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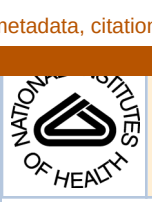

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Antimalarial drug resistance of *Plasmodium falciparum* in India: changes over time and space

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Abstract

After the launch of the National Malaria Control Programme in 1953, the number of malaria cases reported in India fell to an all-time low of 0·1 million in 1965. However, the initial success could not be maintained and a resurgence of malaria began in the late 1960s. Resistance of *Plasmodium falciparum* to chloroquine was first reported in 1973 and increases in antimalarial resistance, along with rapid urbanisation and labour migration, complicated the challenge that India's large geographical area and population size already pose for malaria control. Although several institutions have done drug-resistance monitoring in India, a complete analysis of countrywide data across institutions does not exist. We did a systematic review of *P falciparum* malaria drug-efficacy studies in India to summarise drug-resistance data and describe changes over the past 30 years to inform future policy. Continued use of chloroquine for treatment of *P falciparum* malaria in India will likely be ineffective. Resistance to sulfa–pyrimethamine should be closely monitored to protect the effectiveness of treatment with artesunate plus sulfadoxine–pyrimethamine, which is the new first-line treatment for *P falciparum* malaria. Strategies to reduce the emergence and spread of future drug resistance need to be proactive and supported by intensive monitoring.

Introduction

India has the largest population in the world at risk of malaria, with 85% living in malarious zones.[1] The combination of *Plasmodium falciparum* and *Plasmodium vivax*, six primary malaria vectors, several ecotypes including urban malaria, and various transmission intensities ranging from unstable to hyperendemic create a challenging epidemiological scenario in India. At the time of Indian independence in 1947, there were about 75 million cases and 800 000 deaths a year.[2] After independence, health care was prioritised, and the control of malaria was one of India's key aims. In 1953, the National Malaria Control Programme was launched and protected a population of about 165 million with dichlorodiphenyltrichloroethane (DDT) spraying.[3,4] The control programme developed into

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Contributors

NV, UA, and NKS contributed to the search of published and unpublished works. NKS extracted the data from the searches, NV, NKS, and SRM analysed the data. NKS drafted the review and all authors provided critical revisions.

Conflicts of interest

We declare that we have no conflicts of interest.

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the National Malaria Eradication Programme in 1958. Reliable surveillance gradually developed during the eradication period, and the programme seemed to be highly eff ective with only 99 667 malaria cases and no deaths reported in 1965.4

However, the long-term success of malaria control could not be sustained. Increasing insecticide resistance in mosquitoes, urbanisation, development projects, population migration, integration with the general health services, financial difficulties, and other operational challenges laid the foundation for a resurgence of malaria. In 1976, malaria cases reached a posteradication peak of 6·47 million cases.[5] A new strategy, the modified plan of operation,[5] was introduced in 1977 after which there has been a steady decline in malaria cases in the country with only 1·4 million reported cases in 2007. However, the decline in malaria was not equal in both *P vivax* and *P falciparum*. The proportion of *P falciparum* cases increased to 49% of the total burden in 2007, from 13% in 1978, even though the annual incidence of *P falciparum* infection decreased from 0·90 to 0·67 cases per 1000 people during the same interval (figure 1). The change in species dynamics is a cause for concern because *P falciparum* is associated with high mortality. Increasing drug resistance in *P falciparum* is a possible cause for the changing scenario in India.[6]

Sehgal and colleagues[7] first documented chloroquine-resistant *P falciparum* in the northeast Karbi-Anglong district of Assam in 1973. Routine monitoring of antimalarial resistance using in-vivo-efficacy trials was initiated in 1978 by 13 regional teams. Although several protocols for drug-resistance monitoring have been used in the past three decades, the test system generally includes patients with defined criteria, supervised treatment, and follow-up for clinical and parasitological outcomes. Initial reports of sulfa–pyrimethamine resistance emerged in 1979, again in Karbi-Anglong, Assam.[8] A national antimalarial-drug policy was introduced in 1982 to improve malaria case management and established sulfa–pyrimethamine as the treatment for chloroquine-resistant areas. Drug effectiveness monitoring by the national programme and others has provided data to guide treatment strategy and update policy. Artesunate plus sulfadoxine–pyrimethamine replaced the latter alone as the second-line drug in 2005 for use in chloroquine treatment failures, and as the first-line antimalarial treatment in areas with documented drug resistance. In 2007, artesunate plus sulfadoxine–pyrimethamine was selected as the first-line treatment in high-risk districts and areas with identified resistance, with the goal of covering most of the nation's *P falciparum* burden. In 2010 this treatment became the first-line treatment throughout India.[9]

Few efficacy trials exist for other antimalarial compounds in India and none for routine monitoring. Resistance to mefloquine and quinine is reported but seems to be rare[10] and cases are not well documented. Trials of artemisinin combination treatments in India have consistently shown treatment success above 95%.[11,12] Only a few case reports—from Mumbai, Uttar Pradesh, and Bihar—of chloroquine-resistant *P vivax* malaria exist.[13] Contrary to these reports, systematic trials from across the country have reported 100% efficacy of standard dose chloroquine (25 mg/kg over 3 days).[14] Chloroquine-resistant *P vivax* is not a serious concern in India.

The Indian public health system responds to antimalarial failures with evidence-based policy; however, variations in resistance within the country and a diverse malaria situation complicate decision making. Furthermore, drug resistance studies have been done by various institutions, but a complete analysis of Indian data across institutions is absent. In this systematic review, we summarise data on antimalarial drug resistance in India and describe temporal and spatial trends, with the aims of informing policy makers and identifying gaps in understanding.

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Methods

Search strategy and selection criteria

We focused our search on the drugs chloroquine and sulfa–pyrimethamine and for the treatment of *P falciparum* malaria. We reviewed data gathered between 1978 and 2007 (the year drug policy changed) from published and unpublished sources. First, we searched PubMed and Medline databases from June 1, 2008, with the following terms: ("India") AND ("malaria", OR "falciparum", OR "Plasmodium falciparum") AND ("resistance", OR "resistant", OR "failure", OR "efficacy", OR "sensitivity"). There were no language restrictions to the search. Second, we retrieved unpublished data from the National Vector Borne Disease Control Programme, National Institute of Malaria Research, and WHO headquarters and its Southeast Asia Regional Office. We examined abstracts (or titles if the abstracts were unavailable) to identify published articles that mentioned any type of *P falciparum* resistance (in vivo, in vitro, or molecular) to chloroquine or sulfa–pyrimethamine. Next, we did a detailed manual review and excluded articles or unpublished studies that did not describe at least 7 days of follow-up for chloroquine and 28 days for sulfa–pyrimethamine treatment, did not use standard dosing (ie, 25 mg/kg over 3 days for chloroquine, or 25 mg/kg of sulfalene or sulfadoxine and 1·25 mg/kg of pyrimethamine as a single dose), had fewer than 30 patients with complete follow-up, included patients with severe malaria, included recrudescent patients, did not give exact or graphical data for the number of patients who completed follow-up and number of treatment failures, and could not geographically disaggregate results to at least the district level.

Data extraction

NKS and NV searched for and recorded the total number of studies. NKS merged the datasets and extracted the following information for each study: study year, administrative divisions (ie, state, district), number of patients, total number of failures, duration of follow-up, and PCR correction (if any). For studies spanning more than 1 year, the year the study started was recorded. The smallest unit of geography recorded was the district (second level administrative unit after the state level, with a population of about 1·0 to 3·5 million). For the provision of health care, the district is the smallest unit at which at least a public secondary-care facility is available. Studies spanning many areas of the same district, but in the same year and by the same investigator were aggregated. Each study was assigned a geographical region on the basis of state—east (Andaman and Nicobar Islands, Bihar, Chhattisgarh, Jharkhand, Orissa, and West Bengal), north-central (Haryana, Madhya Pradesh, and Uttar Pradesh), northeast (Arunachal Pradesh, Assam, Meghalaya, Mizoram, Nagaland, and Tripura), south (Andhra Pradesh, Karnataka, and Tamil Nadu), and west (Dadra and Nagar Haveli, Goa, Gujarat, Maharashtra, and Rajasthan).

Drug-resistance monitoring

Since 2005, the cutoff point for routine use of second-line malaria treatment in an area has been more than 10% total treatment failure with first-line therapy in a minimum sample of 50 patients.[15] Before adopting this threshold, routine monitoring of drug effectiveness was done according to WHO in-vivo protocols. However, most 7-day trials were done according to the method used by Prasad and colleagues,16 and the cutoff point for treatment change was 25% or greater RII and RIII resistance in at least 30 patients, which is comparable to early failures according to new protocols. Currently, WHO-recommended standard test for therapeutic-drug efficacy provides the information needed for decisions about changes to treatment policy. Duration of follow-up is determined by the half-life of the drug being tested but was 28 days for chloroquine and sulfa–pyrimethamine studies done through routine monitoring. Classification of treatment response varied from study to study, with most studies using the prevailing WHO criteria at the time. Presently, outcomes are

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classified as early-treatment failures, late-treatment failures, or adequate response according to the most recent guidelines.15 For our purposes we used a composite definition of treatment failure, which included the classic RI, RII, and RIII criteria,17 and the revised WHO criteria,[18] which form the basis of current standards. For 28-day follow-up studies this covers recrudescence after clearance of parasitaemia (RI, late-treatment failure), reduction in parasitaemia by more than 75% of baseline without clearance (RII, early-treatment failure), failure to reduce parasitaemia to less than 25% of baseline (RIII, early-treatment failure), and fever or signs of severe malaria. The follow-up day at which the criteria were assessed varied between the classic RI, RII, and RIII criteria, in which daily blood smears were collected up to day 7 versus the revised protocol, which does not. We used the outcome designated at the time of study, since detailed data for individual patients were not available precluding reclassification.

Analysis

The proportion of treatment failures was calculated per protocol for each study. The total number of treatment failures (uncorrected by PCR) was divided by the number of patients, excluding those lost to follow-up. We recorded the proportion of treatment failures by study state, region, decade, and follow-up period. We examined the change in chloroquine resistance by plotting the proportion of failures in each 28-day study by the study year. Since the strategy is to change policy at 10% or greater total treatment failure with first-line therapy, the comparison of the proportion of 28-day studies exceeding a certain proportion of failures by year was done by use of this cutoff. We used Fisher's exact test to analyse the change in the proportion of studies exceeding the 10% treatment failure cutoff from when routine monitoring began to the end of the study period. Change in the proportion of sulfa–pyrimethamine failures was calculated with the χ^2 test. To identify differences in proportion of chloroquine-treatment failure between regions we did a Kruskal-Wallis non-parametric test for K-independent samples with SPSS version 14.0. Study periods for comparison were determined by observation of the slope of change in the proportion of treatment failures. To produce a national map of existing resistance, we identified districts where a study exceeded 10% treatment failure in any length of follow-up. If a high proportion of failures occurred in a short study, even more failures would be expected in a longer follow-up period. Districts endemic for *P falciparum* were identified by examining surveillance data and selecting areas with annual incidence greater than 1 per 100 000 population. Maps were produced with Health Mapper software, version 4.2.

Results

We identified 738 articles, of which 649 were not eligible for detailed review (figure 2). Of the 89 articles manually reviewed, 41 were included in the review. Some articles reported the results of multiple studies (ie, in-vivo trials done in different districts). We also compiled 334 unpublished studies of which 315 were included in the analysis. In both published and unpublished sources, not all studies reported the number lost to follow-up. Some studies included single-dose primaquine (0·75 mg/kg) for gametocytocidal effect, in accordance with national policy. PCR-corrected results were available for three studies, but were not used in our analysis; in these studies, the proportion of treatment failures classified as reinfections was 0–8%, but not all samples were successfully genotyped. As malaria transmission in most of India is low to moderate, we expect low rates of reinfection. 161 trials were completed since 2000 compared with 121 in the 1990s, 64 in the 1980s, and 18 in the late 1970s. 134 studies were done in the eastern region, 72 in the northeast, 64 in the west, 60 in the south, and 34 in the northcentral area. 119 studies had 7-days of follow-up, four had 14-days, and 240 had 28-days.

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337 studies investigated chloroquine efficacy in 17 189 patients. The number of studies and proportion of failures varied between regions and in states within a region (table 1). The median proportion of chloroquine failure was 35·1% (IQR 13·0–58·2) in studies with a 28-day follow-up. Studies with 7-day follow-up, which largely detected early treatment failures, were phased out from 2000 and the last 7-day study was done in 2003. The proportion of failures detected is higher in 28-day follow-up studies than in 7-day follow-up studies done in the same areas, because late treatment failures are detected in 28-day follow-up studies.

Studies done between 1978 and 2007 show an increasing proportion of failures to chloroquine over time (slope=0·73, r^2=0·07; figure 3). When routine monitoring of drug resistance began in 1978–79, two of 17 studies exceeded the 10% threshold used in India to switch an area to the second-line treatment. In 2006–07, the proportion of chloroquine studies exceeding 10% treatment failure increased to 35 of 40 studies (p<0.0001; figure 4).

Drug-efficacy studies of chloroquine, with at least 30 patients in any follow-up period, have exceeded 10% treatment failure in 115 districts (figure 5). These districts represent 20 of 28 states and two of five union territories. The remaining states and territories have low incidence of *P falciparum*, or have not done any trial of antimalarial drug resistance. Chloroquine-efficacy studies done in eight districts did not have more than 10% treatment failure; however, only three had been done since 2000 and parasite sensitivity might have changed since. From 1978 to 1985, the median proportion of treatment failure between regions (northeast > east > west > south > north-central) were significantly different (p=0·001). For data from 1986–2007, the median proportion of treatment failures increased substantially in all regions, but the difference was not significant (p=0·06).

Between 1978 and 2007, 26 studies of sulfa–pyrimethamine efficacy including 1431 patients were done. Three studies, all in Assam, used sulfalene, whereas the rest used sulfadoxine (National Vector Borne Disease Control Programme, unpublished). The median proportion of sulfa–pyrimethamine failure was 15% (IQR 0·7–33·1) after 28 days of follow-up. 19 (7·7%) of 246 patients failed sulfa–pyrimethamine treatment in 1984–96 compared with 307 (25·9%) of 1185 in 1997–2007 (p<0·0001; table 2). Most studies were done in northeastern states, and Arunachal Pradesh on the Chinese and Burmese borders had the highest rates of treatment failure.

Discussion

Efficacy studies of antimalarial drugs done in India since 1978 show that resistance of *P falciparum* to chloroquine increased over time and is present across all regions of the country. Efficacy of sulfa–pyrimethamine for treatment of *P falciparum* was reduced in some recent studies, largely in the northeast.

Nationally, treatment failures of chloroquine increased between 1978 and 2007. However, the programme of drug-resistance monitoring was designed to detect foci of antimalarial drug resistance where treatment policy can be changed if needed. Longitudinal trends were only obtained in a few areas. Study sites were purposely sampled because they fulfilled several criteria: clinical case reports, outbreak prone areas, high *P falciparum* burden, development project areas, reported malaria fatalities.[4] Thus, each year there was broad variation in treatment failure because studies were done in diverse settings. Heterogeneity in location and frequency of studies created challenges in aggregating data and drawing broad conclusions. Yet, we saw an increase in the proportion of failures over time; this trend persisted with the inclusion of 7-day follow-up studies, in which we identified a low mean proportion of failures because of a short follow-up period. The proportion of studies exceeding a predefined threshold of treatment failures also increased over time. Before

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2005, a 25% treatment-failure threshold determined the need to change the first-line treatment. A 10% threshold for first-line therapy was adopted in line with WHO recommendations and it proved a cost-effective cutoff in India.[19] In 2006–07, 88% of trials done exceeded the 10% treatment-failure threshold for switching an entire area to the second-line drug. This finding suggests further studies of chloroquine resistance, in the few areas that have not yet adopted treatment with artesunate plus sulfadoxine–pyrimethamine, will have little use. Finally, the increase in chloroquine-resistant *P falciparum* has contributed to the growing proportion of *P falciparum* related malaria cases.[20] The reversal of this increase could serve as an indicator of the likely effects of broad treatment with artesunate plus sulfadoxine–pyrimethamine, which is now used in more than 90% of reported *P falciparum* cases.

The median proportion of chloroquine resistance initially varied by region. Most treatment failures arose in the northeast—the original focus of drug resistance—followed by the eastern and then western regions. Drug resistance in the northeast likely originated from neighbouring countries (Thailand 1962, Burma 1969, Bangladesh 1970) that reported chloroquine-treatment failures before India.[21–24] Drug-resistant strains of *P falciparum* might have then spread across India through host movements, particularly through migrant labourers travelling from eastern India to the western states.[25] Thus, chloroquine resistance in India is now widely distributed, and our data show a geographical clustering of resistant areas rather than isolated foci. Few studies have been done in most places that have not identified chloroquine resistance. Changing treatment policy so that second-line drugs are given at smaller administrative levels, such as primary-health centres, blocks, or cluster of blocks, has helped India to limit malaria mortality and morbidity in patients who receive care at government facilities. However, such a policy shift does not seem to have stemmed the spread of drug resistance. In the face of continued selection pressure, strains of drug-resistant malaria will spread. Without geographical barriers, transportation between nearby areas and interactions between catchment populations assures an exchange of vectors and parasite strains. Even when drug sensitivity remains, if the area is close to sites with drug resistance then strains will interact, and with continued chloroquine use, resistant strains will proliferate due to a competitive advantage. Conversely, effective treatments implemented on large scales can reduce malaria transmission and might even reduce existing drug resistance in other settings.[26–28] Thus, minimisation of uneven drug pressure through use of an effective drug throughout a large geographical unit, such as a district or even cluster of districts, is an effective strategy to prevent the spread of drug resistance. Such a change in treatment policy will also need fewer drug-efficacy studies and reduce operational challenges related to drug supply.

As in other control programmes, the dose and choice of sulfa derivative used in India has changed over time.[29] Originally, several sulfa derivatives were used, including sulfalene, but these were gradually replaced by sulfadoxine. The two-tablet adult dose was as efficacious as the three-tablet dose in initial trials; however, the three-tablet dose became the standard.[29] Studies we surveyed were done with the full dose only. Effectiveness of sulfa–pyrimethamine was reduced in parts of the country, particularly the northeast region. These study results might be a conservative estimate because sulfa–pyrimethamine failures can occur after 28 days, and a 42-day follow-up is now recommended. Since a widespread use of sulfa–pyrimethamine would increase resistance, artesunate plus sulfadoxine–pyrimethamine replaced monotherapy because combination treatments, particularly artemisinin-based treatments, are promoted as a means for both the provision of effective treatment and the prevention of drug resistance.[30] There is concern that as the partner drug, pre-existing resistance to sulfa–pyri methamine could compromise combination treatment. Additionally, although age-group blister packs of artesunate plus sulfadoxine–pyrimethamine pills are being made available, in principle, a coformulated drug would be ideal. Although these

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constraints were recognised at the time of inclusion of artesunate plus sulfadoxine–pyrimethamine into the national drug policy, this was the only option available because coformulated artemisin-based combination treatments were not registered. Treatment with artesunate plus sulfadoxine–pyri methamine has shown adequate safety and efficacy in India and is available in sufficient quantities. Trials with several fixed-dose combinations, such as artesunate–mefloquine, artesunate–amodiaquine, artemether–lumefantrine, dihydroartemisinin–piperaquine, and artesunate–pyronaridine, have been completed to provide local efficacy data for other options. Determination and preparation of back-up combination treatments is high priority. In the meantime, effectiveness of treatment with artesunate plus sulfadoxine–pyrimethamine needs careful monitoring.

Our study has two main limitations. First, a range of quality-control issues varied between studies or were not reported, including selection criteria, microscopy techniques, drug quality, and record keeping. Our results are derived from a per-protocol analysis and differences in the proportion of patients completing follow-up and reasons for loss to follow-up could affect estimates of treatment failure. Although exact numbers are not available for most studies, in our experience loss to follow-up rarely exceeded 10%, and in most studies was zero. This low proportion is because of the mass-fever survey approach used for recruitment in many studies, by which study teams enrol the entire study population at once and then remain in the area until the completion of the trial.

Second, the variability in study methods is small compared with differences in the number of studies and their location each year. Diversity in time scales and sites in which studies were done make data aggregation difficult. Operational factors influenced the number and location of studies. Treatment failure is an indirect measure of true parasite resistance, because host immunity and pharmacokinetics contribute to outcomes. Expected variation in such factors between different areas could cause some of the variation in treatment failure rather than any difference in resistance. Caution should be exercised in attempting to interpret any summary estimate of treatment failure across time and place. Thus, we did not produce a meta-analysis, but rather we focused on overall trends with systematic review. The large number of studies analysed should mitigate the limitation posed by the temporal and spatial variability of the data.

Current initiatives and future steps

The National Vector Borne Disease Control Programme has responded to the challenge of drug resistance with several strategies.[31] Rational drug use is being promoted to reduce overall drug pressure—eg, phasing out presumptive treatment, strengthening microscopy services, and extending the availability of rapid diagnostic tests to peripheral areas using the nationwide community health worker system (Accredited Social Health Activists [ASHA]) under the National Rural Health Mission.[32] Inadequate dosing or the use of improper treatments, such as the use of parenteral artemisinin derivatives for treating uncomplicated malaria, can promote resistance. New guidelines have been developed and are being updated in cooperation with the National Institute of Malaria Research,[31,33] which present treatment policy in an accessible format for public and private physicians to improve compliance. Regulation is in place that bans the sale of oral artemisinin monotherapy. A group of 15 alternating sentinel sites were selected in 2009 to enable the longitudinal monitoring of antimalarial-drug resistance. Molecular techniques, such as PCR correction of treatment failures, are now used in trials of antimalarial-drug efficacy, with help from research institutions such as the National Institute of Malaria Research.

Further research and programmes are needed to combat antimalarial-drug resistance in India. Previously, chloroquine treatment, with primaquine as a gametocytocidal drug, was standard. Artemisinin combination treatments show useful gametocytocidal properties but

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do not eliminate mature gametocytes.[30] How the addition of single-dose primaquine to artesunate plus sulfadoxine–pyrimethamine will affect malaria transmission or the spread of drug-resistant strains in India is unclear. In-vitro susceptibility and molecular markers mirror intrinsic antimalarial resistance to a drug and their changes precede clinical resistance.[34] Molecular and in-vitro monitoring could supplement efficacy trials and provide early warning of drug resistance.

Finally, introduction of resistant malaria into non-immune populations such as refugees or migrants increases the opportunity for spread of resistance, because parasites with low or moderate resistance would be cleared in semi-immune populations.[35] In India, antimalarial resistance for chloroquine and sulfa–pyrimethamine was fi rst reported near the international border with Burma.[36] Reports of tolerance of malaria to artemisinin along the Thai–Cambodian border, and the historical westward spread of drug-resistant strains, generate concern about the long-term effectiveness of artemisinin-combination therapies in India.[37] Best practices for malaria control along border areas and in migrant populations in India need to be established. Overall, a robust and specific plan to combat drug-resistant parasites will be fundamental in fulfilling our commitment to malaria control in India.

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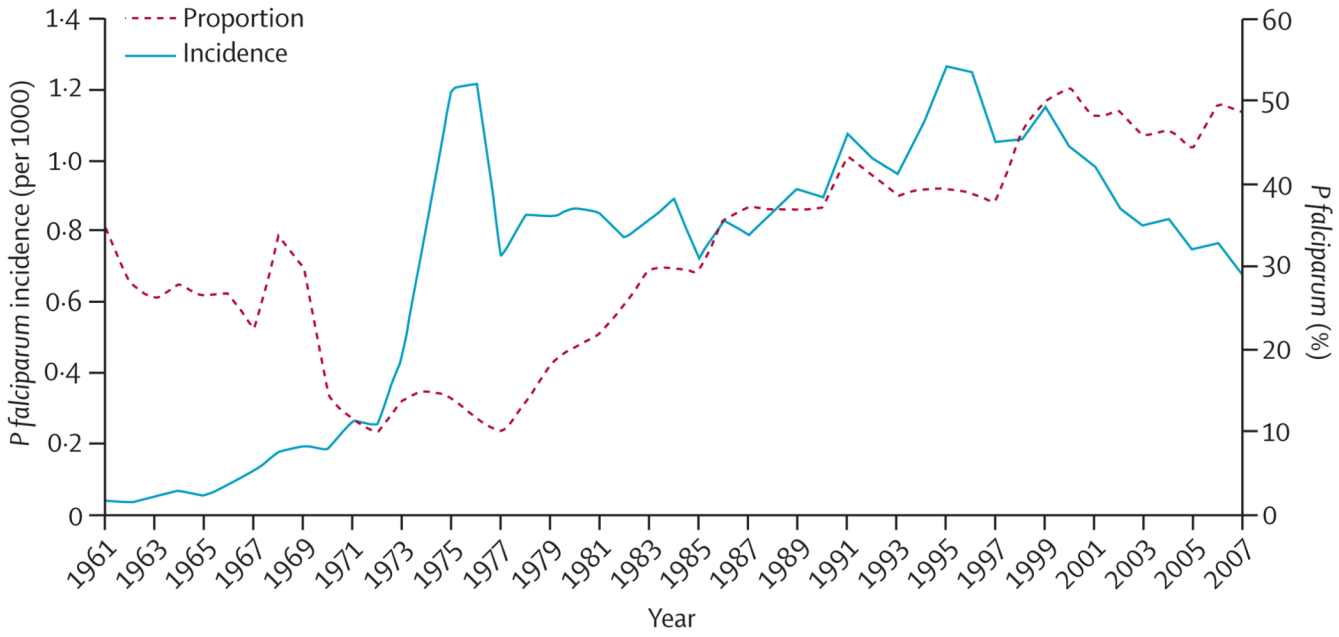

Figure 1.

Incidence and proportion of malaria cases caused by *Plasmodium falciparum* in India between 1961 and 2007

Data from the National Vector Borne Disease Control Programme (unpublished).

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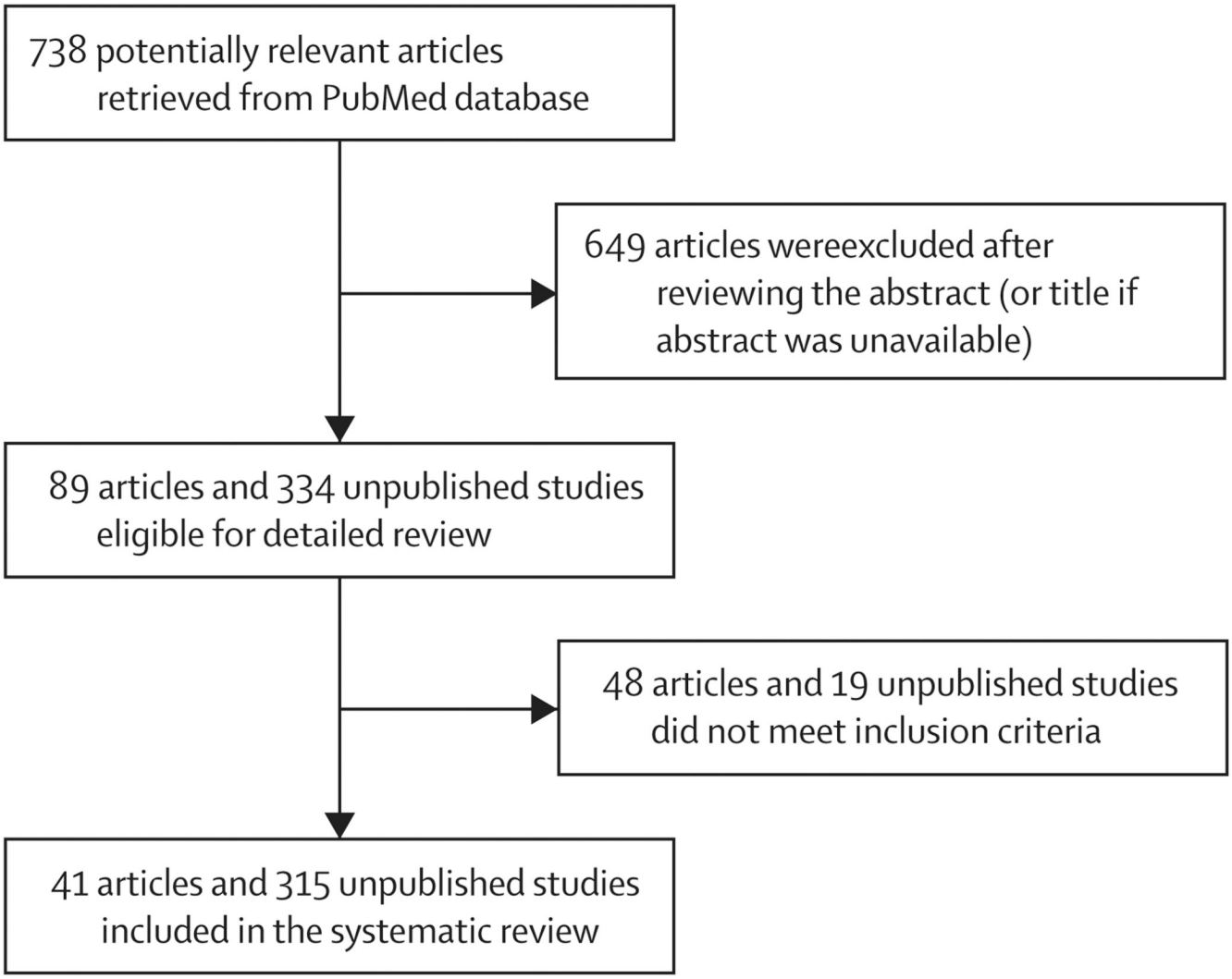

Figure 2.
Study selection

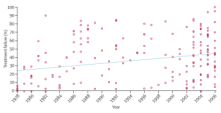

Figure 3.
Studies of chloroquine resistance with 28-day follow-up and the proportion of treatment failures in India between 1978 and 2007

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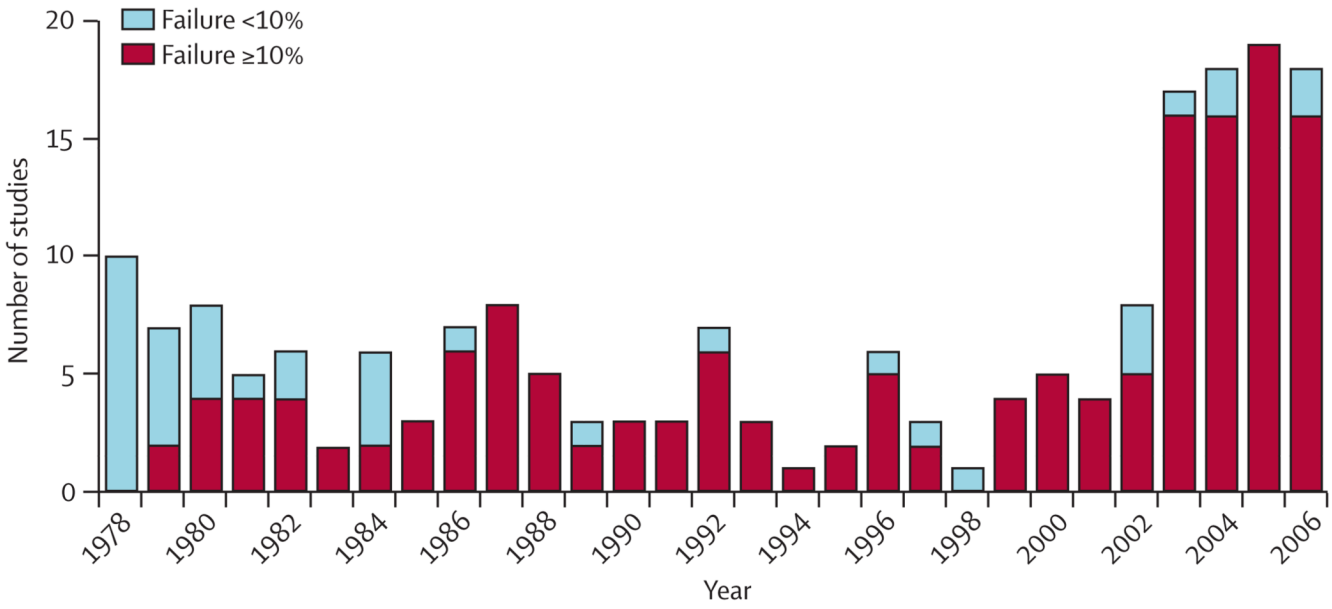

Figure 4.
Number of studies of chloroquine resistance with 28-day follow-up in India between 1978 and 2007 and the proportion of treatment failures greater than or equal to 10%

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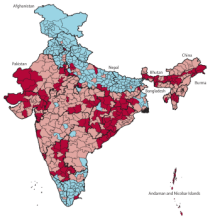

Figure 5.
Districts with 10% or greater chloroquine-treatment failure (red) in any study between 1978 and 2007 and in *Plasmodium falciparum* endemic areas (pink), and districts without reported *P falciparum* transmission (blue)

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Table 1

Results of chloroquine-efficacy studies done in India between 1978 and 2007 by area, year, and duration of follow-up

	All follow-up*			7-day follow-up only			28-day follow-up only		
	Studies	n	Failures (%)	Studies	n	Failures %	Studies	n	Failures (%)
North central	33	2723	687 (25%)	16	741	116 (16%)	17	1982	571 (29%)
Haryana	3	113	21 (19%)	1	38	0 (0)	2	75	21 (28%)
Madhya Pradesh	17	1922	556 (29%)	12	591	86 (15%)	5	1331	470 (35%)
Uttar Pradesh	13	688	110 (16%)	3	112	30 (27%)	10	576	80 (14%)
Northeast	54	2541	893 (35%)	13	446	58 (13%)	38	1946	759 (39%)
Arunachal Pradesh	7	290	174 (60%)	1	30	1 (3%)	6	260	173 (67%)
Assam	37	1909	607 (32%)	10	356	54 (15%)	24	1404	477 (34%)
Meghalaya	5	159	20 (13%)	2	60	3 (5%)	3	99	17 (17%)
Mizoram	1	47	28 (60%)	..	..	..	1	47	28 (60%)
Nagaland	1	34	10 (29%)	..	..	..	1	34	10 (29%)
Tripura	3	102	54 (53%)	..	..	..	3	102	54 (53%)
East	126	5830	1471 (25%)	61	2613	299 (11%)	64	3079	1130 (37%)
Andaman and Nicobar	2	115	15 (13%)	..	..	..	2	115	15 (13%)
Bihar	1	37	0 (0)	1	37	0 (0)	..	..	..
Chhattisgarh	12	454	87 (19%)	4	141	9 (6%)	8	313	78 (25%)
Jharkhand	21	971	212 (22%)	13	588	67 (11%)	8	383	145 (38%)
Orissa	58	2914	719 (25%)	23	1113	122 (11%)	34	1663	555 (33%)
West Bengal	32	1339	438 (33%)	20	734	101 (14%)	12	605	337 (56%)
South	60	3124	1007 (32%)	6	277	20 (7%)	54	2847	987 (35%)
Andhra Pradesh	17	775	95 (12%)	5	236	20 (8%)	12	539	75 (14%)
Karnataka	39	2184	836 (38%)	1	41	0 (0)	38	2143	836 (39%)
Tamil Nadu	4	165	76 (46%)	..			4	165	76 (46%)
West	64	2971	1074 (36%)	23	1049	198 (19%)	41	1922	876 (46%)
Dadra and Nagar Haveli	3	175	19 (11%)	2	121	12 (10%)	1	54	7 (13%)
Goa	4	183	96 (52%)	1	34	10 (29%)	3	149	86 (58%)

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	All follow-up*			7-day follow-up only			28-day follow-up only		
	Studies	n	Failures (%)	Studies	n	Failures %	Studies	n	Failures (%)
Gujarat	29	1297	392 (30%)	13	645	141 (22%)	16	652	251 (38%)
Maharashtra	9	594	297 (50%)	1	45	2 (4%)	8	549	295 (54%)
Rajasthan	19	722	270 (37%)	6	204	33 (16%)	13	518	237 (46%)
Year									
1978–79	18	783	59 (8%)	1	39	0 (0)	17	744	59 (8%)
1980s	63	3900	1292 (33%)	10	466	65 (14%)	53	3434	1227 (36%)
1990s	114	5265	1190 (23%)	81	3578	475 (13%)	33	1687	715 (42%)
2000–07	142	7241	2591 (36%)	27	1043	151 (14%)	111	5911	2322 (39%)
Total	337	17 189	5132 (30%)	119	5126	691 (13%)	214	11 776	4323 (37%)

..No data available.

*Includes four 14-day trials.

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Table 2

Results of 28-day studies of sulfa–pyrimethamine efficacy done in India between 1978 and 2007

	Year	n	Total failures (%)
Arunachal Pradesh			
Changlang	1992	57	4 (7%)
Changlang	1999	43	19 (44%)
Changlang	2002	65	35 (54%)
Changlang	2006	67	38 (57%)
Lohit	2002	70	12 (17%)
Lohit	2006	212	81 (38%)
Assam			
Darrang	1993	36	0 (0)
Darrang	2004	37	4 (11%)
Karbi-Anglong	1984	30	8 (27%)
Karbi-Anglong	2001	51	18 (35%)
Nagaon	2002	78	0 (0)
Nagaon	2003	32	0 (0)
Nalbari	1992	30	1 (3%)
North Lakhimpur	2007	47	6 (13%)
Sonitpur	2001	49	21 (43%)
Sonitpur	2003	32	0 (0)
Madhya Pradesh			
Mandla	1997	114	42 (37%)
Orissa			
Kandhamal	2004	38	1 (3%)
Keonjhar	2002	61	0 (0)
Sundargarh	1991	60	6 (10%)
West Bengal			
Bankura	2005	35	6 (17%)
Jalpaiguri	1996	33	0 (0)
Jalpaiguri	2001	58	11 (19%)
Puruilia	2000	30	7 (23%)
Puruilia	2003	31	0 (0)
Total		1431	326 (23%)