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The 1985 *Plasmodium vivax* malaria elimination campaign in Santa Catarina, Brazil: the feasibility of using serology amid other integrated tools in the last mile

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Abstract

This report outlines the process of malaria elimination in two municipalities, São Francisco do Sul and Araquari, located in Santa Catarina, Southern Brazil, from 1980 to 1985. Before 1948, Santa Catarina reported an annual average of nearly 60,000 malaria cases. The primary vector responsible for transmission was *Anopheles* (*Kerteszia*) *cruzii*, which exhibited high infestation levels in endemic areas. Malaria control measures in the state began in 1941 with the involvement of the National Malaria Service. The elimination process initially targeted *Plasmodium falciparum* and *Plasmodium malariae* infections, followed by a focus on *Plasmodium vivax* infections in 1962. Between 1980 and 1985, comprehensive efforts were undertaken in both municipalities to control and eliminate malaria. These efforts included bromeliad removal, DDT spraying, Malathion fogging, enhanced active and passive detection measures, and serological surveys to guide the radical cure of vivax malaria with chloroquine and primaquine. As a result of these interventions, both cities witnessed a significant decline in malaria incidence, going from 6.7 cases per 1000 residents to 0 cases in 1985. This report documents the first use of serology testing and treating in malaria elimination actions, demonstrating its potential to optimize resources by targeting treatment. The success of the combined interventions underscores the importance of significant resources, sustained effort, and political commitment to achieving elimination. The feasibility of serology-guided strategies in the 1980s highlights their continued relevance today as a model for achieving malaria elimination in endemic regions.

Keywords Brazil, Malaria, *Plasmodium vivax*, Serology, Active search, Elimination

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Background

In 1979, the Brazilian National Malaria Eradication Programme (NMEP) was still striving to eliminate malaria nationwide. While significant progress had been made in most Brazilian territories, the Northern region, predominantly covered by the tropical Amazon forest, remained a challenge [1]. However, malaria cases continued to be reported in the extra-Amazonian areas, including the state of Santa Catarina (SC), which is characterized by a subtropical climate [2, 3]. Until the 1980s, malaria control efforts in Santa Catarina were successful, although some regions, such as the Joinville area, remained challenging [4]. By that time, the decrease in malaria infection indicators had stalled in 14 out of 18 regional municipalities, with São Francisco do Sul and Araquari being the most affected. Between 1977 and 1980, malaria incidence rates (IR) in São Francisco do Sul and Araquari increased from 3.0 to 9.6 cases per 1000 residents. In the remaining 12 municipalities of the Joinville region, the IR stabilized at 2.0 cases per 1000 residents.

This retrospective descriptive analysis draws on epidemiological and operational data from the original records of the local malaria control programme. It aims to report the process of malaria elimination in the municipalities of São Francisco do Sul and Araquari in Santa Catarina between 1980 and 1985.

Study site and population

Santa Catarina is one of the three southern states in Brazil, covering an area of over 95,000 km^2. In 1980, the state had an estimated population of 3,628,292 residents and was divided into 197 municipalities. São Francisco do Sul and Araquari, two of these municipalities, had populations of 20,599 and 9674 residents, respectively [5]. Both municipalities are located on the state's northern coast, with a combined area of approximately 1054.4 km^2. The geographical coordinates for São Francisco do Sul are 26° 14′ 38′′ S, 48° 38′ 17′′ W, while those for Araquari are 26° 22′ 10′′ S, 48° 43′ 20′′ W (Fig. 1).

The climate in this region is characterized by high temperatures throughout the year, with a noticeable drop during June, July, and August. Rainfall is frequent year-round but intensifies during the summer months. The Atlantic Forest predominantly covers the study area, which includes several bromeliad species [2, 6]. Urban areas are situated on the fringes of these forests, and the Atlantic Forest extends across all cities in the state. During the study, one of the prominent economic activities

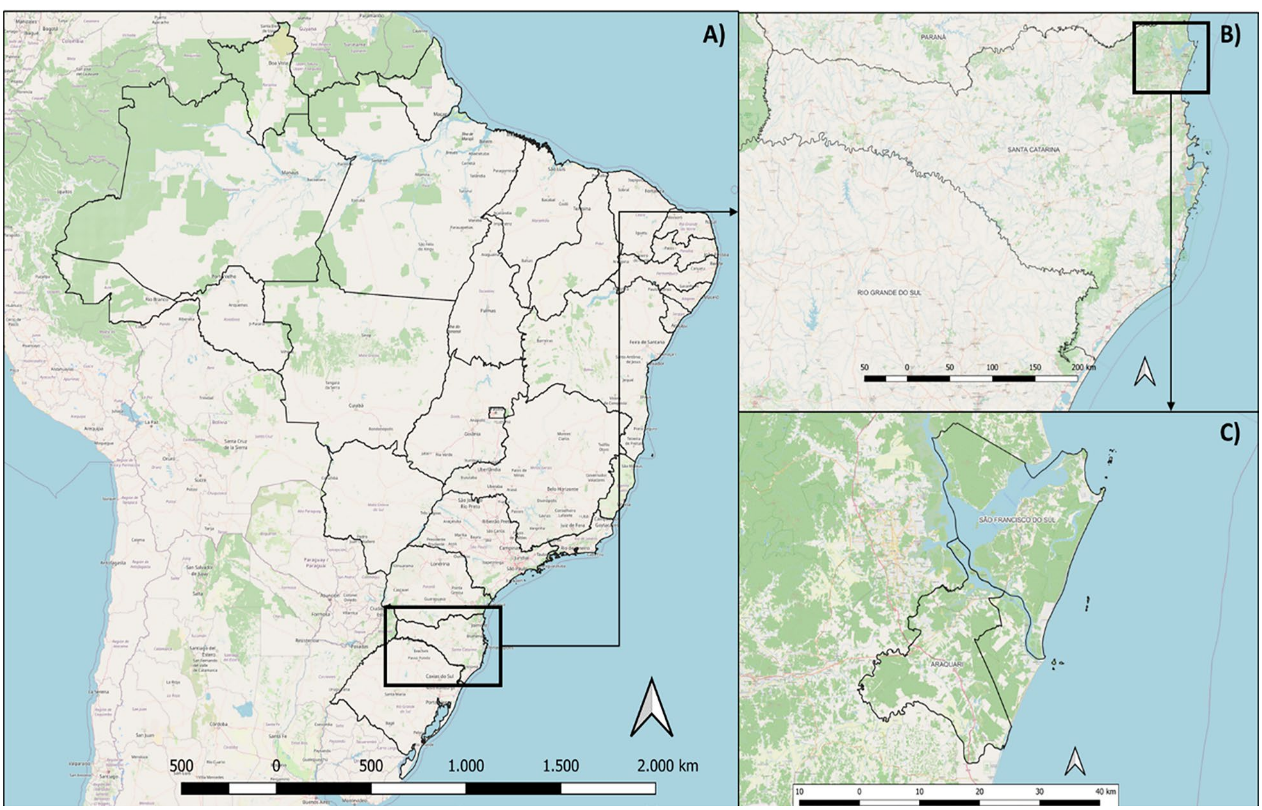

Fig. 1 Santa Catarina, São Francisco do Sul, and Araquari location, Brazil. **A** Santa Catarina's state location; **B** Santa Catarina's north coast region; **C** São Francisco do Sul and Araquari locations. Source: Google Maps plugin – Qgis software

was extracting wood and firewood for commercial purposes, a regular and economically significant practice.

Malaria control in Santa Catarina

The efforts to control and eliminate malaria in the São Francisco do Sul and Araquari region were part of a broader initiative to combat malaria throughout Santa Catarina. At the beginning of the twentieth century, malaria posed a significant threat in southern Brazil, comparable to the current impact in the Amazon region. Before 1948, Santa Catarina reported nearly 60,000 malaria cases annually, with a population of around 1,560,000 at the time. In 1944, São Francisco do Sul reported 3482 malaria cases despite having a population of less than 20,000 residents [7].

Malarial infections in the state were caused by *Plasmodium falciparum, Plasmodium vivax,* and *Plasmodium malariae*, with *Anopheles (Kerteszia) cruzii, Anopheles (K.) bellator*, and *Anopheles (K.) homunculus* serving as the primary vectors [4, 6]. *Anopheles (K.) cruzii* was the most prominent vector due to its high infestation levels in endemic areas [8, 9].

Systematic malaria control measures in the state began in 1941 with the involvement of facilities and consultants from the National Malaria Service (SNM) [10–12]. The SNM was responsible for epidemiological surveillance, case diagnosis, and treatment. Additionally, the SNM implemented intensive bromeliad removal as part of their efforts [3] (Fig. 2).

By 1943, due to bromeliad removal and extensive deforestation between 1946 and 1950, malaria incidence had dropped to near-zero levels in some municipalities. By 1962, infections caused by *P. falciparum* and *P. malariae* were no longer detected throughout the state. These species were eliminated before *P. vivax* infections most probably because with the proper control tools used timely, parasites which do not develop hypnozoites are easier to control. On the other hand, *P. falciparum* gametocytes usually are released in the peripheral circulation after seven days of clinical disease, as compared with *P. vivax*, which releases infectious gametocytes earlier during infection [13]. However, in 1950, the removal of bromeliads and deforestation ceased due to criticism and various pressures, leading to the initiation of reforestation actions.

In 1947, deforestation measures were replaced by DDT, which proved effective in reducing malaria cases in the region [14]. The SNM also established diagnostic facilities and provided free treatment to infected individuals through volunteer efforts.

By 1980, the state's malaria elimination plan still needed to be completed. São Francisco do Sul and Araquari were among the few municipalities that continued to report malaria cases. The incidence rate (IR) in São

Fig. 2 Bromeliads removal team, 1945. Source: Picture taken by the first author

Francisco do Sul had decreased from 122.8 cases per 1000 residents in 1962 to 9.6 cases in 1979, while Araquari's IR had reduced from 38.4 to 2.0 cases per 1000 residents over the same period. However, in 1980, both municipalities experienced an increase in their IRs, with São Francisco do Sul reporting an IR of 10.3 and Araquari reporting 8.1 cases per 1000 residents.

The malaria elimination plan of 1980

The malaria elimination plan implemented in 1980 focused on strengthening screening efforts to identify human cases. The frequency, speed, and coverage of active and passive detection operations by microscopy [15] were increased to eliminate malaria. Health agents conducted more house visits in high-risk communities, and support in health centres was enhanced to improve the detection and management of passively detected cases. By this time, only *P. vivax* infections were present.

Administrative and operational measures were taken to ensure insecticide spraying and active case detection. Mass diagnosis and treatment of seropositive cases were implemented to cover both symptomatic and presumed silent cases. A serological survey was conducted, followed by appropriate treatment. Additionally, although no longer widely used, bromeliad removal actions were reinstated in the region.

The combination of DDT use, bromeliad removal, malathion fogging, mass screening, and treatment was expected to be sufficient for malaria elimination in both municipalities. After one year of these actions, the incidence rate of malaria cases began to decrease. By February 1984, the region registered its last autochthonous case, with subsequent cases imported and effectively controlled.

Vector control measures

In both municipalities, DDT spraying was conducted at least twice a year in each household, following a six-month cycle. Trained teams performed daily bromeliad removal within a 200-m radius of urban areas. In São Francisco do Sul, malathion fogging was implemented in 14 municipalities, while Araquari served as the control group for this measure. Malathion fogging occurred in four annual cycles from 1981 to 1984, primarily in the third quarter of each year and continuing until May of the following year. During each cycle, approximately 1378.4 acres in endemic areas were fogged once a week.

The first serological survey (1981)

To address the challenge of identifying asymptomatic reservoirs of *P. vivax*, two serological surveys were conducted in 1981 and 1982. Detected cases received prompt *P. vivax*-radical cure with chloroquine over three days and 14 days of primaquine (0.25 mg/kg/day), particularly during the low transmission season.

The first survey began in May 1981 and was preceded by awareness campaigns on local media. Educational sessions were held with teachers, parents, and community leaders from March to October 1981. The survey spanned from late June to mid-October and involved 26,301 participants, representing 86.9% of the population in the targeted municipalities. Samples were collected from various locations, including homes, workplaces, and public spaces.

Biological material was gathered using both passive and active search teams. Additional personnel were recruited from other municipalities in Santa Catarina to ensure efficient sample collection. Blood samples were obtained via finger-prick using sterilized lancets. Two drops of blood were collected per individual, one for microscopy examination and the other for serological analysis. The blood for microscopy was dried on glass slides, while samples for serology were placed on filter paper and packaged for laboratory analysis.

Slides for microscopy were sent to local programme laboratories, and filter paper samples for serology were dispatched to specialized laboratories. To ensure proper identification, participants completed a brief questionnaire during collection. This information aided in correlating test results with individuals, enabling timely treatment in the case of a positive diagnosis.

The field laboratories in São Francisco do Sul and Florianópolis conducted the thick smear microscopy, following the Gram staining method technique. Each slide was examined under a microscope across 300 fields. Quality control was performed on 10% of the slides re-examined at the central laboratory.

Blood samples on filter paper were shipped by air, reconstituted with saline, and incubated with conjugates containing parasite antigens for subsequent indirect immunofluorescence (IIF) analysis. *P. vivax* antigens, isolated from local untreated cases, were used to detect antibodies. Serum dilutions were examined until no fluorescence was detected, and results were reported as antibody titres. Titres of 1/16 for IgG or 1/8 for IgM were indicative of infection.

The survey identified 509 individuals with positive serology and four with positive microscopy. Among the latter, two were seropositive, and two were seronegative. All seropositive cases (n = 509) involved IgG detection, with no positive IgM results reported (Table 1). Serum positive and microscopic positive individuals were promptly located and administered radical treatment for *P. vivax*.

That strategy was to treat seropositive populations (i.e. using serology as a surrogate marker of previous

Table 1 Number of samples and results of serological surveys in São Francisco do Sul and Araquari, 1981 and 1982

	Number of blood samples or serum					
	Survey 1981			**Survey 1982**		
	São Francisco	**Araquari**	**Total**	**São Francisco**	**Araquari**	**Total**
Examined localities	34	18	52	13	3	16
Collected	18,254	8047	26,301	5086	1401	6487
Examined	18,254	8047	26,301	4958	1367	6325
Seropositive	389	120	509	417	112	529
Hemopositive	4	–	4	1	–	1

exposure to *P. vivax* infection) regardless of a negative thick blood smear. That strategy probably has treated many people unnecessarily, but it was the most sensitive approach available at the time to tackle hypnozoite carriers, even lacking specificity.

In early 1982, the persistence of positive malaria slides indicated ongoing endemic transmission. A second serological survey was proposed to address the potential presence of cryptic cases. The decision was driven by concerns about continued transmission in two municipalities, fuelled by active transmission mechanisms. The primary goal was to obtain reliable epidemiological data to accurately map the extent of the endemic activity, which was necessary due to incomplete records from the first survey. This led to misclassifying infection cases and compromised identification of high- and low-risk areas. The new survey aimed to rectify these inaccuracies by ensuring precise location attribution of positive cases through home-based sample collection.

The methodology of the second survey closely mirrored that of the first. The main differences were the scope of the survey, and the device used for serum collection. Conducted between July and October 1982, this survey targeted 13 locations in São Francisco do Sul and 3 in Araquari, focusing exclusively on high transmission areas. Unlike the first survey, no samples were collected outside participants' homes. Field agents made repeated home visits, as necessary, to collect samples from individuals absent during previous attempts. When positive results were detected, this ensured accurate mapping of the infection's likely location.

Blood and serum samples from 6487 individuals were examined, representing over 95% of the population in the surveyed areas. Blood for serological testing was collected via finger-prick and drawn into seven-centimetres glass capillary tubes. The tubes were sealed and transported to the laboratory for processing. Serum recovery was performed through microcentrifugation, and seropositive cases were identified using indirect immunofluorescence microscopy utilizing the same *P. vivax* antigens as in the 1980 survey. As with the previous survey, IgG titters of 1/16 or greater and IgM titters of 1/8 or greater were indicative of infection.

The second survey identified 529 seropositive cases and one positive microscopy case, which was also seropositive. Notably, only one IgM-positive case was identified in the second survey, which tested negative for microscopy.

Table 1 summarizes the number of samples collected and examined, as well as positive results obtained in the 1980 and 1982 surveys. A comparison of the two surveys highlights differences in the number of individuals studied, as well as the geographical scope of the procedures. Also, Table 2 demonstrates the varying performance of the surveys regarding sample collection and positive serological results in both municipalities.

Table 2 Results of serological surveys in São Francisco do Sul and Araquari, 1981 and 1982

	Number of detected and treated cases							
	First survey (1981)				**Second survey (1982)**			
	São Francisco do Sul		**Araquari**		**São Francisco do Sul**		**Araquari**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Detected cases	389	100	120	100	417	100	112	100
Treatments initialized	380	97.7	120	100	391	93.8	108	96.4
Treatments concluded	371	95.4	118	98.3	388	93	108	96.4

Notably, all four positive microscopy cases from the first survey were found exclusively in São Francisco do Sul.

Reinforcement of active detection actions

Passive and active detection measures were intensified in both municipalities. Daily examination of blood slides became a routine practice. In the final two years of the intervention, health agents started visiting houses every three days to promptly identify symptomatic cases and investigate suspected cases. This approach ensured no infected person could transmit malaria for more than eight days. Suspected cases received treatment until it was confirmed that they had no current infection.

An indication of the intensification of active case detection is the improvement in treatment timeliness, as measured by the time interval between diagnosis and treatment initiation. In 1979, the time between diagnosis and treatment initiation was 13.7 days or more in 90% of cases, which decreased to 6.0 and 3.8 days in 1983 and 1984, respectively (Table 3).

Between 1980 and 1984, active searches were conducted to screen for individuals presenting symptoms. When individuals were suspected of malaria infection, they received radical treatment. There were no records of treatment failures, malaria relapses, the development of drug resistance, or deaths related to haemolysis caused by G6PD deficiency [16, 17]. Healthy residents did not receive treatment or preventive treatment.

Both municipalities' combined incidence rate (IR) was 6.7 cases per 1000 residents in 1980, which decreased to 0.2 by the end of 1984. From 1984 onwards, no malaria cases were registered in either of the municipalities. São Francisco do Sul went from 212 cases (IR 10.3) in 1980 to five cases in 1984 (IR: 0.2); Araquari registered 78 cases in 1980 (IR: 8;1) and 1 case (IR: 0.1) in 1984. Both municipalities registered zero cases in 1985 (Fig. 3).

Table 3 Number of malaria cases by *Plasmodium vivax* infections and time elapsed (days) between diagnosis and treatment

Year	Detected cases	Median (in days)	Percentile 90 (in days)
1979	151	4.9	13.7
1980	310	5.7	15.0
1981	192	3.7	11.0
1982	39	2.5	8.1
1983	21	1.3	6.0
1984	4	1.5	3.8

Treatment procedures

All identified cases were treated for 14 days following the Global Malaria Elimination Programme recommended regimen for *P. vivax*. The treatment protocol included administering chloroquine for the first three days, followed by primaquine at 0.25 mg/kg/day for 14 consecutive days.

The treatment regimen for patients aged 15 years and older involved taking four 150 mg chloroquine tablets on the first day, followed by three tablets on the second and third days. Additionally, one 15 mg primaquine tablet was taken daily for the entire 14-day treatment period. During the first three days, all pills for the day were taken together, preferably avoiding divided doses. In cases where vomiting occurred after medication intake, the treatment was repeated with daily doses divided into up to three separate doses. For children, therapeutic tables provided by the eradication programme were used to determine the appropriate dosage fractions.

Discussion

The low incidence rates (IR) of malaria in Araquari (0.4/1000 residents) and São Francisco do Sul (4.2/1000 residents) in 1977 suggest that these municipalities missed an opportunity to eliminate malaria during that period. Consequently, intensified control measures were necessary by 1980 when the reduction in malaria IR plateaued, with a specific focus on eliminating *P. vivax* infections.

It is crucial to recognize that the observed reductions in malaria transmission levels in the state before 1962 cannot be solely attributed to the use of DDT. DDT was consistently implemented with active and passive case detection, chemotherapy treatment, and often manual removal of bromeliads, particularly before 1962. These collective efforts in Santa Catarina led to the elimination of *P. falciparum* and *P. malariae* infections.

In São Francisco do Sul, malathion fogging was applied in 14 localities, targeting open spaces around existing dwellings. Epidemiological results were compared with data from three untreated localities (control sites) in Araquari during the intervention. However, there were significant shortcomings in selecting communities for malathion fogging. In the first cycle, only six out of the 14 high transmission areas were treated, while seven unnecessary locations received treatment. Four non-experimental locations were treated in the second and fourth cycles, and high transmission areas were never included in any cycle. These factors suggest fogging did not influence endemic activity beyond the treated areas. It is implausible for fogging to produce any effect in areas

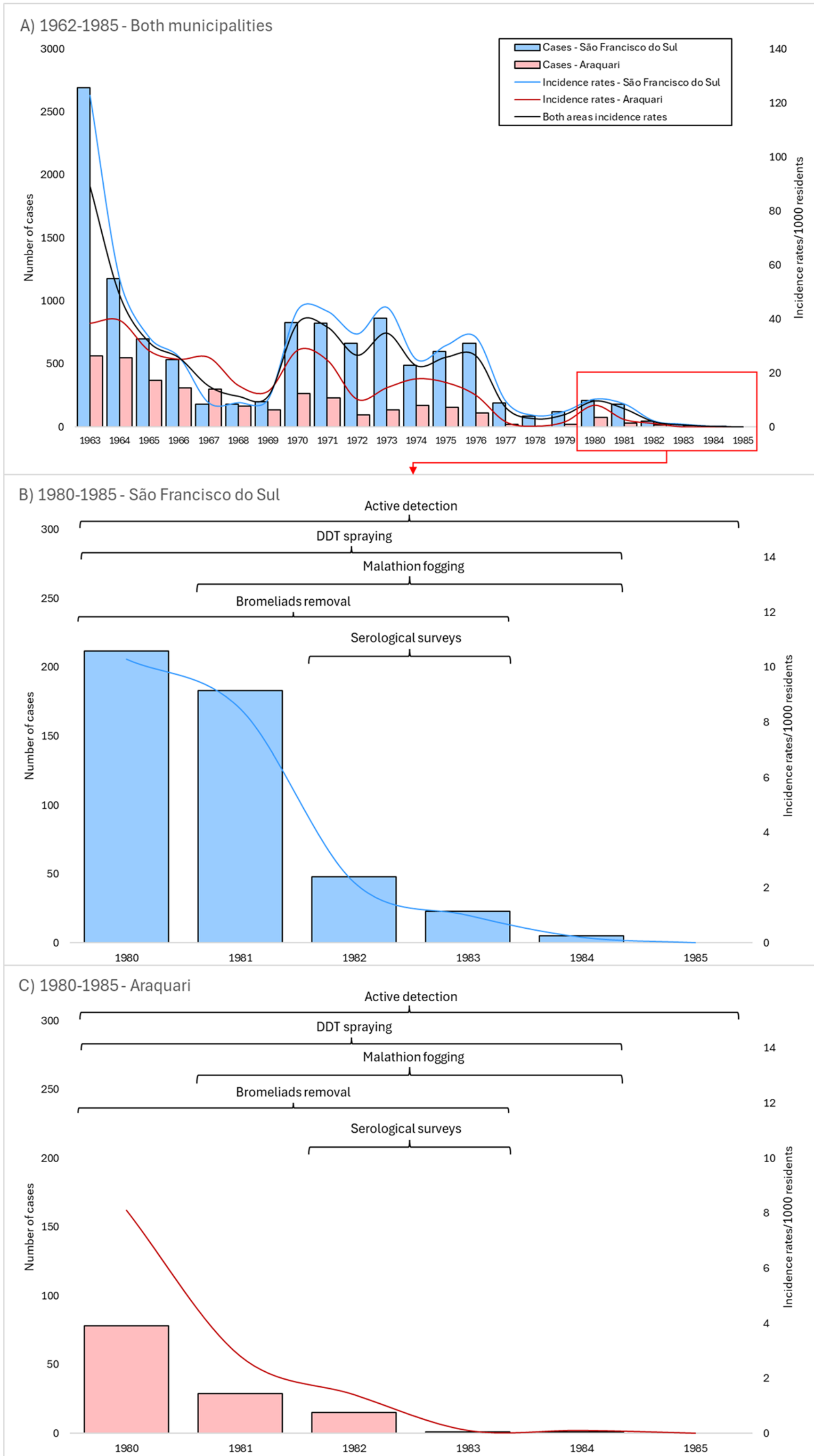

Fig. 3 Malaria cases and incidence rates per 1000 residents in São Francisco do Sul and Araquari, Santa Catarina—Brazil (1963–1985). **A** Both municipalities, period: 1963–1985; **B** São Francisco do Sul, zoom in 1980 to 1985; **C** Araquari, period: 1963–1985; **D** Araquari, zoom in 1980 to 1985

where it was not applied, even when exclusively targeting the high transmission area of São Francisco do Sul.

Bromeliad removal in the locality of Iperoba was the least extensive territorial measure applied during the intervention period. It was also the shortest duration, rapidly decreasing intensity until it ceased entirely in 1984. These factors suggest that bromeliad removal likely did not significantly reduce malaria transmission during the intervention period, particularly considering that Iperoba represented only one of the 17 high transmission locations in the two municipalities and accounted for less than one-fifth of the population exposed to high local transmission. It is unclear if deforestation and bromeliad removal were sustainable and effective tools for malaria control at the time. It is also vague in which period the impact was more prominent.

Two different forms of drug intervention were implemented: one focused on serological diagnosis followed by treatment (serological surveys), and the other involved treating patients detected through active case detection. These interventions were preceded by an extensive public awareness campaign to encourage resident participation and support.

The absence of seropositive individuals for IgM antibodies in the first serological survey and the detection of only one IgM-positive case in the second survey indicated that most seropositive individuals had chronic infections or had previously contracted malaria but were no longer infected. These results were expected, as the surveys were conducted during winter when malaria incidence is typically lower than in other seasons, making acute cases rarer.

Regarding the drug intervention guided by serology, it is essential to note that it involves mass testing and treatment (MTaT) [18]. Compared to the classic Mass Drug Administration (MDA), this approach reduces the number of people receiving treatment and eliminates the need for unnecessary treatments [19]. However, a positive serology result does not guarantee the presence of parasites in the patient's blood at the testing time. Moreover, the intervention did not cover the entire population of both municipalities. Therefore, it cannot be concluded that serology was the primary tool responsible for controlling malaria, although its highly sensitive method should not be overlooked among the many tools used.

Indeed, the strategy used in Santa Catarina appears to be one of the few reported cases of serological screening-guided treatment. The detection of IgM against the whole parasite was the only available tool at the time. More recently, specific antibodies associated with recent *P. vivax* infections have been identified and could be used more specifically to aid in treating positive cases in the context of elimination.

Given the discontinuous nature of serological surveys and anti-vector measures, which cannot solely account for the decline in transmission intensity and eventual eradication of the parasite, the drug intervention guided by active and passive case detection emerges as the primary factor contributing to the elimination or substantial reduction of malaria in the two municipalities. The intensification of active detection and the reduction in treatment delays, initiated in 1980, likely contributed significantly to the effectiveness of the drug intervention guided by active detection in achieving either the elimination or substantial reduction of malaria [20–22].

Thus, it can be concluded that the success of the drug intervention guided by active detection in São Francisco do Sul and Araquari was primarily due to the reduction in the infection period and the ability to maintain this period below the threshold necessary for the elimination of the last case [23].

Considering the variations in temperature and precipitation, natural factors are unlikely to have significantly influenced the effectiveness of the activities carried out in both municipalities between 1980 and 1985. There were no notable changes in mosquito infestation or water levels in breeding grounds. Furthermore, there are no reports of changes in forest size or population demographics during this period. Lastly, entomological data did not indicate any changes in vectorial capacity in the region or about zoonotic reservoirs influence on cases transmission.

It is important to mention that zoonotic malaria has been described in the Atlantic Forest region and linked to autochthonous cases [24, 25]. However, there are no historical evidence or documented reports of *P. simium* infections or transmission from zoonotic reservoirs to humans during the 1980–1985 elimination campaign in São Francisco do Sul and Araquari cities [26, 27].

It is also important to acknowledge that the combination of all five intervention measures likely contributed to the observed outcomes. However, the use of several tools over many years does not allow for the conclusion of causality about the most effective control measure. However, the experience from Santa Catarina shows, for the first time, that even in adverse conditions and with limited sensitivity, serology was feasible and might have contributed to detecting hypnozoite carriers. Today, ultrasensitive PCR, LAMP, or multivalent serology tools could be more successful. There is also a knowledge gap about whether the local populations prefer testing and treating over MDA strategies in residual transmission areas.

Limitations

Due to the historical nature of this study, accessing specific references from over 30 years ago posed significant challenges. As a result, alternative methods were employed to validate findings. While this study provides a thorough overview of the historical context and malaria control measures in Santa Catarina, it is vital to acknowledge the absence of specific references for some aspects. This gap highlights the limitations arising from the unavailability of specific historical data.

To strengthen future research in this area, it is crucial to prioritize preserving historical data and ensure the availability of specific references to enhance the robustness of the findings.

Conclusions

The experience in São Francisco do Sul and Araquari highlights the pivotal role of resource optimization and strategic implementation in malaria elimination efforts. Combining serology testing and treating with active case search, this historical intervention represents the first documented use of serological screening to guide malaria elimination actions. This innovative approach allowed for targeted treatments reduced unnecessary interventions and maximized the efficiency of available resources.

Achieving elimination demands significant resources and sustained effort. The success of this five-year campaign underscores the importance of political will and coordinated actions in overcoming the challenges posed by malaria. While bromeliad removal, malathion fogging, and the treatment of positive cases had limited standalone impact before 1980, their integration with enhanced detection and serology-guided treatment proved essential to interrupting transmission.

The results achieved in the 1980s demonstrate that malaria elimination was feasible even under the technological and operational constraints of the time. This precedent reinforces the potential for similar strategies to succeed today, provided there is sufficient political commitment and prioritization of elimination goals. The experience in São Francisco do Sul and Araquari serves as a valuable model, demonstrating that malaria elimination is an attainable objective with the right combination of strategies.

Abbreviations

DDT	Dichlorodiphenyltrichloroethane
IR	Incidence rates
MDA	Mass Drug Administration
MoH	Brazilian Ministry of Health
NMEP	National Malaria Eradication Program
SC	Santa Catarina
SNM	National Malaria Service
G6PD	Glucose-6-phosphate dehydrogenase

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Author contributions
DFR and AMS are responsible for the study's conception. KKSG and DFR conceived the review the compilation of background material, and drafted the manuscript. DFR, KKSG, IM, CD, PLT, MVGL, and AMS supported the review and contributed to the critical review. All authors read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study did not require approval by ethics committees following Brazilian National Health Council resolution nº 446/2011.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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