Invited review

The Vivax Surveyor: Online mapping database for *Plasmodium vivax* clinical trials

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ABSTRACT

Introduction: Recurrent *P. vivax* infections are associated with significant morbidity and mortality. Although radical cure can reduce recurrent infection, it is confounded by antimalarial resistance and the lack of safe and effective hypnozoitocidal treatment. This study documents the available literature of published clinical trials of *P. vivax*, providing an up to date, online, open access tool to view and download available information.

Methods: A systematic review was conducted according to PRISMA guidelines to identify prospective *P. vivax* therapeutic clinical trials with at least 28 days follow-up published between 1st January 1960 and 12th October 2016. Treatment arms and evidence of chloroquine resistance were mapped to trial sites.

Results: Since 1960, a total of 1152 antimalarial clinical trials with a minimum 28 days follow-up have been published, of which 230 (20.0%) enrolled patients with *P. vivax* and were included. Trials were conducted in 38 countries: 168 (73.0%) in the Asia-Pacific, 13 (5.7%) in Africa and 43 (18.7%) in the Americas. The proportion of antimalarial trials assessing *P. vivax* rose from 10.7% (12/112) in 1991−1995, to 24.9% (56/225) in 2011−2015. Overall, 188 (81.7%) *P. vivax* trials included a chloroquine treatment arm, either alone or in combination with primaquine, and 107 (46.5%) trials included a chloroquine treatment arm with early primaquine to assess radical cure. There has been a recent increase in treatment arms with artemisinin derivatives. Of the 131 sites in which chloroquine resistance could be quantified, resistance was present in 59 (45.0%) sites in 15 endemic countries.

Conclusions: Over the last 20 years there has been a substantial increase in clinical research on the treatment of *P. vivax*, which has generated a greater awareness of the global extent of chloroquine resistance. The WWARN open access, online interactive map provides up to date information of areas where drug resistant *P. vivax* is emerging.

Contents

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1. Introduction

Until recently *Plasmodium vivax* was regarded as a relatively benign infection, however, over the last decade this paradigm has shifted. *P. vivax* is now recognised to cause severe and fatal malaria (Baird, 2007, 2013; Barcus et al., 2007), although the underlying aetiology of this is debated (Anstey et al., 2009; Chu and White, 2016). A key pathological process of *P. vivax* is its ability to recur, with recurrent parasitaemia arising from reinfection, recrudescence (from treatment failure) or relapse (from dormant liver stages - hypnozoites) (White, 2011). Each recurrent episode of parasitaemia is associated with haemolysis and a cumulative risk of anaemia (Price et al., 2009; Douglas et al., 2012), particularly in infants and pregnant women (Douglas et al., 2013), which is associated with both direct and indirect morbidity and mortality (Poespoprodjo et al., 2009; Douglas et al., 2014), as well as preterm delivery and stillbirth (Poespoprodjo et al., 2008; Moore et al., 2016).

Chloroquine remains the mainstay of schizontocidal treatment for *P. vivax* (World Health Organisation, 2015), although this is now under threat from the emergence and spread of chloroquine resistant *P. vivax* (CQR Pv). CQR was first observed in the Island of Papua in 1989 (Rieckmann et al., 1989), with subsequent documentation in many vivax endemic countries (Price et al., 2014). This has prompted increasing study of artemisinin combination therapies for *P. vivax* infection and in some locations, this has led to the adoption of a universal policy of ACT treatment for both *P. vivax* and *P. falciparum* (Douglas et al., 2010).

Primaquine remains the only widely available hypnozoitocidal drug, but its use is hampered by the risk of haemolysis in people with G6PD deficiency and the risk of reduced adherence with the currently recommended 14 day treatment course (Grietens et al., 2010; Fernando et al., 2011). The majority of *P. vivax* recurrences is estimated to be secondary to relapses from the parasites' dormant hypnozoite stages (Adekunle et al., 2015; Robinson et al., 2015). Hence, as countries progress towards elimination of all malaria species, there is an increasing imperative to achieve safe and effective radical cure to tackle both the blood and liver stages of the parasite.

Previous systematic reviews have addressed the evidence of chloroquine efficacy against *P. vivax* (Price et al., 2014) and primaquine antirelapse efficacy (John et al., 2012) and the methodologies used in these clinical trials. This paper extends these systematic reviews to all published *P. vivax* clinical trials currently available and presents these using an online open access tool known as the Vivax Surveyor. The Surveyor will be maintained and regularly updated, providing the research community and policy makers with contemporary knowledge of *P. vivax* therapeutics. The aim is that the WWARN Vivax Surveyor will support the growing research agenda on *P. vivax* and facilitate the design and implementation of future clinical trials, through provision of a flexible, up to date repository of clinical trials.

2. Methods

2.1. Study design

Medline, Web of Science, Embase, the Cochrane Database of Systematic Reviews, clinicaltrials.gov and the International Clinical Trials Registry Platform were systematically searched to identify prospective therapeutic efficacy trials of uncomplicated *Plasmodium* infection published between Jan 1, 1960 and October 25, 2016 with a minimum of 28 days follow up. The following search terms were used: ((malaria OR plasmodium) AND (artefenomel OR arterolane OR amodiaquine OR atovaquone OR artemisinin OR arteether OR artesunate OR artemether OR artemotil OR azithromycin OR artekin OR chloroquine OR chlorproguanil OR cycloguanil OR clindamycin OR coartem OR dapsone OR dihydroartemisinin OR duo-cotecxin OR doxycycline OR halofantrine OR lumefantrine OR lariam OR malarone OR mefloquine OR naphthoquine OR naphthoquinone OR piperaquine OR primaquine OR proguanil OR pyrimethamine OR pyronaridine OR proguanil OR quinidine OR quinine OR riamet OR sulphadoxine OR tetracycline OR tafenoquine)) (WorldWide Antimalarial Resistance Network, 2016c). Only trials enrolling patients with *P. vivax* monoinfection were included (WorldWide Antimalarial Resistance Network, 2016b). Trials were excluded for the following reasons: the trial data had been presented in a previous publication, the trial focused on severe malaria, data were extracted retrospectively from medical records outside of a planned trial, schizontocidal treatment was unsupervised (if not specified treatment was assumed to have been supervised), trials did not involve active follow up, or assessed prophylaxis, intermittent preventive treatment or intermittent screening and treatment. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42016053228).

2.2. Data extraction

Data on trial characteristics, treatment arms and efficacy were extracted systematically by two independent investigators and entered into Excel v15.20. Trial characteristics included the study type (see Section 2.3), study date, site locations within the study and number of patients included. Treatment arms within each trial were documented including number of patients, drug regimens, dosing (including total dose (mg per kg)) and treatment duration, as well as the risk of recurrence at day 28 for patients treated with chloroquine (with or without primaquine).

Trial site locations were identified using Google Earth (https://www.google.com/earth/). For trials including returned travellers, returned soldiers or experimental infections, the site location was defined as the site where the patients were enrolled.

2.3. Definitions

Chloroquine resistance (CQR) was assessed from: the risk of

recurrent *P. vivax* by day 28 (calculated from the number of patients with recurrent parasitaemia, divided by the number of patients followed until treatment failure or at least 28 days), whole blood chloroquine concentrations at the time of recurrence, and trial enrolment criteria as described in Box 1 (Price et al., 2014). CQR categories were derived for each site reported within a trial. When separation of multiple trial sites was not possible, the CQR category was located to the largest trial site. Chloroquine resistance was not categorised in studies of returned travellers or returned soldiers.

Primaquine administration was defined as early if it was initiated within 14 days of enrolment and dosing was defined according to the total dose given as very low dose ($\leq$2.5 mg/kg), low dose (>2.5–<5.0 mg/kg) or high dose ($\geq$5.0 mg/kg). Trial types are defined in Box 2.

2.4. Analysis

The analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Analysis was undertaken in Excel v15.28. Categorical variables were described by annual frequency, cumulative frequency and proportion where appropriate. Recurrence by day 28 was calculated for chloroquine arms according to site, using per protocol analysis with 95% confidence intervals derived using the Wilson procedure without continuity for correction (Newcombe, 1998). Trial site latitude and longitude were mapped onto an electronic platform and linked to trial details with filters for country, year of publication, drug treatment, trial size and trial type.

Box 1

Categories of evidence for chloroquine resistance (Price et al., 2014)

Category 1 evidence: includes trials with greater than 10% recurrences by day 28 (with a lower 95% CI of >5%), irrespective of confirmation of adequate blood chloroquine concentration. Recurrence by day 28 is calculated from the number of patients with recurrent parasitaemia, divided by the number of patients followed until treatment failure or at least 28 days. Occasional breakthrough recurrences do occur within 28 days of chloroquine treatment, but a risk greater than 10% in a large enough sample is very suggestive of resistance.

Category 2 evidence: includes trials with at least 5% recurrences by day 28 in the presence of whole-blood chloroquine concentrations greater than 100 nm (irrespective of the lower 95% CI) or trials with at least 5% recurrences by day 28 and lower 95% CI of >5% (irrespective of confirmation of adequate blood chloroquine concentration).

Category 3 evidence: includes trials with at least 5% recurrences by day 28 (lower 95% CI of <5%), irrespective of confirmation of adequate blood chloroquine concentration; this category provides potential evidence of chloroquine resistance, which may have arisen from other factors such as poor drug absorption or drug quality.

Category 4 evidence (chloroquine susceptible): includes trials of at least 10 patients with symptomatic malaria, where patients were treated with chloroquine monotherapy (no primaquine before day 28) at greater than or equal to 15 mg/kg total dose and fewer than 5% recurrences occurred within 28 days.

3. Results

In total 1152 antimalarial clinical trials were identified with a minimum follow up of 28 days up to October 25th, 2016. Of these 230 (20.0%) studies, enrolling 76,134 patients, fulfilled the criteria for this *P. vivax* review (Fig. 1). Eighty-nine *P. vivax* trials were registered on the clinicaltrials.gov registry or the International Clinical Trials Registry Platform, of which 25 (28.1%) had been published and were included in the 230 studies identified in this literature review.

The trials were conducted in 38 countries, with 99.6% (229) designed to assess antimalarial treatment efficacy against blood stage parasites (schizontocidal efficacy) and 57.4% (132) to assess efficacy against hypnozoites by monitoring relapse in patients after initial treatment (anti-relapse efficacy). The majority of these trials were conducted in the Asia-Pacific (73.0%, 168/230), with 18.7% (43/230) in the Americas and 5.7% (13/230) in Africa (Fig. 2). The median time between completion of a trial and its publication was two years, with a range of 1–12 years.

The number of *P. vivax* trials published each year ranged from 0 to 17 with an increase in publications since the mid-1990s, and the first trials conducted in Africa in 2008 (Fig. 2). Overall 84.3% (194/230) of trials have been published since 1995 and 69.6% (160/230) since 2001. Relative to all antimalarial clinical trials, the proportion of *P. vivax* trials increased from 10.7% (12/112) between 1991 and 1995 to 24.9% (56/225) between 2011 and 2015 and this was apparent in all regions, particularly in the Americas (Fig. 3).

The duration of each study could be determined in 228 trials (99.1%), including 227 schizontocidal efficacy studies and 131 anti-relapse studies. One hundred and twenty-eight schizontocidal efficacy trials (56.4%) followed patients for 28 days, 25 (11.0%) for between 29 and 42 days, 7 (3.1%) for between 43 and 63 days, 7 (3.1%) for between 64 and 120 days and 60 (26.4%) for more than 120 days. In comparison, anti-relapse trials followed patients for 28 days in 51 trials (38.9%), 29–42 days in 11 (8.4%), 43–63 days in 3 (2.3%), 6 (4.6%) for between 64 and 120 days and more than 120 days in 60 (45.8%) (Fig. 4).

3.1. Treatment regimens

A total of 417 treatment arms among the 230 studies were studied, of which 241 (57.8%) were in trials of early recurrence (duration up to 42 days), 172 (41.2%) were in trials of late recurrence

Box 2
Types of trials

Schizontocidal (blood stage) trials: are trials that assessed the effect of treatment on parasite clearance and recurrence within 28 days. They include i) an arm with a schizontocidal agent or ii) studies of the sole administration of an agent with hypnozoitocidal and schizontocidal activity (eg primaquine).

Anti-relapse trials: are trials including administration of a hypnozoitocidal agent prior to the final follow up of the trial, either alone or with a schizontocidal agent.

Trials assessing early recurrence: are defined as having a follow up of less than or equal to 42 days.

Trials assessing late recurrence: are defined as having a follow up of greater than 42 days.
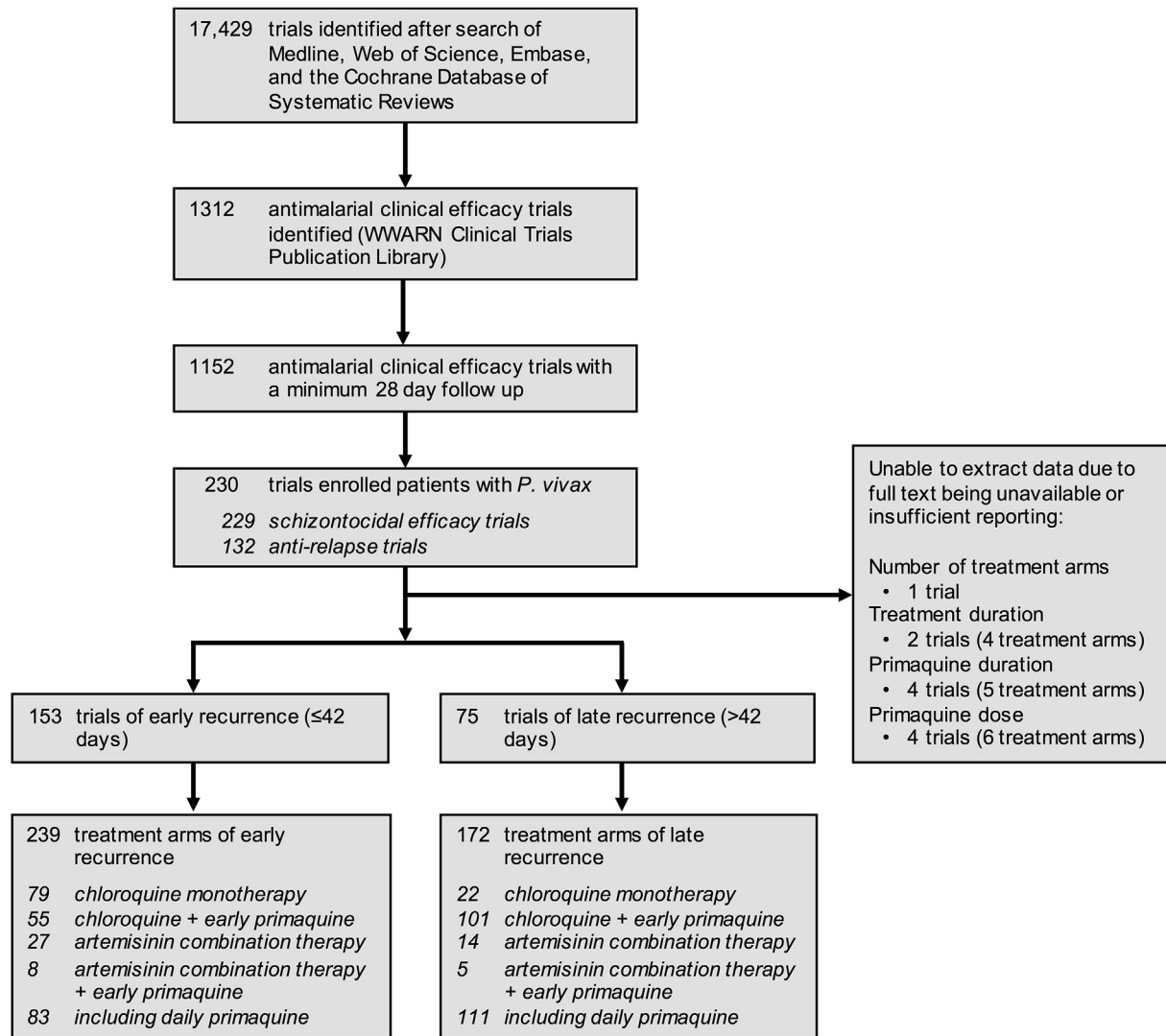
| 17,429 | trials identified after search of Medline, Web of Science, Embase, and the Cochrane Database of Systematic Reviews |

| 1312 | antimalarial clinical efficacy trials identified (WWARN Clinical Trials Publication Library) |

| 1152 | antimalarial clinical efficacy trials with a minimum 28 day follow up |

230	trials enrolled patients with *P. vivax*
229	*schizontocidal efficacy trials*
132	*anti-relapse trials*

Unable to extract data due to full text being unavailable or insufficient reporting:

Number of treatment arms
• 1 trial
Treatment duration
• 2 trials (4 treatment arms)
Primaquine duration
• 4 trials (5 treatment arms)
Primaquine dose
• 4 trials (6 treatment arms)

| 153 | trials of early recurrence (≤42 days) |

| 75 | trials of late recurrence (>42 days) |

239	treatment arms of early recurrence
79	*chloroquine monotherapy*
55	*chloroquine + early primaquine*
27	*artemisinin combination therapy*
8	*artemisinin combination therapy + early primaquine*
83	*including daily primaquine*

172	treatment arms of late recurrence
22	*chloroquine monotherapy*
101	*chloroquine + early primaquine*
14	*artemisinin combination therapy*
5	*artemisinin combination therapy + early primaquine*
111	*including daily primaquine*

Fig. 1. Trial selection.

(duration greater than 42 days) and the duration of treatment could not be extracted from four arms (full text unavailable) (Table 1). Chloroquine was administered in 67.9% (283/417) and artemisinin combination therapy in 9.8% (41/417) of treatment arms. Of the 241 trials of early recurrence, chloroquine was administered in 144 (59.8%), and of these, 38.2% (55/144) included early primaquine treatment (Table 1). Since 1995, the proportion of trials including a chloroquine monotherapy treatment arm has declined (Fig. 5). A total of 41 treatment arms of *P. vivax* have assessed artemisinin combination therapies since 1993, with this proportion increasing in more recent trials, and of these, 31.7% (13/41) included early primaquine treatment.

Primaquine treatment was administered at any stage during the study period in 53.2% (222/417) of treatment arms. In the 111 primaquine treatment arms which assessed late parasite recurrence and used daily dosing, 107 (96.4%) started primaquine treatment within 14 days of enrolment, with 43.0% (46/107) administering a 14 day regimen. Very low dose primaquine regimens were assessed in 40 (37.4%) treatment arms, low dose primaquine in 54 (50.4%) and high dose primaquine in 13 (12.1%). High dose primaquine treatment regimens in trials of late recurrence were given over 14 days or more in all except for one trial (15/16). Of the 88 treatment arms assessing late recurrence where primaquine supervision

could be assessed, primaquine administration was supervised in 83 (94.3%). Four other hypnozoitocidal agents (tafenoquine, bulaquine, elubaquine, tinidazole) were assessed in six trials.

3.2. Chloroquine efficacy

Chloroquine efficacy could be categorised at unique time points from 131 sites in 15 countries. Reduced chloroquine efficacy was documented in 45.0% of trial sites, with category 1 evidence present in 35 sites (26.7%), category 2 in 9 sites (6.9%), and category 3 in 15 sites (11.5%) (See Box 1 for definitions of the categories and Fig. 6 for trial site locations). Chloroquine efficacy was not able to be categorised at 136 sites with reasons for this including administration of early primaquine (102/136 (75%)), no day 28 data being available (31/136 (22.8%)), less than 15 mg/kg total dose of chloroquine (19/136 (14.0%)) and less than 10 patients at the site (8/136 (5.9%)) (some sites had multiple reasons for efficacy not being able to be categorised).

3.3. The Surveyor

All the trials in this systematic review are summarised on the WWARN Vivax Surveyor (WorldWide Antimalarial Resistance
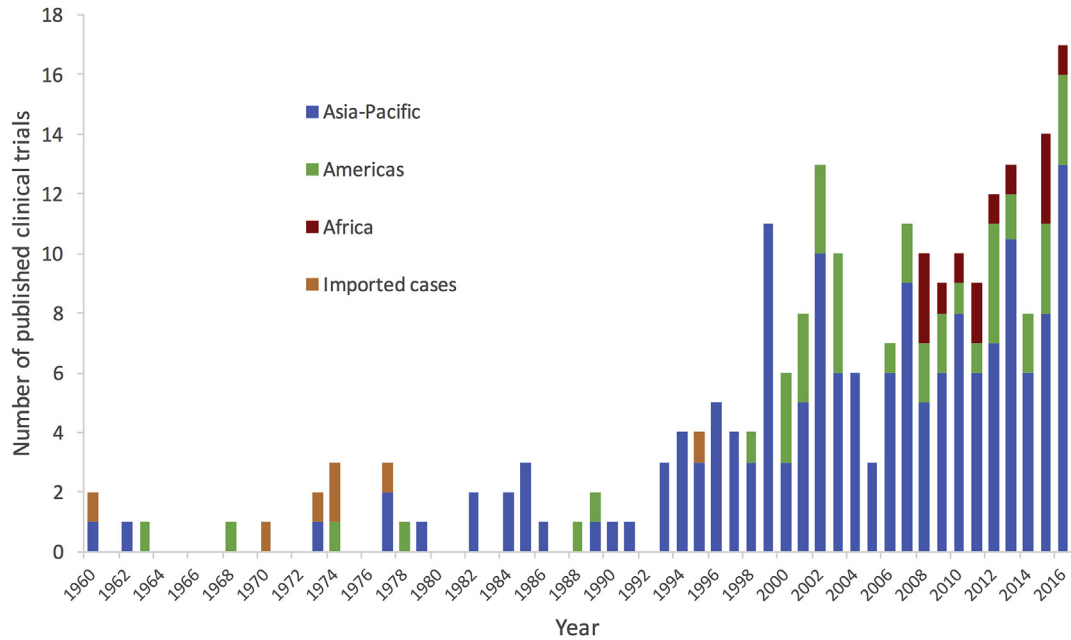
Fig. 2. Number of clinical trials of *P. vivax* monoinfection published each year according to region.
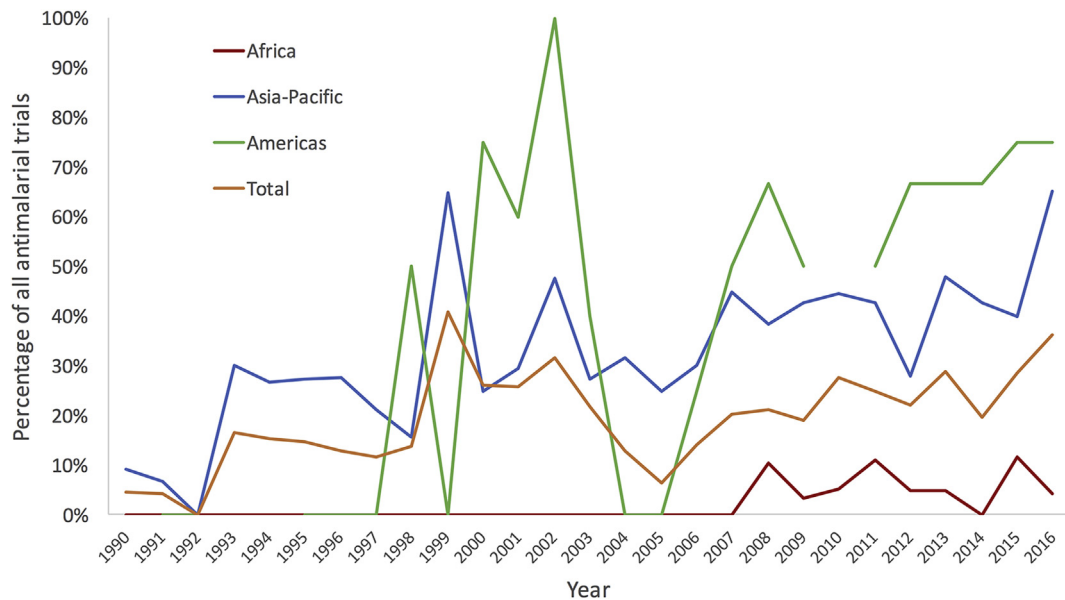

Fig. 3. Temporal trends in the percentage of all antimalarial clinical efficacy trials that include patients with *P. vivax* monoinfection, by region.

Network, 2016a). This open access electronic map uses colour coded pins to identify sites where trials have been undertaken, according to the category of chloroquine resistance. Specific data for each study site are presented including trial type, years of recruitment, number of patients enrolled, treatment arms, primaquine use and timing, chloroquine efficacy estimates, chloroquine resistance category and publication details. Filters are available to select data by year, sample size, country, trial type, treatment regimens and category of chloroquine resistance. The data presented are linked to the published reference and include details on chloroquine and primaquine dosing, timing and supervision. Direct comparison between sites, and at one site over different time periods, can also be undertaken.

4. Discussion

This systematic review highlights an increasing volume of literature on antimalarial efficacy against *P. vivax*. Over the period surveyed, there has been a progressive increase in the number of *P. vivax* trials, particularly in the Asia-Pacific, which contributes almost 81% of the disease burden (World Health Organization, 2016b). The proportion of antimalarial trials involving *P. vivax* has risen, reflecting the proportional increase in *P. vivax* malaria in coendemic countries and recognition of the challenges of controlling and eliminating this important human pathogen. This trend is most apparent in the Americas where *P. vivax* now accounts for 69% of all malaria cases (World Health Organization, 2016b) and is the focus of 75% of all antimalarial trials (Fig. 3).
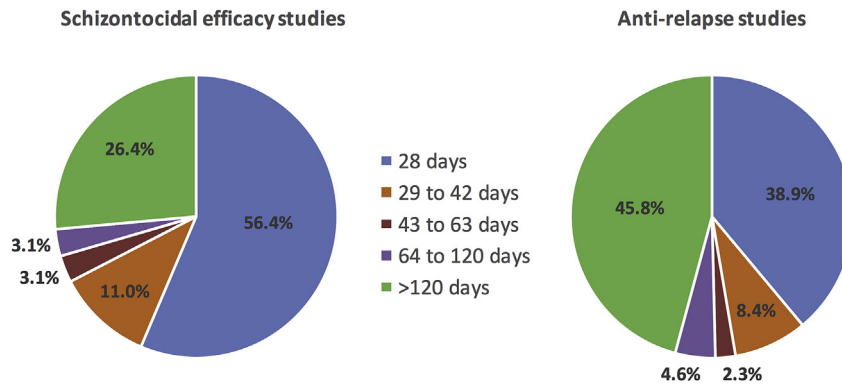
Schizontocidal efficacy studies

56.4% 28 days
11.0% 29 to 42 days
3.1% 43 to 63 days
3.1% 64 to 120 days
26.4% >120 days

Anti-relapse studies

38.9%
45.8%
8.4%
4.6%
2.3%

Fig. 4. Duration of follow up in *P. vivax* clinical trials.

Chloroquine has been the mainstay of treatment of *P. vivax* for 60 years, however the emergence of chloroquine resistant *P. vivax* now poses a serious threat to this policy (Price et al., 2014). Almost half of the sites in which chloroquine efficacy could be categorised, demonstrated evidence of reduced chloroquine efficacy. Among these, 27% of sites, throughout 13 countries (Bolivia, Brazil, Cambodia, Colombia, Ethiopia, India, Indonesia, Madagascar, Malaysia, Myanmar, Papua New Guinea, Turkey, Vietnam), reported treatment failure in greater than 10% of patients enrolled in the trial; four of these countries (Cambodia, Indonesia, Malaysia, Papua New Guinea) have now changed national guidelines to a universal policy of ACT and malaria elimination has been achieved in Turkey.

Despite an increasing number of reports of CQR *P. vivax*, there are many countries where the local efficacy of chloroquine is yet to be assessed. Of the 95 potentially vivax endemic countries (Gething et al., 2012), 45 reported indigenous *P. vivax* during 2015 (World Health Organization, 2016b), and only 24 (53%) of these have assessed efficacy of chloroquine monotherapy since the start of 2011 (20 of these studies are published and a further 4 are unpublished WHO therapeutic efficacy studies;

Fig. 7 and Table 2). The majority of countries without chloroquine efficacy studies are in the Americas and Africa and report relatively few *P. vivax* cases each year (Table 2), suggesting that *P. vivax* is either not considered a public health priority in these countries or that conducting a reliable antimalarial efficacy study is not feasible. However, it is important to emphasise that the absence of locally generated efficacy data should not necessarily be construed as evidence that local regimens remain efficacious, particularly as the remaining parasites in a declining total parasite population are often the most resistant. A particular example is Sabah, Malaysia, which is close to eliminating vivax malaria, but in 2015 revealed surprisingly high levels of recurrence (>30%) following chloroquine treatment of *P. vivax* (Grigg et al., 2016).

Treatment regimens with artemisinin combination therapies (ACTs) are now standard policy for *P. falciparum* and are part of national policy as first line therapy in more than 94% (80/85) of countries reporting *P. falciparum* infections (World Health Organization, 2016b). The widespread deployment of ACTs provides an alternative treatment option for *P. vivax* and an

Table 1
Treatment regimens in *P. vivax* clinical trials.

	Trials (number (%))			Treatment arms (number (%))			Patients (number (%))		
	Early recurrence trials (≤42 days)	Late recurrence trials (>42 days)	Total	Early recurrence trials (≤42 days)	Late recurrence trials (>42 days)	Total	Early recurrence trials (≤42 days)	Late recurrence trials (>42 days)	Total
Overall totals	153 (66.5%)	75 (32.6%)	230[a] (100%)	241[b] (57.8%)	172 (41.2%)	417[b,c] (100%)	23,121[d] (30.4%)	52,345 (68.8%)	76,134[a] (100%)
Chloroquine monotherapy	76 (49.7%)	20 (26.7%)	96 (41.7%)	79 (32.8%)	22 (12.8%)	101 (24.2%)	8,691[d] (37.6%)	5916 (11.3%)	14,607[d] (19.2%)
Chloroquine + early primaquine	50[e] (32.7%)	56 (74.7%)	107[e, f] (46.5%)	55[g] (22.8%)	101 (58.7%)	157[g, h] (37.6%)	5811 (25.1%)	42,623 (81.4%)	48,560 (63.8%)
Including chloroquine	123 (80.4%)	64 (85.3%)	188[f] (81.7%)	144 (59.8%)	138 (80.2%)	283[h] (67.9%)	15,389[d] (66.6%)	49,302 (94.2%)	64,817[d, i] (85.1%)
Artemisinin combination therapy	21 (13.7%)	10 (13.3%)	31 (13.5%)	27 (11.2%)	14 (8.1%)	41 (9.8%)	2827 (12.2%)	1331 (2.5%)	4158 (5.5%)
Artemisinin combination therapy + early primaquine	7 (4.6%)	3 (4.0%)	10 (4.3%)	8 (3.3%)	5 (2.9%)	13 (3.1%)	928 (4.0%)	526 (1.0%)	1454 (1.9%)

[a] Duration of treatment could not be extracted from two trials.
[b] Individual treatment arms could not be extracted from one study.
[c] Duration of treatment could not be extracted from four treatment arms.
[d] Number of patients unable to be extracted from one study.
[e] Chloroquine and primaquine were combined with an artemisinin derivative in the sole treatment arm of one trial.
[f] Duration of treatment could not be extracted from one trial.
[g] Chloroquine and primaquine were combined with an artemisinin derivative in two treatment arms.
[h] Duration of treatment could not be extracted from one treatment arm.
[i] Duration of treatment unable to be extracted for 126 patients.
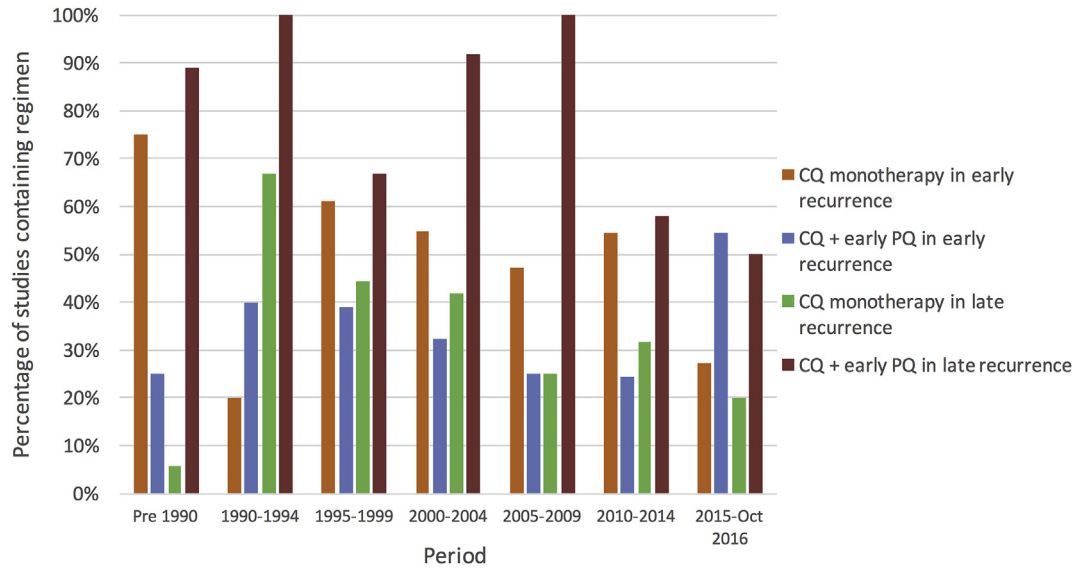
Fig. 5. Temporal trends in the proportion of *P. vivax* clinical trials assessing efficacy of chloroquine monotherapy or chloroquine combined with early primaquine.

opportunity to consolidate and simplify malaria treatment regimens for different malaria species (Douglas et al., 2010). However, the efficacy of ACTs against early and late relapsing *P. vivax* infections varies considerably. ACT regimens rely on the prolonged half-life of their partner drugs to remove the residual parasite biomass following an initial exponential reduction by the artemisinin derivative. Prolonged therapeutic drug concentrations protect patients from relapse and reinfection, but the half-life of some partner drugs, such as lumefantrine, is considerably shorter than chloroquine (3–6 days compared to 2–3 months) (Bassat, 2011). This difference is reflected in a higher risk of early recurrences after artemether-lumefantrine compared to chloroquine (Karunajeewa

et al., 2008). Molecular analysis suggests that the majority of these recurrences are heterologous infections (Hwang et al., 2013), consistent with either hypnozoite relapse from earlier infections or reinfections, rather than true treatment failures (recrudescences). The use of a partner drug with a longer half-life, or the concurrent use of a hypnozoitocidal agent, reduces this recurrence risk (Ratcliff et al., 2007). Our review also highlights an increase in the number of trials of ACTs, with a third of these (10/31) assessing an ACT in combination with early administration of primaquine and 41.9% (13/31) using partner drugs with a half-life greater than 28 days. Ongoing assessment of such combinations is warranted to ensure that substitution of chloroquine with ACTs does not result in an

Fig. 6. Vivax Surveyor map (www.wwarn.org/vivax/surveyor/) identifying trial sites where chloroquine resistance has been identified in clinical efficacy trials of *P. vivax* mono-infection (WorldWide Antimalarial Resistance Network, 2016a).
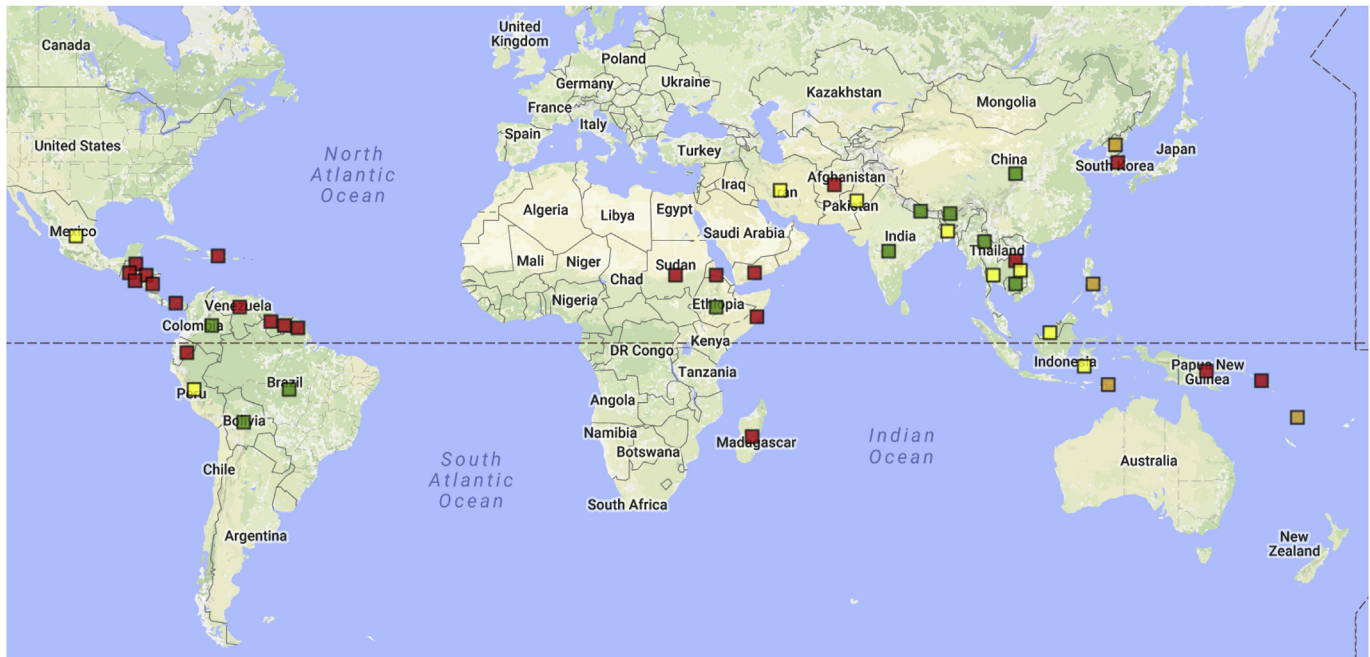
Fig. 7. Map of 45 countries reporting indigenous *P. vivax* during 2015 — categorised according to published clinical trial information or WHO recorded therapeutic efficacy studies assessing chloroquine efficacy since 1 January 2011.

Green - Both published clinical trials and WHO recorded therapeutic efficacy studies assessing chloroquine efficacy against *P. vivax* since 1 January 2011;

Yellow - Published clinical trials but no WHO recorded therapeutic efficacy studies assessing chloroquine efficacy against *P. vivax* since 1 January 2011;

Orange - WHO recorded therapeutic efficacy studies but no published clinical trials assessing chloroquine efficacy against *P. vivax* since 1 January 2011;

Red — No published clinical trials nor WHO recorded therapeutic efficacy studies assessing chloroquine efficacy against *P. vivax* since 1 January 2011. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increased incidence of *P. vivax*.

The risk and timing of *P. vivax* relapses vary considerably with geographical location. In some equatorial regions relapse occurs early (within 21–42 days) and frequently (in over 70% of patients) (Adekunle et al., 2015; Robinson et al., 2015). Conversely, in temperate climates the risk of relapse is considerably lower and recurrent infections occur much later (White, 2011). As the momentum for the elimination of malaria increases, the prevention of relapses becomes a priority, since the reactivation of dormant liver stages plays a key role in sustaining *P. vivax* transmission and results in a slower reduction of *P. vivax* infections compared to *P. falciparum* following intensive control activities (Robinson et al., 2015; Howes et al., 2016). Although primaquine radical cure is recommended in all vivax endemic settings (World Health Organisation, 2015), few clinical trials have addressed its antirelapse efficacy in suitable studies with a long follow up. As described in this review, the majority of primaquine treatment regimens that have been assessed include low or very low total doses that are often associated with poor efficacy (John et al., 2012). In addition, the majority of high dose primaquine regimens that have been assessed are administered over 14 days or longer, a duration of treatment that risks poor adherence in routine practice (Maneeboonyang et al., 2011).

The concurrent administration of schizontocidal and hypnozoitocidal regimens confounds assessment of the risk of recurrent parasitaemia, thus the design and interpretation of clinical trials quantifying both schizontocidal and anti-relapse efficacy can be complex. However, there are potential measures of chloroquine efficacy other than the risk of recurrent parasitaemia. Previous analyses suggest a relationship between resistance and delayed parasite clearance (defined as prevalence of microscopy detectable parasitaemia at 48 h) immediately after chloroquine treatment (Price et al., 2014). If this can be

confirmed prospectively, then trials of short duration with precise determination of the early therapeutic response could be a simple and reliable method for the early detection of declining chloroquine efficacy.

Our review is limited by its reliance on published or registered clinical trials. It is likely that many national and regional malaria programs or research groups have undertaken clinical efficacy trials to screen for emergence of chloroquine resistance, but that these are unpublished or unavailable in the public domain. Timely dissemination of such results is key to identifying early emergence of resistance, improving global research into *P. vivax* management and informing regional and global policy. Furthermore, we adopted strict inclusion criteria for this review, requiring supervised schizontocidal treatment, and active follow up for at least 28 days. Limiting data collection to such trials improves the quality and validity of extracted results, but potentially risks loss of other information relevant to the clinical and research malaria communities. Moreover, there is a risk of publication bias if studies demonstrating poor antimalarial efficacy have a decreased chance of publication.

Despite these constraints, it is clear that chloroquine is no longer suitable as a universal treatment of *P. vivax*. To facilitate individually tailored analyses, details for the studies in this literature review are available on WWARN's open access, online Vivax Surveyor (WorldWide Antimalarial Resistance Network, 2016a). This electronic platform enables easy analysis of available clinical studies, and identification of gaps in our current knowledge. The data are freely available, and will be updated regularly, allowing enhanced scrutiny of antimalarial efficacy against both the blood and liver stages of *P. vivax*. The Vivax Surveyor permits the user to filter studies by year, country and treatment regimen, and to review geospatial and temporal trends in the data. The ability to filter by the level of evidence of chloroquine resistance may be of particular

Table 2
Comparison of published *P. vivax* clinical trials and WHO recorded therapeutic efficacy studies assessing chloroquine efficacy in countries reporting indigenous cases of *P. vivax* in 2015.

Country	Published trials[a]		Therapeutic efficacy studies[b]		Number of estimated vivax cases in 2015[d]
	Total	Since 1 Jan 2011	Total	Since 1 Jan 2011[c]	
Afghanistan	3	0	6	0	370,500
Bangladesh	1	1	0	0	588
Belize	0	0	0	0	<50
Bhutan	1	1	33	1	<30
Bolivia	2	2	6	1	9801
Brazil	16	6	14	2	158,400
Cambodia	4	3	11	1	3600
China	5	3	14	5	<40
Colombia	12	2	14	1	31,600
North Korea	0	0	10	10	7700
Dominican Republic[e]	0	0	0	0	17
Ecuador	0	0	1	0	456
El Salvador	0	0	4	0	<10
Eritrea	0	0	0	0	16,250
Ethiopia	9	6	14	1	1,008,000
French Guiana	0	0	0	0	387
Guatemala	0	0	0	0	10,890
Guyana	1	0	1	0	12,000
Honduras	0	0	0	0	5400
India	33	10	12	6	4,290,000
Indonesia	20	2	0	0	572,000
Iran	5	2	8	0	155
Laos	0	0	0	0	51,040
Madagascar	1	0	3	0	96,000
Malaysia	3	2	2	0	84[f]
Mexico	2	1	1	0	560
Myanmar	5	2	26	12	81,600
Nepal	1	1	8	1	18,720
Nicaragua	0	0	0	0	3910
Pakistan	4	1	5	0	810,000
Panama	0	0	0	0	653
Papua New Guinea	4	0	0	0	189,000
Peru	4	3	7	0	118,500
Philippines	2	0	10	3	1820
Republic of Korea	2	0	3	0	1400
Solomon Islands	1	0	3	0	19,890
Somalia[e]	0	0	0	0	35,000
Sudan[e]	0	0	0	0	70,000
Suriname	0	0	0	0	92
Thailand	26	8	0	0	9880
Timor-Leste	0	0	1	1	36
Vanuatu	1	0	1[g]	2[g]	533
Venezuela	0	0	9	0	170,200
Viet Nam	5	3	19	0	6630
Yemen	0	0	0	0	1349[h]

[a] Published trials identified during the current review and presented in the Vivax Surveyor.
[b] Studies recognised and documented by the WHO (World Health Organization, 2016a).
[c] Studies identified from the WHO therapeutic efficacy of antimalarial therapy treatment against *P. vivax* map (World Health Organization, 2015).
[d] Calculated using the estimated total malaria cases in 2015 and the proportion of malaria cases due to *P. vivax* (World Health Organization, 2016b).
[e] Despite no reported *P. vivax* cases being recorded in the 2016 World Malaria Report (World Health Organization, 2016b), the country specific profiles record a proportion of total cases related to *P. vivax* (World Health Organization, 2016c).
[f] No individual country profile available; values taken from confirmed *P. vivax* cases recorded in the 2016 World Malaria Report (World Health Organization, 2016b).
[g] The number of therapeutic efficacy studies in Vanuatu differs between (World Health Organization, 2016a) and (World Health Organization, 2015).
[h] Proportion of *P. vivax* calculated from figures of confirmed *P. vivax* in 2016 World Malaria Report (World Health Organization, 2016b).

relevance to clinicians, researchers and policy makers. The data presented on the Vivax Surveyor are also available in a tabulated format and a complete database can be downloaded as an Excel file (Supplementary file 1).

In summary, our review documents the changing landscape of clinical research into antimalarial efficacy for *P. vivax*, highlighting an increasing number of *P. vivax* clinical trials and increased investigation into efficacy of the artemisinin combination therapies. It also highlights some of the barriers to *P. vivax* elimination; increasing chloroquine resistance and the lack of appropriate trials into effective hypnozoitocidal regimens. The Vivax Surveyor provides an accessible, regularly updated platform to identify trends and knowledge gaps for all parties interested in researching, treating and eliminating vivax malaria. While gains in malaria control are rapidly being made in *P. falciparum*, malaria elimination will not be possible without substantial investments into the clinical management of *P. vivax*.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ijpddr.2017.03.003.

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