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Burden and clinical characteristics of recurrent *Plasmodium vivax* infections, and impact of primaquine for radical cure: a systematic scoping review in India

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Background: India accounts for the bulk of *Plasmodium vivax* burden in South East Asia. Primaquine (PQ) is the only currently available drug for treating relapses in *P. vivax* malaria.

Methods: Here, we provide an overview of the epidemiology and clinical characteristics of *P. vivax* recurrent infections in India and discuss current knowledge gaps and priority research areas for further investigations, with emphasis on relapses and their radical cure with PQ.

Results and discussion: A total of 27 studies involving ~27,000 *P. vivax* infected patients were finally included. Recurrent infections with *P. vivax* malaria are common, especially in young males. The burden of *P. vivax* relapse greatly varies across Indian regions, with a proportion range of 1.47 to 6% based on the included studies which all used low (very low) PQ dose. There is a need for more empirical data on the effectiveness and safety of weekly administration of PQ at 0.75 mg/Kg for eight weeks in G6PD–deficiency patients in India, especially in children. Further research priorities should also be focused on the epidemiology of confounding factor, such as CQ-resistance, mixed infections, or *Pv* genetic diversity are needed. The clinical impact of *P. vivax* relapses (e.g., severe malaria, mortality) is also of valuable interest in upcoming studies. More studies addressing the above-mentioned missing links should be implemented to inform malariologists, clinicians, populations, and policy makers on real situation of *P. vivax* relapses and the clinical impact of PQ in India. All taken together, these would have important implications for *P. vivax* malaria control and elimination in endemic areas.

KEYWORDS

epidemiology, India, *Plasmodium vivax*, primaquine, recurrent infections

1 Introduction

In 2022, malaria was responsible for ~249 million cases and ~ 608,000 deaths worldwide, which were mostly reported in sub-Saharan Africa (sSA) and South east Asia (SEA) (WHO, 2023). This infectious disease is caused by protozoan parasites of the *Plasmodium* genus transmitted to humans via infecting bites of female *Anopheles* mosquitoes (Cowman et al., 2016). Five species are currently associated with human morbidity and mortality: *P. falciparum* (*Pf*), *P. ovale* (*Po*), *P. vivax* (*Pv*), *P. malariae* (*Pm*) and *P. knowlesi* (*Pk*) (Cowman et al., 2016). Other species such as *P. cynomolgi* and *P. brasilianum* are emerging in humans and are associated with asymptomatic to mild infections (Kojom Foko et al., 2023). *Pf* and *Pv* are the main malarial species in endemic regions, though in very few countries such as Malaysia, *Pk* contributes largely to the malaria burden (Cooper et al., 2019; WHO, 2023).

Malaria is still a cause of concern in India despite the tremendous efforts and achievements made by the country over the last two decades. India and Indonesia accounted for ~94% of *Pv* malaria related total mortality seen in 2022 in the SEA region (WHO, 2023). The epidemiology of malaria in India is complex, diverse, and led by *Pf* and *Pv* while *Po*, *Pm* and *Pk* are reported to a lesser extent (Figure 1A) (Anvikar et al., 2016; Kojom Foko and Singh, 2023). Even though *Pv* is the most geographically distributed species in the world, the current literature on *Pv* is much fewer than that dedicated to its *Pf* counterpart (Gething et al., 2012; Garrido-Cardenas et al., 2019). The control of *Pv* is tricky owing to peculiarities intrinsically linked to its biology, namely (i) high chances for transmission to *Anopheles* mosquitoes due to early triggering of gametocytogenesis and efficient transmission at low parasite densities, (ii) potential to elicit severe malaria and deaths, and (iii) ability to induce relapsing infections via reactivation of dormant stages called hypnozoites (Sattabongkot et al., 2004; Bousema and Drakeley, 2011; Douglas et al., 2013; Matlani et al., 2020; Kojom Foko et al., 2021; Kojom Foko et al., 2022).

Reports on the contribution of *Pv* relapses to malaria transmission, morbidity, and mortality are increasingly published (White et al., 2014; Liu et al., 2021; Phyo et al., 2022). Relapsing *Pv* malaria is associated with a high proportion of recurrent infections and transmittable gametocytaemia (Douglas et al., 2013). The co-administration of schizonticidal and hypnozoiticidal drugs is adopted for the radical cure of *Pv* malaria and thus prevents relapses (Chu and White, 2021). Primaquine (PQ) is the only hypnozoiticidal drug currently recommended by the World Health Organization (WHO) for the radical cure of *Pv* infections (WHO, 2023). In the late 1950s, PQ was included in national Indian guidelines for *Pv* malaria treatment (Figure 1B) (Anvikar et al., 2014; NIMR and NVBDCP, 2014). Unfortunately, utilisation of PQ is greatly jeopardised by the high risk of severe haemolytic anaemia in patients with a deficiency in glucose-6-phosphate dehydrogenase (G6PD) (Peters and Van Noorden, 2009; Chu and White, 2021).

Little is known about recurrent *Pv* infections (i.e., recrudescence, reinfection, and relapses) in India, and filling this gap could be helpful for efficiently controlling *Pv* malaria in the country. In the present scoping review, we systematically summarised and analysed Indian literature on *Pv* malaria recurrences, especially relapses in the context of radical cure with primaquine. Practical implications, knowledge gaps, solutions, and future prospects are also discussed.

Abbreviations: ACT, Artemisinin-based combination therapy; AQ, Amodiaquine; CQ, Chloroquine; *csp*, Circumsporozoite gene; G6PD, Glucose-6-phosphate dehydrogenase; G6PD-d, Glucose-6-phosphate dehydrogenase deficiency; HPLC, High pressure liquid chromatography; IRR, Incidence rate ratio; JBI, Joanna Briggs Institute; LC-MS, Liquid chromatography coupled with mass spectrometry; LM, Light microscopy; MS, Microsatellites; *msp1*, Merozoite surface protein 1 gene; *msp3-α*, Merozoite surface protein 3 alpha gene; n.a, Not available; NVBDCP, National Vector Borne Disease Control Programme; PCR – SSCP, Polymerase chain reaction – Single strand conformational polymorphism; PCR – RFLP, Polymerase chain reaction – Restriction fragment length polymorphism; PRISMA-ScR, The Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; PQ, Primaquine; *Pf*, *Plasmodium falciparum*; *Pk*, *Plasmodium knowlesi*; *Pm*, *Plasmodium malariae*; *Po*, *Plasmodium ovale*; *Pv*, *Plasmodium vivax*; *Pvcrt-o*, *Plasmodium vivax chloroquine carrier transporter orthologue*; PYR, Pyrimethamine; QBC, Quantitative buffy coat; QN, Quinine; RDT, Rapid diagnostic test; SEA, South East Asia; sSA, sub-Saharan Africa; WHO, World Health Organization.

2 Materials and methods

2.1 Guidelines and registration

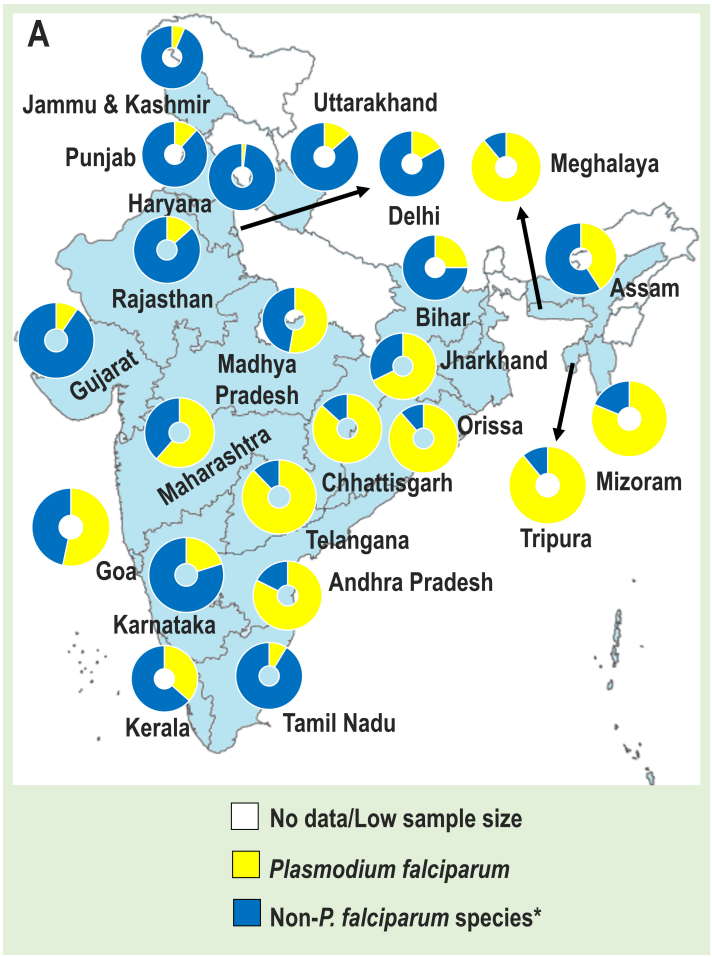
This scoping review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist as well as general related guidance (Supplementary File 1) (Pham et al., 2014; Tricco et al., 2018). The project was registered with the Open Science Framework (https://osf.io/shku4/) (Foster and Deardoff, 2017).

2.2 Identifying research questions

The scoping review approach is considered particularly relevant and useful for analysing, identifying, and synthesising a range of complex health public concerns, such as the management of relapsing malaria (Munn et al., 2018; Peters et al., 2020). The research question examines the literature that exists on the burden and treatment of recurrent *Pv* malaria in India, with an emphasis on relapses. Second, identifying causes/determinants of relapses in the Indian context was also addressed. Third, we also investigated the efficacy and safety of primaquine for the radical cure of *Pv* malaria infections. The knowledge gaps, practical implications, solutions, and future prospects of *Pv* malaria treatment are also discussed.

2.3 Search strategy

The searches were conducted from September to December 2022 and March to April 2023 without any restriction period in six electronic databases, including PubMed, Wiley Online Library, clinicaltrials.gov, the International Clinical Trials Registry



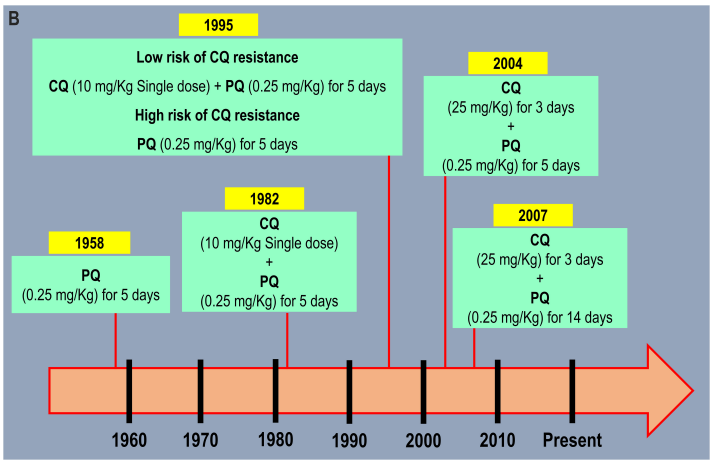


FIGURE 1
(A) Relative contribution of *Plasmodium* species to malaria infections in different states and union territories of India, 2022, and **(B)** Evolution of utilization of primaquine in national drug policy for radical cure of laboratory confirmed *Pv* malaria, India. CQ, Chloroquine; PQ, Primaquine; *P. vivax*, *Plasmodium vivax*. In **(A)**, *Non-falciparum species are mainly due to *P. vivax*. The data were retrieved from official website of the National Vector Borne Disease Control Programme (https://nvbdcp.gov.in). The map was retrieved from official website of Ministry of External Affairs of the Government of India (https://mea.gov.in/india-at-glance.htm). In **(B)**, Primaquine is contraindicated to pregnant women. The figure was generated using national data (Anvikar et al., 2014; NIMR and NVBDCP, 2014).

Platform, ScienceDirect, ResearchGate and Google scholar. Official websites of local journals and scientific associations were also scrutinised. Search terms were used in combination with Boolean terms (i.e., AND, OR) (Table 1). The full texts of open access publications were retrieved from each electronic database. Principal investigators and editors-in-chief of local journals were contacted by email or phone call to request a full-length paper and/or more details on the relevant studies. The papers were purchased in case of absence of feedback or refusal. Full texts were scrutinised for eligibility in the PRISMA-ScR. Also, the reference list of relevant papers was examined to find more potentially relevant papers.

2.4 Selection of the studies on *Pv* recurrences

Only papers published from 1913 to 2022 and written in English were included. Quantitative and interventional studies were considered of interest if they addressed any aspect of recurrent Pv malaria including type (i.e., recrudescence, reinfection, and relapse), prevalence, clinical presentation, biology, determinants, outcomes, diagnostics, prevention, and treatment. The cut-off of 1913 was chosen as the oldest Indian medical journal, i.e., the Indian Journal of Medical Research, started its first releases circa 1913.

We excluded studies i) with a qualitative-based design (narrative review, conference, letter, correspondence, comment), ii) protocol studies, iii) conducted outside India, iv) having evaluated antimalarial drug efficacy against *Pv* malaria without addressing *Pv* recurrences, v) having evaluated antimalarial drug efficacy against recurrent *Pf* malaria, vi) having evaluated presumptive treatments of *Pf* and/or *Pv* infections, and vii) having used animal models. Titles and abstracts of potentially relevant papers were evaluated independently by the authors. Some publications were excluded at this step of the screening strategy, while duplicates were removed.

2.5 Data charting

First, one author (L.P.K.F.) initially extracted the relevant information from eligible studies using an Excel standardised form. The data charting process mapped study findings according to the attributes which could be categorised into five groups namely i) study details (first author's name, year of publication, paper title, collection area, malaria endemicity, state/territory union and year of data collection); ii) design details (setting, study design, study population, parasitological diagnosis method, definition used to identify *Pv* relapses); iii) drug details (number of treatment arms, number of patient in each treatment arms, number of anti-relapse regimens, comparative control regimen, nature of blood schizonticidal and liver anti-relapse drugs, dose of blood schizonticidal drug, total dose of liver anti-relapse drug, daily dose and duration of anti-relapse treatment, G6PD profile, method used to determine blood level of anti-relapse drug); iv) follow-up details (type, frequency and duration), and v) outcomes (number of recurrent parasitaemia events in each treatment arms,

TABLE 1 Search strategy in the different international electronic databases.

Databases	Documents	Search strategy
PubMed	Peer-reviewed	("vivax malaria"[Title/Abstract] OR "Plasmodium vivax"[Title/Abstract] OR "P. vivax"[Title/Abstract]) AND ("recurrence"[Title/Abstract] OR "recurrent"[Title/Abstract] OR "relapse"[Title/Abstract] OR "relapsing"[Title/Abstract]) AND ("primaquine"[Title/Abstract] OR "radical cure"[Title/Abstract] OR "anti-relapse drug"[Title/Abstract] OR "anti-hypnozoite"[Title/Abstract] OR "therapeutic response"[Title/Abstract]) AND ("efficacy"[Title/Abstract] OR "effectiveness"[Title/Abstract] OR "impact"[Title/Abstract]) AND ("safe"[Title/Abstract] OR "safety"[Title/Abstract] OR "inocuity"[Title/Abstract]) AND ("India"[Title/Abstract] OR "Indian"[Title/Abstract] OR "Andaman and Nicobar"[Title/Abstract] OR "Assam"[Title/Abstract] OR "Andhra Pradesh"[Title/Abstract] OR "Bihar"[Title/Abstract] OR "Chandigarh"[Title/Abstract] OR "Chhattisgarh"[Title/Abstract] OR "Daman and Diu"[Title/Abstract] OR "Goa"[Title/Abstract] OR "Delhi"[Title/Abstract] OR "Gujarat"[Title/Abstract] OR "Himachal Pradesh"[Title/Abstract] OR "Jammu and Kashmir"[Title/Abstract] OR Jharkhand"[Title/Abstract] OR "Kerala"[Title/Abstract] OR "Kolkata"[Title/Abstract] OR "Karnataka"[Title/Abstract] OR "Lakshadweep"[Title/Abstract] OR "Maharashtra"[Title/Abstract] OR "Manipur"[Title/Abstract] OR "Mizoram"[Title/Abstract] OR "Madhya Pradesh"[Title/Abstract] OR "Meghalaya"[Title/Abstract] OR "Nagaland"[Title/Abstract] OR "Odisha"[Title/Abstract] OR "Pondicherry"[Title/Abstract] OR "Rajasthan"[Title/Abstract] OR "Sikkim"[Title/Abstract] OR "Tamil Nadu"[Title/Abstract] OR "Tripura"[Title/Abstract] OR "Uttarakhand"[Title/Abstract] OR "Uttar Pradesh"[Title/Abstract] OR "Punjab"[Title/Abstract] OR "Haryana"[Title/Abstract] OR "West Bengal"[Title/Abstract]))
Wiley Online Library	Peer-reviewed	Plasmodium vivax AND primaquine AND relapse AND India; Title, abstract or keywords Plasmodium vivax AND radical cure AND relapse AND India; Title, abstract or keywords
ScienceDirect	Peer-reviewed	Malaria AND (Plasmodium vivax OR vivax) AND (primaquine OR radical cure) AND (relapse OR recurrence) AND (efficacy OR effectiveness) AND (India OR Indian); Title, abstract or keywords
ResearchGate	Peer-reviewed and not peer-reviewed	Plasmodium vivax AND primaquine AND relapse AND India Plasmodium vivax AND radical cure AND relapse AND India
Google scholar	Peer-reviewed	allintitle: "vivax" AND "relapse" AND "primaquine" OR "radical cure" AND "India"

number of recurrent events in each treatment arms, month of recurrent/relapse event in each treatment arms, sociodemographic and clinical characteristics of patients with recurrent event, number of haemolytic anaemia event). The recurrent event included relapse, recrudescence, and reinfection. The design of this extraction form was piloted and refined by all authors.

2.6 Collating, summarising, and reporting the results

Data were explored and summarised in congruence with scoping review objectives, along with narrative analysis. The selected evidence based on the source, study characteristics, and major findings were mapped and presented in tabular and/or graphical forms. For instance, the geographical distribution of studies was mapped by Indian states/union territories. Also, pie charts were used to present the distribution of included studies by setting (research institute, health facility, and community), study design (case report, randomised clinical trial – RCT, and prospective study), and study population (children, adults, and general population). The term "not specified" was used if details on one of the above-mentioned items were not mentioned in the included studies. PQ total dose was classified as very low (≤ 2.5 mg/Kg), low (> 2.5 – < 5 mg/Kg) and high (≥ 5 mg/Kg) as described earlier (John et al., 2012). The multiplication of blood stages of early relapses is suppressed by slowly eliminated drugs, and thus, relapses become microscopically patent 3 weeks after QN or artesunate, 3 – 6 weeks after artemether + lumefantrine, and 5 – 7 weeks after CQ treatment (White, 2011; Chu and White, 2021). In this context, we categorised *Pv* malaria recurrences and/or relapses as frequent (~3 – 7 weeks) and long (~8 – 9 months).

2.7 Determination of *Pv* relapse burden

We used the approach proposed by Commons and colleagues to appraise the proportion of *Pv* recurrences caused by relapse, with slight modifications (Commons et al., 2020). In this approach, the primary outcome was the incidence rate of *Pv* recurrences over 365 days following a given treatment. The incidence rate ratio (IRR) was calculated as the ratio of the incidence rate of *Pv* recurrences in the treatment arm with PQ to the ratio of incidence rate of *Pv* recurrences in the treatment arm without PQ. The minimum proportion of recurrences due to relapse was calculated by subtracting the IRR from 1 (Commons et al., 2020). This approach assumes that PQ has an anti-relapse preventive efficacy of 100% and does not improve the killing effect of asexual blood stage parasites (Commons et al., 2020).

In this section, only RCTs that included PQ in one of the regimen arms, followed up patients actively regardless of duration of follow-up, supervised PQ administration daily, and had an extractable incidence rate were included to assess *Pv* relapse burden. We used these stringent criteria to reduce any ambiguity about the distinction between reinfection, recrudescence, and relapses and thus give a consistent estimate of the proportion of *Pv* recurrence attributable to relapse in the Indian context. Also, *Pv* relapse estimates as calculated in each individual study were extracted and stratified by definition used for relapse, time of follow-up, and PQ dosing.

2.8 Bias risk assessment

Two reviewers (L.P.KF. and V.S.) independently assessed the bias risk of the RCTs included to determine *Pv* relapse burden. The methodological quality of RCTs was evaluated using Joanna Briggs Institute - JBI critical appraisal tools designed for RCTs (https://jbi.global/critical-appraisal-tools). This tool consists of 13 questions on four types of methodology-related bias viz. i) selection, ii) performance, iii) attrition, and iv) reporting. A choice between four answers ("Yes", "No", "Unclear" and "Not applicable") was proposed for each question as per the JBI tool. Thus, the risk of bias was categorised as "low" if the answer was "Yes", "high" if the answer was "No" and "unclear" if the answer was "Unclear or Not applicable" (Arya et al., 2021). Disagreements between reviewers were resolved through discussion and consensus.

2.9 Ethical statements

The data used in this review was retrieved from publicly accessible databases. Thus, ethics committee approval was not requested.

3 Results

3.1 Selection process for the studies

A total of 2,106 potentially relevant records were retrieved from electronic databases. Of these records, 1504 were retained after removing duplicates. We excluded 1478 records after analysing titles and abstracts based on the above mentioned exclusion criteria: i) studies conducted outside India (n = 154), ii) studies on recurrent *Pf* malaria (n = 96), iii) anti-relapse drugs were not tested (n = 7), iv) reviews (n = 5), v) *Pv* relapses were not addressed (n = 5), vi) studies on presumptive malaria treatment (n = 4), vii) protocols (n = 3), viii) correspondence (n = 1), ix) animal-based studies (n = 1), full-text not found (n = 1), and xi) irrelevant studies (n = 1201) (Figure 2). Twenty-six publications were evaluated for eligibility. We identified three more publications through the bibliographic references listed in the 26 publications, thereby giving a total of 29 potentially eligible publications. Of these, two records were excluded because of evidence of duplicate (i.e., same findings published in different journals). Thus, 27 studies involving ~27,000 *Pv*-infected patients treated with PQ-based treatment regimens were finally included to analyse *Pv*

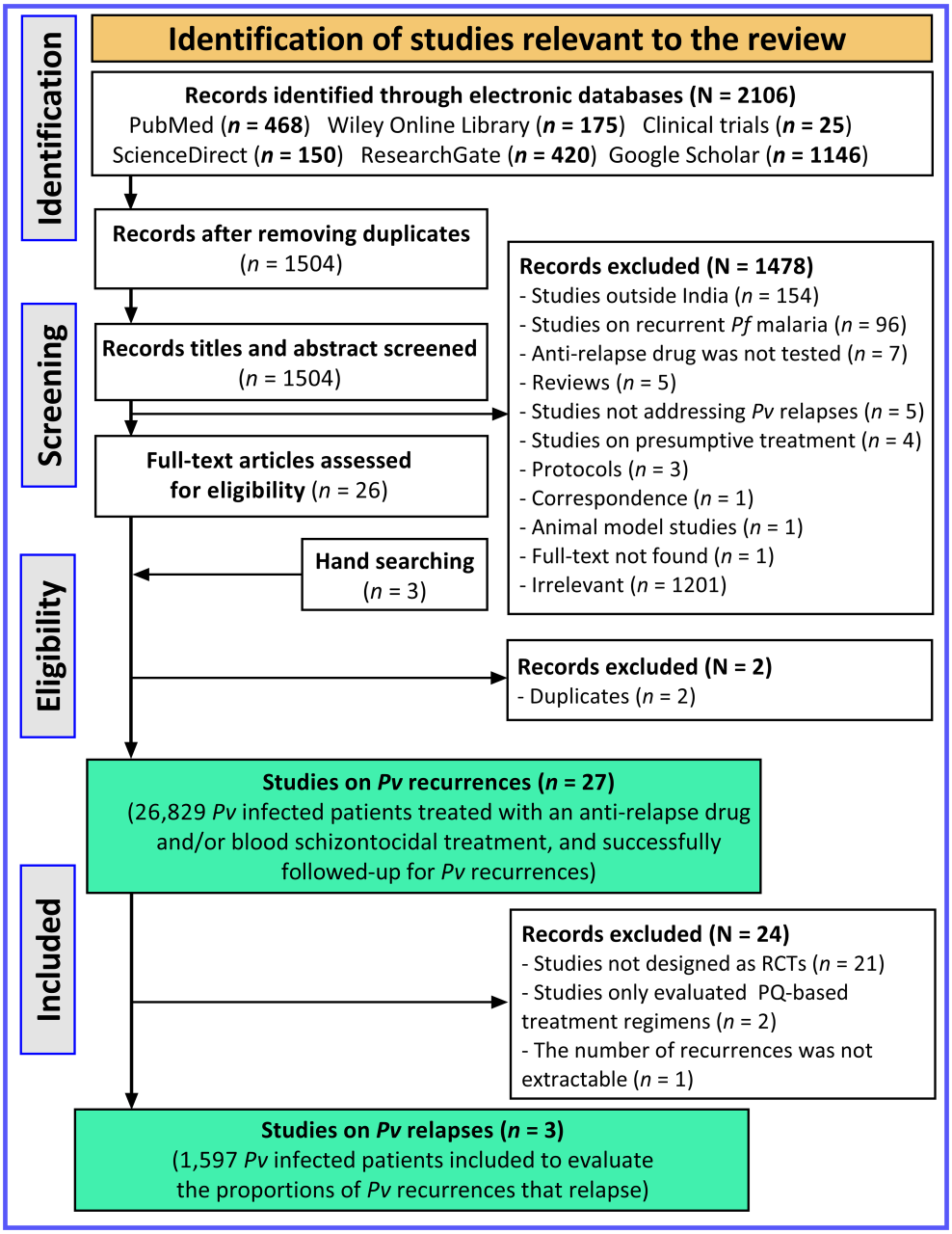


FIGURE 2
PRISMA flow diagram depicting the selection process of studies. *Pf*, *Plasmodium falciparum*; *Pv*, *Plasmodium vivax*; PQ, Primaquine.

recurrences (Figure 2) (Singh et al., 1953; Basavaraj, 1960; Sharma et al., 1973; Roy et al., 1977; Roy et al., 1979; Appavoo et al., 1984; Sinha et al., 1989; Sharma et al., 1990; Prasad et al., 1991; Srivastava et al., 1996; Gogtay et al., 1998; Gogtay et al., 1999; Adak et al., 2001; Dua and Sharma, 2001; Yadav and Ghosh, 2002; Rajgor et al., 2003; Imwong et al., 2007; Saifi et al., 2010; Kim et al., 2012; Rajgor et al., 2014; Pareek et al., 2015; Savargaonkar et al., 2015; Kumar et al., 2016; Savargaonkar et al., 2017; Saravu et al., 2018; Kishore et al., 2020; Gandrala et al., 2022). In order to determine the proportion of *Pv* recurrences due to relapse, 24 studies were excluded due to three reasons: 21 studies were not designed as RCTs, 2 studies evaluated PQ-based treatment regimens, and recurrence data were not extractable in one study (Figure 2).

3.2 Characteristics of studies on *Pv* recurrences

Details of the included studies are presented in Figure 3 and Supplementary File 2. Studies included were published over changes in PQ drug policies in India, with 23.1% of them published from 1960 – 1990, during which *Pv* infections were treated using CQ

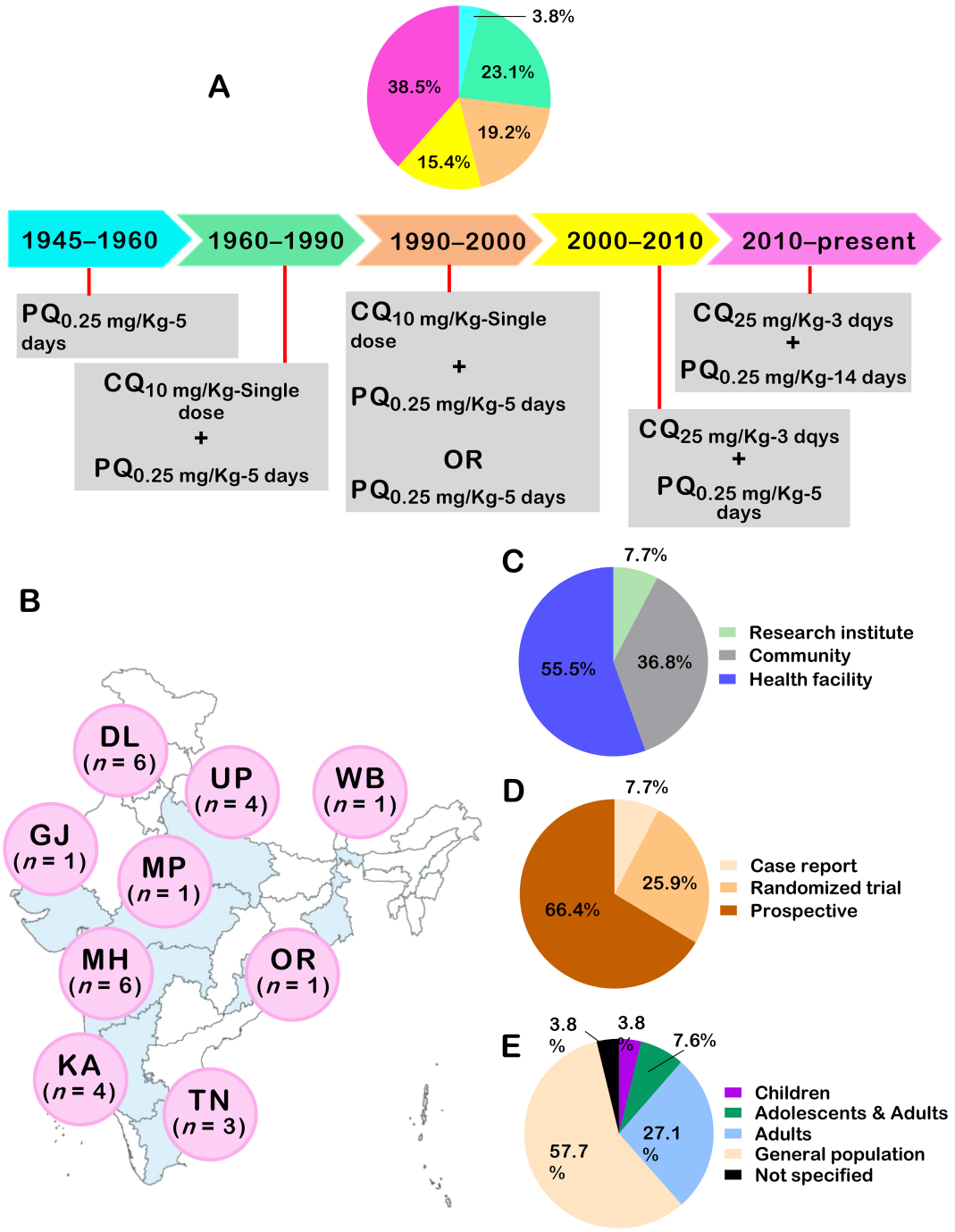


FIGURE 3
Characteristics of studies on *P. vivax* recurrences in India. In **(A)**, proportion of studies with respect to changes in PQ related policies in India. In **(B)**, international codes for Indian areas were used (DL, Delhi; GJ, Gujarat; KA, Karnataka; MH, Maharashtra; MP, Madhya Pradesh; OR, Orissa; TN, Tamil Nadu; UP, Uttar Pradesh) Number of studies conducted in areas is presented. The distribution of studies as per setting **(C)**, study design **(D)**, and study population **(E)** is also depicted.

given as a single dose followed by PQ at a dose of 0.25 mg/Kg for five days (Figure 3A). More than one third (38.5%) of the studies were published from 2010 – present. Most studies were conducted in Maharashtra (n = 6), Delhi (n = 6), Uttar Pradesh (n = 4), and Karnataka (n = 4) (Figure 3B). The bulk of studies were conducted in a health facility setting (55.5%), designed as prospective studies (66.4%), and included patients of all ages (57.7%) (Figures 3C–E).

3.3 Therapeutic strategies used to prevent *Pv* recurrences

CQ was the main blood-stage antimalarial drug associated with PQ regimens, while some studies used artemisinin-based combination therapies (ACT), amodiaquine (AQ), quinine (QN), and pyrimethamine (PYR). The majority of studies (n = 22, 81.5%)

TABLE 2 Characteristics of therapeutic regimens evaluated to prevent recurrent *P. vivax* parasitaemia.

Regimen	Total dose of blood stage drug (mg)*	Total PQ dose (mg base/Kg)	PQ dose/day (mg base/Kg)	Duration (days)	Follow-up duration (days)	Periodicity of the follow up	G6PD status	Diagnosis	Determined blood level of PQ?	Ref.
PQ	-	70 mg	10 mg	7	365 to 730	Not specified	Not specified	LM	no	(Singh et al., 1953)
Pentaquine + QN[a]	-	70 mg	10 mg	7	365 to 730					
Pamaquine + QN	-	140 mg	20 mg	7	180					
AQ (Camaquin) + PQ	600 (D0)	75 mg	15 mg	5	210 to 365	Every 8 weeks	Not specified	LM	no	(Basavaraj, 1960)
CQ + PQ	600 (D0)	75 mg	15 mg	5	365	Every 6 weeks	Not specified	LM	no	(Sharma et al., 1973)
CQ + PQ	600 (D0)	75 mg	15 mg	5	365	Every 4 weeks	Not specified	LM	no	(Roy et al., 1977)
CQ + PQ	600 (D0)	75 mg	15 mg	5	365	Every 4 weeks	Not specified	LM	no	(Roy et al., 1979)
CQ + PQ	600 (D0)	75 mg	30 mg (D1) + 30 mg (D2) + 15 mg (D3)	3	365	Every 4 weeks	Not specified	LM	no	(Appavoo et al., 1984)
CQ + PQ	900 [600 (D0) + 300 (D1)]	75 mg	15 mg	5	548	Weekly	Not specified	LM	no	(Sinha et al., 1989)
CQ + PQ	600 (D0) and 1500 [600 (D0) + 600 (D1) + 300 (D2)]	75 mg	15 mg	5	1460	Passive follow	Not specified	LM	no	(Sharma et al., 1990)
CQ + PQ	600 (D0)	75 mg	15 mg	5	Not specified	Not specified	Not specified	LM	no	(Prasad et al., 1991)
CQ alone	600 (D0)	–	–	–	365	Every 4 weeks	Not specified	LM	no	(Srivastava et al., 1996)
CQ + PQ	600 (D0)	75 mg	15 mg	5	365					
CQ + PYR	600 (D0)	50 mg	–	–	365					
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	75 mg	15 mg	5	180 to 365	Every 4 weeks	Exclusion of patients with G6PD-d	LM	no	(Gogtay et al., 1998)
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	75 mg	15 mg	5	180	Every 4 weeks	Exclusion of patients with G6PD-d	LM	no	(Gogtay et al., 1999)
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	210 mg	15 mg	14	180					
CQ alone	25 [10 (D0) + 10 (D1) + 5 (D2)]	–	–	–	180					

(Continued)

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TABLE 2 Continued

Regimen	Total dose of blood stage drug (mg)*	Total PQ dose (mg base/Kg)	PQ dose/day (mg base/Kg)	Duration (days)	Follow-up duration (days)	Periodicity of the follow up	G6PD status	Diagnosis	Determined blood level of PQ?	Ref.
CQ + PQ	1500 [500 (D0) + 500 (D1) + 500 (D2)]	75 mg	15 mg	5	365	Fortnightly (Active)	Exclusion of patients with G6PD-d	LM	no	(Adak et al., 2001)
CQ + Bulaquine	1500 [500 (D0) + 500 (D1) + 500 (D2)]	125 mg	25 mg	5	365					
CQ + Placebo	1500 [500 (D0) + 500 (D1) + 500 (D2)]	-	-	5	365					
CQ + Bulaquine + PQ	1500 [500 (D0) + 500 (D1) + 500 (D2)]	125 mg & 75 mg	25 mg & 15 mg	5	365					
CQ + PQ	900 [600 (D0) + 300 (D1)]	75 mg	15 mg	5	–	–		LM	no	(Dua and Sharma, 2001)
CQ alone	600 (D0)	-	-	-	365	Passive follow	Not done	LM	no	(Yadav and Ghosh, 2002)
CQ + PQ	600 (D0)	75 mg	15 mg	5	365					
CQ alone	25 [10 (D0) + 10 (D1) + 5 (D2)]	–	–	–	180	Every 4 weeks	Exclusion of patients with G6PD-d	LM		(Rajgor et al., 2003)
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	210 mg	15 mg	14	180				yes[d]	
CQ alone	10 mg of base/kg, followed 6 h later by 5 mg/kg, and then by 2 doses of 5 mg/kg every 24 h	-	-	-	540	Weekly until day 28 and then monthly thereafter for 18 months	Exclusion of patients with G6PD-d	LM	no	(Imwong et al., 2007)[g]
CQ + PQ	10 mg of base/kg, followed 6 h later by 5 mg/kg, and then by 2 doses of 5 mg/kg every 24 h	75 mg	15 mg	5	540	Weekly until day 28 and then monthly thereafter for 18 months				
CQ + PQ	10 mg of base/kg, followed 6 h later by 5 mg/kg, and then by 2 doses of 5 mg/kg every 24 h	210 mg	15 mg	14	540	Weekly until day 28 and then monthly thereafter for 18 months				
CQ alone	1500 [600 (D0) + 300 (after 8 hrs) + 300 (D1) + 300 (D2)]	–	–	–	365	Passive follow	Not done	LM	no	(Saifi et al., 2010)
CQ + PQ	600 (D0) + 300 (after 8 hrs) + 300 (D1) + 300 (D2)]	75 mg	15 mg	5	365					

(Continued)

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TABLE 2 Continued

Regimen	Total dose of blood stage drug (mg)*	Total PQ dose (mg base/Kg)	PQ dose/day (mg base/Kg)	Duration (days)	Follow-up duration (days)	Periodicity of the follow up	G6PD status	Diagnosis	Determined blood level of PQ?	Ref.
CQ alone	25 [10 (D0) + 10 (D1) + 5 (D2)]	-	-	-	450	Every 1 to 2 month for 15 months	G6PD status was evaluated	LM	no	(Kim et al., 2012)
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	75 mg	15 mg	5	450					
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	210 mg	15 mg	14	450					
CQ alone	25 [10 (D0) + 10 (D1) + 5 (D2)]	–	–	–	180	Every 4 weeks	Exclusion of patients with G6PD-d	LM/PCR	no	(Rajgor et al., 2014)
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	210 mg	15 mg	14	180					
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	210 mg	30 mg	7	180					
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	420 mg	30 mg	14	180					
PQ	-	210 mg	15 mg	14	180	Days 7, 14, 21, 28 and then monthly for the next five months	Exclusion of patients with G6PD-d	LM/PCR	no	(Pareek et al., 2015)
PQ-Sustained release	-	210 mg	15 mg	14	180					
PQ-Sustained release	-	210 mg	30 mg	7	180					
CQ alone	25 [10 (D0) + 10 (D1) + 5 (D2)]	–	–	–	365	Passive follow (the patients were asked to come back if fever)	G6PD status was evaluated and PQ was given only to normal G6PD patients	LM	no	(Savargaonkar et al., 2015)
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	210 mg	15 mg	14	365					
CQ + PQ or ACT-PQ[b]	25 [10 (D0) + 10 (D1) + 5 (D2)]	210 mg	15 mg	14	450	Every 1 to 2 month for 15 months	Exclusion of patients with G6PD-d	LM/PCR	no	(Kumar et al., 2016)
CQ + PQ[c]	25 [10 (D0) + 10 (D1) + 5 (D2)]	210 mg	15 mg	14	450					
CQ + PQ	25 [10 (D0) + 10 (D1) + 5 (D2)]	360 mg	45 mg	8[h]	–	–	G6PD status was evaluated and PQ	LM/PCR	no	(Savargaonkar et al., 2017)

(Continued)

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TABLE 2 Continued

Regimen	Total dose of blood stage drug (mg)*	Total PQ dose (mg base/Kg)	PQ dose/day (mg base/Kg)	Duration (days)	Follow-up duration (days)	Periodicity of the follow up	G6PD status	Diagnosis	Determined blood level of PQ?	Ref.
							was given to the patient			
CQ + PQ (Low dose)	25 [10 (D0) + 10 (D1) + 5 (D2)]	210 mg	15 mg	14	180	Every 4 weeks	G6PD status was evaluated and PQ was given to the patient	LM/PCR	yes[e]	(Saravu et al., 2018)
CQ + PQ (High dose)	25 [10 (D0) + 10 (D1) + 5 (D2)]	420 mg	30 mg	14	180					
CQ + PQ	–	Not specified	Not specified	14	–	–	G6PD status was evaluated	LM/RDT	no	(Kishore et al., 2020)
CQ alone	25 [10 (D0) + 10 (D1) + 5 (D2)]	-	-	-	690	Every 4 weeks + passive (report back if fever)	G6PD status was evaluated	LM/QBC	yes[f]	(Gandrala et al., 2022)
CQ alone	25 [10 (D0) + 10 (D1) + 5 (D2)]	-	-	-	690					
CQ + PQ (weekly)	25 [10 (D0) + 10 (D1) + 5 (D2)]	120 mg	15 mg	8[h]	690					
CQ + PQ (daily low dose)	25 [10 (D0) + 10 (D1) + 5 (D2)]	210 mg	15 mg	14	690					
CQ + PQ (daily high dose)	25 [10 (D0) + 10 (D1) + 5 (D2)]	420 mg	30 mg	14	690					

ACT, Artemisinin-based combination therapy; AQ, Amodiaquine; CQ, Chloroquine; G6PD, Glucose-6-phosphate dehydrogenase; G6PD-d, Glucose-6-phosphate dehydrogenase deficiency; HPLC, High pressure liquid chromatography; LC-MS, Liquid chromatography coupled with mass spectrometry; LM, Light microscopy; PCR, Polymerase chain reaction; PQ, Primaquine; PYR, Pyrimethamine; QBC, Quantitative buffy coat; QN, Quinine; RDT, Rapid diagnostic test.
D0: The day which treatment was started, D1(day 1): D0 + 1, D2 (day 2): D0 + 2.
*Blood stage antimalarial drug was either ACT, AQ, CQ or PYR.
[a]This therapeutic combination is commercially known as quiniplex.
[b]CQ + PQ or ACT + PQ were given to patients recruited in Manipal.
[c]CQ + PQ was given to patients recruited in Udupi.
Some authors determined blood concentration of PQ during their evaluation.
[d]LC-MS,
[e]Reverse HPLC,
[f]Method of PQ determination was not specified.
[g]Patients were followed up for 18 months, and we considered that 1 month = 30 days and thus a follow up of 540 days were computed.
[h]PQ was given weekly for 8 weeks.

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evaluated CQ + PQ to prevent *Pv* recurrences. Other studies associated PQ with other 8-aminoquinolines such as pentaquine, pamaquine and AQ while one study evaluated the ACT + PQ association to prevent *Pv* recurrences (Table 2). Two studies evaluated the anti-recurrence potential of different PQ monotherapies (i.e., standard and sustained release) (Singh et al., 1953; Pareek et al., 2015). Another study evaluated the anti-relapse effect of bulaquine, a PQ analogue, in patients from Delhi (Adak et al., 2001).

PQ posology greatly varied between studies, with the majority of studies testing very low PQ dose regimens (total dose < 2.5 mg/Kg). PQ was administered daily mostly for 5 days (n = 16, 59.3%), followed by daily administration for 14 days in 10 studies (37%), and 7 days in 3 studies (11.5%) (Table 2). Patients were either followed up actively or passively for durations ranging from 180 to 1460 months. Regarding active follow-up, patients were followed up either fortnightly, weekly or every 4/6/8 weeks.

Light microscopy (LM) was invariably used for *Pv* detection in patients, while some studies coupled it with polymerase chain reaction (PCR), rapid diagnostic test (RDT), and quantitative buffy coat (QBC). While if G6PD status of patients was not specified or evaluated in the bulk of the study, we noted that recent studies either excluded G6PD-d patients or evaluated G6PD status (Table 2). In addition, two studies determined the blood level of PQ using liquid chromatography – mass spectrometry (LC-MS) and reverse high-pressure liquid chromatography (HPLC) while the technique was not specified in one study (Rajgor et al., 2003; Saravu et al., 2018; Gandrala et al., 2022).

3.4 Approaches used to determine the burden of relapse attributable to *Pv* recurrences

The approach used to analyse recurrent infections was either not specified or inexistent in 34.6% and 26.9% of the included studies, respectively. For the remaining studies, six types of approaches were proposed, and based on patterns of recurrences following the primary infection, genotyping, parasitological evidence, clinical symptoms, and mathematical modelling (Table 3).

A genotyping-based approach relied on molecular amplification and/or sequencing of genetic markers (genes, microsatellites) in order to distinguish between relapse (heterologous infections) and recrudescence (homologous infections). The assumption behind this approach is that recurrent infections are classified as relapses if they are genetically distinct from primary infections. One study from Karnataka used molecular markers such as microsatellites (MS7 and MS10) to analyse *Pv* recurrence in adults treated with CQ + PQ (Saravu et al., 2018). In an RCT conducted in Maharashtra, genetic markers were associated with a linear regression-based mathematical model to determine the attributable fraction of *Pv* recurrence caused by relapse in patients treated with CQ alone or in association with PQ for 5 and 14 days (Table 3) (Kim et al., 2012).

Before the advent of molecular methods, earlier studies identified relapses using an approach based on patterns of recurrences, clinical symptoms, and parasitological evidence. In Uttar Pradesh, one study defined relapses as follows: "Patient became positive again, a few weeks after clearance of parasitaemia and in spite of a full course of CQ and PQ, associated with the analysis of periodicity to distinguish relapses from fresh infections" (Sinha et al., 1989).

3.5 Demographics of patients with recurrent *Pv* infections

Few studies analysed demographic characteristics of *Pv* recurrences and only data was extracted from five community-based studies and one case report conducted in Karnataka, Uttar Pradesh, Gujarat, Delhi, and Orissa states (Basavaraj, 1960; Sinha et al., 1989; Prasad et al., 1991; Srivastava et al., 1996; Yadav and Ghosh, 2002; Savargaonkar et al., 2017), even though several attempts were made to contact the corresponding and supervising authors of unavailable studies. Most *Pv* recurrences were found in males and those aged > 14 years old. In Karnataka, the proportion of *Pv* recurrences was higher in males (71.8%) and patients aged > 14 years (53.8%) compared to their female and younger counterparts, respectively (Basavaraj, 1960). Likewise, two studies from Uttar Pradesh reported a higher proportion of males (≥ 66%) and aged > 14 years (≥ 60%) (Sinha et al., 1989; Prasad et al., 1991). In contrast, Yadav and Ghosh found no statistically significant difference in *Pv* recurrence proportion between males and females in Orissa (Yadav and Ghosh, 2002).

3.6 Latency patterns of recurrent *Pv* infections

The number of *Pv* recurrences with regard to treatment arm and latency type is presented in Figure 4. Recurrences were observed for all arm treatments analysed (CQ, PQ, AQ + PQ, QN + Pentaquine, CQ + PYR, and CQ + PQ). Most *Pv* recurrences had intermediate and long latency. In patients treated with PQ monotherapy, *Pv* recurrences had frequent latency, while *Pv* recurrences had intermediate and long latency in those treated with CQ + PYR (Figure 4).

3.7 Characteristics and methodological quality of studies used to determine *Pv* relapse burden

As stated previously, three studies met inclusion criteria to determine the fraction of *Pv* recurrences caused by relapse (Rajgor et al., 2003; Kim et al., 2012; Rajgor et al., 2014). Although similarities between the three RCTs were noted for a place (Maharashtra), design (open label RCT), control arm (CQ) and follow-up (active), there were some differences found for population, number of treatment arms, PQ total dosing evaluated, duration of follow-up, parasitological method, and determination of PQ blood level (Supplementary File 3). For instance, patients were followed-up for 180 days in two studies and 450 days in the remaining study. Only one study determined the blood level of PQ in its design. Overall, the risk of bias was low for all evaluation

TABLE 3 Approaches used to discriminate the different types of *Plasmodium vivax* recurrences (relapse, reinfection, recrudescence).

Approaches	*n*	%
Not specified	9	33.3
• Not specified.	9	33.3
None[a]	7	25.9
• Relapses and reinfection were not differentiated.	7	25.9
Genotyping (homologous infections *vs* heterologous infections)[b]	5	18.5
• PCR genotyping was performed for such patients to allow differentiation between relapse and reinfection.	2	7.4
• Relapses were identified using polymerase chain reaction-single strand conformational polymorphism (PCR-SSCP).	1	3.7
• Relapses were identified by genotyping the *pvcsp* gene, the central fragment (F2) of the *pvmsp1* gene, and three microsatellites.	1	3.7
• Relapses were identified by genotyping MS7 and MS10 microsatellites.	1	3.7
Patterns of recurrence + Clinical symptoms + Parasitological evidence	2	7.4
• Patients who reported back to the clinic within 1.5 months to one year with renewed clinical symptoms (mild) along with a periodic alternate day fever (not observed in the primary cases) and found to be microscopically positive for *Pv* infection.	1	3.7
• Patients who reported back to the clinic within 1 month to one year with renewed clinical symptoms (mild) along with a periodic alternate day fever (not observed in the primary cases) and found to be microscopically positive for *Pv* infection.	1	3.7
Genotyping (homologous infections vs heterologous infections) + Mathematical model (Pattern of recurrence)	1	3.7
• Genotyping of three genes (*csp*, *msp3* alpha, and *msp1*) and three microsatellites. Linear regression was used to assess the temporal pattern of recurrent infections. The excess of early heterologous recurrences was attributed to relapse. As reinfection with a similar genotype had a probability = 0.002, recurrences of the same genotype were considered all to be relapses. The recurrences with different genotypes presumably resulted from both relapses and reinfections. It was assumed that genetically heterologous early relapses shared similar periodicity to the genetically homologous relapses in relation to the primary infection, whereas reinfections occurred at a much lower constant rate after four months and did not have any periodicity.	1	3.7
Patterns of recurrence + Genotyping	1	3.7
• The cases of recurrence were classified as relapse or reinfection based on i) The month of recurrence [relapse if it occurred between January and June (low transmission season), and reinfection if it occurred between July and December (active transmission season)], and ii) Two genotyping method - PCR-RFLP and PCR sequencing (*pvmsp3* alpha and beta) – (The detection of same parasite with such a polymorphic region indicates presence of same parasite clones in the paired sample which means relapse. The presence of different clones as indicated with another restriction enzyme probably points to either the presence of multiple clones in one of the samples or reactivation of one of the clones from primary infection).	1	3.7
Patterns of recurrence + Parasitological evidence	1	3.7
• Patients became positive again, a few weeks after clearance of parasitaemia and in spite of a full course of CQ and PQ, associated with analysing of periodicity to distinct relapses from fresh infections.	1	3.7
Clinical symptoms + Parasitological evidence	1	3.7
• Patient became febrile and was confirmed blood smear-positive within 18 months of the complete clearance of parasitaemia, despite receiving a full course of treatment.	1	3.7
Total	**27**	**100**

csp, Circumsporozoite gene; *msp1*, Merozoite surface protein 1 gene; *msp3-α*, Merozoite surface protein 3 alpha gene; PCR – SSCP, Polymerase chain reaction – Single strand conformational polymorphism; PCR – RFLP, Polymerase chain reaction – Restriction fragment length polymorphism.
[a]Relapse and reinfection were not differentiated (Patient became positive again after complete cure with CQ + PQ).
[b]Relapse was defined as homologous genotypes found before and after PQ treatment.

components, with the exception of concealment and blinding to drug treatment (Supplementary File 4).

3.8 Burden of *Pv* malaria relapse

In the included studies, estimates of the proportion of *Pv* malaria recurrences that relapsed were based on different approaches (genotyping, mathematical model, temporal pattern of recurrence). Using the Commons and colleagues-based adapted approach, the proportion estimates was ~0 – 60% across the three RCTs included. These estimates were higher than those found based on approaches defined by the authors of each individual study. Using two PCR-based approaches, Rajgor et al. found *Pv* relapses at proportions of 6% and 2 – 5% in CQ + PQ-treated adults from Maharashtra (Table 4) (Rajgor et al., 2003; Rajgor et al., 2014).

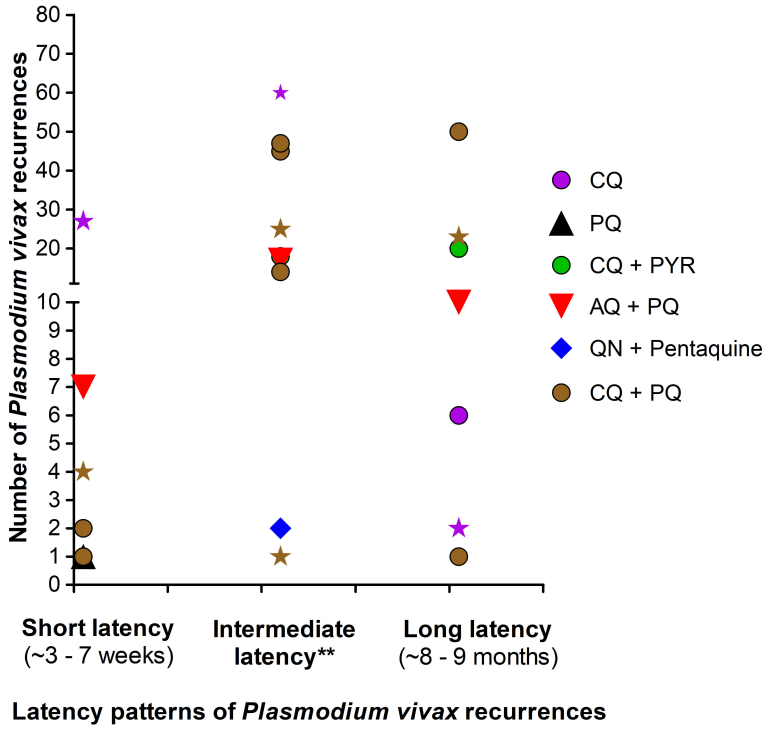

FIGURE 4
Latency patterns of *P. vivax* recurrences in treatment arms. AQ, Amodiaquine; CQ, Chloroquine; PQ, Primaquine; PYR, Pyrimethamine; QN, Quinine. Points depicted as star represent the number of relapses from studies with passive follow up of *P. vivax*-infected patients treated with CQ (purple star) or CQ + PQ (brown star). Points depicted as round, diamond and triangle represent the number of relapses from studies with active follow up of *P. vivax*-infected patients. Latency period of *P. vivax* recurrences was defined as frequent and long as proposed earlier (White, 2011; Chu and White, 2021). **These recurrences were subjectively termed "intermediate" by authors of the included studies. All treatment arms with PQ were very low dose (i.e. PQ total dose ≤ 2.5 mg/Kg).

TABLE 4 Comparative analysis of estimates of *Pv* relapses based on approaches used by authors of individual studies and adapted from the Commons and colleagues' study.

Approaches	Rajgor et al. (2003)	Kim et al. (2012)		Rajgor et al. (2014)		
	CQ + PQ (0.15 × 14 = 2.1 mg/kg)[a]	CQ + PQ (0.15 × 5 = 0.75 mg/kg)[b]	CQ + PQ (0.15 × 14 = 2.1 mg/kg)[a]	CQ + PQ (0.15 × 14 = 2.1 mg/kg)[a]	CQ + PQ (0.30 × 7 = 2.1 mg/kg)[c]	CQ + PQ (0.30 × 14 = 4.2 mg/kg)[d]
Author adapted approach	55%	10%	0%	51%	39%	60%
Genotyping (PCR - SSCP)	6%	–	–	–	–	–
Genotyping (PCR - RFLP)	-	-	-	2%	5%	3.68%
Genotyping (Sequencing)	–	–	–	1.47%	2%	3%
Genotyping (*csp*, *msp3-α* and *msp1* and three microsatellites) + Mathematical model	-	n.a	n.a	-	-	-
Month of recurrence	–	–	–	1.55%	4%	2.84%

CQ, Chloroquine; *csp*, Circumsporozoite gene; *msp1*, Merozoite surface protein 1 gene; *msp3-α*, Merozoite surface protein 3 alpha gene; PCR – SSCP, Polymerase chain reaction – Single strand conformational polymorphism; PCR – RFLP, Polymerase chain reaction – Restriction fragment length polymorphism; PQ, Primaquine; n.a, Not available.
For definitions based on genotyping, PCR-RFLP or PCR-SSCP were used in either the two studies.
[a]PQ arm include patients treated with 2.1 mg/Kg total dose over 14 days (Very low PQ dosing).
[b]PQ arm include patients treated with 0.75 mg/Kg total dose over 5 days (Very low PQ dosing).
[c]PQ arm include patients treated with 2.1 mg/Kg total dose over 7 days (Very low PQ dosing).
[d]PQ arm include patients treated with 4.2 mg/Kg total dose over 14 days (Low PQ dosing).

3.9 Haemolytic anaemia associated with PQ administration

In one study from Delhi, PQ was administered at 0.75 mg/Kg/week for eight weeks in a 23-year-old male with G6PD-d who had presented three episodes of relapses 4, 5 and 6 months after the primary *Pv* infection. No haemolytic anaemia event was reported in the patient (Savargaonkar et al., 2017).

4 Discussion

It is evident that recurrent malaria parasitaemia is an important impediment to malaria control strategies and that accurately determining the burden and patterns of relapsing *Plasmodium* infections is a key determinant to evaluating the clinical impact of *Pv* malaria and informing policy makers on the utility of PQ-based national strategies in India. However, there are several missing links and solutions presented below and in Figure 5, that should be addressed in the future.

Various approaches, such as genotyping, patterns of recurrence and statistical models, were used in individual studies, and this increases uncertainty over the true epidemiology of relapse burden and patterns in India. Distinguishing relapses and reinfections using genotyping is still problematic given that relapse–associated genotypes can be identical, closely similar, or different from those of the primary infection (Imwong et al., 2007; White, 2011; Imwong et al., 2012; Popovici et al., 2018; Chu and White, 2021). In Thailand, Imwong et al. showed that the first relapses of life in babies are genetically similar to the primary infections (Imwong et al., 2012). Using denoting protocols, Popovici and colleagues showed that most *Pv* relapses were polyclonal and closely related genotypes that caused acute infection in Cambodian individuals (Popovici et al., 2018). More recently, Xu and colleagues showed the possible utility of the circumsporozoite protein gene for tracing the origin of *Pv* relapse among Chinese patients (Xu et al., 2023). In community settings, the utilisation of genotyping methods is challenging and thus requires the development of point-of-care testing for the detection of relapse risk as recently proposed by the WHO (2024).

On analysis of the periodicity of *Pv* recurrence events, it was observed that these showed frequent and long latency phenotypes. It is plausible that some *Pv* recurrences observed in Indian studies were relapses. Both frequent and long latency types coexist in India (White, 2011). PQ has a narrow therapeutic window and a short half-life (~4 – 7 hours) which requires daily administration for up to two weeks (Pareek et al., 2015). Thus, this may result in poor adherence and explain some recurrent infections. In some included studies, recurrent infections appeared within less than 28 days of

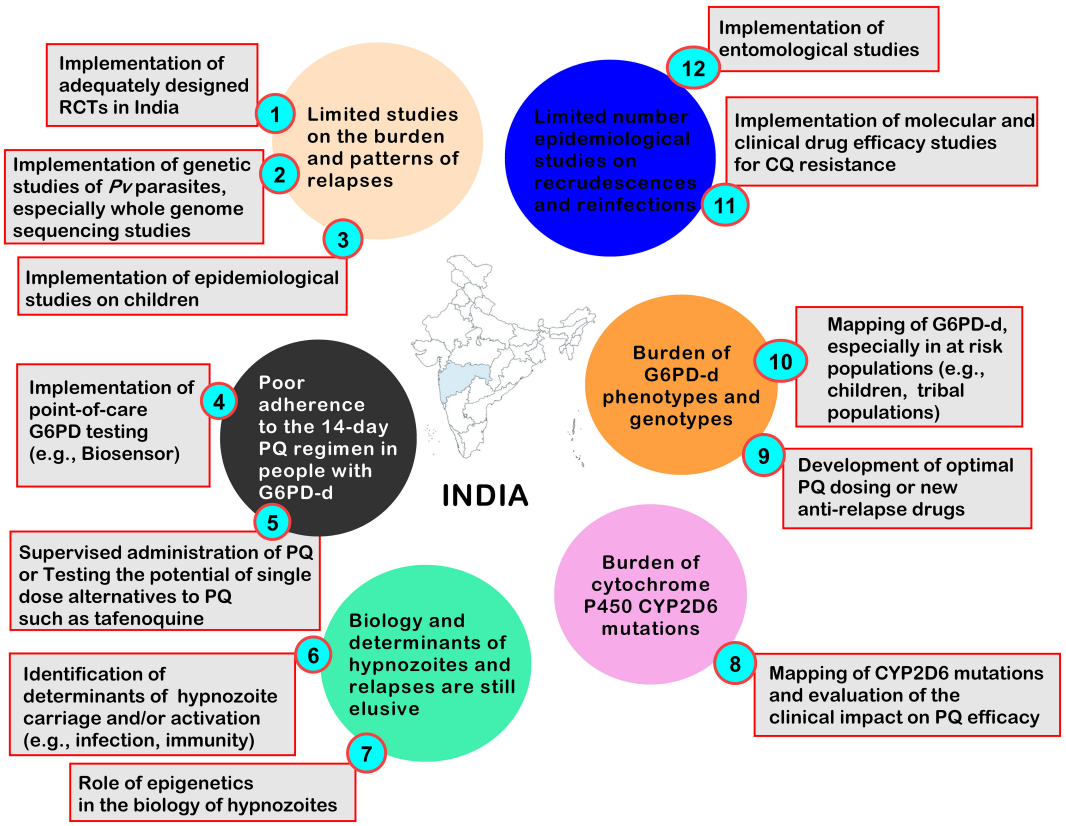

FIGURE 5
Current challenges to appraise and control *Pv* recurrences caused by relapses, and some proposed solutions. CQ, Chloroquine; G6PD, Glucose-6-Phosphate dehydrogenase; G6PD-d, Glucose-6-Phosphate dehydrogenase deficiency; PQ, Primaquine; *Pf*, *Plasmodium falciparum*; *Pv*, *Plasmodium vivax*; RCT, Randomised controlled trial.

follow-up, thereby suspecting a possible CQ-resistance of the *Pv* parasite and/or suboptimal blood levels of the PQ active metabolite.

Recurrences of *Pv* malaria were mostly seen in young males, and this is consistent with previous studies in Brazil (Daher et al., 2019), but contradictory to other investigations (Cuong et al., 2006; Vieira et al., 2020). In addition to the male sex, Douglas and colleagues found that young age, *Pf*/*Pv* mixed infections at enrolment, lower haematocrit, higher *Pf* asexual parasite density, *Pf* gametocytaemia at enrolment, and drug partner in the ACTs were risk factors for *Pv* recurrence after treatment of acute *Pf* malaria in individuals from the Thai-Myanmar border (Hossain et al., 2020). The role of age on the risk of *Pv* recurrence is a bit less elusive than that of gender. Higher rates of *Pv* recurrences observed in young individuals are likely due to immunity levels that are known to increase with age with the lowest levels during infancy and the highest during adulthood, thereby reducing the number of *Pv* recurrences in increasing age groups (White, 2011). Regarding gender, its relationship with *Pv* recurrences is still elusive, and thus, further studies are necessary to understand how this variable could modulate *Pv* recurrence.

The proportion of *Pv* recurrences that relapse in India varied from 0 to 60% using the adapted Commons and colleagues' approach, but from 1.47 to 6% using the methods described in the included studies. Relapse burden was estimated earlier to be minimally at 66%, using the Commons and colleagues' approach, across *Pv* malaria endemic regions (Afghanistan, Ethiopia, Indonesia, Nepal, Pakistan, Thailand, and Vietnam) (Commons et al., 2020). This is not surprising as the approach proposed by Commons and colleagues has some limitations as outlined by them previously (Commons et al., 2020). For instance, the approach assumes that the risk of recrudescence is similar between individuals treated with or without PQ. It is known that PQ has a schizonticidal activity against early recurrent infection that likely derivate from relapse and/or recrudescence (White, 2008). In areas where *Pv* isolates have reduced CQ susceptibility, it is probable to observe lower rates of recurrent infections in individuals treated with PQ, and in this scenario, the proportions of recurrences that relapses can be overestimated (Commons et al., 2020). Furthermore, as we adapted the Commons' approach (for instance, we included all studies regardless of the duration of follow-up), this inevitably introduced another bias in the estimation of relapse rates, thus explaining the differences observed. Also, it is evident that between-study differences may explain this large range of estimates, even though the studies included for analysis were all conducted in Maharashtra, and this limits our estimates to this area and not at the country level. Huber and colleagues recently pointed out that differences in the conditions under which clinical trials are conducted may explain difficulties in comparative analyses of efficacy estimates between clinical trials and underestimate the effect of radical cure on *Pv* hypnozoites (Huber et al., 2021). More importantly, it should be important to mention that this large variation in the prevalence of relapse is likely due to the fact that PQ was given at a low dose in the included studies. In general, if proper treatment is given, relapse rates may be lower than 5%, as is evidenced by their studies using genotyping techniques. Also, some of the included studies did not follow the Indian Government guidelines for the treatment of *Pv* malaria which in itself is cause for concern. India adopted the WHO guidelines for dealing with Pv relapses which consists of administering PQ for 14 days. Very low doses of PQ will not eliminate the hypnozoites, which are dormant and are in the liver cells. This is why the PQ doses should be standardised and would help eliminate dormant stages so that no relapse occurs. Adequate PQ dosing is a key factor to reduce the chances of relapses. Several studies reported that the chances of relapses were decreased with increasing PQ doses (Galappaththy et al., 2013; Verma et al., 2023). Some of the current questions are about the duration of the PQ regimen (e.g., 3 days, 7 days, 14 days) and the impact of adjustment variables (e.g., age, weight, G6PD activity level, G6PD-d) of the PQ doses (Taylor et al., 2021; Moore et al., 2023; Pukrittayakamee et al., 2024; Rajasekhar et al., 2024). Besides, the included studies did not use the same definitions for *Pv* relapses, and this has also introduced bias in comparative analysis (Xu et al., 2023).

Besides, the drug resistance profile of infecting *Pv* strains is also an important confounder in the ability to distinguish the different types of recurrent infections. Drug resistance profile is particularly important in areas where high rates of drug-resistant *Pv* parasites, especially CQ-resistant parasites, are documented. CQ is the drug of choice for treating *Pv* infections in India. Even though, there are no validated molecular markers of *Pv*-related CQ-resistance till now, clinical efficacy studies may reveal valuable help to appreciate the burden of both CQ-resistance and *Pv* relapse (Popovici et al., 2019; Twohig et al., 2019; Kojom Foko et al., 2024). Unfortunately, this aspect was not addressed in the included studies that evaluate the burden of *Pv* relapses. Also, measuring the G6PD activity of individuals is crucial to evaluating both severe haemolysis risk and the effectiveness and efficacy of PQ against relapse. Again, these aspects were not evaluated in the included studies and should be investigated in future. A recent study by Rajasekhar and colleagues concluded the safety of PQ radical cure at doses 0.25–0.5 mg/kg in patients with G6PD activity of 30% or higher, and 0.25–1 mg/kg per day regimens in patients with G6PD activity of 70% or higher, in comparison with patients treated without PQ (Rajasekhar et al., 2024). Finally, host-related factors such as pharmacogenetics should also investigated in future. Indeed, three main genetic polymorphisms, i.e., cytochrome P450 2D6 (CYP2D6), monoamine oxidase (MAO), and cytochrome P450 NADPH: oxidoreductase, can affect the PQ metabolism and its conversion to active form, and thereby possibly impairing its efficacy or effectiveness and increasing the chances of relapses (Nain et al., 2022). Thus, it would be crucial to conduct proper clinical studies, combining correct doses of PQ, sensitive genotyping techniques, and evaluation of G6PD activity, clinical CQ resistance, and host-related genetic factors to better understand the real burden of *Pv* recurrences that relapse in India.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

LK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft. VS: Conceptualization, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Supplementary material

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