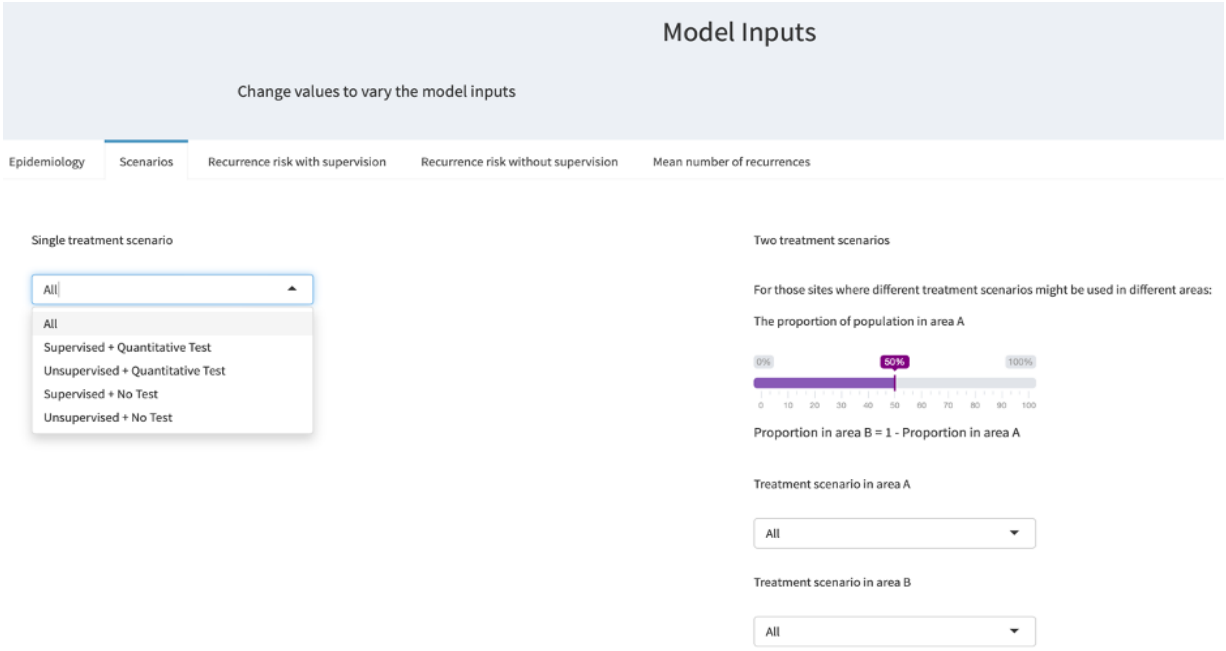


Figure 5a: Shiny App model inputs, Single treatment scenario, considering all scenarios

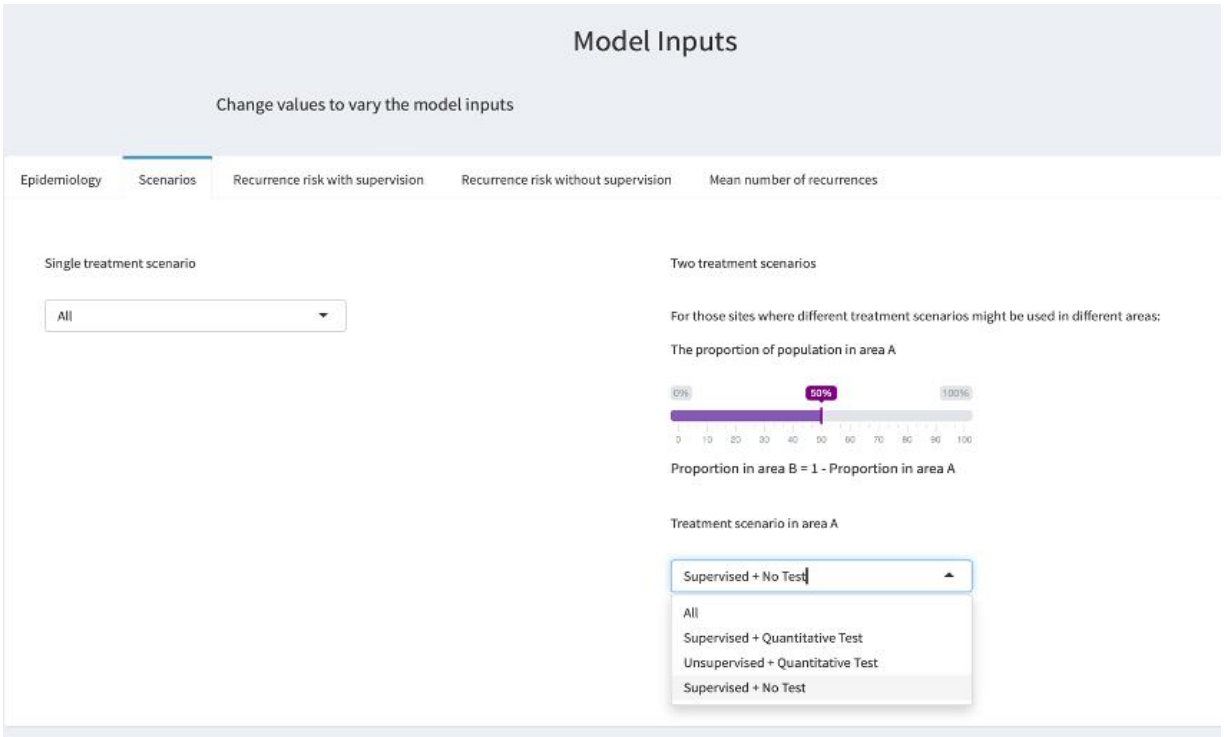


Figure 5b: Shiny App model inputs, Two different treatment scenarios, Supervised+No Test (Scenario 2) selected for Area A

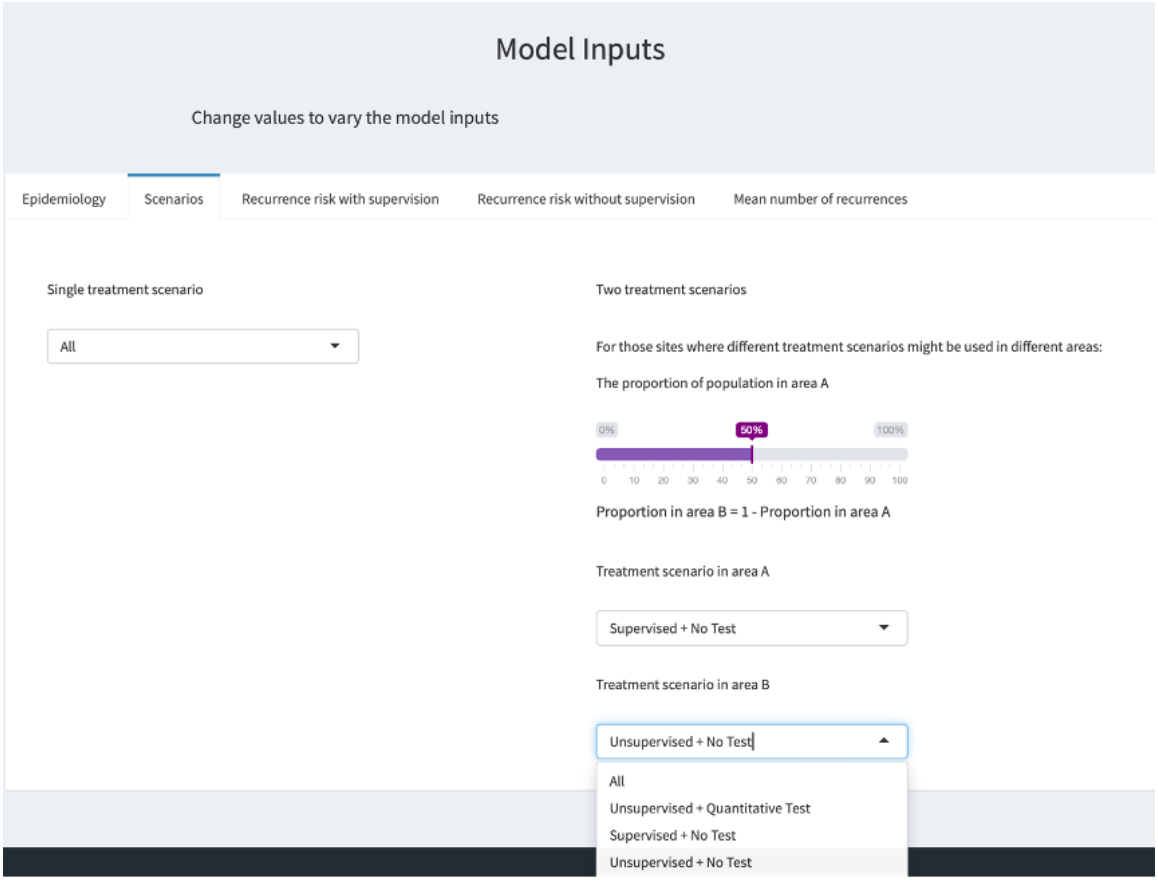


Figure 5c: Shiny App model inputs, Two different treatment scenarios, Unsupervised+No Test (Scenario 4) selected for Area B

Step 3: Review default inputs regarding recurrences and modify as indicated

For the different treatment regimens, default values are provided for recurrence risk when administration is supervised, recurrence risk when administration is unsupervised, and mean number of recurrences. The default values, which are based on a review of the published literature at the time of writing, can be used, or the values can be modified if the program has alternative sources or expert opinions that inform different inputs. See Figures 6a, 6b, and 6c.

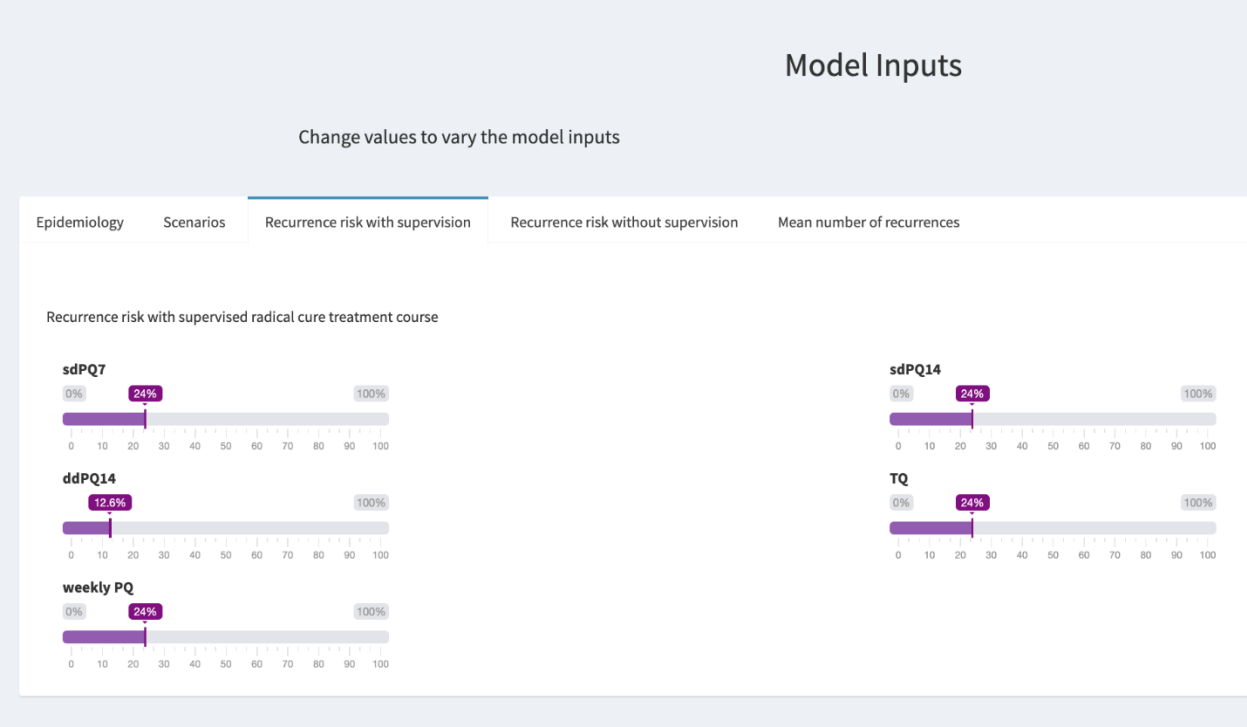


Figure 6a: Shiny App model inputs, Recurrence risk with supervision

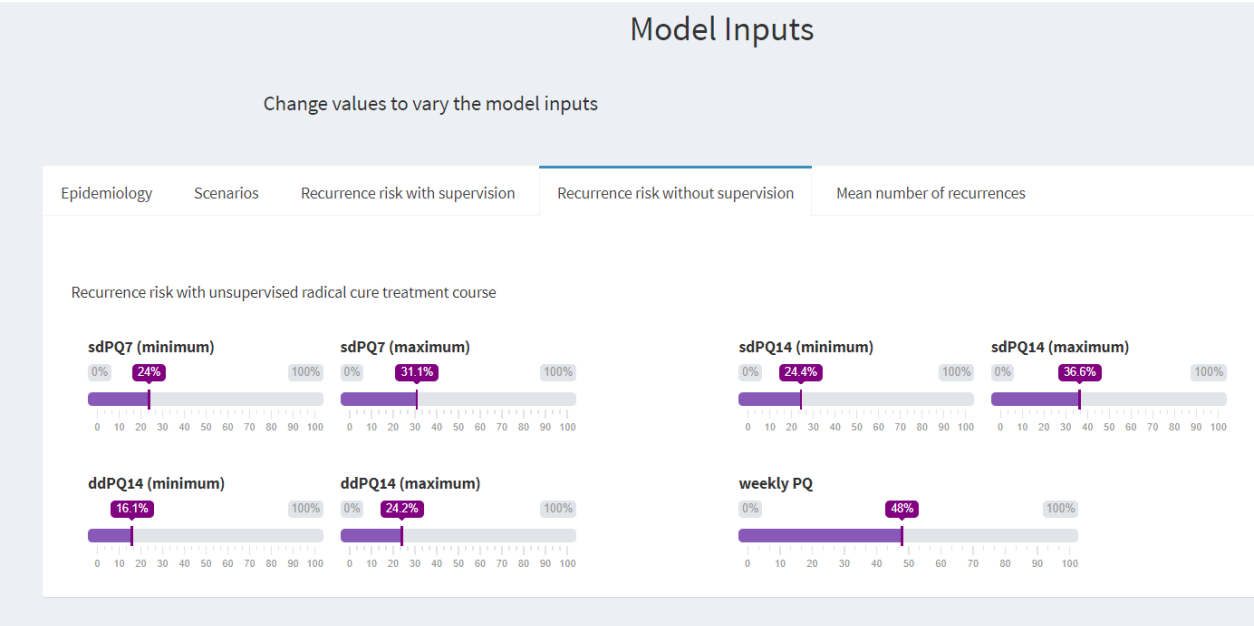


Figure 6b: Shiny App model inputs, Recurrence risk without supervision

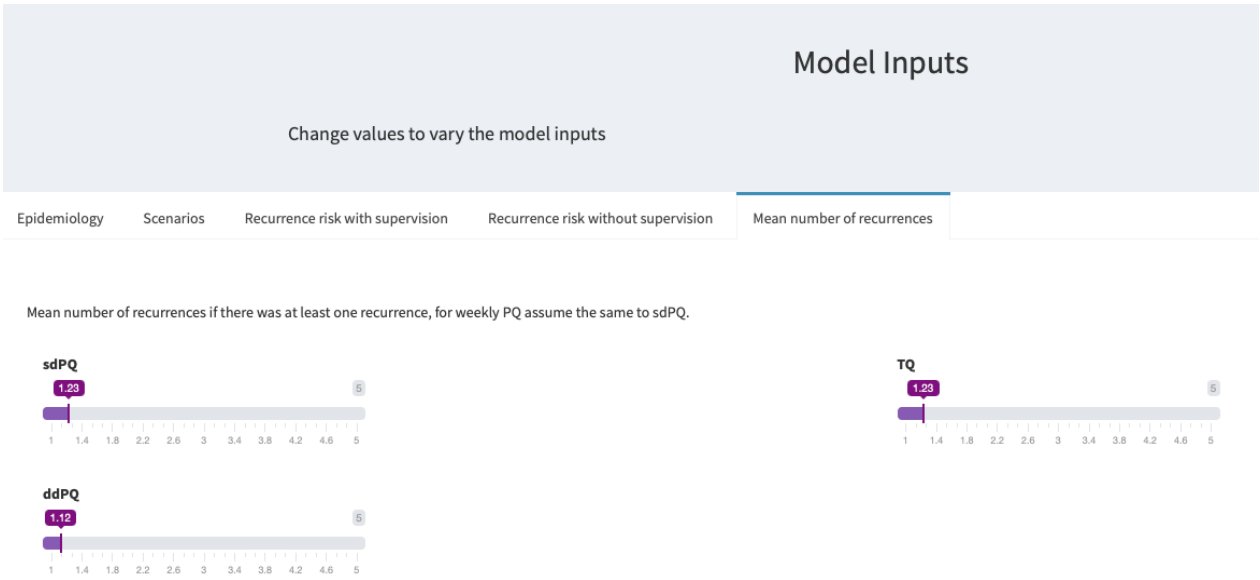


Figure 6c Shiny App model inputs, Mean number of recurrences

The recurrence risk with supervision tab refers to the risk of recurrence with certain treatment regimens given as part of supervised administration. Globally, *P. vivax* strains have different relapse patterns and, where possible, treatment efficacy data should be obtained regionally, or within the country of interest if these data are available.[21,24] In some settings, high quality surveillance data from clinical cases and their follow-up can be used for these estimates. The recurrence risk without supervision tab refers to the risk of recurrence with certain treatment regimens administered without supervision. These values can be obtained directly from studies that measure effectiveness. However, due to limited data on effectiveness, the tool largely makes estimates using risk ratios from trials comparing supervised and unsupervised regimens. The tool then applies those risk ratios to data from the region regarding recurrence risk of supervised treatment to generate an estimate of recurrence risk with unsupervised treatment, and assuming 20% precision around that estimate. The tool also assumes that an unsupervised regimen cannot be more effective than a supervised regimen in preventing recurrences.

Step 4: Generate outputs to compare treatment schemes for a single scenario

After inputting data from Steps 1 to 3, the tool will generate graphs comparing outputs for all treatment schemes in a radical cure scenario. The tool provides a single table with the recurrences reported for the site(s) of interest that would be expected to occur in the subsequent year. Outputs are also provided as a proportion of the *P. vivax* cases. An example with mock input data is shown in Appendix B.

While this tool aims to quantify and compare recurrences associated with different radical cure treatment regimens and delivery strategies, the tool is not intended to be used in isolation to determine treatment policy for a country. Rather, findings from the assessment should inform decision-making, alongside considerations of contextual factors such as risk aversion, cost, and indirect effects of decreased recurrences or health system strengthening activities (e.g., G6PD testing or supervision of treatment) on improving quality of life, health system strengthening, trust in the health system, and malaria elimination and eradication goals (Appendix E).

Step 5: Generate outputs to compare treatment schemes for two scenarios

The tool has a tab whereby up to two scenarios can be compared (Appendix C). The user enters the proportion of the area that reflects one delivery strategy scenario, and then the remaining area will receive an alternative delivery strategy scenario. The tool then compares recurrences for all possible schemes given the proportion entered.

Limitations

There are several limitations of the tool that users should consider. First, the evidence is limited regarding 8-aminoquinoline associated hemolytic risk, precluding accurate estimates of hemolysis or deaths for the different regimens. Further, data regarding G6PDd prevalence are limited, and where available, these data are from community surveys, which may not reflect G6PD activity level in individuals presenting with malaria and recurrence risk with treatment. Level of hemolysis may also vary based on G6PDd variants, though there is limited evidence in this area.[25] Nonetheless, as data become available, the tool can be improved and in the meantime, the delivery strategies proposed in this tool, namely G6PD testing and supervision of treatment, can help to mitigate risk of hemolysis.

The evidence regarding recurrence risk associated with different treatment regimens, and especially unsupervised treatment, are also limited. Studies with more controlled data from the region are difficult to fund and conduct. Also, these studies can be difficult to power, particularly in LAC where transmission is declining. Where data are not available from LAC, the tool uses data from outside the region. The tool also allows for a sensitivity analysis whereby a range of input values for this variable are considered.[16] Another intended goal of the tool is to identify areas where more rigorous data are needed. If there is considerable uncertainty around specific inputs, and the sensitivity analysis suggests that this variable is a major driver of benefit or risk, studies to generate more accurate estimates of these inputs should be considered.

Another limitation of the tool is that many difficult-to-measure factors influence risk and benefit and are not captured in this tool (Appendix E). Appendix E of the tool provides a worksheet where these difficult-to-quantify factors can be prioritized and considered as part of the decision-making process. Users are encouraged to work through the questions in Appendix E to identify other factors that might affect the results.

Future Steps

Transferability

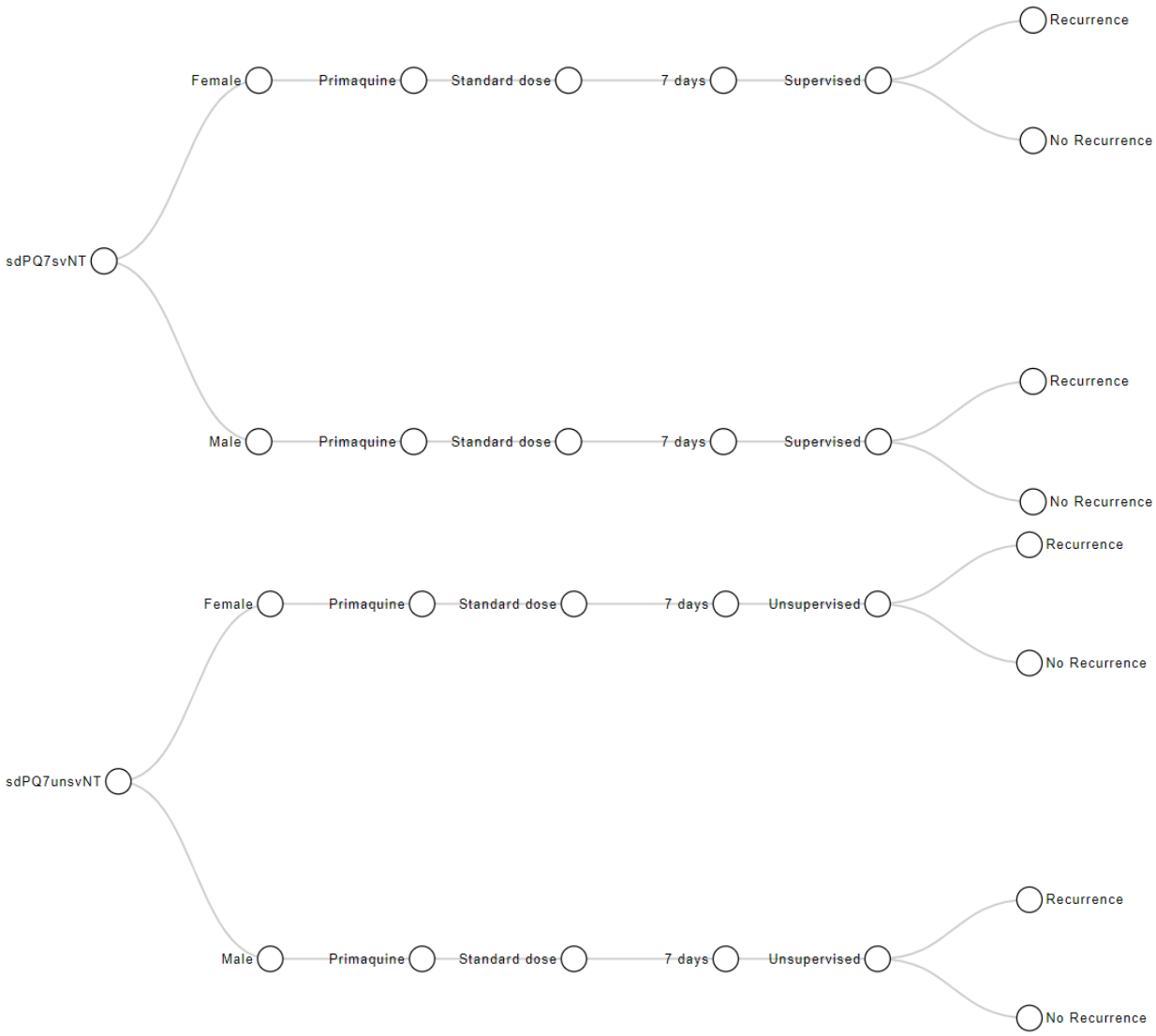
The Risk Benefit Assessment Tool can be used in other *P. vivax* endemic areas outside of the LAC region. The tool may also be adapted to mass drug administration (MDA) programs. While benefits in terms of reduced transmission cannot be quantified (due to lack of controlled data regarding MDA for *P. vivax*), the tool could be used to quantify risks of severe hemolysis and associated deaths using the total population that is being targeted for MDA as the population size of interest.

Appendices

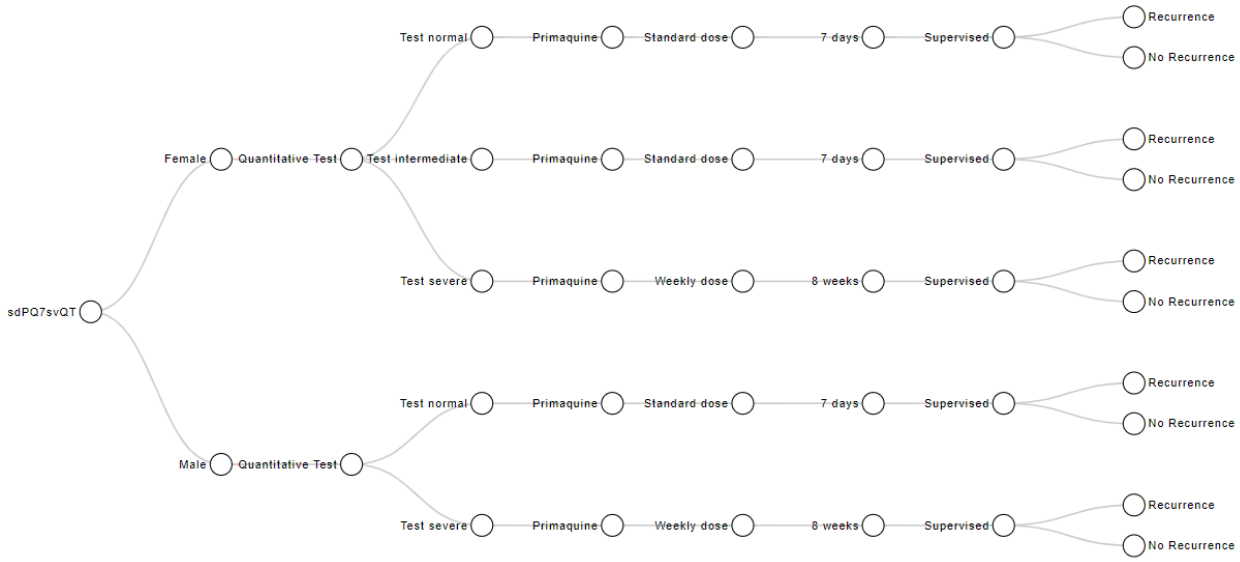
Appendix A. Decision algorithm trees for 11 treatment schemes

1. sdPQ7 treatment schemes

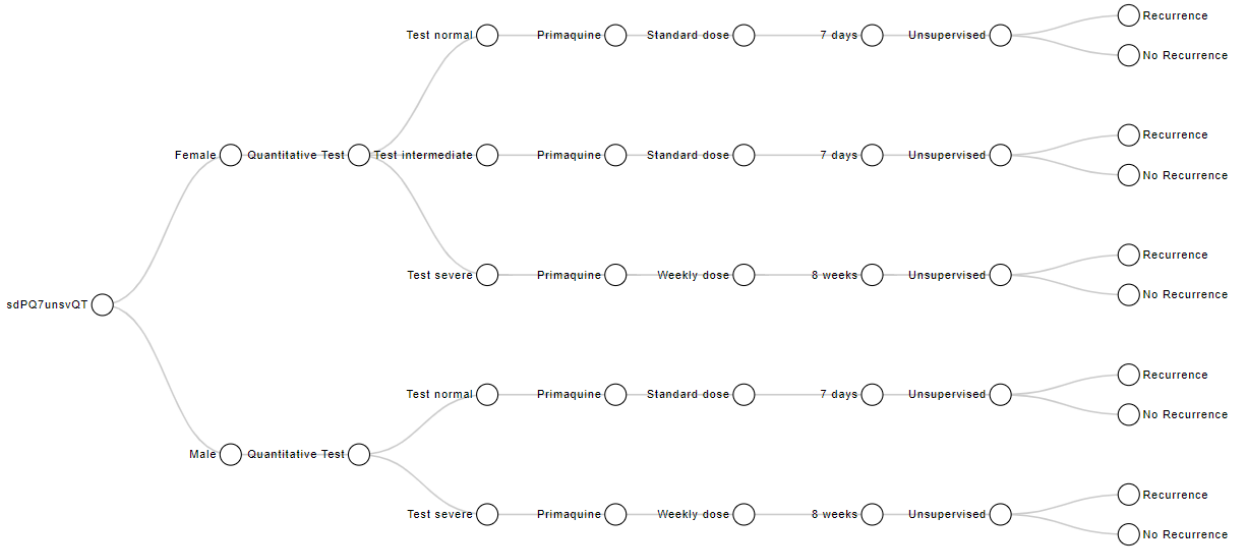
A. No Testing, Supervised



B. Quantitative G6PD Testing, Supervised

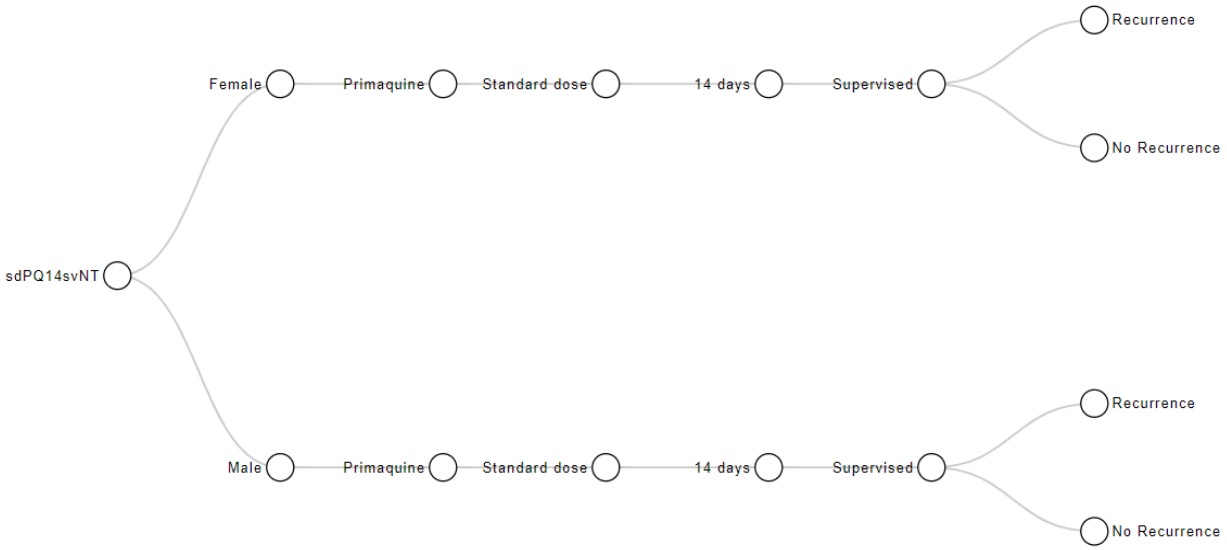


C. Quantitative G6PD Testing, Unsupervised

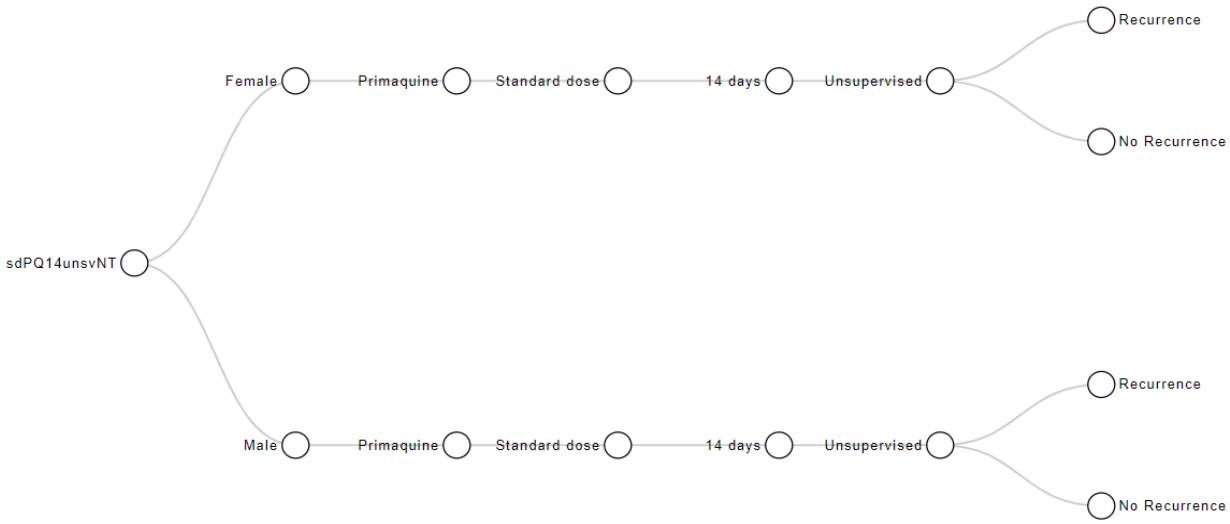


2. *sdPQ14 treatment schemes*

A. No Testing, Supervised

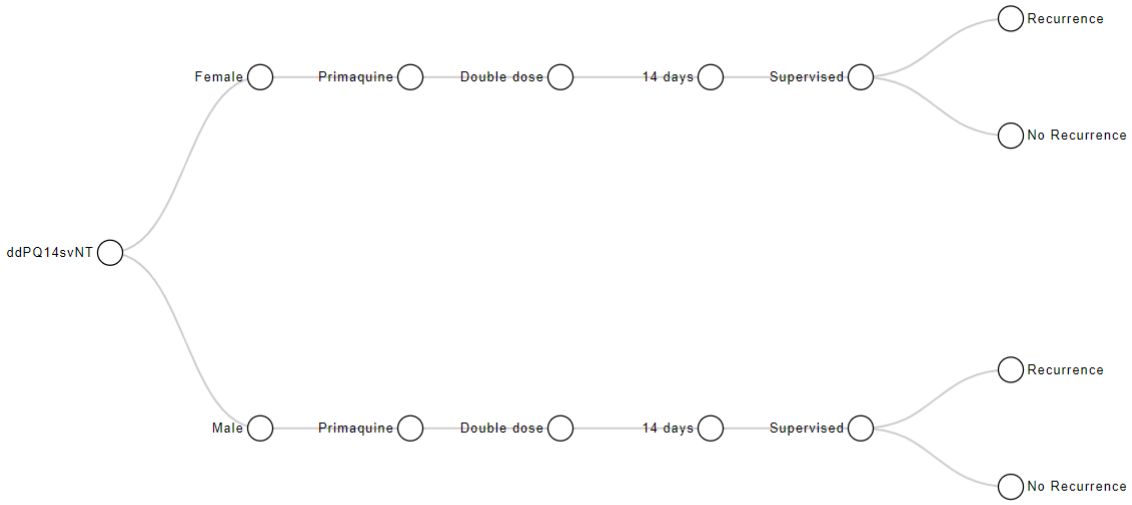


B. No Testing, Unsupervised

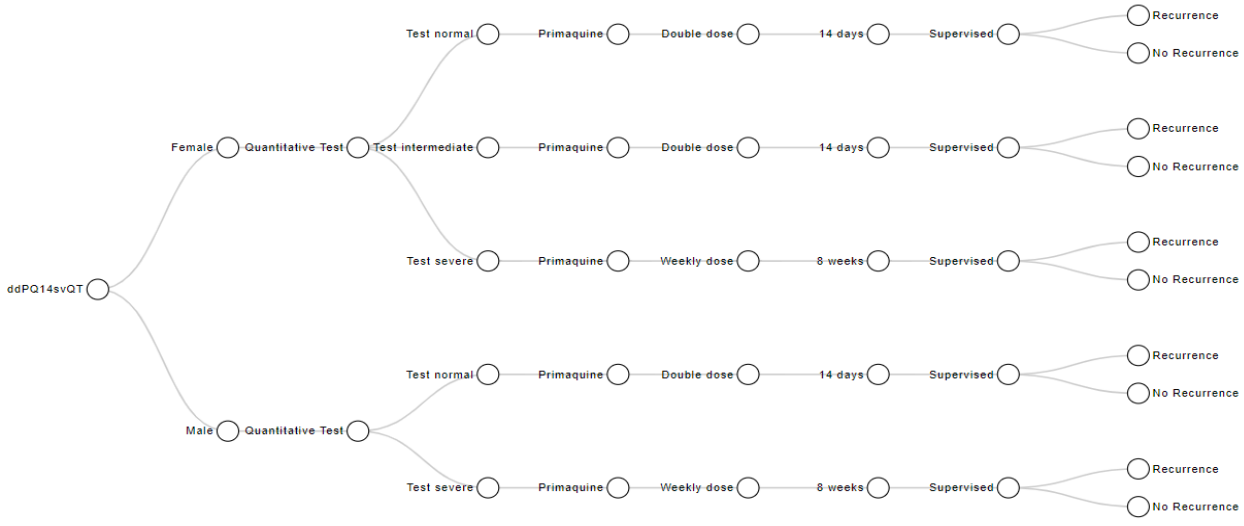


3. *ddPQ14 treatment schemes*

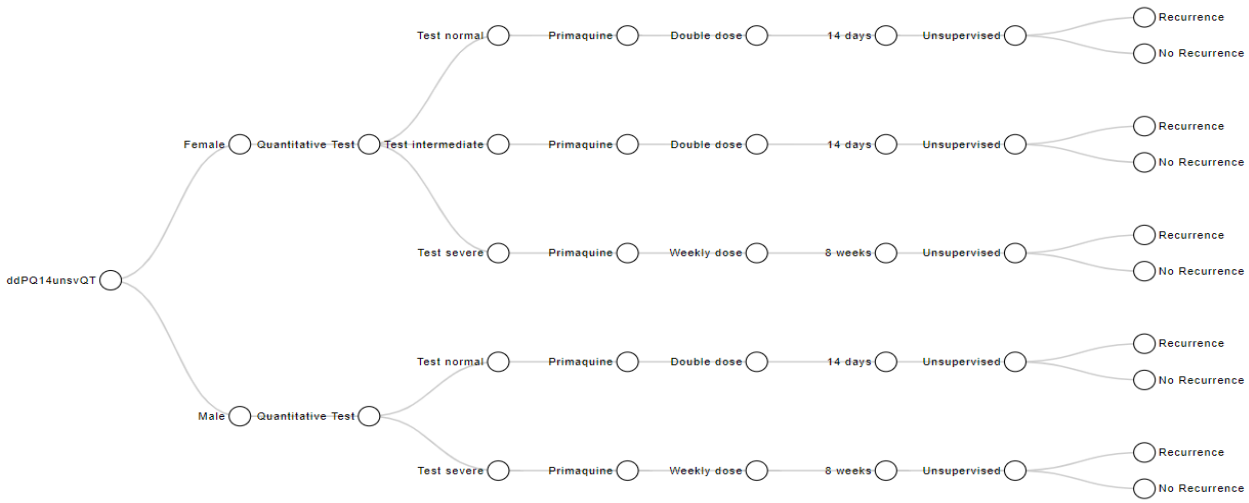
A. No Testing, Supervised



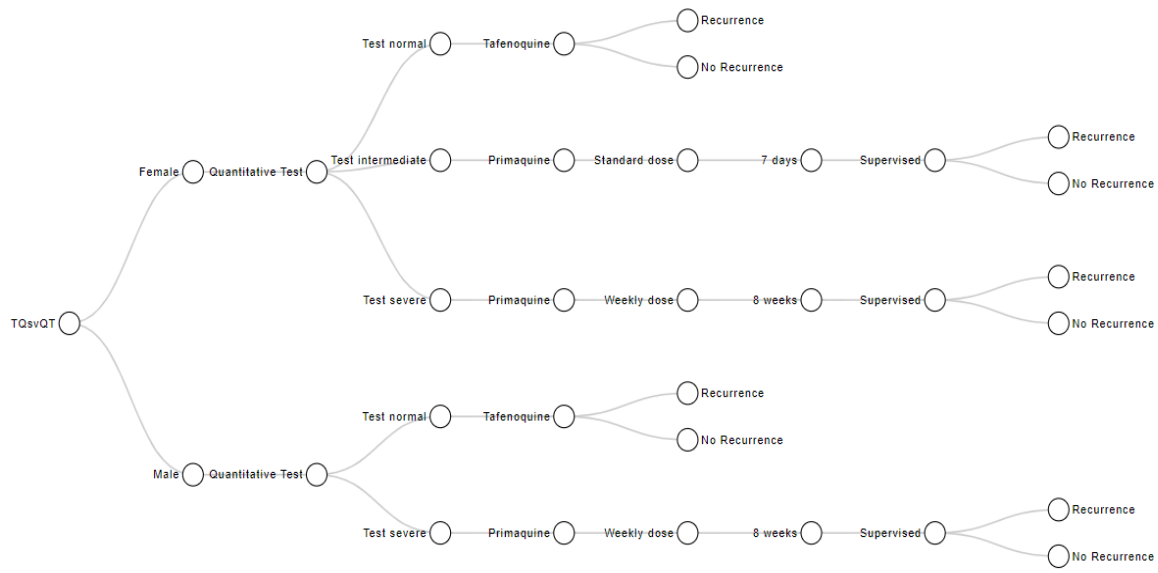
B. Quantitative G6PD Testing, Supervised



C. *Quantitative G6PD Testing, Unsupervised*

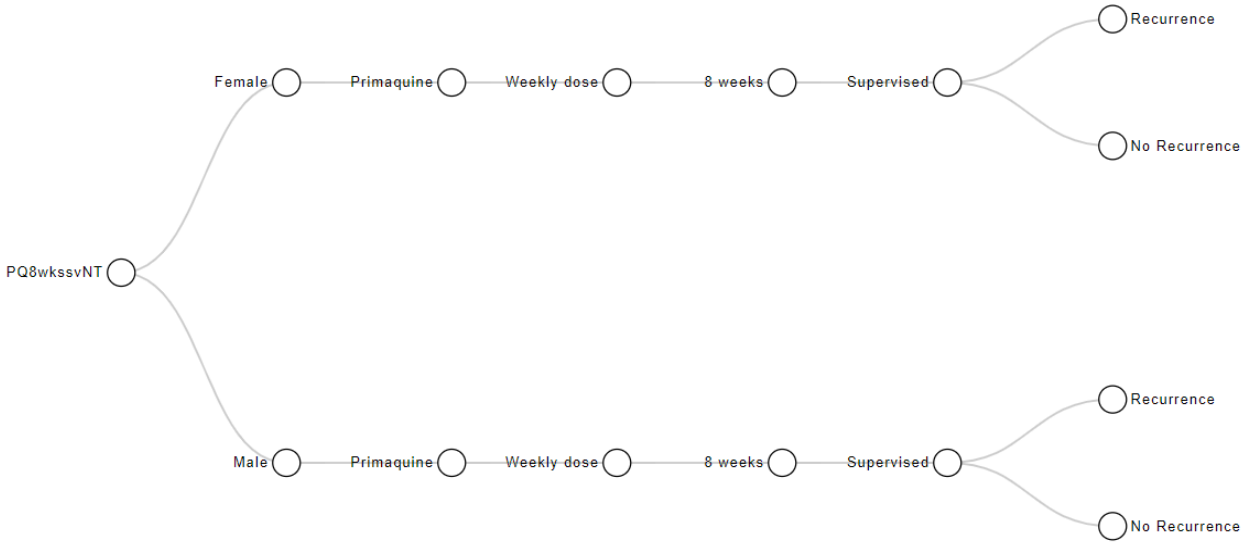


4. *TQ, Supervised, Quantitative G6PD Testing*

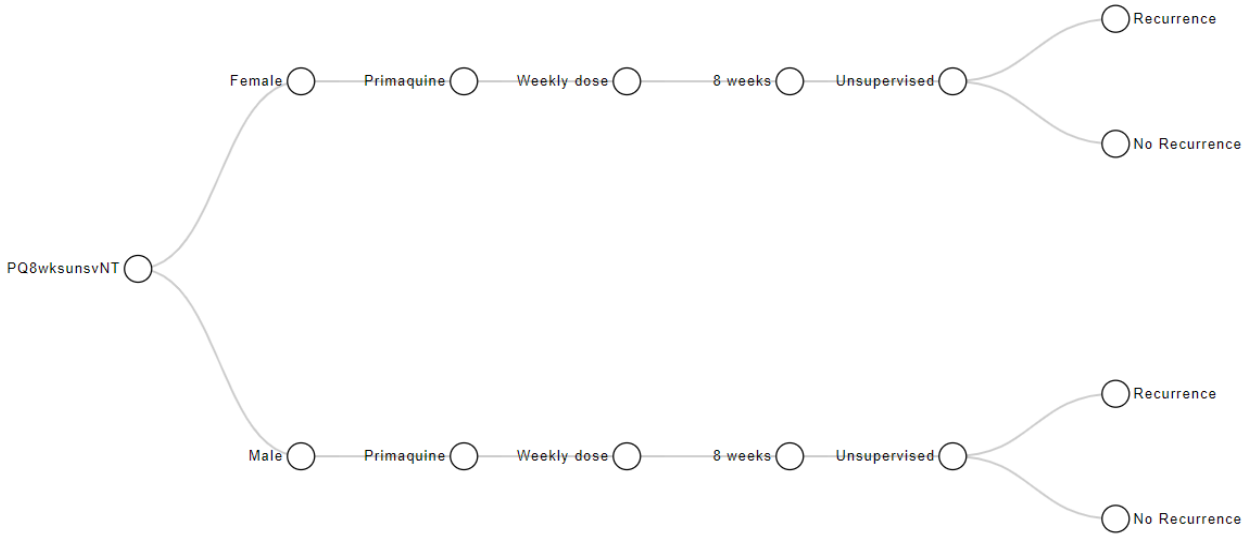


5. PQ8wks treatment schemes

A. No Testing, Supervised



B. No Testing, Unsupervised



Appendix B. Site Pre-test, Single Scenario

In this hypothetical site, the number of annual *P. vivax* cases is 10,000. Of the cases, 60% are male. Default input values for recurrences are also shown.

Appendix B, Table 1. Data inputs for hypothetical site, Single Scenario

Categories	Label name *	Inputs	Input value	Reference/Notes
General information		Country	Example	Non-Amazonian strain
		Administrative unit of interest	Example	Administrative unit at the country, regional, or district level
	Num	Number of *P. vivax* cases	10,000	Hypothetical
	P1.1	Percentage of patients that are male	60%	Assumption, in malaria endemic settings in Latin America, males at high risk[26]
Treatment scheme considerations		Currently used radical cure scheme (indicate if supervised or unsupervised)	sdPQ14 (unsupervised)	0.25 mg/kg x 14 days
		Health system can provide supervised treatment, Yes/No	Yes/No	Both considered
		Health system can conduct G6PD testing at the point of care according to protocol	Yes/No	Both considered
		Other radical cure scheme(s) being considered	All	All radical cure schemes considered in the tool are being considered.
G6PD deficiency epidemiology	P2.1 P2.2	Prevalence of G6PDd (≤70%), lower and upper range	0-4.9%	0-4.9%
Scenario	P3.1	Hemolytic risk	Low/High	Both considered
	P3.2	Scenario	No Test, Supervised	All considered
			No Test, Unsupervised	

				Quantitative Test, Supervised	
				Quantitative Test, Unsupervised	
Recurrence	Recurrence risk with supervised treatment**	P4.1	sdPQ7	24%	References: Zuluaga-Idárraga *et al.*,[27] Alvarez *et al.*[28] (Default value from non-Amazonian setting in Colombia)
		P4.2	sdPQ14	24%	References: Zuluaga-Idárraga *et al.*,[27] Alvarez *et al.*[28] (Default value from non-Amazonian setting in Colombia)
		P4.3	ddPQ14	12.6%	Reference: Chamma-Siqueira *et al.*[20]
		P4.4	TQ	24%	References: Zuluaga-Idárraga *et al.*,[27] Llanos-Cuentas *et al.*[23]
		P4.5	PQ8wks	24%	Ley-Thriemer (personal communication); WHO guidelines for malaria[8]
	Risk ratio of recurrences with unsupervised versus supervised treatment**	P4.6	sdPQ7	1.02-1.52 24.5%-36.5%	Reference: Chamma-Siqueira *et al.*[20], Dinelly *et al.*[29] (Risk ratio 1.02-2.0 in references, but upper limit not to exceed upper limit in P4.7)
		P4.7	sdPQ14	1.01-1.52 24.5%-36.5%	Reference: Leslie *et al.*[30] (Risk ratio 1.27, data from Pakistan)
		P4.8	ddPQ14	1.28-1.92 16.1%-24.2%	Reference: Poespoprodjo *et al.*[10] (Risk ratio 1.60, data from Indonesia)
		P4.9	PQ8wks	2 48%	Ley-Thriemer (personal communication); WHO guidelines for malaria;[8] Assumption that adherence will be poor, resulting in same recurrence risk as no treatment
	Mean number of recurrences in a year if there was at least one recurrence	P4.10	sdPQ7 or sdPQ14 or PQ8wks	1.23	References: Zuluaga-Idárraga *et al.* (mean 1.38),[27] Alvarez *et al.* (mean 1.08)[28]
		P4.11	ddPQ14	1.12	Reference: Abreha *et al.*[31] (Ethiopia: sdPQ associated with 2.375 recurrences during a year of follow-up), Taylor *et al.*,[18] (Ethiopia: ddPQ associated with 2.6

					recurrences). RR 0. 91 applied to P.4.10
		P4.12	TQ	1.23	Reference: Llanos-Cuentas *et al.*[23]
Two scenario comparison (Area A and Area B)		%	Proportion in area A	50%	Hypothetical

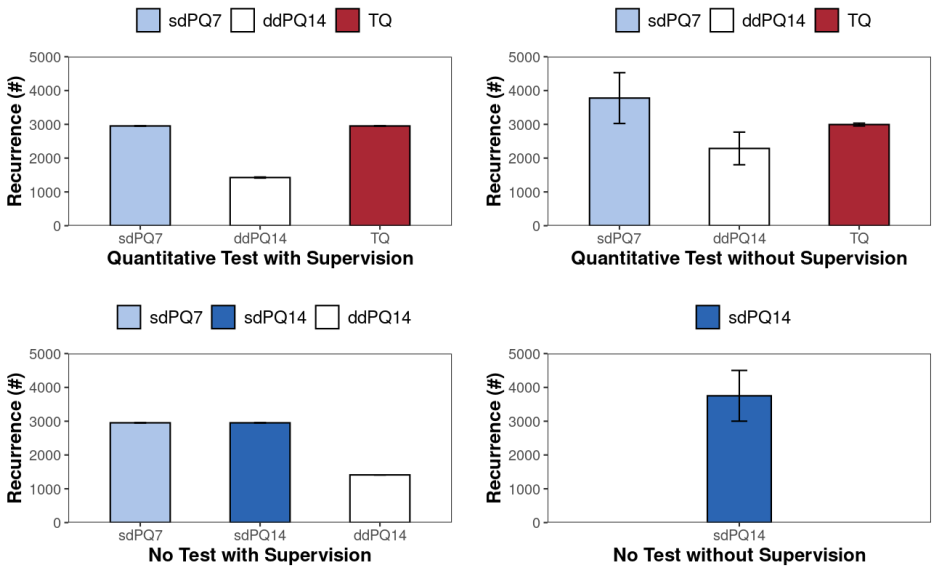
**Label name used in Shiny App code*

***Recurrence risk with unsupervised treatment is calculated by the tool using these input values. Values for recurrence risk with supervised treatment, as well as risk ratios of recurrences with unsupervised versus supervised treatments, were obtained from published studies. Where feasible, these values were obtained from studies conducted in the LAC region. Recurrence risk for unsupervised treatment was calculated as the product of: [recurrence risk with supervised treatment] * [risk ratio of recurrences with unsupervised versus supervised treatment]. For the estimate of risk ratio of recurrences with unsupervised versus supervised treatment, IM assumed a precision of 20% and that the estimate would be ≥1.0.*

Appendix B, Table 2. Table of Scenarios for low hemolytic risk settings.

	G6PD Testing	No G6PD Testing
Supervision	Scenario 1 sdPQ7, ddPQ14, TQ	Scenario 2 sdPQ7, sdPQ14, ddPQ14
No supervision	Scenario 3 sdPQ7, ddPQ14, TQ	Scenario 4 sdPQ14

Appendix B, Figure 1. Single treatment scheme, Comparison of recurrences for treatment schemes in each scenario of low hemolytic risk settings.



Appendix B, Table 3. Outputs for all scenarios in low hemolytic risk settings.

Scenario	Risk	Delivery Strategy	Regimen	Recurrence: Mean	Recurrence: Min	Recurrence: Max
1	Low	Supervised + Quantitative Test	sdPQ7	2,952	2,952	2,952
	Low	Supervised + Quantitative Test	ddPQ14	1,426	1,411	1,440
	Low	Supervised + Quantitative Test	TQ	2,952	2,952	2,952
2	Low	Supervised + No Test	sdPQ7	2,952	2,952	2,952
	Low	Supervised + No Test	sdPQ14	2,952	2,952	2,952
	Low	Supervised + No Test	ddPQ14	1,411	1,411	1,411
3	Low	Unsupervised + Quantitative Test	sdPQ7	3,777	3,026	4,528
	Low	Unsupervised + Quantitative Test	ddPQ14	2,287	1,803	2,770
	Low	Unsupervised + Quantitative Test	TQ	2,993	2,952	3,035
4	Low	Unsupervised + No Test	sdPQ14	3,751	3,001	4,502

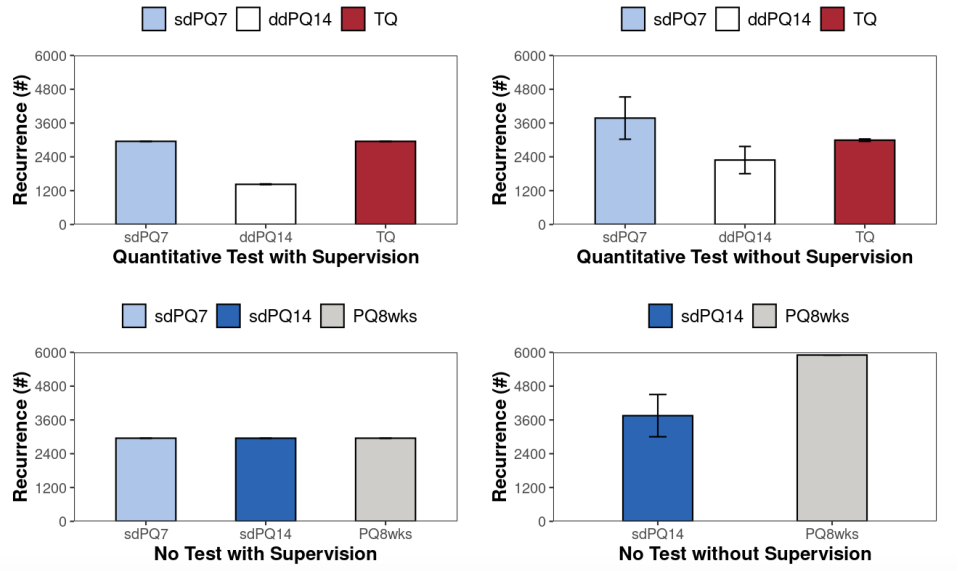
Interpretation

Overall, the treatment regimen associated with the lowest number of recurrences is ddPQ14. See table 3 output where the recurrences estimated with ddPQ14 are shown in light blue. Among the ddPQ14 options, the unsupervised regimen with G6PD testing is associated with the most recurrences (2,287 recurrences) due to expected challenges with adherence and thus effectiveness. Supervised ddPQ14 with G6PD testing is associated with more recurrences than with supervised ddPQ14 without G6PD testing because with the former scheme, those identified as G6PD deficient will receive supervised PQ8 weeks, which is less effective than ddPQ14. However, supervision for 14 days may be operationally and/or cost prohibitive. In the Shiny App table outputs, the user can sort results by clicking the column header, e.g., by "Recurrence: mean," "Regimen," or "Delivery strategy," to consider other situations relevant to the site. For example, if the program is currently using sdPQ14 in Scenario 4, transitioning to sdPQ7 in Scenario 2 (no testing with supervision for seven days) may be feasible and affordable and still result in fewer recurrences (3,751 versus 2,952 recurrences, respectively). See light versus dark orange in table 3. Of note, sdPQ7 unsupervised with G6PD testing is associated with more recurrences than sdPQ14 unsupervised without G6PD testing (3,777 versus 3,751 recurrences, respectively). sdPQ14 and sdPQ7 have the same effectiveness when supervised. However, for either regimen, when unsupervised, G6PD testing is associated with more recurrences than no G6PD testing because those identified a G6PD deficient will receive PQ8weeks unsupervised, for which adherence and thus effectiveness is expected to lower than for sdPQ7 or sdPQ14.

Appendix B, Table 4. Table of scenarios for high hemolytic risk settings.

	G6PD Testing	No G6PD Testing
Supervision	Scenario 5 sdPQ7, ddPQ14, TQ	Scenario 6 sdPQ7, sdPQ14, PQ8wks
No supervision	Scenario 7 sdPQ7 ddPQ14 TQ	Scenario 8 sdPQ14, PQ8wks

Appendix B, Figure 2. Single treatment scheme, Comparison of recurrences for treatment schemes in each scenario for a high hemolytic risk setting.



Appendix B, Table 5. Outputs for all scenarios in high hemolytic risk settings.

Scenario	Risk	Delivery Strategy	Regimen	Recurrence: Mean	Recurrence: Min	Recurrence: Max
5	High	Supervised + Quantitative Test	sdPQ7	2,952	2,952	2,952
	High	Supervised + Quantitative Test	ddPQ14	1,426	1411	1440
	High	Supervised + Quantitative Test	TQ	2,952	2,952	2,952
6	High	Supervised + No Test	sdPQ7	2,952	2,952	2,952
	High	Supervised + No Test	sdPQ14	2,952	2,952	2,952
	High	Supervised + No Test	PQ8wks	2,952	2,952	2,952
7	High	Unsupervised + Quantitative Test	sdPQ7	3,777	3,026	4,528
	High	Unsupervised + Quantitative Test	ddPQ14	2,287	1,803	2,770
	High	Unsupervised + Quantitative Test	TQ	2,993	2,952	3,035
8	High	Unsupervised + No Test	sdPQ14	3,751	3,001	4,502
	High	Unsupervised + No Test	PQ8wks	5,904	5,904	5,904

Interpretation

Overall, the scheme associated with the lowest number of recurrences is ddPQ14. See table 5 output where the recurrences estimated with this regimen are shaded in light blue. If the program currently uses sdPQ14 in Scenario 8 (No Supervision, No G6PD testing), and a priority moving forward is to decrease recurrences, they can pick ddPQ14 in Scenario 5 (Supervision and G6PD Testing) or Scenario 7 (No supervision, G6PD testing). But they may also consider other schemes that would result in the next fewest recurrences; these include any other regimens in Scenario 5 or 6, as these all would result in 2,952 recurrences (shaded in dark orange) compared to the current regimen which results in 3,751 recurrences (shaded in light orange).

Appendix C. Site Pre-test with Two Scenarios

For health facilities with different capacities for supervision and/or G6PD testing, the tool can also consider two different scenarios in one site. The Shiny App has an option to show outputs for all possible combinations of treatment schemes for two scenarios. However, this produces many outputs that may be difficult to interpret. Thus, it is recommended that for two scenarios, the user choose two specific drug regimens. The proportion of patients in Area A can be set as any value between 0%–100%. Shown below are examples of outputs for a situation where the proportion is set at 50% for Area A and 50% for Area B.

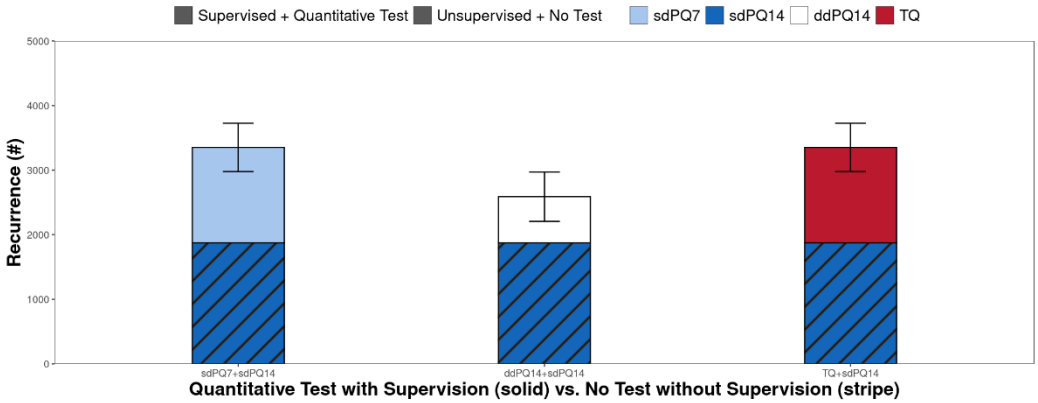
Two scenarios for a site with low hemolytic risk

For a site with low hemolytic risk (G6PDd prevalence 0-4.9% with capacity to manage hemolytic events), quantitative testing with supervision (Scenario 1) is being considered for Area A, which serves 50% or half of *P. vivax* cases. The current standard of care radical cure scheme is unsupervised sdPQ14, without G6PD testing (Scenario 4). and this will be continued in Area B, which the rest of the *P. vivax* cases.,

Appendix C, Table 1. Table of low hemolytic risk setting delivery strategies.

	G6PD Testing	No G6PD Testing
Supervision	Scenario 1 sdPQ7, ddPQ14, TQ	Scenario 2 sdPQ7, sdPQ14, ddPQ14
No supervision	Scenario 3 sdPQ7, ddPQ14, TQ	Scenario 4 sdPQ14

Appendix C, Figure 1. Recurrence in low hemolytic risk setting with two scenarios.



Note: light blue: sdPQ7, dark blue: sdPQ14, white: ddPQ14, red: TQ, top of bar without stripe: Area A, bottom of bar with stripe: Area B

Appendix C, Table 2. Low hemolytic risk setting, two treatment scenarios, Output table for all combinations.

Risk	Delivery strategy A	Regimen A:	A Mean:	A Min:	A Max:	Delivery strategy B	Regimen B:	B Mean:	B Min:	B Max:	Sum Mean:	Sum Min:	Sum Max:
Low	Supervised + Quantitative Test	sdPQ7	1,476	1,476	1,476	Unsupervised + No Test	sdPQ14	1,876	1,501	2,251	3,352	2,977	3,727
Low	Supervised + Quantitative Test	ddPQ14	713	706	720	Unsupervised + No Test	sdPQ14	1,876	1,501	2,251	2,589	2,206	2,971
Low	Supervised + Quantitative Test	TQ	1,476	1,476	1,476	Unsupervised + No Test	sdPQ14	1,876	1,501	2,251	3,352	2,977	3,727

Interpretation

Overall, the regimen associated with the lowest recurrences is the middle bar, colored white in Area A (top part of bar, ddPQ14, Scenario 1) and dark blue with stripe in Area B (bottom part of bar, sdPQ14, Scenario 4). Use of these schemes together will result in a sum mean of 2,971 recurrences (shaded in light blue box). The two other combinations result in a sum mean of 3,727 recurrences (See light orange shaded boxes). If Area A serves a mobile population where 14 days of supervision may be challenging, the program may opt for TQ or sdPQ7 which would require fewer days of supervision. Note that the proportion in Area A versus Area B can be changed so that a program may consider different proportions.

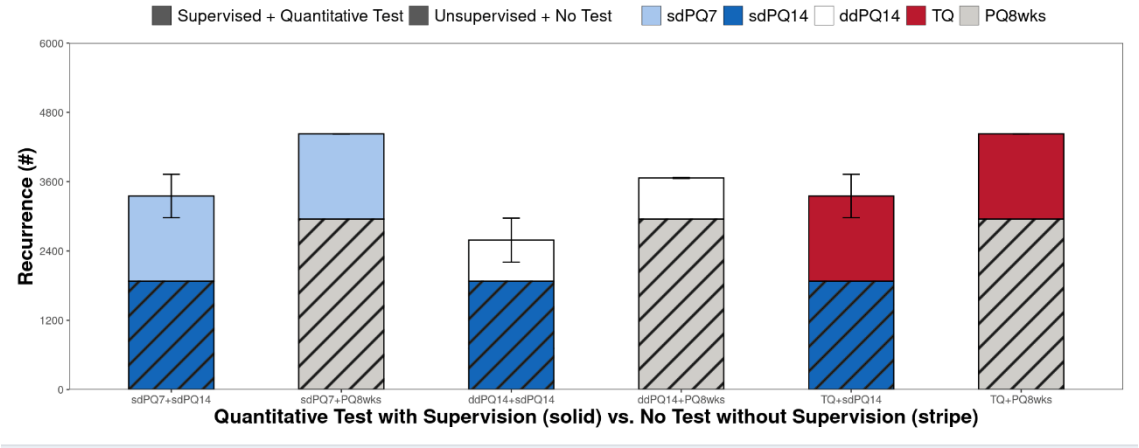
Two scenarios for a site with high hemolytic risk

For a site with high hemolytic risk (G6PDd prevalence is five - 10% and capacity to manage hemolytic events is limited), Area A is considering G6PD testing, and supervision (Scenario 5) and this area serves 50% or half of *P. vivax* cases. In the rest of the setting (Area B) radical cure is not supervised and there is no G6PD testing (Scenario 8)

Appendix C, Table 3. High hemolytic risk setting delivery strategies.

	G6PD Testing	No G6PD Testing
Supervision	Scenario 5 sdPQ7, ddPQ14, TQ	Scenario 6 sdPQ7, sdPQ14, PQ8wks
No supervision	Scenario 7 sdPQ7 ddPQ14 TQ	Scenario 8 sdPQ14, PQ8wks

Appendix C, Figure 2. The recurrence in high hemolytic risk setting with two scenarios.



Note: light blue: sdPQ7, dark blue: sdPQ14, white: ddPQ14, red: TQ, top of bar without stripe: Area A, bottom of bar with stripe: Area B

Appendix C, Table 4. Low hemolytic risk setting, two treatment scenarios, Output table for all combinations.

Risk	Delivery Strategy A	Regimen A	A Mean:	A Min:	A Max:	Delivery Strategy B	Regimen B	B Mean:	B Min:	B Max:	Sum Mean:	Sum Min:	Sum Max:
High	Supervised + Quantitative Test	sdPQ7	1,476	1,476	1,476	Unsupervised + No Test	sdPQ14	1,876	1,501	2,251	3,352	2,977	3,727
High	Supervised + Quantitative Test	sdPQ7	1,476	1,476	1,476	Unsupervised + No Test	PQ8wks	2,952	2,952	2,952	4,428	4,428	4,428
High	Supervised + Quantitative Test	ddPQ14	270	258	281	Unsupervised + No Test	sdPQ14	1,876	1,501	2,251	2,145	1,759	2,532
High	Supervised + Quantitative Test	ddPQ14	270	258	281	Unsupervised + No Test	PQ8wks	2,952	2,952	2,952	3,222	3,210	3,233
High	Supervised + Quantitative Test	TQ	1,476	1,476	1,476	Unsupervised + No Test	sdPQ14	1,876	1,501	2,251	3,352	2,977	3,727
High	Supervised + Quantitative Test	TQ	1,476	1,476	1,476	Unsupervised + No Test	PQ8wks	2,952	2,952	2,952	4,428	4,428	4,428

Interpretation

Overall, the regimen associated with the lowest recurrences is the third bar from the left, colored white above and dark blue with stripe below: ddPQ14 in Area A (Scenario 5) with sdPQ14 in Area B (Scenario 8). Use of these schemes together will result in a sum mean of 2,532 recurrences (shaded light blue). However, area A has a large migrant population whereby 14 days of supervised treatment may be challenging. The combination in the fourth bar from the left (white above and grey with a stripe below) would result in the next fewest recurrences (sum mean 3,233, see white box) but the program has

reservations about eight weeks of unsupervised treatment for Area B given limited evidence regarding the risk of recurrence for this regimen. The next fewest recurrences would be reached using the regimens in the first bar (sdPQ7+sdPQ14) or the fifth bar from the left (TQ+sdPQ14) in Areas A and B, respectively. These combinations each result in a sum mean of 3,727 recurrences (See orange shaded boxes). If Area A serves a mobile population where seven days of supervision may be challenging, the program may opt for single dose TQ instead. Note that the proportion in Area A versus Area B can be changed so that a program may consider different proportions.

Appendix D. Programmatic data inputs worksheet

Categories		Label name*	Inputs	Input value	Reference/ Notes
General information		P1.1	Country		
			Administrative unit of interest		
			Number of *P. vivax* cases		
			Percentage of male patients		
Treatment scheme considerations			Currently used radical cure scheme (indicate if supervised or unsupervised)		
			Health system can provide supervised treatment, Yes/No		
			Health system can conduct G6PD testing at the point of care according to protocol		
			Other radical cure scheme(s) being considered for case management (indicate if supervised or unsupervised)		
G6PD deficiency epidemiology		P2.1 P2.2	Prevalence of G6PDd (≤70% activity) lower and upper range		
Scenario		P3.1	Hemolytic risk	Low/High	
		P3.2	Scenario	No Test, Supervised	
				No Test, Unsupervised	
				Quantitative Test, Supervised	
				Quantitative Test, Unsupervised	
Recurrence	Recurrence risk with supervised treatment**	P4.1	sdPQ7	24%	27, 28 (Default value from non-Amazonian setting in Colombia)
		P4.2	sdPQ14	24%	27, 28 (Default value from non-Amazonian

					setting in Colombia)
		P4.3	ddPQ14	12.6%	20
		P4.4	TQ	24%	23, 27
		P4.5	PQ8wks	24%	Ley-Thriemer (personal communication), 8
	Risk ratio of recurrences with unsupervised versus supervised treatment**	P4.6	sdPQ7	1.02-1.52 2.5%-36.6%	20, 29 (Risk ratio 1.02-2.0 in references, but upper limit not to exceed upper limit in P4.7)
		P4.7	sdPQ14	1.01-1.52 24.5%-36.6%	30 (Risk ratio 1.27, data from Pakistan)
		P4.8	ddPQ14	1.28-1.92 16.1%-24.2%	10 (Risk ratio 1.60, data from Indonesia)
		P4.9	PQ8wks	2 48%	Ley-Thriemer (personal communication), 8
	Mean number of recurrences in a year if there was at least one recurrence	P4.10	sdPQ7 or sdPQ14 or PQ8wks	1.23	27, 28
		P4.11	ddPQ14	1.12	18, 31
		P4.12	TQ	1.23	23
Two scenario comparison (Area A and Area B)		%	Proportion in area A		

**Label name used in Shiny App code*

***Recurrence risk with unsupervised treatment is calculated by the tool using these input values. Values for recurrence risk with supervised treatment, as well as risk ratios of recurrences with unsupervised versus supervised treatments, were obtained from published studies. Where feasible, these values were obtained from studies conducted in the LAC region. Recurrence risk for unsupervised treatment were calculated as the product of: [recurrence risk with supervised treatment] * [risk ratio of recurrences with unsupervised versus supervised treatment]. For the estimate of risk ratio of recurrences with unsupervised versus supervised treatment, a precision of 20% was also assumed and that the estimate would be ≥1.0.*

Appendix E. Other considerations worksheet

Other benefits	Relationship between other benefits	Rank variable by importance to the program (1-5)
Quality of life	Fewer vivax cases and fewer 8-aminoquinoline associated hemolytic events will lead to lower burden of disease and improved quality of life and positive socioeconomic effects for the individual and community.	
Health system strengthening	The inclusion of a program to improve adherence, pharmacovigilance, or adverse event management leads to fewer vivax cases and 8-aminoquinoline associated hemolytic events and strengthens the overall health system.	
Trust in health system	Fewer vivax cases and 8-aminoquinoline associated hemolytic events lead to decreased transmission, and trust/satisfaction with the health system (by community and providers)	
National malaria elimination goal	Fewer vivax cases lead to decreased transmission, facilitating achievement of malaria elimination locally	
Regional malaria elimination goal, global eradication goal	Fewer vivax cases lead to decreased transmission, facilitating achievement of malaria elimination regionally and globally	

Appendix F. Instructions to set up the *P. vivax* Radical Cure Risk Benefit Assessment Shiny App Tool using "R" on your device

1. Install the RStudio program if you don't already have it.

2. Go to: https://github.com/XueWuUCSF/Risk-Benefit-Tool to download the R code titled "Risk Benefit Tool.r" and a zip file titled "Strategy.csv" to your device.

3. Double click the file RB_App.r which will then open the file in RStudio.

4. Note that for the interactive Decision Tree panel to work, you will need to replace the yellow highlighted areas on lines 679-729 in the code (for Tree 02 to Tree 13) to the path name on device for where the csv file is located. For a PC device, an example path name is "D:/foldername." For a Macintosh device, an example path name is "/Users/username/Documents/foldername"

5. Click the arrow in the upper right of the screen as shown in the screenshot below.

NOTE: The first time the code is run, you will need to accept the window prompts to allow for installation of the ShinyApp R package and other tools such as "command line developer tools." This will take a few minutes. You also need to accept the prompt to download various R packages (prompt will be in yellow at the top of your R screen). This will take a few minutes.

6. After all the tools and packages are installed, click the arrow again to Run the App.

7. Have fun!

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