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Assessing tafenoquine implementation in Brazil: a qualitative evaluation of perceptions of healthcare providers and *Plasmodium vivax* patients (QualiTRuST Study)

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Abstract

Background To eliminate malaria by 2035, Brazil must address *Plasmodium vivax*. Previously, first-line treatment was chloroquine plus 7-day primaquine (PQ) without glucose-6-phosphate dehydrogenase (G6PD) deficiency testing. In 2021, point-of-care quantitative G6PD testing and single-dose tafenoquine (TQ) were piloted in two municipalities. This study evaluated healthcare professional (HCP) and patient perceptions of TQ implementation.

Methods This qualitative observational study in Manaus and Porto Velho municipalities evaluated the pilot implementation of the new *P. vivax* malaria treatment algorithm in high/medium-complexity healthcare units (phase one), then low-complexity units (phase two). Qualitative data collection began 30 days after the first TQ treatment in each phase, i.e., October 2021 and March 2022. Perceptions of TQ were assessed using semi-structured in-depth interviews and field notes until saturation. Data were analysed through debriefing sessions, and systematic organization in Excel and MAXQDA, with themes derived by inductive and deductive analysis.

Results The study included 55 patients who received TQ and 94 HCPs. HCPs viewed the TQ single-dose regimen as a significant advancement over 7-day PQ, enhancing adherence. Patients appreciated the shorter duration of treatment and perceived a rapid clinical recovery and fewer side effects. HCPs also noted that TQ resulted in fewer recurrences of *P. vivax*. The single-dose administration of TQ facilitated complete supervision of the treatment, reduced HCP workload and ensured that patients received the necessary care and did not share the medication with family members. TQ packaging instilled patient trust, though HCPs working in the community found the packaging too bulky. Prescription insecurities among HCPs after initial training prompted requests for additional training. While some patients initially doubted single-dose efficacy, confidence grew with experience. TQ implementation increased awareness of pharmacovigilance and enhanced patient communication, with HCPs adhering to protocols for monitoring haemolysis symptoms.

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Conclusion Single-dose TQ for *P. vivax* malaria in Brazil's Amazon region was positively received by HCPs and patients. Positive perceptions of the medication may aid in improving patient adherence to malaria treatment, thereby reducing malaria recurrences. The findings underscore the importance of adaptive training to optimize *P. vivax* radical cure implementation.

Keywords Malaria, *Plasmodium vivax*, Qualitative study, Tafenoquine

Background

Malaria continues to present significant challenges for its elimination, in addition to its considerable and meaningful impact on people's lives worldwide, sustaining a substantial social burden, especially in low-and middle-income countries [1]. Between 2000 and 2022, malaria incidence in the Americas decreased by approximately 64%, and mortality rates declined by 60% in the population at risk [2]. However, countries across the Amazon basin continue to exhibit high malaria incidence, primarily due to *Plasmodium vivax* [2]. Notably, Venezuela, Brazil and Colombia contribute 73% of the malaria cases on the continent [2]. The concentration of cases in these nations underscores the complex interplay of factors contributing to the sustained transmission of the disease, including socio-economic challenges, healthcare infrastructure limitations, and the tropical forest environment which is highly receptive to malaria-carrying mosquitoes [3, 4].

In 2022, Brazil, with support from the Pan American Health Organization (PAHO), initiated a malaria elimination plan with the aim of reducing autochthonous cases to less than 68,000 per year by 2025 and achieving malaria elimination by 2035 [5]. The plan is strategically targeted at the Amazon region, where most malaria transmission occurs (99%) and focuses on new approaches for malaria treatment and diagnosis targeted at accelerating elimination [6]. In the case of *P. vivax* malaria, universal implementation of radical cure is the cornerstone of control and elimination efforts. Radical cure involves the administration of a schizontocidal drug to clear the blood stage infection and an 8-aminoquinoline to eliminate the dormant hypnozoite stage of the parasite. In Brazil, hypnozoite reactivation usually occurs within 2–3 months of the initial infection and may cause repeated relapses which significantly contribute to the burden of disease and transmission [7]. Hence, addressing relapses is a critical element of the malaria elimination programme.

Since the mid-1990s, the standard treatment protocol in Brazil for *P. vivax* malaria has been a combination therapy, consisting of chloroquine (CQ) administered over three days to all patients at a total dosage of 25 mg/kg, accompanied by primaquine (PQ) for seven days at 0.5 mg/kg/day [8]. This regimen applies to all cases, except when a probable relapse occurs within 60 days, when the same daily PQ regimen is given for 14 days. A key barrier to implementation is that PQ causes haemolysis in individuals who are glucose-6-phosphate dehydrogenase (G6PD) deficient. However, despite a 5% prevalence of G6PD deficiency in the Amazon [9], PQ was routinely administered without prior G6PD screening. This practice has been a significant cause of hospitalization among individuals with *P. vivax* malaria, often resulting in life-threatening acute haemolytic anaemia (AHA) and acute renal failure in endemic regions [10]. In Manaus, the incidence of primaquine-induced AHA was estimated to be as high as 85.2 cases per 100,000 primaquine users [10].

To enhance safety for G6PD deficient patients and support treatment adherence, in 2021, the Brazilian Ministry of Health (MoH) piloted revised guidelines for the management of *P. vivax* malaria in two municipalities. The new treatment algorithm included single-dose tafenoquine (TQ) and quantitative G6PD testing using SD Biosensor technology prior to administering radical cure for malaria [11]. The administration of PQ or TQ depended on patient age, breastfeeding status and G6PD activity. Pregnant women and infants <6 months of age were excluded from PQ or TQ treatment and received CQ alone. Single-dose TQ treatment (300 mg) was recommended for patients ≥16 years of age who were not breastfeeding with normal G6PD activity (≥6.1 U/g Hb). 7-day PQ (0.5 mg/kg/day) was recommended for patients ≥6 months of age, not breastfeeding or breastfeeding >1 month, with intermediate G6PD activity (4.1–6.0 U/g Hb), or those who were G6PD normal and not eligible for TQ. Weekly primaquine (0.75 mg/kg per week) for 8 weeks was recommended for G6PD deficient patients (≤4.0 U/g Hb) who were ≥6 months old and not breastfeeding or breastfeeding >1 month [12].

Brazil was the first malaria-endemic country to incorporate these new tools for *P. vivax* radical cure into the public health system [13]. To support effective implementation, two municipalities—Manaus (Amazonas) and Porto Velho (Rondônia)—were chosen to pilot the treatment algorithm. These municipalities were chosen because of the high incidence of *P. vivax* and the presence of two reference hospitals for the treatment of severe malaria cases and the management of AHA cases. Both hospitals participated in the phase IIb/III multi-center clinical trials of TQ [14–16]. The pilot implementation

found that point-of-care quantitative G6PD testing and TQ were highly feasible within the Brazilian national health service [12]. Additionally, in terms of the prevention of recurrence, treatment effectiveness was at least as high as recurrence-free efficacy demonstrated in clinical trials [14–17].

In the implementation of a new strategy for disease control, the importance of local, cultural, and individual aspects cannot be overstated, as they profoundly influence the outcome of such initiatives [18]. Understanding healthcare professionals' (HCPs) and patients' perceptions of TQ within Brazil's national health system is essential for effectively implementing innovative treatment and prevention strategies [19]. Community understanding and perception of the medication are fundamental to ensuring the success of treatment regimens, while the support of HCPs directly impacts the quality of care provided and the effectiveness of the treatment [20, 21]. Negative HCP perceptions about new tools impair implementation, undermining patient trust [22]. Conversely, positive perceptions, supported by intensive training and evaluation of understanding, can accelerate the implementation of new tools and improve patient trust and perceptions.

The introduction of point-of-care quantitative G6PD testing before providing radical cure demands a significant change in the current practice of HCPs and the experience of patients. HCPs must learn and adopt new skills to perform the G6PD test, interpret the results, and provide patients with the correct treatment, as well as counseling patients about G6PD testing and informing them of their treatment. Understanding and confidence of HCPs and patients regarding new tools is essential for their systematic use. The QualiTRuST study was a mixed-methods qualitative study conducted in parallel to the pilot implementation of the new *P. vivax* radical cure algorithm in Manaus and Porto Velho. It aimed to assess HCP and patient perceptions to identify factors that would facilitate or impair the timely adoption of the intervention. The operational feasibility and effectiveness of the new treatment algorithm were assessed in the TRuST study using observational methods [12, 17]. A qualitative investigation of HCP perspectives on training for quantitative G6PD testing has also been published [23]. This paper specifically examines HCP and patient perceptions of TQ within the Brazilian national health system.

Methods

Study context and study sites

Single-dose TQ (300 mg) for *P. vivax* was implemented in Brazil with the objective of improving patient adherence to malaria treatment, promoting a simple and effective radical cure, thus contributing to a reduction in the number of disease recurrences in the country. The Brazilian MoH conducted the implementation in 2021 in two distinct phases in two endemic municipalities with high transmission of vivax malaria in the Brazilian Amazon, Manaus and Porto Velho (Fig. 1). The incidence of malaria caused by *P. vivax* in these municipalities is concentrated especially in peri-urban and rural areas.

In phase one, TQ was implemented in high-complexity healthcare units such as hospitals, emergency rooms and urgent care units. Three months later, in phase two, the implementation was extended to low-complexity healthcare units, including primary and malaria-specific health units. From 2021 to 2022, 43 health facilities implemented quantitative G6PD testing and TQ. In total, during this period, 6075 patients with *P. vivax* malaria were treated in these units and 2685 (44.6%) received 3-day

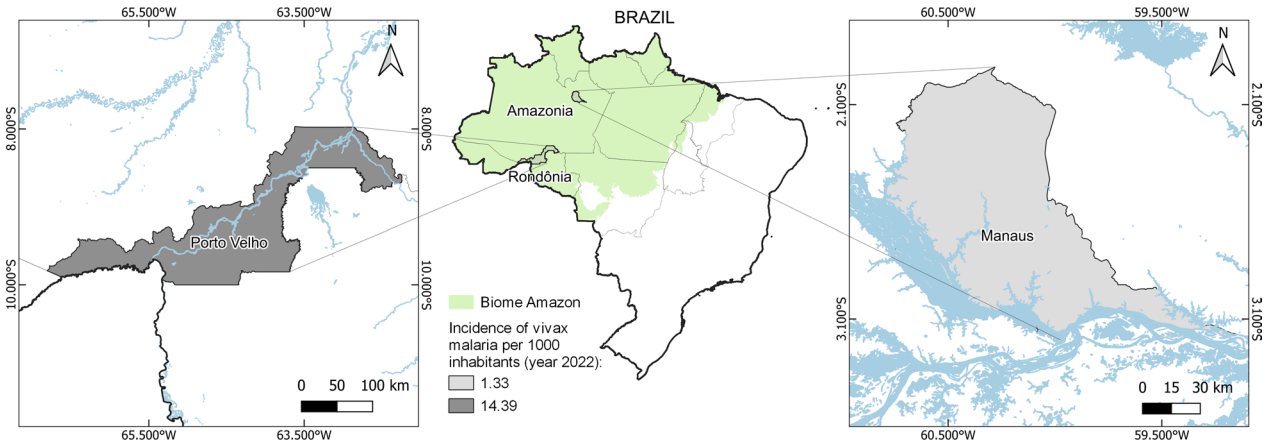

Fig. 1 Study sites (Manaus and Porto Velho). The image base used to create the map is from the IBGE (Brazilian Institute of Geography and Statistics), which is freely accessible for creative uses in shapefile format, in accordance with the Brazilian Access to Information Law (12,527/2011)

CQ together with single-dose TQ [12]. The implementation was supported by HCP training, including online resources, in-person sessions, practical sessions, peer-to-peer learning and updates and support via WhatsApp [23]. An overview of the clinical process for delivering *P. vivax* radical cure under the new treatment algorithm is provided in Fig. 2 [23].

Study design

A rapid qualitative study using in-depth interviews (IDIs) was adopted to understand HCP and patient perceptions and experiences of TQ during implementation [24]. TQ implementation started in high-complexity units in September 2021 (phase 1) and in low-complexity units February 2022 (phase 2). Qualitative data collection took place in October 2021 (phase 1) and March 2022 (phase 2), 30 days after the first patient received treatment with TQ (Fig. 3).

The research team chose the study design to provide rapid and valid responses, allowing timely feedback to the MoH during TQ implementation, facilitating essential adjustments in the communication strategy with HCPs and patients. Furthermore, this approach allowed for a larger number of interviews and enabled the identification of patterns and trends simultaneously with data collection, supporting robust data analysis [25].

Study objectives were to determine the barriers and enablers supporting wider implementation of TQ at the national scale by assessing the satisfaction, intent to continue use, and integration within the organization of care, including the perceived positive and negative effects of the intervention [26]. The framework of objectives was mirrored between HCPs at all levels or the organization and patients to generate a comprehensive and unified analysis (Fig. 4).

Data collection procedures

Data were collected via individual face-to-face IDIs using two semi-structured interview guides directed for HCPs and patients, reflecting the framework of objectives. The guides were developed by the research team, and included open-ended questions, allowing the interviewer to delve deeper into a topic as necessary (Tables 1, 2). Both guides were previously validated in a smaller sample of volunteers with the same characteristics as the study population to adjust the language and ensure a good understanding of the questions. The interviews took place during the first and second phases of TQ implementation (Fig. 3).

The research team had expertise in qualitative research methods and malaria. IDIs were led by FLGM, APCS, EARTS, APSO and HSSG, all of whom are HCPs and field researchers, with training and experience in qualitative data collection. IDIs were scheduled with the participants, according to their availability and lasted on average 35 min. For HCPs, IDIs were conducted in quiet locations at their workplace, and patient IDIs were done in their home environments. During the interviews, only the researchers, observers and participants were present at the location. The IDIs were audio recorded, transcribed into Word, and field notes and observations were made by the observers for data triangulation during the analysis. No repeat IDIs were conducted and participants did not have access to transcripts or provide feedback on the study findings.

Participant selection and recruitment

HCPs and patients were intentionally included in the study according to pre-selected criteria [27]. For patients, criteria were diagnosis of vivax malaria, known G6PD status and prescribed medication (TQ). These criteria were established to capture the diversity of specific knowledge and heterogeneous experiences relevant to the context. HCP selection criteria included working daily with malaria diagnosis, treatment, and health education or overseeing a facility that treats malaria patients and having been trained in the use of the new tools. None of the participants had an established relationship with any member of the study team prior to study commencement. Participant sample size was determined based on the principle of theoretical saturation, observed during the fieldwork, when the information obtained in IDIs begins to repeat, revealing a consistent pattern of responses, and no new information emerges [28].

Data analysis

Data analysis occurred concurrently with data collection after debriefings sessions. The debriefing sessions provided immediate insights into the data content, and informed necessary adjustments during data collection, addressing unforeseen issues in the local context. Moreover, debriefings enhanced the real-time quality and reliability of the data, thereby assisting in the analysis process [29]. Data analysis initially involved researchers engaging in discussions, and reviewing interviews, audio recordings and field observations, aiming to achieve an immersive understanding of the data. Additionally, a table was used to systematically organize all the acquired data through both inductive and deductive analysis. This table, structured based on the interview script for both HCPs and patients, featured columns for participant identifiers (usually designated as IDI 01 in ascending order) and topics requiring prompt responses. These topics generally covered aspects related to TQ impressions, incorporating participants' statements. The extracted data were then entered into MAXQDA software for deeper analysis and

Fig. 2 Summary of the clinical process for *P. vivax* radical cure. Example of training material used during the TRuST study implementation [23]

theme construction. Two researchers (APCS and FLGM) reviewed the data and reached consensus on the formed categories and themes. Subsequently, the interviews were fully transcribed to deepen the analysis and validate the initial findings.

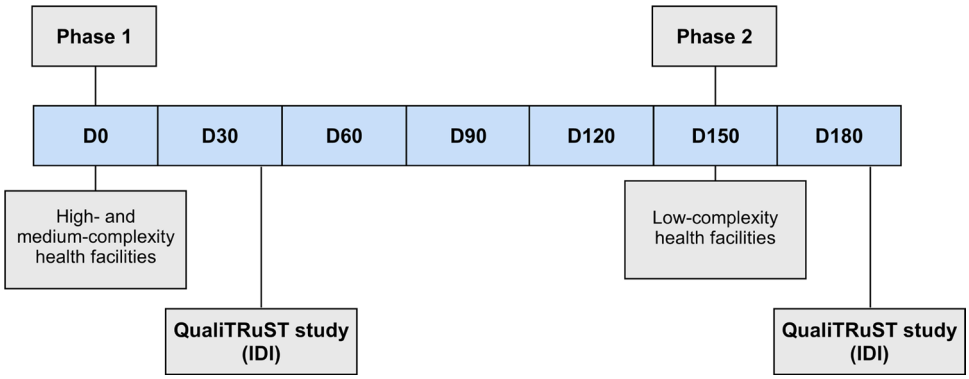

Fig. 3 Timeline of TQ implementation and QualiTRuST study. *IDI* in-depth interview

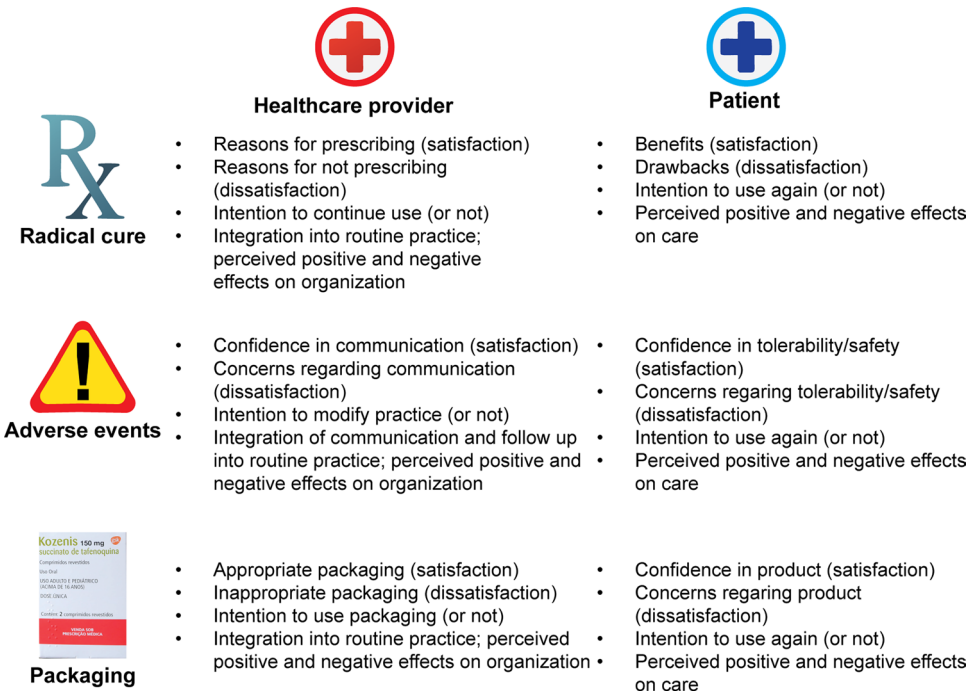

Fig. 4 Framework of objectives for the qualitative analysis

Research team and reflexivity

The study team consisted of nine qualitative researchers, including five women (APCS, APSO, RND, EARTS, PCSB) and four men (MAMB, FLGM, HSSG, HAAJ), all with expertise in studies focused on neglected tropical diseases. FLGM, APCS, and MVGL had previously conducted qualitative research with malaria healthcare providers in the Amazon region [19, 23, 30]. The team members made efforts to ensure that their subjectivity did not influence the collection and analysis of data. The study team had no prior relationship with the participants.

Ethics statement

The Ethics Review Board at the *Fundação de Medicina Tropical Dr Heitor Vieira Dourado* in Manaus and the National Research Ethics Committee (CONEP) in Brasília, Brazil (CAAE: 47598921.2.0000.0005) approved the protocol for both study sites. Eligible patients and HCPs provided their signed consent prior to participation. Participants were briefed on the purpose of the study and understood that it was a research project. All consolidated criteria for reporting qualitative research (COREQ) were followed in the production of this manuscript [31] (Additional file 1).

Table 1 Individual in-depth interview guide for healthcare providers

Questions	Objective
Radical cure	
• What do you think about tafenoquine in general? • How was your experience following the new treatment guidelines? • Are there any factors or barriers that you have experienced using tafenoquine that impact on the delivery to the patients?	Understand perception regarding tafenoquine
Adverse events	
• How do you inform patients about possible adverse events? • What would you do if a patient complains of any adverse events? • How do patients react when you inform them about adverse events?	Assess understanding of adverse events with radical cure and experience with informing patients
Packaging of tafenoquine	
• What do you think of the packaging of tafenoquine? • How does the packaging of tafenoquine compare to other malaria medications? • Does the packaging format contribute to the work routine in any way?	Evaluate the interviewee's perception of the tafenoquine packaging and how its features are perceived

Table 2 Individual in-depth interview guide for patients

Questions	Objective
Radical cure treatment	
• What treatment did you receive? • Do you know why this treatment given? Describe • Do you already know the treatments for malaria? If so, which one do you prefer? Why? • Have you heard of tafenoquine before? • What do you think about tafenoquine? • Do you understand why this change in care occurs? What is your opinion on this? Do you have any suggestions for improvements in care/testing/treatment?	Understand perception regarding tafenoquine
Adverse events	
• How was your treatment? • Do you know what side effects that you should watch out for? • What should you do if you notice any of these signs?	Understand of adverse events with radical cure and patients' experience
Packaging of tafenoquine	
• What do you think of the tafenoquine packaging? • Was there anything specific that caught your attention regarding the packaging? • Do you have any suggestions for changes in the packaging?	Evaluate the interviewee's perception of the tafenoquine packaging and how they perceive its characteristics

Results

Overall, 149 people participated in the study, including 55 patients (29 male, 26 female) who received single-dose TQ and 94 HCPs. This represented approximately 2.1% of the 2685 patients and 10% of the HCPs trained in total throughout the TRuST pilot implementation across Manaus and Porto Velho [12]. Table 3 contains information about the HCPs and the type of health unit they work in; low-, medium- or high-complexity. In phase one (high- and medium-complexity health facilities) HCPs were mostly medical doctors, nurses, pharmacists, and microscopists, while in phase two (low-complexity health facilities), the HCPs interviewed were mostly health agents and microscopists [23]. All participants remained engaged and did not withdraw from the study. Three main themes and four sub-themes were extracted, with the findings summarized in Fig. 5.

Theme 1: key treatment adherence factors for TQ

Overall, the perception of HCPs and patients regarding adherence to TQ was positive in both phases of the study.

Sub-theme 1a: simplified therapy

According to the HCPs interviewed across all levels of the health system, TQ represents a significant advance in malaria treatment, primarily because of the reduced number of pills patients need to take and the single-dose

Table 3 Characteristics of the HCP participants

Job title	Phase one: high/medium-level facilities			Phase two: low-level facilities			Overall N = 94
	Manaus n = 20	Porto Velho n = 21	Total n = 41	Manaus n = 28	Porto Velho n = 25	Total n = 53	
Physician	5	5	10	0	5	5	15
Microscopist	3	5	8	7	5	12	20
Nurse	1	4	5	0	4	4	9
Laboratory technician	2	2	4	0	0	0	4
Biochemist	3	0	3	0	0	0	3
Pharmacist	4	4	8	0	1	1	9
Health agent	2	0	2	18	8	26	28
Nursing technician	0	1	1	0	0	0	1
Supervisor	0	0	0	2	1	3	3
Reporter	0	0	0	1	1	2	2

duration of treatment compared with 7 days for PQ. This reduction in complexity was thought to reduce the potential for patient non-adherence. HCPs reported that TQ improves adherence especially for patients who are socially vulnerable, such as those with alcohol addiction and mental health issues.

> *The positive points really are the reduction in the tablets. I also think that, just as we mentioned before, I felt a greater acceptance of patients in relation to the treatment, precisely because of the reduction [treatment time] in days. HCP 6_pharmacist_male_Manaus_phase one.*
> *There is nothing better than taking a single dose and it is already solved [patient improvement]. Usually, patients end up not getting the full treatment, they end up coming back with [the same] malaria as before. So, this is really bad, and TQ is ideal, because you took it that day and you don't have to worry about it the next day. HCP 4_microscopist_male_Porto Velho_phase one.*

Regarding patient's perceptions, the shorter treatment duration significantly contributed to the positive feedback. These patients found taking many PQ tablets for several consecutive days uncomfortable, often causing nausea and a lack of appetite. Many patients perceived TQ as efficient, leading to a quicker recovery compared to previous vivax malaria treatments. This perception was particularly strong among those who had experienced vivax malaria multiple times. Similarly, patients reported that TQ treatment led to faster symptomatic improvement compared to PQ treatment.

> *The first treatment [PQ], I knew it, I've even taken it a lot when I was young, but this other [TQ] I didn't know, it's a new medication, but for me, it worked and didn't give me any reaction... I didn't feel anything, on the contrary, the only reaction I had was that the fever went away immediately, and that was a good reaction. Patient 34_male_Porto Velho_phase one.*
> *[...] I was taking this medicine [TQ], and it was better. I thought it was great because it didn't have that bitter taste. When we take that old medicine [PQ], we get a bitter taste in our mouth. This one had none of that; I didn't feel anything. [...] It's because you don't have to take a lot of medicine, and when I took that old medicine, I felt more side effects like vomiting and trouble keeping food down. With this one, it wasn't the same. I ate well and didn't feel as many effects; I thought it [TQ] was great. Patient 26_male_Manaus_phase one.*
> *I found that it [TQ] was much more efficient than treatments in the past. I believe that you recover faster, you understand? Patient 3_female_Manaus_phase one.*

Sub-theme 1b: outcomes and treatment supervision

This sub-theme was identified in HCPs only but was important at all levels of the health system. HCPs in both municipalities reported that another positive aspect of TQ was the reduction in the number of *P. vivax* recurrences. They emphasized that the complete course of TQ treatment can be supervised by HCPs at the initial visit. In contrast, only the first dose of 7-day PQ was usually supervised. This supervision is particularly important for patients with drug addiction or a history of withdrawing from treatment. A single supervised TQ dose also prevents patients from taking the drug inappropriately, such as on an empty stomach or taking all their PQ at the same time. These perceptions

Theme 1: key treatment adherence factors for tafenoquine (TQ)

- **Sub-theme 1a: simplified therapy**
  - *Finding*: reduced pill count and single-dose nature boost adherence, especially for vulnerable patients.
  - *Evidence*: positive HCP and patient feedback on fewer side effects and high acceptance.
- **Sub-theme 1b: outcomes and supervision**
  - *Finding*: TQ reduces *P. vivax* recurrence and supports better initial supervision.
  - *Evidence*: supervised single doses prevent incomplete courses and self-medication issues.
- **Sub-theme 1c: packaging and trust**
  - *Finding*: unique packaging bolsters patient trust and ease of use.
  - *Evidence*: patients feel more confident with sealed packaging.
- **Sub-theme 1d: practical packaging issues**
  - *Finding*: HCPs in rural areas find packaging impractical.
  - *Evidence*: logistics challenges cited by low-level unit HCPs.

Theme 2: single dose and prescription insecurities

- *Finding*: initial TQ use led to HCPs' prescription concerns due to limited training, whereas patients were sceptical of single-dose efficacy.
- *Evidence*: HCPs sought further training for clarity, while patients adapted with time following observations of few adverse events and rapid recovery.

Theme 3: monitoring haemolysis risks

- *Finding*: greater attention to haemolysis signs emphasized; patient follow-ups often missed due to logistics.
- *Evidence*: monitoring protocols explained to patients but challenges noted in adherence to follow-up when patients are clinically well and find the drug well tolerated.

Fig. 5 Summary of qualitative analysis thematic results

are primarily from HCPs in low-complexity units. In these units, HCPs tend to have more frequent contact with the same patients, unlike in high- and medium-complexity units where patients may not return for multiple visits.

> *It is more difficult to have a positive malaria case within 30 days if the patient was treated with TQ, from what we have seen here. When the treatment is done correctly, according to our instructions [...]. HCP 27_nurse_female_Porto Velho_phase two.*

> *There is a challenging [vivax malaria] patient who was treated with PQ. My colleagues often told me: 'This patient took the medicines for the first 3 days, but then he stopped taking them.' One day, his neighbor mentioned that he only took the medication for 3 days before drinking and getting drunk, neglecting the rest of the treatment [...] As a result, we had to visit his house every single day during his treatment and insist, 'Get a glass of water and take the medicines in front of us' With TQ, we*

no longer had any problems with this patient. HCP 35_pharmacist_female_Manaus_phase two.

HCPs from high/medium- and low-complexity units reported that another benefit of TQ was the reduction of intra-family self-medication. This occurred when patients that received CQ+PQ stopped the treatment after clinical improvement and distributed the remaining medication to family members with malaria symptoms. In contrast, with TQ, the patient takes the whole course of treatment with no left-over drugs available to share with relatives after clinical improvement.

I saw this happen in a family. One person had malaria and took the medication provided in the package, which included detailed instructions. He then shared the medication with another person who was also showing symptoms, saying, 'I'll take half, and you take half.' This was how it was done. HCP 53_biochemist_female_Manaus_phase one.

There was the case of a lady who came here in the afternoon on a Friday [...]. Over the weekend, her son felt bad, and she took a dose of her medicine [PQ and CQ] and gave it to him. On Monday, we went there and told her, 'You can't do this; this medicine is yours.' HCP 39_microscopist_male_Porto Velho_phase two.

Subtheme 1c: packaging and trust

For all anti-malarials given in Brazil, boxes with multiple blisters are distributed to the municipalities. This saves space in the stocks and in the health posts. When patients receive the treatment, it is not unusual for the health agent to take the pills out of the blisters and distribute the right number of pills per day in improvised paper envelope packs, as shown for PQ in Fig. 6A. Therefore, malaria patients usually have no access to the label of the drug or individual sealed packaging. According to the HCPs from all levels of the health system, the specific TQ packaging (Fig. 6B) instilled a sense of trust in patients and, in some cases, assisted with storage and distinguishing between medications (CQ and TQ). They noted that individualized packaging also aided in treating patients with learning difficulties and/or low literacy levels, as these patients may struggle with reading medical prescriptions and understanding the dosage instructions.

When we deliver the medication (PQ and CQ), we divide them and place each dose in different improvised packages, organizing them for the first, second, and third days. If it's the TQ box, we label it 'single dose.' If it's PQ, we cut the 14 tablets and label up to number 7, so the patient knows they need to take 2 tablets for 7 days. We provide everything together with the medical prescription. HCP 11_physician_male_Porto Velho_phase one.

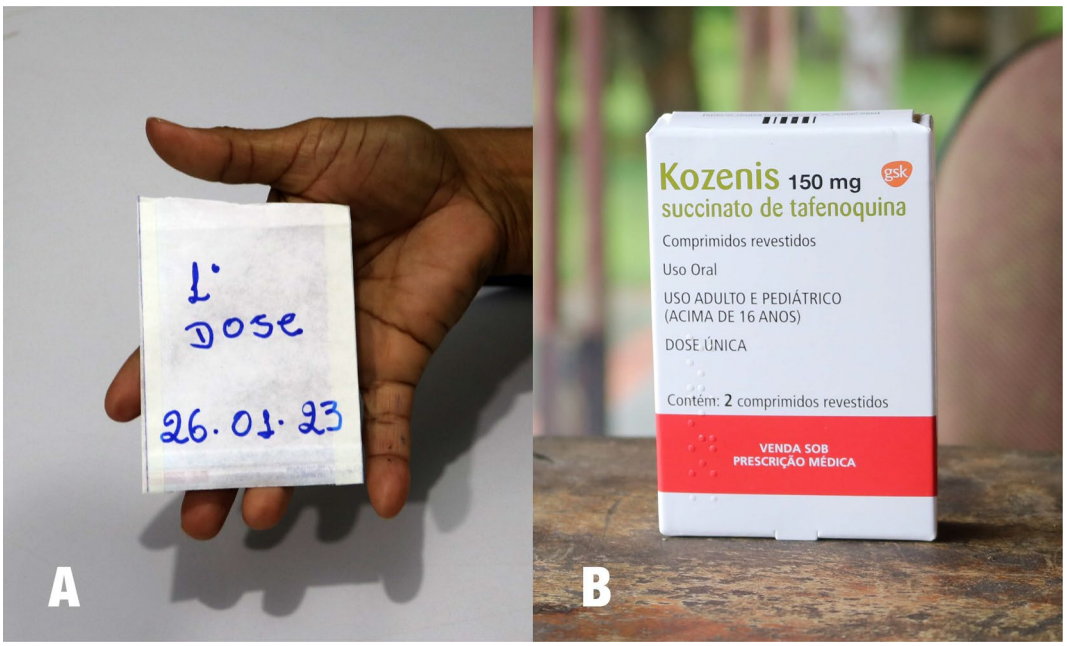

Fig. 6 **A** Improvised paper envelopes by the HCPs for PQ. **B** TQ packaging

Patients also mentioned that the medication packaging provided a sense of security. Those who did not receive it in sealed boxes for logistical reasons expressed that they would also like to receive it sealed.

> *The little boxes they give the medicine [TQ] in is sealed [...]. I think that's the right way. Because, if it's been messed about with [medicine], even I would be surprised [...]. When it's out of the package already, it's like when you go in the store and buy the pills – they're already out of the package. I think it's wrong. Patient 31_male_Manaus_phase two.*
> *For me it should come all in plastic, like in one of those little bags that has the zipper to slide. But they come in the packaging all in paper, in that stapled paper thing, those little bags come like this [...] For me, it should come in the sealed box. Patient 43_female_Manaus_phase two.*

Subtheme 1d: practical packaging issues

HCPs in high/medium-complexity units did not raise any limitations regarding TQ packaging. However, the HCPs from low-level units who work in rural, riverside and forest areas indicated that the TQ packaging is not practical because of space constraints. This was based on the need to carry numerous boxes along with other work materials such as notebooks, forms and pens, as well as the collected slides and the equipment for the G6PD test, in the same backpack. Consequently, these HCPs must remove the medications from their boxes. Moreover, they mentioned that there is limited space available on the luggage racks of the motorcycles.

> *The tafenoquine goes to them out of the box, only in the blister, so our colleagues can carry it because the space [in the bag] is small [...] and our colleagues will be full of materials such as: slides, scalpel, paper, a lot of stuff, so taking it out of the box decreases the volume for transportation [...] the packaging should be smaller, like with chloroquine, to reduce the volume. It would be much more practical for our work. HCP 40_physician_female_Porto Velho_phase two.*

Theme 2: single dose and prescription insecurities

Some HCPs from high/medium-level health units revealed feeling insecure at the beginning of the TQ implementation due to issues related to the initial training, particularly concerning the limited number of training days. These situations created insecurities at the time of prescribing the medication. As a result, some HPCs requested new training to solidify their acquired knowledge and address any uncertainties effectively.

> *[...] if I ask for a thick blood smear exam and it doesn't come with the G6PD [...] then I have this doubt "Do I prescribe or don't I prescribe?', in doubt I do not prescribe, I prescribe classical scheme? HCP 3_physician_male_Manaus_phase one.*
> *I think everyone felt this insecurity [...] there are people with comorbidities that we don't know, we're not sure if there will be any reaction or not, you know? So, if the patient is hypertensive or diabetic. What will be different about this person? So, what do I do? Can I give this medication to them without worrying? Or not? You know? Because this is not clear to us, so it's always an unknown like this [...]. HCP 17_physician_female_Porto Velho_phase one.*

Many patients noted the change in the malaria treatment algorithm during the initial phase of TQ implementation, particularly those with previous experiences of multiple malaria episodes treated with daily PQ. While the majority perceived the change positively, some patients expressed concerns about the reduced medication dosage due to their prior experiences with PQ.

> *In the beginning, I wanted to say, 'Man, will this [TQ] really work since it's fewer days taking medicine?' But it did work... I thought that because I've had malaria more than six times. Now I became worried that it might not work because there wasn't enough medication to cure it. Patient 38_male_Porto Velho_phase one.*

However, in the second phase, there was a significant improvement in patients' understanding of the medication's effectiveness. Unlike the first phase, there were no doubts about the effectiveness of the medication related to the quantity of pills received for treatment. On the contrary, there were numerous inquiries, particularly from patients on weekly PQ treatment, about why they did not receive TQ, as the treatment was shorter, and in their view cured malaria more quickly.

> *They said that this one [weekly PQ] was for me to take, that it was a more complete treatment and did less harm, because the other one I would feel a lot of pain. I was even afraid to take that pill there. I looked for the medicine [TQ] to take at once, because my colleague went to the health unit and took it in a single dose, and it was already good...*

I wanted to go to the pharmacy and buy it [TQ], even if it was expensive, I would buy it. Patient 40_male_Manaus_phase two.

Theme 3: monitoring haemolysis risks

The implementation of TQ brought greater concern for HCPs regarding pharmacovigilance in both cities across all health system levels. They reported that following the implementation, especially in the second phase, they began asking patients to observe the colour of their urine and initiated a monitoring process to detect potential signs and symptoms of haemolysis. When any sign or symptom was observed, the HCPs revealed that they followed the prescribed protocols from their training appropriately.

You tell them that they are going to take a new medication [TQ], and with this medication we must be following them, and when they go to urinate, they have to see if they are normal, if their eyes have not turned yellow. HCP 40_physician_female_Porto Velho_phase two.

The question, after taking TQ, is about urine. We tell the patient to observe their urine, but I have never seen it [...] This is a reaction of the body due to the medicine, sometimes the body reacts to the medication and, in this case [of TQ], it has the possibility of occurring in this situation. HCP 36_microscopist_male_Porto Velho_phase one.

It is only if the patient presents some symptoms, such as dark urine, that they must report. Something that the patient reports, we put it on the SIVEP form [...]. This is so that when the microscopist observes the patient, they will check what is the appropriate medication they need to dispense [...]. the dark urine, but these effects are only after the patient takes the medication and if they present the symptoms, we also put it on the SIVEP form. HCP 30_health agent_female_Manaus_phase two.

However, patients often do not return for the day 5 follow-up due to their perception of recovery from malaria and the logistical challenges associated with attendance in the Amazon context. However, this follow-up is important as it involves microscopic confirmation of blood stage parasite clearance and the assessment of signs and symptoms of acute haemolytic anaemia, such as jaundice and dark urine.

They [health professionals] told me to come back for a follow-up, but I didn't go... I saw that I was feeling better, so I didn't go back because I spent most of my time at the farm [far from the health center], then the date passed, and I didn't go. I wasn't feeling anything, so I thought the malaria was gone. Patient 2_female_Manaus_phase one.

Although follow-up visits presented logistical challenges for patients, many understood the importance of monitoring signs of haemolysis, especially dark urine. They reported that HCPs had advised them about these signs and symptoms and the necessity of returning to the health facility. Additionally, they mentioned that the educational material provided with the medication reinforced this information through illustrative icons.

She [HCP] said that the colour of the urine could change, I don't remember if it was blood-colored or Coca-Cola-colored, but she said that if it happened, I should return as soon as possible. Patient 29_male_Porto Velho_phase one.

There is a booklet [educational material] that the healthcare professionals gave, which explains the issue of dark urine, yellowed skin, and eyes. These symptoms need attention, especially during treatment. Patient 5_male_Manaus_phase one.

Summary framework

The study findings were analysed within the framework of objectives to identify the key barriers and facilitators to TQ implementation in the Brazilian Amazon as perceived by HCPs and patients (Fig. 7).

Satisfaction related to the convenience of the regimen and its perceived effectiveness and good tolerability, with the packaging enhancing the overall perception of quality. Dissatisfaction around the belief that a single-dose medicine would not be strong enough was addressed following good outcomes from therapy. Similarly, concerns from HCPs originating from the impression that their initial training was insufficient were alleviated with additional training and through experience. However, the impractical packaging for community use persists as an area of dissatisfaction. Both patients and HCPs confirmed their intention to continue to use TQ, and this was reinforced as experience increased. Although at first, the need to integrate TQ prescribing and patient communication were perceived as negative effects on the organization, with increased training and experience these were flipped to positive effects, with HCPs having greater understanding of pharmacovigilance and patients benefiting from enhanced education on radical cure and recognizing the symptoms of haemolysis. HCP workload was initially higher as training was completed and adjustments were made. Also, the need to communicate to patients the new treatment algorithm and symptoms of haemolysis was more time consuming. However, the benefits of not having to follow patients

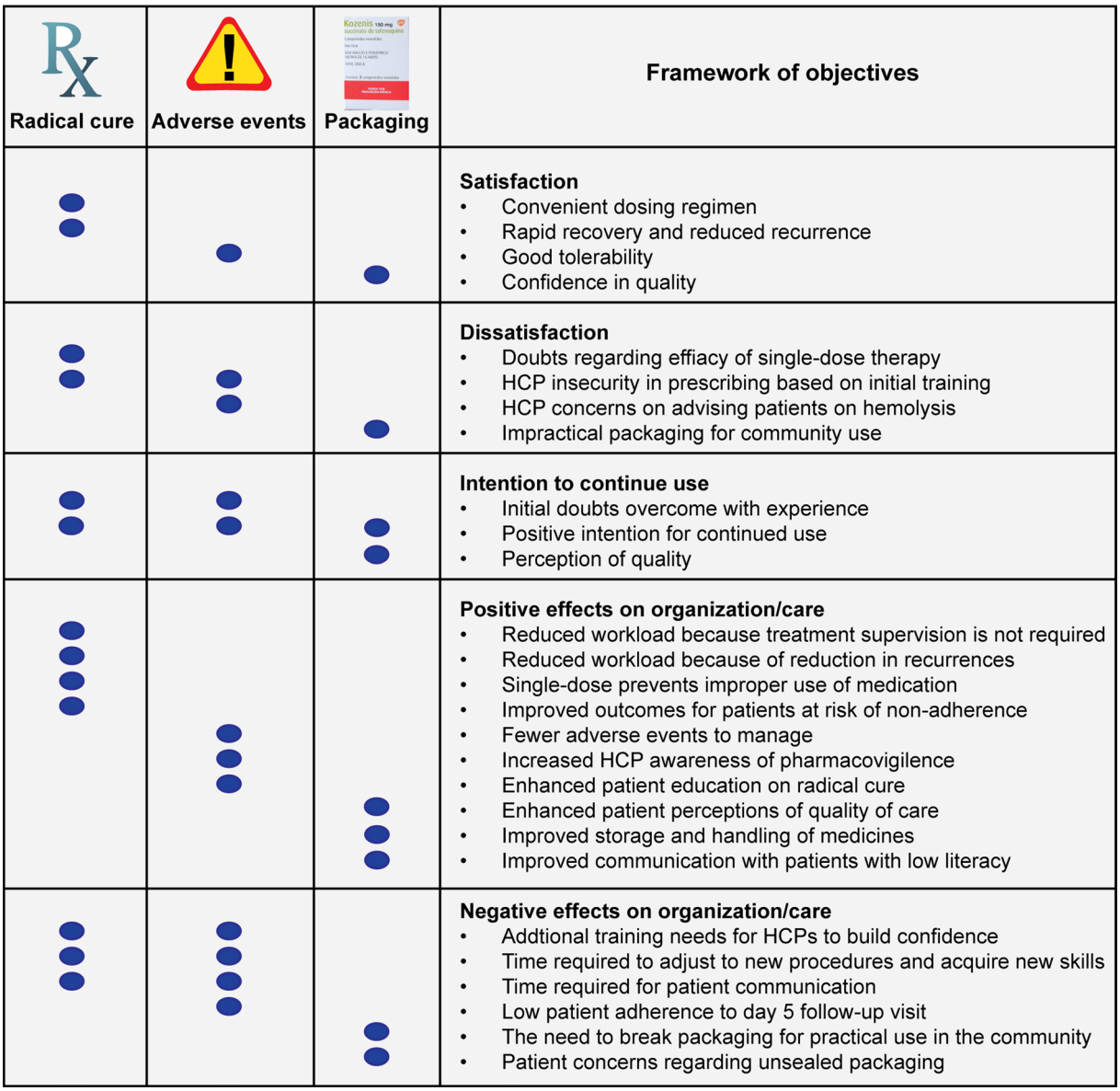

Fig. 7 Summary of outcomes with the framework of objectives

to ensure adherence and the reduction in recurrence rates following effective therapy were soon perceived as positive to the organization, with a reduction in HCP workload. Vulnerable patients who struggle to adhere to medication were thought to particularly benefit from single-dose therapy. In terms of patient care, positive effects were a reduction in gastrointestinal adverse events, rapid recovery and the prevention improper medication use. However, despite improvements in their understanding of the risks of haemolysis, patients did not adhere to day 5 follow-up routinely, only returning if they had specific concerns. Overall positive perceptions were supported by the impression that TQ was a quality medicine based on sealed packaging. However, where packages were broken for convenience of HCP use in the community, this benefit was not realized.

Discussion

This qualitative study examined the perceptions of HCPs and patients regarding the introduction of TQ in Brazil as a single-dose alternative to PQ for G6PD normal adult *P. vivax* patients. The feasibility and effectiveness of the intervention and perspectives of HCPs on training for

quantitative G6PD testing have already been published [12, 17, 23].

One of the main challenges for the elimination of *P. vivax* malaria is non-adherence to the complete treatment regimen with PQ. In Brazil, PQ is administered for 7 consecutive days, in combination with CQ for 3 days [14, 32]. Estimated non-adherence rates to this treatment regimen in Brazil can reach 33% [32]. This reflects various issues, such as the clinical improvement perceived by patients in the first days of treatment due to the reduction of the blood stages of the parasite, the high number of PQ+CQ pills, and the long duration of the treatment. Furthermore, it was reported that treatment abandonment is linked to poor social conditions, high rates of alcoholism and drug use, and low educational levels among the affected population [33]. As the study was conducted in a malaria endemic region where PQ had been previously used for many years, and until recently without G6PD testing, HCPs and patients were familiar with the limitations of treatment. Thus, their impressions of TQ were influenced by their prior experience of PQ regimens.

The perceptions of HCPs and patients indicate that TQ implementation has significant promise in addressing the existing challenges to delivering effective radical cure in the Brazilian Amazon. By reducing the number of pills and shortening the duration of treatment, TQ enhances patient adherence. HCPs highlighted the positive effect of single-dose therapy on their workload, as they no longer had to make daily visits to those patients who were at risk of non-adherence and treatment failure. Additionally, HCPs often see the same patients returning with repeated recurrences caused by poor adherence to therapy. Ensuring adherence supports clinical effectiveness, contributes to better health outcomes. The perceived greater effectiveness of TQ versus PQ also reinforces the benefits of health-seeking behaviour in patients. These perceptions are corroborated by observational findings in the TRuST study which showed that single-dose TQ was significantly more effective than 7-day PQ in preventing the *P. vivax* recurrence in the first 90 days after the start of treatment, i.e., within the timeframe between treatment and IDI within this study [17].

Notably, patients also reported that TQ was better tolerated compared to their prior experience with PQ. Neither HCPs nor patients reported any adverse events that were concerning. TQ is not specifically contraindicated in alcoholism, and although psychiatric adverse reactions have been observed in patients with a previous history of psychiatric conditions at TQ doses higher than the approved dose, the risk:benefit of TQ when used as a single-dose therapy for *P. vivax* radical cure favours treatment of patients with mental illness [34, 35]. In this study, patients who were addicted to alcohol and/or had mental illness were treated with TQ in line with the prescribing information [34], and there were no reports of any psychiatric adverse events or worsening of their symptoms. This is consistent with the clinical trials conducted for TQ and PQ in the region and the well described safety profile [14–16, 34, 35].

During the first phase of TQ implementation, many HCPs felt insecure about prescribing the new medication due to doubts about its efficacy given the reduced number of tablets required for complete treatment. The limited number of training days and the need for more practical sessions for professionals contributed to these insecurities [23]. To address these issues, additional practical training sessions and follow-ups were provided, which helped increase HCP confidence in prescribing and communicating the new treatment algorithm to patients [23]. Furthermore, the training format was modified to include active learning methodologies to reinforce the knowledge and skills of the professionals [23]. In the second phase of the study, after this feedback and the new training sessions, these perceptions were no longer evident.

The patients treated with TQ in the first phase of the study reported uncertainties regarding the medication's efficacy, particularly due to the reduced number of tablets compared to their previous experiences with PQ. However, these doubts were not observed in the second phase of the study. The rapid building of trust in the medication may be attributed to the established relationship between HCPs and patients in primary healthcare units. These professionals serve the communities and have been following families for years. Thus, even though TQ is a new treatment, it was introduced into the patients' routines by someone they already knew and trusted. Studies on community engagement demonstrate that interventions and tools developed and implemented in partnership with local agents are more likely to succeed, largely due to the establishment of trust [36, 37]. Similarly, personal involvement of the HCP is associated with patient trust [38]. On the contrary, many patients with G6PD deficiency questioned why they had not received TQ, as the treatment was shorter and they perceived that their relatives who received TQ treatment were cured more quickly.

The TQ packaging played a significant role in patient confidence and adherence to treatment. In contrast, the PQ packaging, often improvised, diminished patient confidence. Well-designed packaging protected the medication, a factor which limits the shelf stability of other anti-malarials in Brazil. It also influenced patients' perceptions of TQ efficacy and safety. Therefore, the individualized and sealed TQ packaging was well received,

making patients feel more secure, especially those with learning difficulties or low educational levels who found it easier to follow treatment instructions with the clear and well-structured packaging. The importance of packaging in treatment adherence is supported by studies showing that well-designed packaging can significantly improve patient adherence by simplifying medication administration and reducing confusion about the dosage regimen [39–41].

By enhancing pharmacovigilance measures, healthcare systems can improve the overall management of malaria by promoting the effective use of anti-malarial drugs while minimizing the occurrence of adverse events [42, 43]. The implementation of TQ increased HCP concern with pharmacovigilance of 8-aminoquinolines in both cities. Before the implementation of the new treatment algorithm, despite the absence of G6PD testing, HCPs often did not recognize the potential for drug-induced haemolysis in patients reporting changes in urine colour and/or jaundice following PQ administration and patients were at risk of severe AHA [10]. However, after TQ implementation, especially in the second phase, HCPs began asking patients to observe the colour of their urine and initiated a monitoring process to detect possible signs and symptoms of haemolysis. When any sign or symptom was observed, the HCPs rigorously followed the protocols established during their training, including referral when necessary. This proactive approach ensured that any adverse events were detected and treated early, increasing patient safety and confidence in the treatment with both PQ and TQ [12]. Thus, the need for pharmacovigilance, though initially a barrier to TQ implementation, was fully adopted by HCPs and enhanced their confidence in the management of *P. vivax* malaria. In contrast, patient engagement in returning for the day 5 visit was sub-optimal, mainly because patients did not feel the need to attend once their malaria symptoms had resolved without adverse events, given the logistical and economic barriers that they face. Further work is needed to determine if more robust risk communication can address this deficit, or whether additional measures are needed, for example: more detailed protocols for initial G6PD screening and monitoring; support or counselling for patients identified with G6PD deficiency; ongoing training and updates for healthcare professionals, emphasizing the importance of screening and effective communication regarding the risks associated with treatment; the development and assessment of culturally adapted health communication materials for segmented populations (based on ethnic group, language, age, sex, etc.); and strengthened pharmacovigilance at all levels of the health service. Despite the low rates of day 5 follow-up, there were no cases of confirmed drug induced AHA reported during the study, probably because of the high rates of adherence to the treatment algorithm [12]. Hence, patients are at low risk of haemolysis when treated appropriately according to G6PD enzyme level [12].

The positive reception of TQ by both patients and HCPs underscores its potential as an effective tool in the ongoing fight against vivax malaria in both cities. However, barriers such as insecurity in prescribing due to limited initial training by HCPs and concerns about the reduced amount of medication compared to PQ by patients need to be continuously addressed. Based on the results, ongoing and improved communication between the MoH, HCPs, and patients were identified as a key factor for accelerating the population's acceptance of TQ in Brazil. In terms of TQ packaging, there is a need to balance security with practicality, which at present is not met in all circumstances.

The qualitative nature of the study is a strength in capturing a diversity of perspectives, but also relies on participants willingness to disclose information, which is a potential limitation. Although theoretical saturation was reached, it is possible that additional experiences and perspectives relevant to TQ implementation exist which were not captured within the sample.

Conclusions

The study indicates that the implementation of single-dose TQ for the treatment of *P. vivax* malaria in Brazil was positively received by both HCPs and patients, particularly due to its simplified regimen and the reduction in the number of pills required compared to 7-day PQ and was perceived to result in quicker symptomatic relief and fewer recurrences of malaria. Additionally, the individualized packaging of TQ enhanced patient trust and adherence, contrasting with the improvised packaging of PQ. Moreover, the introduction of TQ heightened HCP awareness and monitoring of potential haemolysis, supporting patient safety through pharmacovigilance practices.

The rapid feedback and adaptation of training between phases one and two was critical in addressing early concerns and insecurities regarding the new medication and treatment algorithm among HCPs and patients [23]. This underlines the need for qualitative evaluation of training and perceptions of new interventions before broader implementation to identify and address unanticipated barriers and enhance facilitators. Ongoing efforts to address remaining challenges, such as developing tailored educational tools and practical packaging solutions, are essential for optimizing TQ implementation and improving malaria treatment outcomes. The positive reception

of TQ suggests its potential as a valuable tool to accelerate *P. vivax* malaria elimination in Brazil.

Abbreviations

AHA	Acute haemolytic anaemia
CONEP	National Research Ethics Committee
COREQ	Consolidated Criteria for Reporting Qualitative Research
CQ	Chloroquine
HCPs	Healthcare professionals
IDIs	In-depth interviews
G6PD	Glucose-6-phosphate dehydrogenase
MoH	Ministry of Health
PAHO	Pan American Health Organization
PQ	Primaquine
TQ	Tafenoquine
SIVEP	Sistema de Informação de Vigilância Epidemiológica [Information System for Epidemiological Surveillance]

Supplementary Information

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Additional file 1.

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Author contributions
The study was designed by FLGM, MAMB, PGD, DBP, CRLP and MVGL. The FGD and IDI guide was developed by APCS, FLGM, PCSB, RR and MVGL. FGDs and IDIs were led by APSO, RND, HSSG, EARTS, HAAJ. Recruitment of participants and database development was performed by MAMB, RR, and APCS. Data analysis was conducted by FLGM, APCS. All authors were involved in data interpretation, and writing and critical review of the manuscript, approved the final version for submission and take responsibility for the publication.

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Availability of data and materials
The data that support the findings of this study are available at Fundação de Medicina Tropical Dr. Heitor Vieira Dourado. However, restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request.

Declarations

Ethics approval and consent to participate
The Ethics Review Board at the *Fundação de Medicina Tropical Dr Heitor Vieira Dourado* in Manaus and the National Research Ethics Committee (CONEP) in Brasília, Brazil (CAAE: 47598921.2.0000.0005) approved the protocol for both study sites. All participants provided written consent for participation in the study and publication of their de-identified contributions.

Competing interests
PGD is a consultant for MMV Medicines for Malaria Venture. All other authors declare that they have no competing interests.

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