Imported malaria in the Northern Territory, Australia – 428 consecutive cases

Timothy J Gray, James M Trauer, Merv Fairley, Vicki L Krause, Peter G Markey

Abstract

Malaria is a notifiable disease in Australia with an average of 600 notifications per year in returned travellers or newly arrived refugees, migrants and visitors. Although endemic disease has been eliminated from the tropical north of Australia, the region remains malaria receptive due to the presence of efficient mosquito vectors. This study analyses enhanced surveillance data collected by the Centre for Disease Control on all cases of malaria notified in the Northern Territory from 1 January 2000 to 31 December 2010. There were 428 malaria episodes notified that occurred in 391 individuals with a median age of 26 years. Of these, 71.4% were male, 40.5% were Australian nationals and 38.0% were prescribed chemoprophylaxis. Primary infection consisted of 196 (51.3%) cases of *Plasmodium falciparum*, 165 (43.2%) *P. vivax*, 2 (0.5%) *P. ovale*, 1 (0.3%) *P. malariae* and 18 were mixed infections. There were 46 episodes of relapsed infection. Residents of non-malarious countries were most likely to have acquired primary infection in East Timor (40.6%), Papua New Guinea (27.8%), Indonesia (18.7%) and Africa (6.4%). Primary infection was diagnosed after a median 19 days (interquartile range (IQR) 7–69) after arrival in Australia for cases of *P. vivax* compared with 4 days for *P. falciparum* (IQR 2–11). Screening protocols led to the diagnosis of 27.2% of cases. Eighty-seven per cent of patients were admitted to hospital at the time of their malaria diagnosis with median duration of 3 days (IQR 2–4) and one patient died. Resettlement of people from endemic countries, as well as military and civilian activities, influences the prevailing notification rates and *Plasmodium* species type. *Commun Dis Intell* 2012;36(1):107–113.

Keywords: malaria, surveillance, Northern Territory, screening

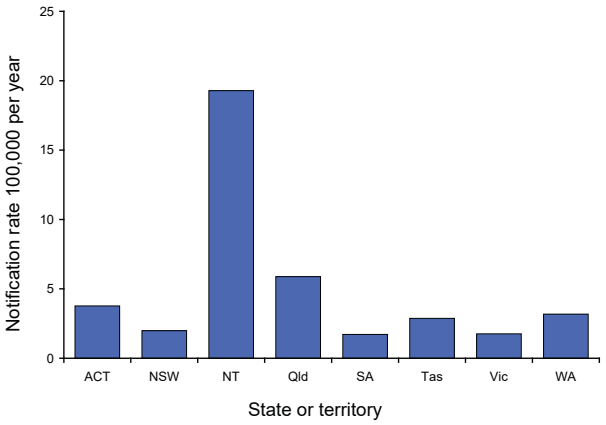
Background

Malaria remains the most frequent cause of fever in returned travellers, being the specific diagnosis in 21% of returned travellers with fever as reported across a worldwide surveillance network, including Australia.[1] Recent migrants and refugees are also at risk of malaria, with a hospital-based survey in Australia reporting 12% of confirmed malaria cases between 1997 and 2001 being from these groups.[2] The last documented case of endemic malaria in the Northern Territory occurred at Roper River in 1962.[3] Subsequently, the World Health Organization (WHO) reported the eradication of malaria from Australia in 1981,[4] but the tropical north remains susceptible to the re-establishment of the disease due to the presence of efficient *Anopheles* mosquito vectors.[5] Two outbreaks of *Plasmodium vivax* infection in northern Queensland[6,7] as well as sporadic introduced cases[8,9] emphasise the public health importance of malaria control in the tropical north.

In the 11 years from January 2000 to December 2010, 6,856 cases of malaria were imported into Australia, with 6.4% of these cases notified in the Northern Territory.[10] The Northern Territory has the highest rate of malaria notifications of all states and territories with 19.3 per 100,000 per year, compared with the national rate of 3.0 per 100,000 per year (Figure 1).[10] Under legislative requirements, laboratories and physicians notify the Northern Territory Centre for Disease Control (NT CDC) of all confirmed or probable cases of malaria. CDC staff routinely interview all individuals diagnosed with malaria and review all hospital medical charts.

Staff from the NT CDC, including those from Medical Entomology, carry out public health risk assessments for each notification and advise on the need for infection control measures such as hospitalisation or avoidance of mosquito exposure.

Figure 1: Average annual notification rates per 100,000 population, Australia, 2000 to 2010[10]



Frequently, mosquito trapping is performed in the vicinity of the case's residence and insecticide fogging is used if necessary.

In addition to the core data items applicable to all notifiable diseases, the NT CDC staff prospectively record additional malaria-specific data incorporating epidemiological, treatment and outcome variables. This report summarises these data for the 428 consecutive episodes of malaria diagnosed in the Northern Territory from January 2000 to December 2010.

Methods

Cases were defined according to the national case definition of laboratory-confirmed malaria, which requires the specific identification of malaria parasites by microscopy on blood film with confirmation of species or the detection of *Plasmodium* species by nucleic acid testing.[11] Probable cases diagnosed by the presence of malaria antigen in whole blood were also included in this analysis.

Malaria data of cases notified between 1 January 2000 to 31 December 2010 were extracted from the Northern Territory Notifiable Diseases System (NTNDS), de-identified and imported into Stata version 11.1 (StataCorp, Texas, USA). Comparisons of the effect of binary exposures on binary outcomes (including gender, chemoprophylaxis use and presence of gametocytes) were performed using the Pearson χ^2 test. Comparisons of non-normally distributed numerical variables (including time to diagnosis, duration of inpatient stay) were performed using the Mann-Whitney U-test (Wilcoxon rank-sum).

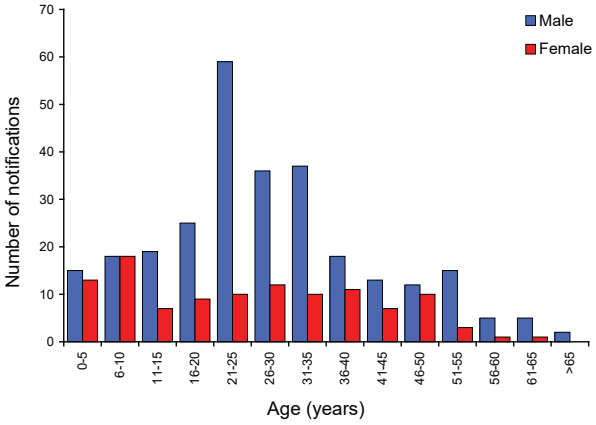
Where two countries are considered possible for acquisition, the most likely was judged at the time of interview. The recorded, but less likely secondary area of acquisition, was excluded from analysis in these cases. Summary demographic statistics were calculated on data from the primary infection or first relapse notified for each individual during the study period. Episodes of infection were judged to be relapses if they had previously been diagnosed with *P. vivax* or *P. ovale* and had not travelled again to a malaria endemic region. When the date of diagnosis was greater than 30 days after the reported date of entry into Australia, original case notes held by the CDC were reviewed to support the documentation of relapsed infection.

Results

Demographics

There were 428 episodes of malaria notified during the study period of which 425 were microscopy confirmed cases and three were probable cases. Of these 428 episodes, 382 were primary infections and 46 were relapse infections. The mean number of primary infections notified per year was 34.7 with a range from 13 to 65. No cases were acquired locally. The 428 episodes occurred in 391 individuals, of whom 279 (71.4%) were males and 112 (28.6%) were females ($P < 0.0001$). The median age was 26 years for males (range 0–80 years) and 25 years for females (range 0–65 years) (Figure 2). Three individuals (0.8%) identified as Indigenous. Over $^2/_5$ of cases were Australian nationals and 24.5% were African (Table 1).

Figure 2: Malaria cases, Northern Territory, January 2000 to December 2010 (n = 391), by age and sex



Classification of species

Primary malaria infections consisted of 196 cases (51.3%) of *P. falciparum,* 165 (43.2%) of *P. vivax,* 2 (0.5%) of *P. ovale* and 1 (0.3%) of *P. malariae.* There were 18 cases (4.7%) of mixed infection proven on microscopy; all were *P. falciparum* co-infection with either *P. vivax* (15 cases) or *P. malariae* (3 cases) (Table 1). There was marked temporal variation in species notified (Figure 3).

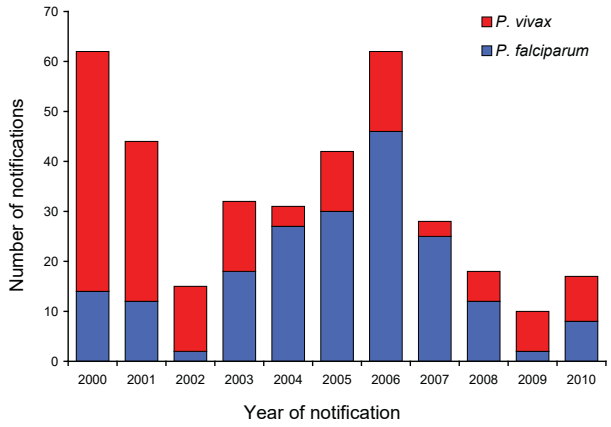
Region of acquisition for primary infections

Throughout the study period *P. falciparum* was the dominant species causing infection in individuals having travelled in, or arrived from Africa (92.0%) and Indonesia (53.8%), while *P. vivax* was the dominant infection in patients travelling to East Timor (68.0%) and Papua New Guinea (PNG) (66.2%). Since 2005 however, *P. falciparum* has been the dominant infection diagnosed in individuals arriving from East Timor (76.9%), leaving only the Pacific Islands and PNG where *P. vivax* continues to dominate in returned travellers.

Table 1: Characteristics of individuals diagnosed with malaria, Northern Territory, 2000 to 2010

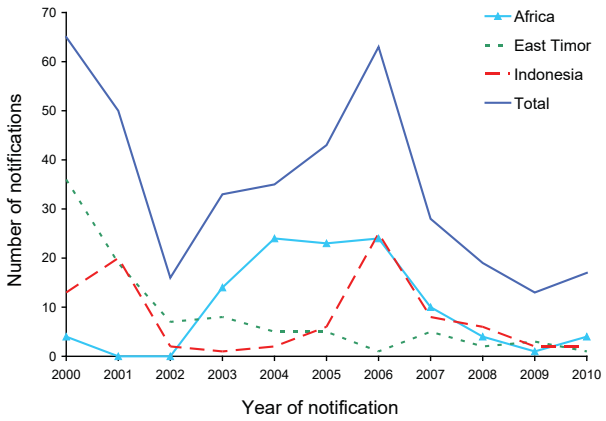
Gender (n = 391)	**n**	**%**
Male	279	71.4
Female	112	28.6
Indigenous status (n = 390)		
Indigenous	3	0.8
Non-Indigenous	387	99.2
Nationality by region (n = 388)		
Australian	157	40.5
African	95	24.5
Indonesian	49	12.6
European	25	6.4
Papua New Guinean	17	4.4
New Zealand	7	1.8
East Timorese	6	1.5
Other	32	8.2
Civilian vs military (n = 373)		
Civilian	306	82.0
Military (n = 67)		
Australian	49	13.1
International	18	4.8
Region of acquisition *primary* infection (n = 382)		
Africa	108	28.3
East Timor	92	24.1
Indonesia	87	22.8
Papua New Guinea	74	19.4
Pacific Islands (other than Papua New Guinea)	8	2.1
Other	13	3.4
***Plasmodium* species in *primary* infection (n = 382)**		
P. falciparum	196	51.3
P. vivax	165	43.2
P. ovale	2	0.5
P. malariae	1	0.3
Mixed	18	4.7
Region of acquisition for *relapsed* infection (n = 37)		
Africa	2	5.4
East Timor	10	27.0
Indonesia	5	13.5
Papua New Guinea	16	43.2
Other	4	10.8
***Plasmodium* species in *relapsed* infection (n = 37)**		
P. vivax	36	97.3
P. ovale	1	2.7
Diagnosed by screening (n = 104)		
Refugee arrival	71	68.3
Co-traveller of malaria case	18	17.3
Apprehended persons in Australian water	6	5.8
Students arriving from endemic country	3	2.9
Other	6	5.8

Figure 3: Primary *Plasmodium vivax* and *Plasmodium falciparum* infections,* Northern Territory, 2000 to 2010



* Other malaria species and mixed infections were excluded.

Figure 4: Primary malaria infections* acquired in Africa, East Timor, Indonesia and total of all regions notified in the Northern Territory, 2000 to 2010



* Includes all species and mixed infections.

Of the 187 individuals (including 150 Australian nationals) who reported a nationality from non-malarious regions, 116 (62.0%) were diagnosed with *P. vivax,* 60 (32.1%) with *P. falciparum* and 11 (5.9%) with mixed *P. falciparum/P. vivax* infection. This group acquired infection in East Timor (40.6%), PNG (27.8%), Indonesia (18.7%), Africa (6.4%), South East Asia (2.1%), Pacific Islands (2.7%) and Central and South America (1.1%). For the 191 individuals who were nationals of countries with endemic malaria, 135 (70.7%) were diagnosed with *P. falciparum,* 46 (24.1%) with *P. vivax,* 7 (3.7%) with mixed infection and 3 (1.6%) with *P. ovale* or *P. malariae* infection.

Notification rates by country of acquisition varied considerably during the study period. East Timor contributed the most cases in 2000 and 2001, Africa dominated in the years 2003 to 2007 and Indonesia contributed a significant number of cases in 2000, 2001 and 2006 (Figure 4).

Chemoprophylaxis

Chemoprophylaxis was prescribed in 145 cases (38.0%) of primary infection. Compliance data were available for 120 of these cases with 71 (59.2%) reporting completion of all doses as per accepted chemoprophylaxis guidelines. Ninety-two of 150 (61.3%) Australian nationals with primary malaria were prescribed chemoprophylaxis. The most commonly prescribed medication was doxycycline (57.2%). Of the 51 individuals who acquired malaria despite reporting compliance with doxycycline, 43 developed *P. vivax* malaria and 8 developed *P. falciparum* malaria. A further 18 cases reported full compliance to chemoprophylaxis agents other than doxycycline, of these, 11 developed *P. vivax* and 7 developed *P. falciparum* infection. Military personnel were more likely to have been prescribed chemoprophylaxis compared with civilians (51/64 vs 94/300, $P < 0.001$). When prescribed prophylaxis, military personnel were more likely to report full compliance compared to civilians (33/45 vs 38/75, $P = 0.014$). Civilians from non-malarious countries were more likely to utilise prophylaxis compared with individuals from malarious countries (105/187 vs 29/191, $P < 0.001$).

Presentation and screening

The date of arrival in Australia was recorded in 368 of the 382 primary malaria infections. The use of prophylaxis had a marked effect on the delay to the date of the first diagnostic test. In the case of *P. vivax* the median time from arrival to diagnosis was 9 days (IQR 4 to 23) in the absence of prophylaxis compared with 32 days (IQR 10 to 95) when prophylaxis of any type was prescribed ($P < 0.0001$). Similarly, *P. falciparum* cases presented after a median of 4 days (IQR 2 to 10) in the absence of prophylaxis compared with 6 days (IQR 3 to 21) when prophylaxis use was reported ($P < 0.0001$) (Table 2). The latest primary presentation of *P. falciparum* was 92 days after arrival in Australia in an African refugee migrating to Australia, who did not report using prophylaxis. The latest presentation of *P. vivax* was 333 days after arrival in Australia, in a member of the military who reported compliance with prophylaxis while deployed in East Timor.

Malaria was diagnosed by screening procedures in 104 of the primary infection presentations (27.2%). Reasons for screening included recently arrived refugee status (71 cases), being identified as a co-traveller of an individual diagnosed with malaria (18 cases), individuals apprehended for illegally fishing or arriving in Australian waters (6 cases) and

Table 2: Showing median days (interquartile range) from arrival into Australia until diagnosis of malaria for all primary malaria infections (n = 347)

	All patients	No prophylaxis	Prophylaxis prescribed
P. vivax	19 days (7–69)	9 days (4–23)	32 days (10–95)
P. falciparum	4 days (2–11)	4 days (2–10)	6 days (3–21)

The use of prophylaxis significantly delayed the diagnosis of *P. vivax* and *P. falciparum*.

students arriving or returning from malarious countries (3 cases) in schools participating in screening programs (Table 1).

The *Plasmodium* gametocyte is the life cycle stage that infects the feeding mosquito vector. Microscopy results reporting the presence or absence of gametocytes on blood films were available in 423 of the 428 episodes of malaria. Gametocytes were less likely to be identified on the films of patients infected with *P. falciparum* compared with *P. vivax* (69/195 vs 110/206, $P = 0.003$).

Hospitalisation, treatment and outcomes

Hospitalisation data were available for 395 of the 428 episodes of malaria with 344 (87.1%) individuals admitted to hospital at the time of their malaria diagnosis. The proportion of patients admitted to hospital varied with year (Figure 5). Infection with *P. falciparum* was associated with overall longer hospital admission with 43 of 183 patients with *P. falciparum* admitted for 5 days or greater compared with 15 of 174 *P. vivax* infected patients ($P < 0.001$). Despite this significant difference the median duration of hospital admission was 3 days, irrespective of the infecting species.

Treatment data were available for 413 of the 428 episodes of malaria. Prior to 2006, artemisinin combination therapy was used to treat 11.8% of cases, chloroquine 57.9%, quinine 15.5% and mefloquine 8.5%. Since 2006, artemisinin combination therapy was used in 77.5% of cases, chloroquine 12.0%, quinine 0.7% and mefloquine 1.4% (Figure 6).

There was a single death attributed to malaria in the Northern Territory during the study period. This occurred in a 32-year-old Malaysian resident evacuated from East Timor in May 2000 with mixed *P. falciparum* and *P. vivax* infection.

Figure 5: Proportion of patients diagnosed with malaria admitted to hospital, Northern Territory, 2000 to 2010

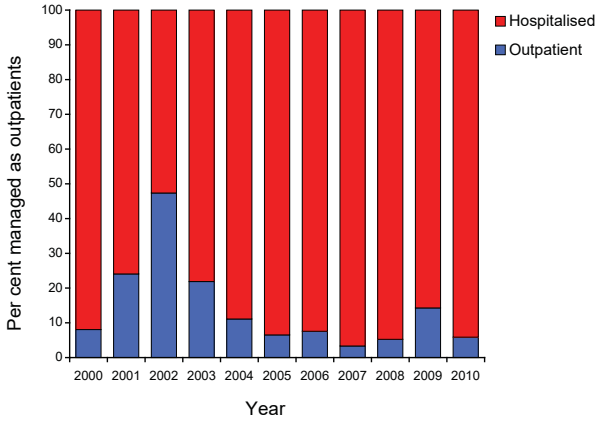
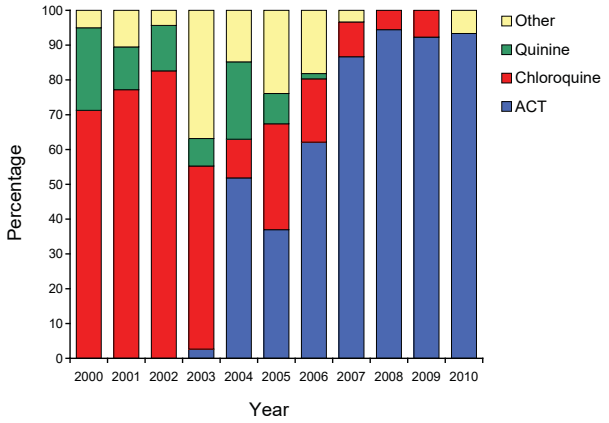


Figure 6: Proportion of malaria cases treated with different antimalarial medication or different antimalarials, Northern Territory, by year



Relapsed infections

There were 46 episodes of malaria identified as relapsed infection in 37 individuals. Microscopy confirmed 45 episodes due to *P. vivax* and 1 episode as *P. ovale*. A single episode of relapse occurred in 31 individuals, 2 relapse episodes occurred in 4 individuals, 3 relapse episodes occurred in 1 individual and 4 episodes in another individual. This group of 37 individuals were compared with the 167 who presented with primary *P. vivax* or *P. ovale* infection. There was no significant difference between the groups (Table 1). Assuming there is a steady state of relapsing individuals moving in and out of the Northern Territory, the approximate proportion of *P. vivax* relapse is 17.9% of primary infections. A 14 day course of primaquine was prescribed for 29 individuals following diagnosis with

relapsed disease, 6 individuals were not prescribed primaquine and the use was unknown in the 2 other cases. Dosage of primaquine and treatment history on cases prior to relapse is not recorded in the NTNDS.

A further 12 patients with previous malaria where categorised as primary infection (presumed reinfection) having travelled back to a malarious area between episodes.

Discussion

This study describes important epidemiological features of 428 consecutively notified cases of malaria in the Northern Territory of Australia. This series includes both hospital and community managed malaria cases and because of legislative requirements requiring laboratories and clinicians to notify the CDC it is unlikely cases have been missed. The surveillance data were collected at the time of diagnosis by chart review and interview of individuals, thus reducing the recall bias of retrospective analysis. Nevertheless, the authors needed to consult original case notes for a small number of incomplete data fields. In particular, case notes were necessary to classify infections as relapsed or reinfection as the NTNDS fails to make a distinction between these cases.

This analysis reveals that the origin of malaria infections in the Northern Territory varies over time and reflects the movement of people from endemic countries to Australia, as shown in the African refugee arrivals from 2005 to 2008 and large scale military and civilian activities following the political transition in East Timor in 2000 and 2001. These same factors have likely contributed to the increased proportion of *P. falciparum* diagnosed in the study period, not just in the Northern Territory but Australia-wide.[12,13] In 2009 and 2010, *P. vivax* was again the predominant species notified in the Northern Territory (Figure 3) as well as nationally, possibly reflecting shifts in refugee populations and implementation of pre-departure screening programs.[14,15]

It is not possible to draw conclusions from this study as to the effectiveness of chemoprophylaxis as the number of persons at risk during the observation period is not known. A number of individuals who reported compliance with appropriate chemoprophylaxis still acquired malaria infection with both *P. vivax* and *P. falciparum,* emphasising that mosquito avoidance and protection is also required.

Males outnumber female malaria cases over 10 years of age, but particularly in those aged between 11 and 35 years. While this may reflect the larger number in this demographic exposed, clinicians should nevertheless target this group with chemoprophylaxis and mosquito avoidance and protection. Current guidelines for prescribing prophylaxis can be found in the *Australian Therapeutic Guidelines,* Version 14.[16]

This study highlights the importance of the CDC policy of screening high risk groups for malaria with 27.2% of all diagnoses arising from screening procedures.[17] Prior to the introduction of refugee pre-departure screening and treatment, the incidence of malaria in recently arrived refugees from Africa was reported between 5%–16%.[18] Pre-departure screening programs promoted through the Department of Immigration and Citizenship (DIAC) have reduced malaria diagnosis in refugees, but some still arrive in Australia with malaria[15] and may present later, presumably because of partial immunity or relapse of subclinical disease. The utilisation of screening in the Northern Territory may explain the shorter period from arrival in Australia to diagnosis of malaria when compared with other Australian and international series.[19,20]

There are minimal available data to compare hospitalisation rates for patients with malaria in other jurisdictions. The seemingly high rate of hospitalisation for patients diagnosed with malaria in the Northern Territory may reflect local treatment guidelines, which aim to reduce the risk of transmission to local mosquitoes and the re-establishment of malaria. Admission is recommended where species identification cannot be made within 24 hours, for all *P. falciparum* disease, if gametocytes are seen in the blood film or screened accommodation is not available.[17] The temporal variation in the hospitalised proportion of malaria infected individuals may reflect the increased number of *P. falciparum* infections between 2003–2008. The observation that hospital duration was longer in patients with *P. falciparum* has been described in other jurisdictions in Australia and is in keeping with the well described natural history of this more pathogenic species.[12,19]

Increasing resistance of *P. vivax* malaria to chloroquine in Indonesia, East Timor and Pacific Island nations has led to local Northern Territory and national guidelines recommending the use of artemisinin-based combination therapy (ACT) or mefloquine, for *P. vivax* infection acquired in these regions.[16,17] This analysis shows there has been a clear shift to using ACT and provides evidence that Northern Territory clinicians are implementing these guidelines (Figure 6).

P. vivax and *P. ovale* are characterised by relapsing infection, which arise from the hypnozoite stage of the life cycle within human hepatocytes. The proportion of infections that relapse is variably reported and is probably a function of the malaria

"strain" as well as sporozoite inoculums and host immunity.[21] The proportion of relapses reported in this study population can only be seen as a snapshot as the diagnosis of primary infections in some cases occurred outside the Northern Territory and also it is possible that some individuals may have relapsed after moving out of the Northern Territory jurisdiction. It is also possible that a proportion of these cases classified as relapse were recrudescent infections.

In conclusion, the use of enhanced surveillance data in the Northern Territory has allowed clinicians and health officials to better understand who is at risk of malaria. This analysis provides compelling support for the Northern Territory active screening program and shows that there are significant temporal shifts in malaria rates and species reflecting movement of people from endemic countries into Australia, influenced by military and civilian activities and changing refugee settlement programs. There is recognition that a close working relationship with DIAC and the Department of Defence would benefit diagnostic possibilities and prevention strategies. Enhanced malaria surveillance to some extent is already operational in Victoria,[22] Western Australia,[12] New South Wales and the Australian Capital Territory.[23] Consideration should be given to the gaps in our present knowledge and what might be gained from timely national enhanced data collection and analysis.

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