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SORT IT: MALARIA ELIMINATION SUPPLEMENT

Advances in malaria elimination in Botswana: a dramatic shift to parasitological diagnosis, 2008–2014

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Background: Malaria elimination requires infection detection using quality assured diagnostics and appropriate treatment regimens. Although Botswana is moving towards malaria elimination, reports of unconfirmed cases may jeopardise this effort. This study aimed to determine the proportion of cases treated for malaria that were confirmed by rapid diagnostic testing (RDT) and/or microscopy.

Methods: This was a retrospective descriptive study using routine national data from the integrated disease surveillance and case-based surveillance systems from 2008 to 2014. The data were categorised into clinical and confirmed cases each year. An analysis of the data on cases registered in three districts that reported approximately 70% of all malaria cases was performed, stratified by year, type of reporting health facilities and diagnostic method.

Results: During 2008–2014, 50 487 cases of malaria were reported in Botswana, and the proportion of RDT and/or blood microscopy confirmed cases improved from 6% in 2008 to 89% in 2013. The total number of malaria cases decreased by 97% in the same period, then increased by 41% in 2013.

Conclusion: This study shows that malaria diagnostic tests dramatically improved malaria diagnosis and consequently reduced the malaria burden in Botswana. The study identified a need to build capacity on microscopy for species identification, parasite quantification and guiding treatment choices.

Botswana has made extraordinary progress in the fight against malaria along the elimination continuum, with overall national malaria incidence falling dramatically by 79%, from 136 cases per 1000 population in 2000 to 29/1000 in 2015, and mortality declining by 57%, from 1069 deaths in 2003 to 462 deaths in 2015.[1] Malaria transmission in Botswana is highly seasonal and unstable, occurring primarily between November and May during the rainy season, and is highly heterogeneous, with transmission primarily seen in the northern and eastern parts of the country.[2] The main vector is *Anopheles arabiensis,* which is widespread across the country. Some members of the *An. funestus* group have also been reported in Botswana.[3] Most rainfall occurs in the northern regions of the country. Over the last decade, the Government of Botswana, through the National Malaria Programme (NMP), has further advanced the goal of reducing morbidity and mortality through the implementation of intensified malaria interventions.[4]

Effective case management remains one of the key interventions for malaria elimination in Botswana. Health workers are trained annually on malaria case management to ensure accurate diagnosis and treatment of identified cases.[3] Health facilities in Botswana still report unconfirmed cases, however, which are treated with artemisinin-based combination therapies (ACTs).[2] This practice can be a major challenge in an elimination programme, because it is important to know whether patients are still harbouring the parasite and are appropriately treated to prevent secondary infections. Accurate diagnosis is therefore key to defining these patients; the training has not, however, been evaluated for efficiency.

Malaria elimination requires that all infections are promptly detected using quality-assured diagnostics, and that they are subsequently treated with ACTs. According to the World Health Organization (WHO) malaria report for 2015,[1] all countries in the African region have adopted either artesunate-amodiaquine (AS/AQ) or arthemether-lumenfantrine (AL) as their first-line treatment policy. While the therapeutic efficacy of both treatments remains high, with a median treatment failure rate of less than 10% observed for both treatments,[1] increased costs and the potential development of strains of *Plasmodium falciparum* resistant to ACTs have resulted in a more careful approach to their use, and it is recommended that ACTs be limited to laboratory-confirmed malaria cases only.

In 2010, the WHO recommended that all patients with suspected malaria undergo serum microscopy or malaria rapid diagnostic testing (RDT), and that only those with a positive result be treated. This was based upon research that showed that as the malaria burden decreases, so does the proportion of fevers due to malaria.[5] The treatment of non-confirmed uncomplicated malaria should be considered only when a parasitological diagnosis is inaccessible or in the event that the results will not be available within <2 h of the patient presenting to a health facility.[6]

Microscopy remains the gold standard for malaria diagnosis, and can be used in peripheral settings with trained and skilled staff. The use of RDT, however, has been embraced in most parts of Africa where malaria is a challenge, as it requires less training and can be used by health care providers at peripheral health facilities and at community levels. The use of RDT is not

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without obstacles, however, as it can only detect parasites within a certain threshold limit, making it less useful in elimination settings where parasites are present in very low densities. In such settings, more sensitive diagnostic methods for the detection and speciation of parasites, such as polymerase chain reaction (PCR), should be considered, although these methods are expensive and require highly skilled staff. This was illustrated in a study conducted on factoring quality laboratory diagnosis into the malaria control agenda for sub-Saharan Africa, which found difficulties in diagnostic testing, including a shortage of skilled workers, inadequate health systems infrastructure and lack of political will.[7] A coordinated approach in offering pre-service clinical and laboratory training together with systems that support scale-up of laboratory services could provide the means not only for effective malaria case management but also for management of non-malaria febrile illnesses, disease surveillance and accurate control programme evaluations.[8]

Another study from Namibia showed that the distribution of RDT in 2005 led to more accurate diagnosis, which explained the sharp decline in malaria cases beginning in 2006.[9] The study indicated, however, that personnel training and supervision in the use of these tests remained problematic. On the issue of excessive use of ACTs in treating clinical cases of malaria, a study conducted in Uganda on the use of RDT to improve malaria diagnosis and fever case management at primary health care facilities resulted in a two-fold decrease in antimalarial drug prescriptions at lower-level health care facilities.[10] The study also demonstrated that RDT use can lead to better targeting of malaria treatment. Finally, a study undertaken in Cote d'Ivoire on the willingness to use RDT for malaria demonstrated that its effective use showed promise to further enhance the control and elimination of malaria, particularly in rural areas where health services are insufficient.[11]

No studies have been completed to date in Botswana to quantify the extent of correct malaria diagnosis and treatment. Limited studies have been undertaken elsewhere on malaria case management in similar elimination settings. The present study focused on determining the proportion of cases treated for malaria and whether they were confirmed by RDT and/or microscopy. This was accomplished through 1) a review of available Integrated Disease Surveillance and Response (IDSR) programme data during 2008–2014 to identify the trends of malaria case reporting, and 2) a review of the Case Based Surveillance (CBS) systems data during 2013–2014 to assess the characteristics of patients presenting with malaria and confirmed by RDT and/or microscopy in the three districts with the highest rates of malaria transmission in Botswana.

METHODOLOGY

General setting

Botswana is a semi-arid, land-locked country that borders Zambia, Namibia, Zimbabwe and South Africa, and has a surface area of approximately 582 000 km^2. The estimated population is approximately 2.1 million.[12] Over the last decade, the Government of Botswana has further advanced the goal of reducing morbidity and mortality secondary to malaria through the implementation of intensified interventions. A significant decrease in malaria cases was observed in Botswana between 2000 and 2012, indicated by a drop in incidence from 0.99% to 0.01% and a decline in deaths attributed to malaria from 12 to 3 per year.[13] With this achievement, a new goal was set to achieve zero local malaria transmission by 2018. This requires implementation of intensified malaria interventions, including diagnostic and therapeutic services.[2]

Botswana has embraced the Universal Health Coverage principles.[4] Nationally, 95% of the total population (89% of the rural population) live within 8 km of a health facility. The public sector is the predominant provider of health care services, serving more than 80% of the population. In the public sector, patients only pay a nominal fee for general health services, including for malaria diagnosis and treatment services.[14] The revised national health policy (2011) places emphasis on health systems strengthening through the integration and coordination of existing policies for the improvement of performance, including malaria management.[4]

Study design

This was a retrospective descriptive study using routine aggregated programme data for patients presenting with possible malaria at health facilities in three target districts.

Study sites

Of the 29 districts in Botswana, only six (Okavango, Ngami, Chobe, Tutume, Boteti and Bobirwa) still report significant cases of malaria.[2] This study was conducted in the three districts with the highest transmission, Okavango, Ngami and Chobe, which report approximately 70% of total annual national malaria cases.

Malaria case management in Botswana

In 2010, Botswana changed its case management policy to align with the WHO recommendations. The diagnosis of uncomplicated malaria is based on a history of fever, with a high index of suspicion for malaria confirmed by RDT or microscopy in the absence of signs of severe malaria and having excluded other possible causes of acute febrile illness. Early detection, correct diagnosis and treatment are key. The diagnosis of malaria is based on clinical criteria (clinical diagnosis) and confirmed by the detection of parasites in the blood (parasitological diagnosis). The first-line treatment of uncomplicated malaria is AL, an ACT that is given together with a single dose of primaquine (0.25 mg/kg) to all *P. falciparum* cases except for pregnant and lactating mothers and children aged <6 months. Parenteral artesunate is recommended for treating severe malaria. Furthermore, since the country embarked on malaria elimination, guidance has been provided for the confirmation of all RDT-positive malaria cases through microscopy, in line with the elimination standards.[15] The RDT used during this study was Paracheck Pf® (Orchid

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Conflicts of interest: none declared.

TABLE 1 Number of cases of malaria reported in Botswana, 2008–2013

Year	Unconfirmed diagnosis *n*	Confirmed diagnosis *n* (%)	Total *n*
2008	17 886	1 201 (6)	19 087
2009	14 878	885 (6)	15 763
2010	12 196	1 046 (8)	13 242
2011	1 141	432 (28)	1 573
2012	115	193 (63)	308
2013	58	456 (89)	514
2014	139	1 341 (91)	1 480

Biomedical Systems, Verna, Goa, India), which has a parasite detection score of 95.9% for *P. falciparum* and 98% for *P. vivax*.[16]

In Botswana, health worker training on accurate malaria diagnosis and treatment is provided annually. Health facilities nevertheless still report high numbers of cases diagnosed via RDT compared to blood smear microscopy, and some cases are unconfirmed and treated with ACTs. This practice can be a major challenge in an elimination programme, where confirmation and accurate treatment of all cases is mandatory and should reflect the true malaria burden to inform intervention targeting in the transmission foci. Good case management also delays the overall development of resistance to ACTs and reduces government spending on malaria.[17]

Data sources

Nationally, data on malaria diagnosis, laboratory confirmation and treatment are collected at health facility level, compiled at district level and forwarded to the national level. These data are housed in the IDSR and the CBS systems. The CBS is a patient-level, malaria specific database implemented in 2012 as part of the goal to achieve malaria elimination, while the IDSR is an aggregated general surveillance system that contains malaria case reports.

The 2008–2013 IDSR data and 2013–2014 CBS data were utilised in this study; data variables were extracted from both databases. During 2008–2014, 50 487 cases of malaria were reported in Botswana; the number of cases diagnosed using RDTs and/or blood microscopy improved from 6% in 2008 to 89% in 2013. This study showed that the use of malaria diagnostic tests improved malaria diagnosis and reduced the number of reported clinical cases (which previously included presumptive and confirmed cases).

Analysis and statistics

Descriptive statistics were used to generate frequencies, percentages and means. The selected data were entered into EpiData v.3.1, and analysis was conducted using EpiData Analysis v. 2.2.2.182 (EpiData Association, Odense, Denmark).

Ethical approval

The Botswana Ministry of Health Research and Development Unit (Gaborone, Botswana) approved the study. Approval and clearance were also obtained from the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease (Paris, France) and the Médecins Sans Frontières Ethics Review Committee (Brussels, Belgium).

RESULTS

During the study period, from 2008 to 2014, 50 487 cases of malaria were reported in Botswana (Table 1). In 2008, only 6% of cases were laboratory-confirmed by RDT or blood microscopy, but by 2013 this had improved to 89%. During the study period, 74% of all cases were reported from three districts: Okavango, Ngami and Chobe. The total number of diagnosed malaria cases decreased by 97% between 2008 and 2014 (Figure).

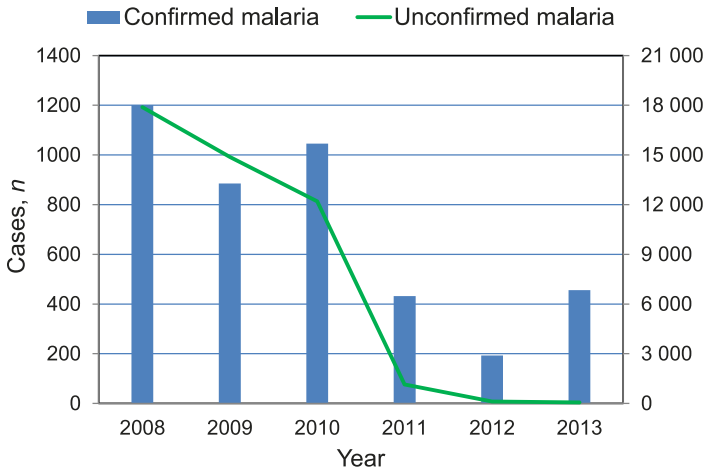

FIGURE Number of malaria cases reported, unconfirmed vs. confirmed, in Ngami, Chobe, and Okavango districts, Botswana, 2008–2013. Unconfirmed = diagnosis based on clinical history and clinical examination alone; confirmed = diagnosis made by rapid diagnostic test and/or blood smear examination.

In 2013, there was a 67% increase in reported malaria cases compared with 2012, while the frequency of laboratory confirmation of malaria diagnoses improved by another 26% (Table 1).

In the districts of Okavango, Ngami and Chobe, 884 cases of malaria were diagnosed in 2013 and 2014, 60% of whom were female. The median age was 17 years (interquartile range [IQR] 9–31). Okavango was the highest reporting district, with 72% of reported malaria cases.

Looking specifically at the use of RDT vs. blood microscopy for laboratory confirmation, there was a trend toward using the latter less frequently (Table 2). Blood smear was used in 10% of cases in 2013 compared to 3% in 2014. Clinical diagnosis alone, without laboratory confirmation, was consistently low, with only eight cases reported for 2013–2014 among the three high-risk districts. During 2013–2014, the majority of cases (59%) in Okavango, Ngami and Chobe districts were diagnosed in a clinic as opposed to a health post or hospital setting (Table 3).

DISCUSSION

The current study reviewed programme data at the national level and in three high malaria transmission districts in Botswana, analysing patterns of malaria diagnosis and treatment before and after the scale-up of RDT to all health facilities. Our investigation reveals for the first time the extent to which malaria cases in Botswana received treatment based on test results (RDT and/or

TABLE 2 Number of malaria cases diagnosed by laboratory test vs. clinical diagnosis in Okavango, Ngami and Chobe Districts, Botswana, 2013–2014

Year	Clinical diagnosis *n*	Rapid diagnostic test *n*	Blood smear *n*
2013	3	192	22
2014	5	683	24

TABLE 3 Proportion of reported malaria cases diagnosed by health facility type in Okavango, Ngami and Chobe districts, 2013–2014

Health facility	Cases (n = 821) n (%)
Health post	288 (35)
Out-patient clinic	486 (59)
Hospital	47 (6)

blood smear) or clinical impression alone. A key component in malaria elimination is the use of confirmation testing for all cases before treatment is initiated.

Our findings show a sharp decline in clinical malaria cases, from 19 087 in 2008 to 514 in 2013, most likely attributable to the shift in the case definition for elimination, which defines a malaria case as a person in whom, regardless of the presence or absence of clinical symptoms, malaria parasites should have been confirmed by quality controlled laboratory diagnosis. In 2010, the Ministry of Health implemented a laboratory-based diagnosis policy that emphasised that all patients with suspected malaria should have parasitological confirmation before treatment.[5] Blood slide microscopy is performed for all patients with suspected malaria, and, where microscopy is not available, RDT is performed. The implementation of this diagnostic policy change and roll-out of RDT was likely the key driver in the 93% decrease in the total number of malaria cases reported between 2008 and 2013. It would therefore appear that the most plausible reason for the significant decrease in the malaria burden in Botswana was the ability to make the correct diagnosis.

Reviewing the data from the three high-risk malaria districts in 2013–2014, the majority of patients were diagnosed by RDT (94%), with very few cases diagnosed by blood smear (6%). It is also of note that, in these districts, patients were much more likely to be diagnosed with malaria at an out-patient clinic (59%) or health post (35%). These findings are consistent with the recommendation that RDT should be the diagnostic tool of choice in these settings.

A significant challenge remains, however, as the number of cases diagnosed by microscopy fell to 3% in 2014 compared to 10% in 2013, despite the recommendation that all positive RDT results undergo confirmatory blood smear for species identification and parasite quantification and to guide treatment choices. There is thus a huge gap in diagnostic compliance between those patients receiving only RDT laboratory screening and those receiving confirmation by blood smear. Gaps in diagnostic compliance may make it difficult to interrupt the malaria transmission cycle, and are likely to impact malaria elimination going forward.

Our study found that the majority of cases (74%) were from three districts: Okavango, Ngami and Chobe. This suggests that focusing future programme efforts on these districts would be most beneficial. Our findings therefore contribute to the body of knowledge on understanding systematic, evidence-based malaria diagnosis and treatment.

Finally, the findings emphasise the need for Botswana to build further capacity, particularly on laboratory services, to strengthen the diagnosis of malaria. The importance of training of health workers at all levels in the preparation and interpretation of RDT and blood smear microscopy should be intensified, including a laboratory quality-assurance system with high-quality diagnostics that pick up all cases. As the number of cases decreases, new recommended diagnostic methods that can be performed at certain levels of the referral system should be implemented.[7]

The strengths of this study are that it is the first in-depth review of trends in malaria testing and treatment in Botswana based on malaria case reports from 2008 to 2014. We utilised routine programme data from two sources, the IDSR and CBS systems. Programme data were compiled and analysed to gain insights into the realities of malaria diagnosis and treatment. Furthermore, by selecting the most affected districts in Botswana, the risk of methodological bias was limited.

Study limitations include the use of retrospective programme data, which has been reported to have inherent challenges.[2] Furthermore, data were sourced from two different malaria reporting systems, which have been noted to have incongruences.[18] Data prior to 2012 would have been useful to better understand trends in testing and treating by health workers across the three levels of health facilities. Finally, no data were available from the private health facilities, which make up a small, but important portion of the health sector.

In conclusion, we found that increased use of malaria testing reduced the number of clinically diagnosed cases and likely contributed to the overall decrease in the reported malaria burden for Botswana. There remains, however, a significant gap in the frequency of microscopy-confirmed malaria cases. To achieve the goal of malaria elimination in Botswana, it will be crucial for all RDT-positive cases to be confirmed by microscopy for species identification, parasite quantification and for guiding treatment choices.

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Contexte : L'élimination du paludisme requiert la détection des infections grâce à des diagnostics de qualité garantie et à des traitements appropriés. Le Botswana évolue vers l'élimination du paludisme, mais des déclarations de cas non confirmés pourraient compromettre cet effort. Cette étude a visé à déterminer la proportion de cas traités pour paludisme et confirmés par des tests de diagnostic rapide (RDT) et/ou microscopie.
Méthodes : Etude rétrospective descriptive qui a utilisé les données nationales de routine des systèmes de surveillance intégrée des maladies et de surveillance basée sur les cas de 2008 à 2014. Les données ont été classées en cas cliniques et confirmés chaque année. Une analyse des données des cas enregistrés dans trois districts déclarant environ 70% des cas de paludisme a été réalisée et stratifiée par année, par type de structure de santé et par méthode de diagnostic.
Résultats : En 2008–2014, il y a eu 50 487 cas de paludisme déclarés au Botswana et les cas confirmés par RDT et/ou la microscopie se sont améliorés de 6% en 2008 à 89% en 2013. De plus, le nombre total de cas a chuté de 97% dans la même période, puis est remonté de 41% en 2013.
Conclusion : Cette étude a montré que l'utilisation des tests de diagnostic du paludisme avaient considérablement amélioré le diagnostic et avaient par conséquent réduit le fardeau du paludisme au Botswana. L'étude a identifié un besoin de renforcement des capacités en matière de microscopie pour l'identification des espèces et la quantification des parasites et pour guider le choix des traitements.

Marco de referencia: La eliminación del paludismo exige detectar el parasitismo con medios diagnósticos de calidad garantizada y administrar esquemas terapéuticos apropiados. Botswana avanza hacia la eliminación del paludismo, pero los informes de casos no confirmados pueden poner en peligro este esfuerzo. En el presente estudio se determinó la proporción de casos tratados por paludismo, con confirmación diagnóstica mediante pruebas de diagnóstico rápido, examen microscópico o ambos.
Métodos: Un estudio retrospectivo descriptivo a partir de los datos corrientes de ámbito nacional de los Sistemas de Vigilancia Integrada de Enfermedades y de Vigilancia Basada en los Casos, del 2008 al 2014. Los datos se categorizaron en casos clínicos y casos confirmados cada año. Se realizó un análisis de datos de los casos registrados en tres distritos que notifican alrededor del 70% de los casos de paludismo, estratificados por año, tipo de establecimiento de salud que notificaba y método diagnóstico.
Resultados: Del 2008 al 2014 se notificaron 50 487 casos de paludismo en Botswana y la proporción de casos confirmados mediante pruebas rápidas o examen microscópico de muestras sanguíneas aumentó del 6% en el 2008 al 89% en el 2013. Además, el número total de casos disminuyó un 97% durante el mismo período y luego aumentó de nuevo un 41% en el 2013.
Conclusión: El presente estudio puso de manifiesto que las pruebas diagnósticas del paludismo mejoraron de manera notable el diagnóstico y con ello disminuyeron la carga de morbilidad por paludismo en Botswana. El estudio reveló la necesidad de fortalecer la capacidad en materia de microscopia con el fin identificar la especie, cuantificar los parásitos y orientar las opciones terapéuticas.

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