Four decades of epidemiological data reveal trajectories towards malaria elimination in Kheda district (Gujarat), western part of India

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ABSTRACT

Background Malaria is a main public health problem in India and was so particularly in the state of Gujarat in the western part of the country. This study assesses the effects of various interventions on malaria cases using data from the last 33 years (1987–2019).

Methods Here we have analysed 33 years of malaria epidemiological data from a malaria clinic in Kheda district in Gujarat. The data were digitised yearly and monthly, age-wise and gender-wise, and descriptive analysis was performed to assess the effects of several interventions on malaria burden.

Results During 1987–2019, our clinic diagnosed 5466 Plasmodium vivax and 4732 P. falciparum malaria cases. Overall, there was a declining trend in malaria cases except for the years 1991, 1994, 2004 and 2005. The year 2004 especially witnessed an epidemic in Kheda as well as throughout Gujarat. Malaria infections were most common (40%) among the 21–40 years age group. Fever was the most common symptom in all age groups.

Interpretation Introduction of revised drug policy and improved surveillance technique (rapid diagnosis kits) have strengthened the diagnosis and treatment of malaria in the district. Use of pyrethroid in indoor residual insecticide spray has also strengthened vector control. Among the various interventions used, long-lasting insecticide nets and introduction of artemisinin-based combination therapy have played significant roles in controlling malaria cases. A more drastic decline in P. falciparum cases versus P. vivax is evident, but the latter persists in high proportions and therefore new tools for malaria control will be needed for elimination.

BACKGROUND

Malaria is an old public health problem in India, which contributes 3% to the global malaria burden. India has the highest malaria burden in the South East Asian region, but cases have shown decline during the last decade. 1-2 Malaria in India remains a major disease, and in 2020 there were 0.15 million cases, with 0.09 million Plasmodium falciparum cases and 55 deaths—the lowest in the last four decades.3 In Gujarat, there were more P. vivax cases compared with P. falciparum in 1990, same time 0.5 million total malaria cases and 0.1 million P. falciparum cases reported. In 2020, malaria cases declined,

Key questions

What is already known?

► Paucity of proper and timely analysis of epidemiological data is an important cause of malaria mortality and morbidity in malaria-endemic districts of India.

► Addressing malaria requires analysis of each malaria parameter to inform policies and decision making authorizes.

► To eliminate malaria, improved programme planning based on microanalysis of malaria parameters is of primacy.

What are the new findings?

► We analysed four decades of data on malaria incidence in Kheda district in central Gujarat, located in western part of India, as a surrogate for the rest of the state.

► We found that patients from all age groups were affected by malaria, and high-risk groups such as children and pregnant women still need special attention.

► Although malaria incidence has declined, the burden of Plasmodium vivax persists in considerable proportions in this area.

► Implementation of integrated vector management and revised drug policy likely resulted in the drastic reduction in cases, but newer intervention tools will still be required.

What do the new findings imply?

► Our findings underline the need to consider microanalysis of all epidemiological parameters when preparing strategies to eliminate malaria.

► Quality and timely analyses of longitudinal data are critical to guide priority setting and resource allocation by the control programme.

► It is essential for state programme managers to strengthen data analysis and information system to disseminate data to technical staff so as to develop evidence-based mitigation methodologies for malaria elimination.
with only 0.003 million cases reported. In Kheda district in central Gujarat, 0.03 million cases were reported in 1990, which declined to only 76 malaria cases in 2020. Anopheles culicifacies and A. stephensi, which are mainly zoophagic in nature, are the known primary vectors in the rural and urban areas of Gujarat.

Despite continuous intervention efforts, malaria outbreaks have occurred intermittently in certain villages and urban areas of Gujarat. A small number of cases in the community may act as reservoirs of malaria and may lead to surge in cases in the future. A retrospective analysis of malaria incidence is warranted to focus on intervention and prevention of malaria. The national goal of India to achieve malaria elimination by 2030 with differential timelines for states and districts depending on their epidemiological situation. Accordingly, the state of Gujarat has set a target of becoming malaria-free by 2022 under the guidelines of the National Vector Borne Disease Control Programme (NVBDCP). Since the commencement of the National Institute of Malaria Research (NIMR) field unit at Civil Hospital Campus, Nadiad in Kheda district in Gujarat in 1984, a malaria clinic has been operational to screen febrile patients for malaria infection. The NIMR malaria clinic examines >5000 febrile patients annually. Patients who report fever and other symptoms are recorded and the results are transmitted on a daily basis to the district malaria officer to undertake effective intervention. Patients with malaria infection are treated according to the National Malaria Drug Policy. Here, we have systematically analysed the malaria epidemiological data over the last four decades (1987–2019). We dissect the local epidemiology, distribution patterns of infections, proportion of malaria species, and age groups of patients with malaria and their symptoms. We also highlight past milestones and efforts in terms of future control and prevention strategies, which need to be understood to target malaria elimination in this state. To our knowledge, this is the first systematic analysis of existing longitudinal malaria data in the last four decades that have been collected by the state’s routine health surveillance system (active and passive) to study the epidemiology of malaria.

**METHODS**

**Study area**

Kheda is situated at 22.75°N 72.68°E, with an average elevation of 21 m (figure 1). The area receives rainfall between the second week of June and September from the southwest monsoon. The average annual rainfall ranges between 500 mm and 700 mm and the mean annual temperature ranges between 25°C and 32°C. Kheda district has a population of 2.29 million and has shown a population growth rate of 13.62% over the last decade (2001–2011). The sex proportion is 937 females per 1000 males, with a literacy rate of 84.31%. The malaria clinic, under the aegis of the Indian Council of Medical Research- National Institute of Malaria Research (ICMR-NIMR), has been operating here since 1987 and caters to the whole Kheda district, while also receiving patients from other districts (viz Anand, Vadodara and Ahmedabad). This clinic has been collecting epidemiological data on key malaria parameters in a structured manner since 1987.

**Data collection**

All febrile patients who reported to us were registered and their symptoms were recorded. Thick and thin smears of each febrile patient were prepared and stained with Jaswant Singh-Bhattacharji stain. The microscopists examined 200 fields in the thick smear before declaring the results of the slide. Month-wise malaria data from 1987 to 2019 were recorded at the NIMR, Nadiad malaria clinic and routine surveillance data were also recorded at the District Malaria Office, Kheda, to assess consistency.

![Figure 1](https://example.com/image1.png)

**Figure 1** Study area. NIMR, National Institute of Malaria Research.
coherence of the NIMR clinic data with those collected under routine surveillance by the District Malaria Office for the same periods. Descriptive analysis was performed using Stata V.15.0 and R V.3.4.4 to assess the effects of past interventions on malaria cases. Bar plots with density of yearly data were constructed to assess the overall trend in time series and the possible decrease/increase in malaria cases due to several interventions used for malaria control. Circular bar plots of monthly data were constructed to assess seasonality. Other variables were expressed in number or percentage.

**Patient and public involvement**

We do not have a patient involvement.

**RESULTS**

**Malaria dynamics**

In 1987 the total number of annual blood slide examinations (BSE) in the malaria clinic was 556, which had increased to 11 053 in 2005. Nearly 7000 patients were screened for malaria infection per year during the last four decades. Overall, there was a gradual decline in malaria cases, from 332 in 1990, 151 in 2000, 71 in 2010, to 23 in 2019 (figure 2). However, in 1991, 1994 and 2004, a sharp rise in cases was evident. Thus, three major yearly peaks in malaria cases were evident over the last four decades. The second peak (malaria cases/BSE: 905/6211) in 1994 was higher than the first peak (malaria cases/BSE: 767/2201) in 1991, and the third highest peak (malaria cases/BSE: 1561/10 053) in 2004 was an outbreak of malaria in Kheda district. Thereafter, malaria cases have gradually declined year after year. The results from the malaria clinic showed coherence with the data reported by routine surveillance in Kheda district during the same period (online supplemental appendix 1). During the last four decades, the proportion of *P. vivax* cases has been ~60%, while the proportion of *P. falciparum* cases showed a maximum of ~46% during the outbreak in 2004.

**Seasonality of malaria**

To make an appropriate assessment of seasonality, the epidemiological data were broken into three equal periods of 11 years, viz from 1987 to 1997, from 1998 to 2008, and from 2009 to 2019. The seasonal prevalence of *P. vivax* and *P. falciparum* cases in the malaria clinic and programme data during the different periods is shown in figure 3A–F and figure 4A–F, respectively. The transmission of *P. vivax* usually starts in the month of May and persists until October, and a similar pattern in the prevalence of *P. vivax* was observed in all time spans (figure 3A–F). The peak in *P. vivax* cases during the first period (1987–1997) was seen in August and September, whereas during the second period (1998–2008) it was highest in August. During the third period (2009–2019), multiple peaks in *P. vivax* cases can be seen. The transmission of *P. falciparum* usually begins in July and remains active until December. The highest *P. falciparum* cases were recorded in September during each period, except during the third period when multiple peaks were found in August and September in different years (figure 4A–F). The Analysis of routine surveillance data revealed a similar pattern in peaks, with a small variation in the peak of *P. falciparum* cases in the few years during the third time span (figure 4E–F).

**Malaria by age group, gender and symptoms**

We could analyse the information available since 2004 for age-wise and sex-wise distribution of malaria cases was analysed (figure 5). Altogether, 2445 confirmed malaria cases who attended the malaria clinic were subjected to this analysis. Out of 2445 patients, 67% were male and the remaining were female of different age groups. Malaria infections were most common (40%) among the 21–40 years age group. The proportion of malaria infections...
among the older age group >60 years (4%) and children 0–5 years of age (5%), the most vulnerable group, was low in this area. In broader view of the age categorisation of malaria cases in 2004, *P. falciparum* cases were high in those aged more than 50 years at 83.9%, followed by 69.5% in those aged 6–15 years, 66.4% in those aged 31–50 years, 64.8% in those aged 16–30 years, and 47.8% in those aged 0–5 years. In 2004, *P. vivax* cases were high among those aged 0–5 years (52.2%), followed by 16–30 years (35.2%), 31–50 years (33.6%) and 6–15 years (30.5%), and lowest at 16.11% in those aged more than 50 years. In all age groups, year-wise from 2004 to 2019, *P. falciparum* cases declined and *P. vivax* cases increased (online supplemental appendix 2A).

In gender wise data shown in year of 2004, *Pf* cases were more in male 70.0% and female 64.4% and *Pv* cases were low in male 29.9% and female 35.3%'. After 2004, *P. falciparum* cases gradually declined in both genders, while *P. vivax* cases increased in both genders (online supplemental appendix 2B). The majority of patients (93%) who reported to the malaria clinic were from Kheda district, while the remaining 7% were from neighbouring districts. In general, fever with headache was the most common symptom in patients with *P. vivax*, *P. falciparum* and mixed malaria; however, most of the patients with *P. vivax* were more likely to have complaints of fever, headache and chills. A few patients had complaints of diarrhoea with fever and headache (online supplemental appendix 3A, B). In general, there were considerable differences in symptoms among the different age groups; however, no difference by gender or season was observed. Fever was the most common symptom in all age groups, followed by fever with headache and fever along with headache and chills. The younger age groups were more

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**Figure 3** Seasonality in *Plasmodium vivax* (*Pv*) cases in three spans of years: clinic data Fig.3 A, C, E and programme data Fig.B,D,F.
likely to have fever and fever with headache as compared with the older groups. Fever with headache and chills were the most common symptoms among many patients from the older groups (online supplemental appendix 3C).

Interventions undertaken during the last four decades (1990–2019)

The major activities for malaria control in Kheda were chemotherapy (with chloroquine + primaquine) and vector control by indoor residual insecticide spraying (IRS) using DDT (dichloro-diphenyl-trichloroethane) up to 1997. Due to the development of resistance of the vector against DDT and the inadequate spray coverage, malaria cases started to increase year after year until 1999. Hence, in 1998 DDT was replaced with malathion, and as a result malaria cases declined to 1245 in 2000. Thereafter, mosquitoes became resistant to malathion and malaria cases gradually increased, resulting in an epidemic in 2004 across the state. To control the epidemic, particularly the chloroquine-resistant *P. falciparum*, a combination of sulfadoxine + pyrimethamine was introduced. For vector control, malathion was replaced with pyrethroid (deltamethrin) in all affected areas and biological control was intensified by a large-scale introduction of larvivorous fish (*Poecilia reticulata*). The integrated vector management and effective chemotherapy made a significant reduction in malaria cases by 2006. After continuous use, the vector developed resistance to deltamethrin and hence this was replaced with alphacypermethrin in IRS and impregnation of net was initiated. Subsequently Long lasting nets (LLNs) were distributed by the NVBDCP in high-risk areas (figure 2).

**DISCUSSION**

The NIMR was established in Nadiad, Kheda district in 1983 and a malaria clinic was set up to provide malaria

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**Figure 4** Seasonality in *Plasmodium falciparum* (Pf) cases in three spans of years: clinic data Fig. A, C, E and programme data Fig. B, D, F.
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(A) Gender Distribution

(B) Gender distribution over the year

(C) Age categories distribution

(D) Age categories distribution over the year

Figure 5  Age (Fig. C,D) and gender (Fig. A,B) distribution of malaria cases from 2004 to 2019.

During the 1990s, districts with >2 Annual Parasitic Incidence (API) were sprayed with malathion for vector control. Therefore, cases gradually declined to a minimum in routine surveillance in 2000. A similar pattern was also observed in clinic cases. In 2002, malaria cases started to escalate in many districts of Gujarat, including Kheda. Prolonged rain, inadequate surveillance in villages and resistance of the vector to malathion resulted in a malaria epidemic in several villages of Gujarat in 2004. To strengthen surveillance, a new tool called rapid diagnosis kit (RDT) was introduced to the programme for prompt detection of malaria infections and treatment in remote areas or in Primary Health Centres (PHCs) where technicians were not available. For vector control, a pyrethroid formulation (deltamethrin) was introduced to curb malaria transmission in most parts of Gujarat.14 19 20

Continuous use of deltamethrin for a long period in the south (since 1996) and central (since 2004) Gujarat had resulted in the development of resistance of *A. culicifacies* by 2007, and as a result deltamethrin was replaced with alphacypermethrin in 2008.14 19 20 It was the same period when *P. falciparum* was also found resistant to chloroquine.
in most parts of Gujarat, and a combination of ACT (artesunate + sulfadoxine-pyrimethamine) was introduced as first-line treatment in *P. falciparum*-dominated areas. Implementation of effective vector control through IRS with alphacypermethrin, scaling up the distribution of long-lasting nets and prompt treatment have led to a sharp decline in malaria cases since 2006.

Malaria is unstable in Gujarat with *P. vivax* and *P. falciparum* prevalence rates depending on the rainfall. Kheda district receives rain in the months of June to September from the southwest monsoon. In general, malaria transmission starts with the onset of monsoon in June or July. However, our work reveals a significant number of *P. vivax* cases have been recorded in the months of April to June, when environmental conditions are adverse for vector survival in Kheda district. This is especially true for *P. vivax* cases, and it is likely that the occurrence of untreated relapse cases maintains an adequate quantity of *P. vivax* reservoirs during the non-transmission period from April to June, as shown by the current analysis. This also leads to increased *P. vivax* infections in Kheda during the subsequent transmission period (August or September) in most years.

In present scenario of National Malaria Drug Policy malaria treatment of *P. vivax* is treated with chloroquine for 3 days and primaquine for 14 days. Therefore, there are higher chances of incomplete treatment. A single dose of tafenoquine drug may be the best option for treatment of reservoir or relapse condition in malaria. The dominance of *P. falciparum* infections has been reported during the monsoon and postmonsoon periods, with the highest number of cases in the month of September or October in this area, depending on early or late monsoon. A similar pattern in *P. vivax* and *P. falciparum* prevalence had also been reported earlier in other states of India. Earlier studies have reported that *P. vivax* cases increased during the monsoon season in July to October.

During the premonsoon and postmonsoon periods, a very low prevalence has been recorded in the clinic as well as by routine surveillance, indicating poor transmission due to extremely adverse weather conditions for vector survival.

In our analysis of the case distribution of malaria by gender, males seem to be at higher risk of malaria in Kheda. There are very few data available on gender-wise and age-wise seasonal prevalence of malaria from various parts of the country. Most of the available studies, age and gender classifications supported our data. Differences in risk of malaria by gender among adults have been reported earlier in different states of India and in other countries. This is mainly attributed to men being involved in more outdoor activities, as well as their clothing and sleeping pattern, and to the different attractiveness of vectors in areas with potentially infected mosquitoes, such as urban areas and forests. In our study, malaria infections were found in all age group categories. The prevalence of malaria infections was significantly higher in the 21–40 years age group, followed by children in the 6–10 years age group. A similar pattern of age-wise malaria distribution has also been described before in India. In the last few decades, rapid urbanisation and quadrilateral development in Gujarat have occurred. Migratory populations from neighbouring districts of Gujarat may be reservoirs for malaria. In an earlier study in 2007, the migratory population working at brick kilns showed *P. falciparum* as 15.5%, *P. vivax* as 81.4% and the mixed species were detected in 3.1%. Another study reported that most of the migratory populations were involved in road construction and cultivation of agricultural crops such as paddy, tobacco, chickory and wheat. Migratory populations stayed in the district for 2–6 months according to the nature of their work. A study from Surat, Gujarat reported the slide positivity rate (44.24%) and *P. falciparum* infections (95.37%) in migratory populations (for the purpose of sugarcane cultivation). In this study a very high incidence of malaria was found due to improper insecticide coverage, poor surveillance and poor awareness. All malaria infections detected in the NMR clinic were symptomatic. The most common symptom was fever or fever with different combinations of symptoms such as headache, chills, vomiting, ache and diarrhoea. Patients with *P. falciparum* infection and mixed infection (*P. vivax* + *P. falciparum*) had more complaints of fever alone compared with patients with *P. vivax* infection; however, no difference by gender was detected. The younger age group had more complaints of fever as compared with the older age groups, as earlier.

To break the transmission of malaria, strong surveillance and effective chemotherapy and vector control are important requisites. Our analysis of data shows that during the 1980s to mid-1990s, different integrals were implemented in isolation in different situations. IRS with DDT was the mainstay of vector control, which was ineffective against *A. culicifacies*, a major malaria vector in many parts of Gujarat, due to its resistance. Therefore, malaria incidence constantly increased until DDT was replaced with malathion in 1969 in Gujarat. Malathion resistance of *A. culicifacies* was first observed in 1973 in Surat district. Therefore, malaria incidence constantly increased until DDT was replaced with malathion in 1996 in Gujarat, and it was continuously used in IRS until 2004 in most of the districts, except in tribal districts where malathion was replaced by deltamethrin under the Enhance Malaria Control Programme (EMCP). The introduction of pyrethroids in IRS and impregnation of mosquito nets then resulted in a significant decline in malaria cases until 2003 in areas under the EMCP. As Kheda district was under malathion spray in 2004, due to prolonged rain and breakdown in surveillance system for malaria cases, *P. falciparum* escalated to an epidemic in most of the villages. It was the time when deltamethrin was introduced in IRS and Insecticide treated nets (ITNs) in central Gujarat. Second, the reduced response or resistance of *P. falciparum* and *P. vivax* to chloroquine
was known to exist in Kheda and some neighbouring districts, and the second-line treatment of choice for chloroquine-resistant *P. falciparum* was sulfadoxine-pyrimethamine until 2006 when it was changed to artesunate combination therapy, artesunate-sulfadoxine-pyrimethamine (ASP). The strengthened surveillance, treatment and integrated vector management using IRS, ITNs, biological control and Information education and communication (IEC) have resulted in a decline in cases in the subsequent years. Early diagnosis using RDT and prompt treatment may have resulted in a decline in malaria cases to as low as <2 API in Kheda and adjoining districts.

Our analysis of NIMR clinic and routine surveillance data indicates that the introduction of ACT as first-line treatment in 2013, coupled with intensive integrated vector management, has reduced the cases to <1 API. Some studies showed that introduction of ACT was highly effective in tackling chloroquine-resistant *P. falciparum* cases. In Bharuch district, Gujarat, treatment of *P. falciparum* cases with chloroquine indicated chloroquine resistance, which was overcome by introducing ACT. A study in Anand district showed complete resistance of *P. falciparum* to chloroquine and resistant cases were eliminated by introducing ACT as a first-line drug treatment. A similar decline in malaria infections in other states of India and neighbouring countries has been reported during the same period. *A. culicifacies* and *A. stephensi* are the primary vectors in the rural and urban set-up in Gujarat, respectively. The high season prevalence and biting rate of these vectors also coincide with greater malaria transmission.

Due to continuous efforts of the Government of Gujarat towards malaria elimination, in 2019 the state API was less than 1. Gujarat is following the guidelines of the ‘State Framework for malaria elimination in Gujarat 2017–22’. The main objectives of the framework are to reduce the incidence of malaria to less than 1 case per 1000 population in all districts and talukas by 2020 and to interrupt indigenous transmission of malaria throughout the state, including all high-transmission districts and corporations, by 2022. All the districts of the state are stratified based on cases per 1000 population into the following categories: (1) elimination districts, (2) transitional districts and (3) burden-reducing districts. The state has framed the elimination document in line with national goals and targets set under the national framework of malaria elimination. The main area of focus is vector control along with effective surveillance to reduce the burden in these districts. In urban areas, house-to-house surveillance is strengthened for case detection, treatment and control of mosquito breeding sites. In the districts, maximum coverage through IRS/long-lasting insecticide net is ensured and monitored by a dedicated team of malaria workers. Intensive IEC/behaviour change communication (BCC) campaigns are done in each community to encourage participation in the programme. High-risk and vulnerable populations, such as construction workers and migrant labourers, are given special attention and are regularly monitored for malaria. Use of RDTs is done for prompt diagnosis in high-risk and inaccessible areas and treatment is started immediately on confirmation. Follow-up treatment cards are provided for monitoring. Concerned authorities at the district/corporation level ensure that there are no vacancies at any level, and intersectoral collaboration mechanism is in place to enable quicker actions.

**CONCLUSIONS**

It is apparent that during the last four decades the incidence of malaria has gradually declined from API >5 in 1990 to <1 API in 2019 in Kheda district in Gujarat. Nonetheless, high prevalence and outbreaks in some villages were witnessed intermittently despite continuous effective control. The high frequency of resistance of *P. falciparum* to Chloroquine (CQ) and/or low compliance to radical treatment and/or poor surveillance were possible reasons behind the outbreak in this district. However, changes in drug policy at regular intervals based on CQ efficacy assessments and improved surveillance with RDTs likely strengthened the malaria diagnosis and treatment services, resulting in a decline in cases particularly of *P. falciparum*. High-risk groups for malaria, such as pregnant women and children below 5 years age, need more attention. Interestingly, the major malaria vector *A. culicifacies* was capable of developing resistance to conventional insecticides as well as to synthetic pyrethroid after a short period of introduction in IRS, but resistance was managed by replacing blunt insecticide with new insecticide molecule for vector control. *A. culicifacies* is a multiresistant species, and due to paucity of alternative insecticides the best current option for its control is the rotation of different groups of insecticides to prevent or delay the onset of resistance. However, despite the catch-up game between the intervention and the evolution of both vectors and parasites, the current situation looks in favour of malaria elimination, but only if the remaining reservoirs of infection are tackled in a coordinated fashion. In particular, the residual *P. vivax* infections need to be addressed by radical cure as much as feasible, and in this light alternatives to 14-day radical cure regimen with primaquine and/or tafenoquine may be considered in haste before the existing vectors start to display new resistance to the insecticides being used. The malaria situation in Kheda district therefore is promising but needs relentless public health attention.

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