

## The burden of imported malaria in Gauteng Province

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**Objectives.** To describe the burden of malaria in Gauteng Province, and to identify potential risk factors for severe disease.

**Design.** We conducted a prospective survey of malaria cases diagnosed in hospitals throughout Gauteng from December 2005 to end November 2006.

**Outcome measures.** Malaria frequency, severity, and treatment.

**Results.** We identified 1 701 malaria cases; 1 548 (91%) were seen at public sector hospitals and 153 (9%) at private hospitals; 1 149 (68%) patients were male. Median age was 27 years (range 1 month - 89 years). Most (84%) infections were presumed to be acquired in Mozambique. Disease severity did not differ by age or sex. Patients who were South African-born were more likely to have severe disease (OR=1.43 (1.08 - 1.91)), as were patients who experienced a delay >48 hours between onset of symptoms and diagnosis or treatment

(OR=1.98 (1.48 - 2.65)). While most patients appropriately received quinine, only 9% of severe malaria cases received the recommended loading dose.

**Conclusions.** The incidence of malaria in Gauteng was higher than previously reported, emphasising the need to prevent malaria in travellers by correct use of non-drug measures and, when indicated, malaria chemoprophylaxis. Disease severity was increased by delays between onset and treatment and lack of partial immunity. Providers should consult the latest guidelines for treatment of malaria in South Africa, particularly about treatment of severe malaria. A change in drug policy to artemisinin combination therapy for imported uncomplicated malaria in non-malaria risk provinces should be strongly considered.

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Malaria, though preventable and treatable, remains a major cause of morbidity and mortality in the developing world. Its greatest toll is exacted on populations in sub-Saharan Africa, resulting in significant morbidity and mortality and impeding economic development in the region. The World Health Organization (WHO) estimated that there were 801 000 malaria deaths in 2006 in Africa, 85% of whom were children <5 years of age.<sup>1</sup> The increase in case-fatality rates in recent years is attributed largely to increasing resistance to antimalarial drugs in *Plasmodium* spp.

As a result of effective malaria control for over 50 years in South Africa, the risk of malaria transmission is low, seasonal, and limited to the low-lying north-eastern areas of the country (KwaZulu-Natal, Mpumalanga and Limpopo provinces); therefore, the South African population living in both malaria-risk and malaria-free areas are non-immune. The burden of disease in malaria-risk areas has been reduced through

regional strengthening of vector control and use of artemisinin-based combination therapy. Patients and health care workers, particularly in malaria-free areas, may be less likely to suspect or recognise malaria because of the pronounced decline in malaria cases nationally. While artemisinin combination therapy (ACT) for uncomplicated malaria and quinine for severe or complicated malaria form part of the national policy in malaria-risk areas in South Africa, ACTs are not available in the public sector outside these areas, and common practice is to administer a 7-day course of quinine treatment.

South African residents and visitors are travelling more frequently within the African sub-region. Gauteng, a malaria-free province and home to approximately 9.7 million people, is the major hub for domestic and international travel. In 2005, an estimated 1 256 000 nationals of mainland African countries entered South Africa, many from the 45 countries endemic for malaria within the WHO Afro region.<sup>1</sup> Data on the travel destinations of South Africans visiting neighbouring countries are sparse, especially at ports of entry where visas are not required.

Imported malaria is well documented in developed countries, particularly in Europe and the Americas.<sup>2</sup> However, few scientific research reports address the burden of malaria imported into non-endemic parts of African countries. This critical information may help to inform the need for health worker training, community health promotion and a change in drug policy.

### Methods

#### Objective

To describe the burden of malaria in Gauteng Province, and to identify potential risk factors for severe disease, we conducted a survey from December 2005 to end November 2006.

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**Case definition**

A case of malaria was defined as illness in any patient seen in a hospital in Gauteng Province and diagnosed and treated as malaria on the basis of clinical suspicion with or without laboratory confirmation of infection with human *Plasmodium* species (by blood smear or rapid antigen detection methods), between 1 December 2005 and 30 November 2006.

**Case ascertainment**

Every hospital in South Africa is required by law to employ at least one Infection Control Officer (ICO) whose responsibilities include the prevention and management of reportable and nosocomial infectious diseases.<sup>3</sup> Since malaria is a nationally notifiable disease, clinicians and laboratories should report hospital-based cases internally to ICOs, who subsequently investigate and report cases to the provincial department of health. ICOs and clinicians were recruited to collect data on all malaria cases in each of the public and private sector hospitals in Gauteng. The provincial department of health encouraged public sector participation during departmental meetings, and private hospital authorities invited participation by their facility personnel through internal circulars and meetings.

**Data collection**

Participating ICOs and clinicians completed a single-page questionnaire for each eligible malaria case. Interviewers obtained the date and country of birth, and the presumed location of malaria infection, when the patient or relative was able to provide that information. Disease severity classification was based on the national guidelines for the treatment of malaria, where severe or complicated malaria was defined as symptomatic malaria with signs of severity or evidence of vital organ dysfunction, while uncomplicated malaria was symptomatic malaria not meeting the criteria of severity.<sup>4</sup>

**Data analysis**

Data were entered into a Microsoft Access database, and we conducted the analysis using EpiInfo version 3.3.2. We calculated age- and sex-specific incidence rates using data from the 2001 national census.<sup>5</sup> We described basic epidemiological parameters and conducted bivariate analysis on independent variables with severity of illness as the dependent variable. We tested for differences in normally distributed continuous variables between groups using Student's *t*-test, and applied non-parametric methods to non-normally distributed data. For categorical variables, we used chi-squared or Fischer's exact test for proportions, defining the level of significance as 95%. We quantified measure of association by odds ratios (OR) and calculated 95% confidence intervals around the ORs.

**Results**

Participants from 47 health care facilities submitted questionnaires on 1 701 malaria cases; 1 548 (91%) were seen at public sector hospitals and 153 (9%) at private sector hospitals. Large public sector tertiary and secondary hospitals, namely Chris Hani Baragwanath Hospital (17%), Leratong Hospital (14%), Edenvale Hospital (12%) and Natalspruit Hospital (10%) reported cases most frequently.

Males accounted for 1 149 (68%) patients; median patient age was 27 years (range 1 month to 89 years). Among 1 580 (93%)

patients for whom data on age and sex were available, there was a bimodal age distribution among males and females, with peaks in children under 10 years and adults between 20 and 49 years (Fig.1). While incidence rates were similar among children of both sexes, rates among males older than 15 years were significantly higher than those of their female counterparts ( $p<0.05$ ). Among 282 female patients between the ages of 13 and 54 years, 39 (14%) were pregnant, 159 (56%) were not pregnant, and pregnancy status was not known in 84 (30%). The majority of malaria cases occurred in the summer months, with a distinct peak in January (Fig. 2). Data on country of birth were available for 1 343 (79%) patients, of whom 612 (46%) were born in Mozambique, 607 (45%) in South Africa, 113 (8%) in other African countries, and 11 (<1%) on other continents.

In 1 593 (94%) cases, the patients or their relatives were able to provide information on the presumed geographic region where infection was acquired; 1 336 (84%) suspected acquisition of infection in Mozambique, 83 (5%) in malaria-risk parts of South Africa, 154 (10%) in other African countries, and 2 (<1%) in south-east Asia. Eight (<1%) patients had not travelled outside Gauteng province; one of these patients was a health care worker who sustained a needle-stick injury from a patient with confirmed malaria. The remaining 7 patients had insufficient data to evaluate the potential for autochthonous transmission.

Among the 1 662 (98%) cases in which the diagnostic method was reported, 1 635 (98%) were diagnosed on the basis of a positive blood smear, 22 (1%) on rapid diagnostic tests, and 5 (<1%) on clinical features alone. In 1 603 (94%) cases where the detected *Plasmodium* species was identified, *P. falciparum*

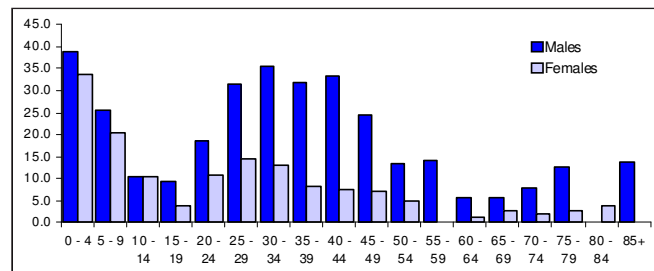


Fig. 1. Incidence of malaria per 100 000 population by age group and sex in Gauteng, December 2005 - November 2006.

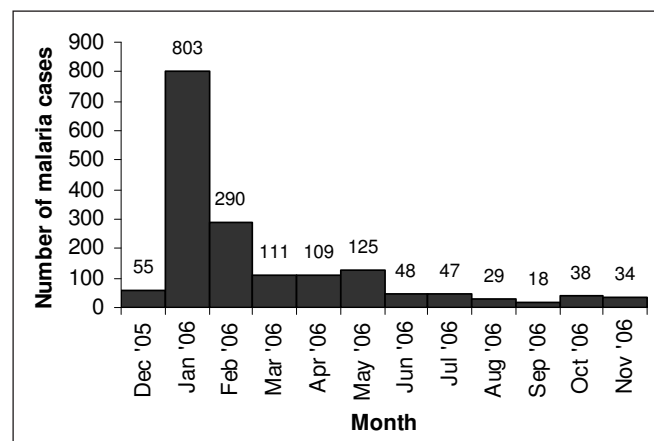


Fig. 2. Malaria cases by month in Gauteng, December 2005 - November 2006.

accounted for 1 537 (96%) infections, *P. malariae* for 39 (2%), mixed infections for 19 (1%), *P. ovale* for 5 (<1%), and *P. vivax* for 3 (<1%).

Among 1 430 cases where the interval between onset of symptoms and diagnosis or treatment was recorded, 98 (7%) cases were diagnosed or treated within 12 hours, 289 (20%) between 12 and 24 hours, and 268 (19%) between 24 and 48 hours, while 775 (54%) indicated delays of more than 2 days. In cases where delays exceeded 2 days, the reasons cited were that the patient did not suspect malaria (77%), that the initial health care provider did not suspect malaria (21%), and that the patient did not have immediate access to health care (2%).

Data on disease severity were available for 1 374 (81%) cases, of which 1 057 (77%) were classified as uncomplicated and 317 (23%) as severe. Disease severity did not differ by age or sex (Table I). Patients who were South African-born were more likely to have severe disease (OR=1.43 (1.08 - 1.91)), as were patients who experienced a delay of greater than 48 hours between onset of symptoms and diagnosis or treatment (OR=1.98 (1.48 - 2.65)).

Treatment data were available for 1 645 (97%) cases. Quinine was administered to 1 555 (95%) patients, of whom 817 (53%) received quinine alone, 565 (36%) received a combination of quinine and doxycycline, 172 (11%) received a combination of quinine and clindamycin, and 1 received quinine together with chloroquine. Four patients with *P. falciparum* malaria received chloroquine alone. Among severe cases, 27 (9%) received loading doses of quinine.

Vital outcome data were reported for 970 (57%) cases. Thirty-eight (4%) patients died, all of whom had severe malaria, of whom males accounted for 25 (66%); their median age was 33 years (range 1 - 75 years). Among the 9 females between 13 and 54 years who died, 1 was pregnant, 3 were not pregnant, and pregnancy status was not known in 5 patients. Among 28 deceased with a recorded country of birth, 17 (61%) were born in South Africa.

## Discussion

This study demonstrates the public health significance of imported malaria infections in Gauteng Province. The incidence of malaria in Gauteng was higher than previously reported to the National Department of Health<sup>6</sup> and, while the increase may be attributable to a real increase in cases, it is probably owing to increased reporting, possibly stimulated by the research project, provincial health department education efforts, and concurrent media reports. However, the cases included in the study were still an underestimate

of disease incidence in the province. A concurrent analysis of laboratory reports estimated that the number of cases that were laboratory confirmed in the province during the study period was almost three times that counted in the survey (personal communication, M Tepper, National Health Laboratory Service).<sup>7</sup> During this period, 6 513 cases were reported from Limpopo Province, 4 794 from Mpumalanga Province, and 1 284 from KwaZulu-Natal. These are all provinces in which the Malaria Control Programme operates, there is greater compliance with malaria case reporting, and accurate quantification of malaria is critical to inform malaria control activities.

Among the Gauteng study population, rates of disease were higher in children and men of economically productive age. The increased rates in children were probably because of increased severity of infection in this age group, raising the likelihood of parents taking them to hospital. In addition, providers may tend to admit children more commonly than adults, raising their opportunity for inclusion in this study. The increased rate in men is consistent with labour-related migration between malaria-endemic regions and Gauteng. The majority of our patients attended public health care facilities, reflecting the appreciable burden of disease among population groups unable to afford private health care, which dispels the notion of imported malaria being confined to affluent recreational travellers. South African guidelines and community education messages encompass the basic principles of malaria prevention, namely: awareness of risk, prevention of bites through application of N,N-diethyl-3-methylbenzamide (DEET)-containing mosquito repellants,<sup>8,9</sup> and chemoprophylaxis when appropriate. The latter intervention is expensive and not readily available from public sector health facilities. Research on South African travellers in the 1990s demonstrated a correlation between increasing use of chemoprophylaxis and a decrease in numbers of reported infections.<sup>10</sup> However, no recent studies have confirmed this finding. In general, even though travellers' adherence to antimalarial chemoprophylaxis is notoriously low, especially on regimens other than the shorter course atovaquone-proguanil combination, this option must be weighed against the risk of becoming infected and developing severe disease.

The burden of severe malaria in the study population is increased by delays in diagnosis or treatment exceeding 48 hours. In addition, the increased severity of illness associated with being born in a non-endemic region emphasises the vulnerability of populations lacking partial immunity to severe malaria. Hospitalisation for uncomplicated malaria is

**Table I. Characteristics of malaria cases by severity in Gauteng, December 2005 - November 2006**

	Uncomplicated malaria (N=1 057)	Severe and complicated (N=317)
Median age, years (range)	27 (<1 - 89)	27 (<1 - 75)
Male (%)	721 (68%)	202 (64%)
Pregnant females (%)	20 (2%)	15 (5%)
South African born (%)	370 (35%)	143 (45%)
Delay >48 hours* (%)	444 (42%)	187 (59%)

\* Between onset and diagnosis/treatment.

unnecessarily prolonged by artemether-lumefantrine not being available in the public sector hospitals in Gauteng (and other malaria-free provinces in South Africa).

Our study was subject to several limitations. We could not fully quantify the incidence of malaria in Gauteng because hospitals might not have submitted questionnaires on all patients. Patients treated as outpatients would have been under-represented in this study, which could explain the difference in cases found in the concurrent analysis of laboratory reports. However, guidelines recommend initial admission of all malaria patients in non-malaria risk areas of South Africa. The association between risk factors and malaria severity might have been subject to confounding or effect modification because we were unable to reliably classify patients as non-immune or semi-immune to malaria, and we had no record of patients' general immune status, including the effects of human immunodeficiency virus (HIV) infection. In a study conducted among 336 patients at Chris Hani Baragwanath Hospital, in Gauteng, Cohen *et al.* found an increased prevalence of severe malaria in HIV-positive patients with CD4 counts less than  $200 \times 10^6$  cells/l, although semi-immunity owing to prior residence in a highly endemic malaria area reduced the risk of severe malaria in both HIV-positive and HIV-negative patients.<sup>11</sup> A similar increase in risk of severe malaria, acute renal failure, and malaria-related mortality was found in KwaZulu-Natal.<sup>12</sup> To keep the questionnaire short and based on prior research indicating inaccuracy in reporting of adherence,<sup>13</sup> we did not collect data on chemoprophylaxis use. The high case-fatality rate among patients with known outcome of illness might have occurred as a result of reporting bias because of increased attention to thorough documentation of cases with fatal outcomes, while cases in which patients survived were less likely to have a specific outcome reported.

The number of travellers moving between non-endemic parts of African countries and malaria-endemic areas is likely to increase as a result of displacement of vulnerable population groups through wars or impoverishment, the development of transport infrastructure, and continued labour-related migration. In addition, South Africa will be hosting the Fédération Internationale de Football Association (FIFA) World Cup soccer tournament this year, which is likely to draw large international crowds with many visitors travelling the sub-region and at risk for malaria infection. These findings indicate the need for health care provider and patient education to prevent malaria through reliable use of non-drug measures and, when indicated, malaria chemoprophylaxis. These measures would include awareness of malaria risk areas (Fig. 3), available prophylactic agents<sup>14</sup> and national treatment policies.<sup>15</sup> National and provincial health departments should consider a change in treatment policy from quinine to ACT for the treatment of patients with uncomplicated malaria at public sector facilities in non-malaria-risk provinces.

We thank the clinicians and nursing personnel who participated in this study by submitting questionnaires, the Gauteng Department of Health, the South African National Health Laboratory Service, and Lancet and Ampath laboratories for providing us with supplementary data to corroborate patient laboratory results.

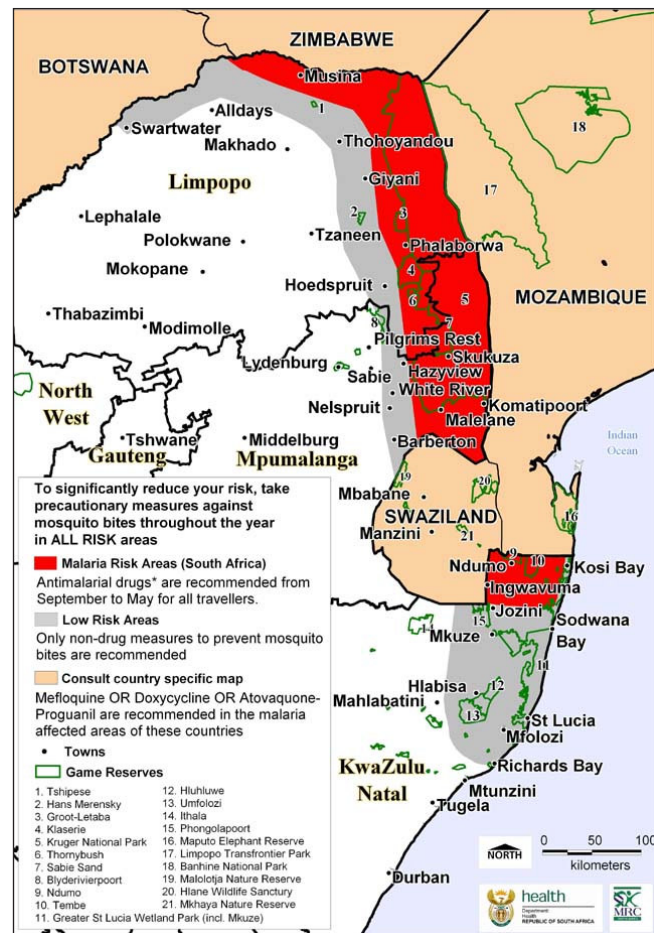


Fig. 3. Malaria risk in southern Africa, January 2007.<sup>14</sup>

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