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Spatiotemporal dynamics of malaria in Zanzibar, 2015–2020

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ABSTRACT

Background Despite high coverage of malaria interventions, malaria elimination in Zanzibar remains elusive, with the annual number of cases increasing gradually over the last 3 years.

Objective The aims of the study were to (1) assess the spatiotemporal dynamics of malaria in Zanzibar between 2015 and 2020 and (2) identify malaria hotspots that would allow Zanzibar to develop an epidemiological stratification for more effective and granular intervention targeting.

Methods In this study, we analysed data routinely collected by Zanzibar's Malaria Case Notification (MCN) system. The system collects sociodemographic and epidemiological data from all malaria cases. Cases are passively detected at health facilities (ie, primary index cases) and through case follow-up and reactive case detection (ie, secondary cases). Analyses were performed to identify the spatial heterogeneity of case reporting at shehia (ward) level during transmission seasons.

Results From 1 January 2015 to 30 April 2020, the MCN system reported 22 686 index cases. Number of cases reported showed a declining trends from 2015 to 2016, followed by an increase from 2017 to 2020. More than 40% of cases had a travel history outside Zanzibar in the month prior to testing positive for malaria. The proportion of followed up index cases was approximately 70% for all years. Out of 387 shehias, 79 (20.4%) were identified as malaria hotspots in any given year; these hotspots reported 52% of all index cases during the study period. Of the 79 hotspot shehias, 12 were hotspots in more than 4 years, that is, considered temporally stable, reporting 14.5% of all index cases.

Conclusions Our findings confirm that the scale-up of malaria interventions has greatly reduced malaria transmission in Zanzibar since 2006. Analyses identified hotspots, some of which were stable across multiple years. Malaria efforts should progress from a universal intervention coverage approach to an approach that is more tailored to a select number of hotspot shehias.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ To progress towards malaria elimination, malaria-endemic countries require developing and operationalising surveillance systems and approaches that allow them to routinely monitor the spatiotemporal dynamics of malaria so that clusters of cases (ie, malaria hotspots) can be—ideally, preemptively—identified, and interventions can be targeted more effectively to mitigate any expansion of those initial clusters.

WHAT THIS STUDY ADDS

⇒ Using routinely collected data from Zanzibar's Malaria Case Notification system, we analysed the spatiotemporal distribution of all health facility confirmed malaria cases reported in Zanzibar, identified malaria hotspots, characterised the hotspots' temporal stability, as well as quantified how much they contribute to overall reported case counts.

⇒ Of Zanzibar's shehias (wards), 20.4% were identified as malaria hotspots in any given year between 2015 and 2020; these hotspots reported 52% of all primary index cases during the study period. Of the 79 hotspot shehias, 12 (3.1% of all shehias) were considered temporally stable, reporting 14.5% of all index cases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Malaria hotspots in the Zanzibar malaria elimination setting were successfully identified, with hotspots disproportionally contributing to Zanzibar's malaria case count.

⇒ Targeting these hotspots with intensified malaria interventions would represent a more effective allocation of programmatic resources and more likely result in greater reductions in malaria transmission—a key prerequisite for Zanzibar and other countries to further progress towards malaria elimination.

INTRODUCTION

Malaria remains a major global public health concern, with an estimated 241 million malaria cases and 627 000 deaths reported across 87 endemic countries in 2020.[1] From 2003 onwards, the Zanzibar Malaria Elimination Program (ZAMEP) gradually introduced and scaled up rapid diagnostic tests (RDTs), artemisinin combination therapies

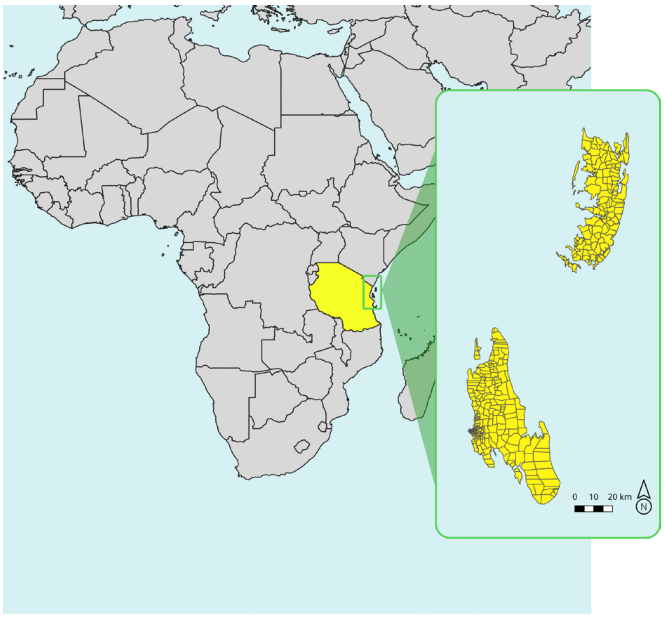

Figure 1 Geographical location of Zanzibar Archipelago, including the main islands Pemba (northern island) and Unguja (southern island).

(ACTs), intensive vector control (long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS)) and case-based surveillance, all of which resulted in a large decline of malaria cases and deaths. Thus, malaria prevalence in children under 5 years of age decreased from 40% before 2002 to less than 1% in 2007/2008, and has remained at those low levels ever since.[2–4] Nonetheless, despite the continued high coverage of malaria interventions, malaria elimination in Zanzibar remains elusive: from 2015 to 2020, the annual number of reported malaria cases and malaria incidence have gradually increased, the annual number of severe malaria admissions increased from 89 to 606, and the annual number of malaria-related deaths increased from 1 to 20.[5] The reasons for this resurgence are likely due to a combination of factors, including residual transmission with more outdoor rather than indoor biting mosquito vectors[6]; asymptomatic (and undetected) malaria infections in the community that remain a possible source for local transmission[7]; fluctuations in travel-associated malaria; insecticide resistance in mosquito vectors that affect the efficacy of LLINs and IRS; and a variability in environmental factors important for mosquito and parasite reproduction and survival.[4 8] ZAMEP currently allocates resources in response to malaria case numbers crossing set shehia-level outbreak thresholds, regardless if cases are travel-associated (and thus possibly imported) or not (ie, are autochthonous).

As countries progress towards malaria elimination, strengthening malaria surveillance systems and using the data collected through these systems to better understand malaria transmission dynamics at a more granular spatiotemporal scale becomes increasingly important.[9] Spatiotemporal heterogeneity in transmission dynamics is likely to occur in elimination settings, with certain locations having no or very little transmission, and other locations (so-called 'hotspots') experiencing comparatively high transmission. Stresman *et al*[10] defined malaria hotspots as areas 'where transmission intensity exceeds the average level', adding that hotspots are, typically, <1 km^2 in size and are often within a focus of active malaria transmission. Furthermore, they argued that a hotspot that is conducive of transmission across both dry and rainy seasons is stable (rather than unstable), and thus should be able to be detected across time. It is assumed that these hotspots disproportionally contribute to maintaining ongoing transmission and that targeting them will achieve greater impact as well as maximise available resource allocation. Consequently, proactively identifying hotspots and characterising whether these hotspots persist over time may help in stratifying Zanzibar epidemiologically, to then determine the level and type of interventions, as well as the amount of programmatic and financial resources that are needed to progress towards malaria elimination.

The objectives of the analyses presented here were to: (1) describe the spatiotemporal dynamics of malaria in Zanzibar between 2015 and 2020 using routinely collected case-based malaria surveillance data and (2) by applying a comparatively simple statistical approach, identify malaria hotspots that would allow ZAMEP and stakeholders to develop an epidemiological stratification for more effective and granular targeting of malaria interventions, thereby maximising programmatic resource allocations.

METHODS

Study setting

The archipelago of Zanzibar is located between longitudes 39.19793 and latitudes −6.16394, 25–50 km off the east coast of the Tanzania mainland in the Indian Ocean (figure 1). There are two main islands, Pemba and Unguja, which cover a total land area of 2461 km^2 and have an estimated population of 1 717 608 people. Zanzibar comprises 11 districts, which are subdivided into 387 shehias, 258 of which are on Unguja and 129 are on Pemba. Shehias are akin to wards and Zanzibar's lowest administrative unit, where many of the public services are planned, managed and implemented, including for health and malaria.

Zanzibar's climate is characterised by two main rainfall seasons: a primary (March–May, called masika) and a secondary (November–January, called vuli) season; rainfall is at its lowest in July. Both rainfall seasons are followed by peak malaria transmission seasons, with the highest malaria case count typically observed in the March–May rainfall season.

Study design and data collection

Data used in this study had been routinely collected by ZAMEP's Malaria Case Notification (MCN) system between 1 January 2015 and 30 April 2020. The MCN

system was established in 2012 to electronically collect detailed sociodemographic, epidemiological and malaria intervention data from all malaria cases in Zanzibar in order to inform programmatic decision-making—both for cases passively diagnosed by microscopy or RDTs at health facility level (defined as primary index cases), as well as cases diagnosed by RDTs during case follow-up and reactive case detection (RACD) activities at household level (defined as secondary cases). By 2014, the system had been progressively scaled up to cover all 189 public and 124 private health facilities on Pemba and Unguja.

Suspected malaria cases access health facilities, where they get tested for malaria. If confirmed as positive, the health provider prescribes ACTs as per national malaria diagnosis and treatment guidelines.[11] Within 24 hours of the index case being detected at facility level, the provider sends an unstructured supplementary service data notification to a central ZAMEP computing server. The notification is forwarded to a District Malaria Surveillance Officer (DMSO), who visits the health facility to confirm the reported index case and collects additional information, including the patient's contact details. Within 48 hours of being notified, the DMSO then follows-up the index case at household level, ensuring they are adhering to prescribed treatment and investigating case details that will inform case classification (eg, whether the case was autochthonous vs possibly imported because of a travel history in the preceding 30 days). DMSOs then use RDTs (in most cases and years the SD Bioline HRP2/pLDH RDT from Standard Diagnostics, Giheung-ku, Republic of Korea, was used) to screen all the index case's additional household members; members with a positive RDT result (ie, secondary cases) are treated with an ACT. Using an electronic, standardised questionnaire that is completed by the DMSO, the case follow-up and RACD data, including for household-based screening and treatment, are linked to each index case through the Coconut surveillance platform (https://coconutsurveillance.org/). The specific variables collected in the questionnaire are individual factors (ie, contact information, age, sex, self-reported history of travel in the last 30 days, self-reported history of fever in the last 2 weeks, RDT positivity and LLIN use the previous night); household factors (ie, number of people residing in the household, number of household LLINs and IRS application in the last 12 months) and geographical factors (ie, household geolocation and weekly rainfall). During the 2015–2020 study period, rainfall data were obtained from 10 meteorological stations managed by Zanzibar's Tanzania Meteorological Agency, with rainfall data measured in millimetres (mm) and recorded daily.

Data analysis

In Zanzibar, malaria transmission occurs throughout the year, and it is characterised by two high-transmission periods after the vuli and masika rainy seasons. The duration of each high-transmission season, as well as the following low-transmission season, varies among the years due to precipitation patterns. To identify the exact duration of each transmission season during the 2015–2020 study period, we used the change point analysis technique to analyse the weekly trend of reported malaria cases.[12] This technique enables to divide times series by identifying those points in time (ie, change points) when substantial changes occur in a data trend. The change points identified by the analysis were used to estimate the duration of each malaria transmission season throughout any given study year.

The spatial pattern of malaria index cases during each transmission season from 2015 to 2020 was assessed using the Global Moran's I to identify the presence of spatial autocorrelation. The Getis-Ord G_i^* local spatial clustering test was used to identify shehia-level hotspots of malaria cases[13 14]; shehia was used as the geographical unit to define hotspots, since it is the lowest administrative unit at which programmatic decision-making occurs. The significance of the computed G_i^* was estimated by comparing observed values to the random case distribution (null hypothesis) by randomly reassigning the weekly cases to the shehias. The statistical significance calculation was based on 100 000 Monte Carlo randomisations ($p<0.05$, with Bonferroni correction). The G_i^* was also used to evaluate the spatial pattern of all reported cases, cases with travel history outside Zanzibar during the previous 30 days, and cases that reported no travels outside and inside Zanzibar. A Kendall's concordance coefficient (W) was calculated to investigate the spatiotemporal overlap of hotspots from 2015 to 2020.[15] Kendall's W measures concordance between two datasets, ranging from+1 (complete agreement) to −1 (no agreement). We considered Kendall's $W<0.4$ as low spatial overlap, $0.4\geq W< 0.6$ as moderate spatial overlap, $0.6\geq W<0.8$ good spatial overlap and $W\geq 0.8$ as very good spatial overlap when comparing spatiotemporal distribution of hotspots.[15] The relationship between reported cases and rainfall was evaluated using the autocorrelation function.[16] Analyses were performed in R language,[17] with spatial analyses using the functions of the *spdep*, *maptools* and *rgdal* packages[18]; maps were created using QGIS GIS software.[19]

Definition of indicators

Based on the G_i^*, hotspot shehias were defined as shehias with a statistically significant higher number of malaria index cases compared with their neighbouring shehias in any given transmission season. We defined hotspot shehias as temporally stable, if during the 5-year study period, they were classified as hotspots either during the high or low transmission season for at least four out of the five study years. The probability of finding a positive secondary case (detection rate) was defined as the number of secondary cases detected through case follow-up and RACD of each primary index case. The probability to find a secondary case and its 95% CI was estimated using a logistic regression.

Table 1 Summary of reported index cases from 1 January 2015 to 30 April 2020, in Zanzibar

	2015	2016	2017	2018	2019	2020*
Cases notified by health facilities	4325	3856	4252	5494	6766	6678
No of index cases followed up to health facilities by DMSOs	3745	2596	2940	3647	5747	4011
No of investigated index cases (%)	2592† (69.2)	2096 (80.7)	2081 (70.8)	2736 (75.0)	4259 (74.1)	2630 (65.6)
Median age (years) of investigated index cases	20 (IQR: 11–29)	19 (IQR: 9–28)	21 (IQR: 13–29)	20 (IQR: 11–29)	22 (IQR: 13–31)	23 (IQR: 15–31)
Fraction of investigated index cases who were male (%)	59.3	57.6	62.6	59.3	64.8	69.8
Fraction of investigated index cases reported in Unguja (%)	81.6	69.7	84	77.1	82.9	80.2
No of index cases with travel history outside Zanzibar (%)	1926 (51.4)	1195 (46.0)	1223 (41.6)	1938 (53.1)	3536 (61.5)	1365 (34.0)
No of index cases with travel history within Zanzibar (%)	139 (3.7)	87 (3.4)	87 (3.0)	154 (4.2)	197 (3.4)	220 (5.5)
No of index cases with no travel history outside their shehia (%)	1680 (44.9)	1314 (50.6)	1630 (55.4)	1555 (42.6)	2014 (35.0)	2426 (60.5)
‡Fraction of index cases reported during January–April who have travel history outside Zanzibar	62.7	51.0	55.2	58.6	69.0	35.1
‡Fraction of index cases reported during January–April who have travel history within Zanzibar	4.4	4.9	3.0	4.6	3.0	5.7
Weekly rainfall year in mm (median (IQR))	9.8 (1.9–30.7)	2.9 (0.0–18.3)	15.5 (3.1–72.6)	21.8 (6.9–63.5)	16.6 (2.4–88.9)	10.9 (6.0–12.9)
Weekly rainfall during the masika season in mm, mid-March to May (median (IQR))	52.4 (12.5–96.3)	19.8 (3.7–55.1)	125.6 (62.7–175.7)	56.3 (25.2–129.3)	43.3 (13.3–84.6)	–
Weekly rainfall during the vuli season in mm, November to mid-January (median (IQR))	11.8 (4.5–43.8)	13.3 (2.6–19.3)	19.2 (9.1–66.3)	17.9 (9.9–24.8)	43.8 (15.7–74.4)	–

*Time period 1 January to 30 April.
†Data available from 1 January to 16 September.
‡Calculated to make comparison among all years from 2015 to 2020.
DMSO, District Malaria Surveillance Officer.

RESULTS

Index cases

From 1 January 2015 to 30 April 2020, 31 371 cases were notified by health facilities in Zanzibar, of which 22 686 were followed up at health facility level by DMSOs and reported through the MCN system (called (DMSO) index cases). The number of these index cases showed a declining trend from 2015 to 2016, followed by an increase from 2017 to 2020 (table 1; figures 2 and 3).

Median age of index cases was 21 (IQR: 12–30) years, with 62.8% of cases being male; neither age nor sex ratio significantly varied across study years. Of index cases, 79.9% were reported in Unguja (range across years: 69.7%–84.0%) (table 1). Comparing index cases reported from 1 January to 30 April of each year from 2015 to 2020, 2019 showed the highest number of reported cases. The proportion of index cases that was followed up to household level was 72.2% for all years, with 2016 being highest (80.7%) (table 1).

Among reported index cases over the entire 2015–2020 study period, 11 183 cases (49.3%) had a travel history outside of Zanzibar in the month prior to testing positive for malaria; 10 619 index malaria cases (46.8%) reported no travel inside or outside Zanzibar in the month prior to testing positive for malaria. The proportion of cases who reported travelling outside of Zanzibar prior to confirmatory testing decreased from 2015 to 2017, increased in 2018 and 2019, before decreasing again in 2020. The fraction of malaria index cases with travel history outside Zanzibar reported in Unguja (9876, 57.5%) was higher compared with those reported in Pemba (1395, 33.8%).

Secondary cases

The percentage of tested household members who were malaria positive (secondary cases) showed a declining trend from 2015 to 2020 (table 2). Comparing secondary cases reported from 1 January to 30 April of each year, 2020 showed the lowest number of tested household members who were malaria positive. The probability of finding a secondary case (detection rate) after index case investigation was approximately 0.04 (ie, 1 additional secondary case was detected for every 25 investigated index cases) and was significantly higher during 2015 compared with the other years. The trend of the secondary case detection rate slightly declined from 0.041 in 2016 to 0.030 in 2020.

Malaria transmission seasons and precipitation

Change point analysis identified—based on case counts reported through the MCN—10 distinct periods of malaria transmission across the study period (figure 3). Although these generally aligned with the expected peak transmission seasons following the masika and vuli rainy seasons, the analysis showed how variable the seasons were across

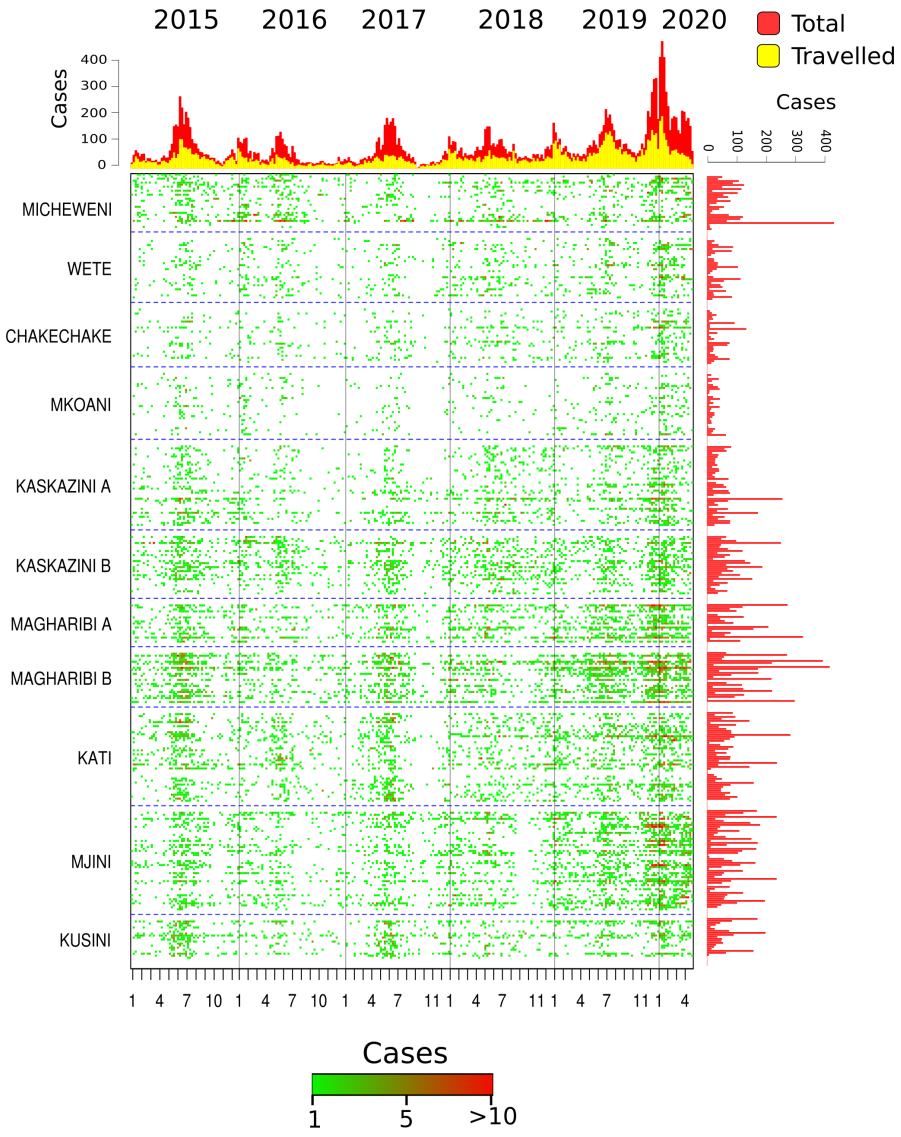

Figure 2 Number of confirmed malaria cases per shehia from 1 January 2015 to 30 April 2020. Each row of the plot represents the time series of reported index cases per week per shehia. The shehias were grouped by district ordered by latitude (from North to South). The image shows the cumulative number of index cases per year split by travel history (top; horizontal) and cumulative number of cases per shehia during the 2015–2020 study period (right; vertical). The numbers on the bottom x-axis represent months.

years, both in terms of onset and duration. From 2015 to 2018, precipitation during the vuli season tended to be lower compared with the masika rainy season. From 2017 to 2020, precipitation increased in both rainy seasons, and in 2019 precipitation during the vuli and masika rainy seasons were similar (table 1). The seasonality of reported index cases was significantly correlated to the amount of precipitation that occurred during the previous rainy season (figures 3 and 4). Cross-correlation analyses showed that the number of index cases had the highest correlations with total precipitation in the 12th and 13th weeks prior to malaria case confirmation (figure 4).

Spatiotemporal dynamics of index cases and identification of hotspots

During peak transmission seasons, Unguja reported more index cases than Pemba (figure 2, online supplemental figures S1 and S2). Additionally, the spatial pattern of the reported index cases on the two islands was different. Most of the index cases reported on Unguja were from shehias in the southern part of the island (figure 2, online supplemental figures S1 and S2). On Pemba, northern shehias reported more cases compared with the rest of the island (figure 2, online supplemental figures S1 and S2). Most of cases that travelled outside Zanzibar were reported in southern Unguja (online supplemental figures S3 and S4). Cases that did not travel inside or outside Zanzibar were mostly reported from shehias in northern Pemba and southern Unguja (online supplemental figures S5 and S6). Of all 387 shehias, 54 (14.0%) did not report any index cases during the entire 2015–2020 study period.

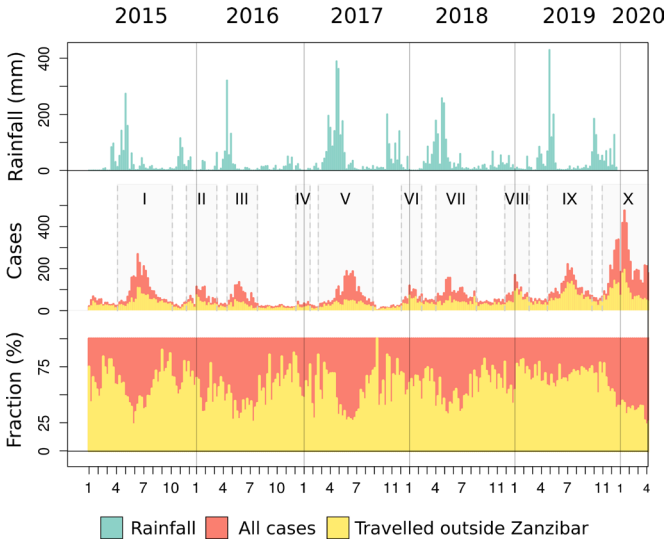

Figure 3 Weekly rainfall and reported malaria index cases in Zanzibar from 1 January 2015 to 30 April 2020. The figure also shows the number and fraction of index cases with travel history outside Zanzibar (yellow bars). The grey boxes indicate the ten high transmission seasons of the study period; transmission seasons were classified using Roman numerals. The numbers on the bottom x-axis represent months.

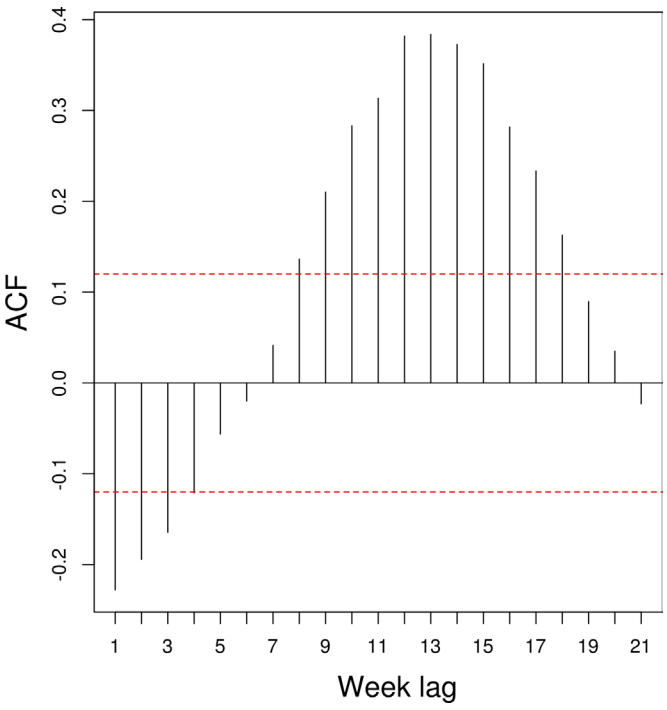

Figure 4 Cross-correlation of weekly reported index cases and weekly precipitation. The black lines passing the red dotted lines are significant correlations, p<0.05.

The results from the spatiotemporal analyses identified shehia hotspots in the north-eastern and the southern part of Unguja during the 2015–2020 study period; hotspot shehias on Pemba were located in the northern part of the island (figure 5, online supplemental figures S1 and S2). In 2019 and 2020, the spatial pattern of index cases reported during the peak transmission season after the masika and vuli rainy seasons (ie, transmission seasons IX and X) were similar (online supplemental figures S1 and S2). In all other years, the transmission season after the masika rainy season was longer compared with the transmission seasons that occurred after the vuli rainy season (online supplemental figures S1 and S2). The spatial analysis showed that—across all transmission seasons—the spatial pattern of all index cases was similar to the pattern shown by index cases reporting no travel, but it was different to the pattern of index cases with a travel history outside Zanzibar. The Kendall agreement test found a slightly higher spatial overlap among all index cases and index cases with no travel history (Kendall's W, mean (MN)= 0.52; IQR=0.46–0.67) compared with index cases with a travel history outside Zanzibar (Kendall's W, M=0.46; IQR=0.29–0.59). Overlap among hotspots across transmission seasons was low when comparing index cases with no travel history and index cases with a travel history outside Zanzibar (Kendall's W, M=0.15; IQR=0.01–0.21) (figure 5).

Across Unguja and Pemba shehias, 64 (24.8%) and 15 (11.6%) shehias were identified as a hotspot in any given year when considering all reported index cases, respectively, that is, reported malaria index cases in either transmission season were observed to significantly cluster spatially and temporally in those shehias. When

Table 2 Summary of reported secondary cases from 1 January 2015 to 30 April 2020, in Zanzibar

	2015	2016	2017	2018	2019	2020*
No of household members tested during index case investigation	11601†	8479	7638	10782	14963	8511
Median age (years) of investigated index cases	–	15 (IQR: 7–25)	16 (IQR: 8–26)	16 (IQR: 7–25)	18 (IQR: 8–28)	17 (IQR: 8–26)
Fraction of index cases who are male (%)	49.7	41.6	43.7	47.4	48.5	53.0
No of positive investigated people (secondary cases) (%)	591† (5.1%)	365 (4.3%)	319 (4.2%)	445 (4.1%)	544 (3.6%)	267 (3.1%)
No of positive investigated people (secondary cases) performed from January to April (%)	169 (6.7%)	167 (4.9%)	74 (4.7%)	164 (4.8%)	177 (5.1%)	267 (3.7%)
Probability to find a secondary case during investigation (95% CI)	0.048† (0.045 to 0.052)	0.041 (0.037 to 0.045)	0.040 (0.036 to 0.044)	0.040 (0.036 to 0.043)	0.035 (0.032 to 0.038)	0.030 (0.027 to 0.034)

*Time period 1 January to 30 April.
†Data available from 1 January to 16 September.

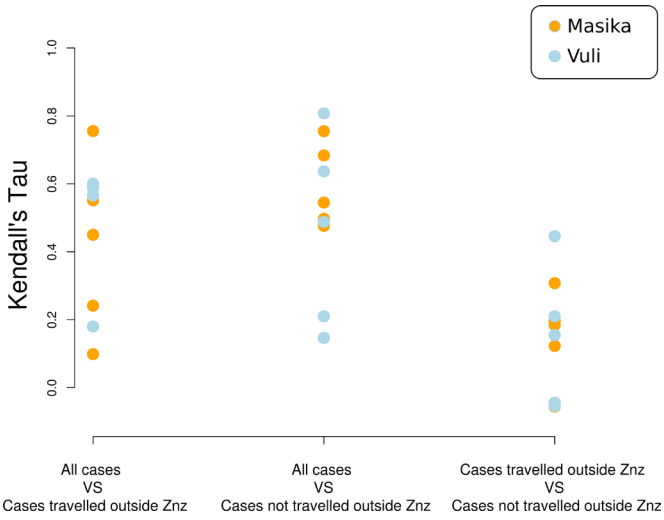

Figure 5 Results of Kendall's agreement test comparing hot-spot spatial pattern of all index cases, index cases with no travel history outside and inside Zanzibar (Znz), and index cases with travel history outside Znz per transmission season. Orange dots represent masika transmission seasons while blue dots represent vuli transmission seasons.

Figure 6 Number of years in which each shehia was identified as hotspot of all reported index cases during peak transmission seasons following the masika (A) and vuli (B) rainy seasons from 1 January 2015 to 30 April 2020. Non-highlighted shehias were not identified as hotspot during the study period as per G_i^* local spatial clustering test . The maps show Zanzibar's major islands: Pemba (northern island) and Unguja (southern island).

the hotspot shehias' temporal stability was examined, it varied greatly between years. Of hotspot shehias, 12 (3.1%) were temporally stable, that is, they were identified as hotpots either during the high or low transmission season for at least 4 out of the five study years (figure 6). The 12 hotspots shehias that were stable reported 3294 (14.5%) of all reported index cases during the study period. Conversely, the 67 shehias that were identified as non-stable hotpots—that is, they were identified as hotpots for <4 years during 2015–2020—contributed to 8519 cases (37.6%) of reported index cases during the study period. The spatial pattern of stable hotspots of all index cases showed a high degree of overlap with those hotspots based on index cases with no travel history (Kendall's W=0.62, p<0.05), compared with those hotspots based on index cases with a travel history outside Zanzibar (Kendall's W=0.47, p<0.05) (figures 6–8).

DISCUSSION

Our analyses confirm the low level of malaria burden in Zanzibar,[2–4] with annual shehia incidence ranging between 0 and 54.5 cases per 1000 population (mean equal to 3.8 cases per 1000) over the 2015–2020 study period. Most of the cases in Zanzibar are passively detected at public or private facilities, with secondary cases detected through RACD being comparatively low: over the entire study period, and bearing in mind the ability of DMSOs to follow-up index cases to household level, the proportion of all cases that were reported through RACD ranged between 4.0% and 13.7% between years, with the probability to detect such a secondary case during RACD ranging from 0.030 to 0.048. We also confirm previous analyses that even in Zanzibar's malaria elimination setting, a significant correlation between monthly rainfall and confirmed malaria diagnosis remains.[2 3 8]

A large proportion of cases (34.0%–61.5% for the entire study period; up to 69.0% in 2019, if reporting is limited to the January–April peak transmission period) have a self-reported history of travel outside of Zanzibar 1 month prior to testing positive for malaria infection.[20] This is within the range of prior mathematical modelling analyses, which—based on mobile phone, transportation and other data—had estimated that 1–12 annual infections per 1000 population were imported.[21 22] Indeed, applying the method used by Cohen *et al*,[23] the reproductive number under control ranges between 0.38 and 0.66, confirming the large contribution of travel-associated malaria to Zanzibar's overall malaria burden, and the generally low malaria receptivity across the archipelago. Currently, no effective approach exists that would allow to quickly and routinely identify those infections that are truly autochthonous versus those that are imported. Whole-of-genome sequencing[24] provides important information on the genetic diversity of circulating parasite populations and can differentiate those infections that are autochthonous versus imported; however, due to infrastructure requirements and cost, this approach is

Figure 7 Number of years in which each shehia was identified hotspot of reported index cases with no travel history outside or inside Zanzibar peak transmission seasons following the masika (A) and vuli (B) rainy seasons from 1 January 2015 to 30 April 2020. Non-highlighted shehias were not identified as hotspot during the study period as G_i^* local spatial clustering test. The maps show Zanzibar's major islands: Pemba (northern island) and Unguja (southern island).

Figure 8 Number of years in which each shehia was identified as hotspot of reported index cases with travel history outside Zanzibar during peak transmission seasons following the masika (A) and vuli (B) rainy seasons from 1 January 2015 to 30 April 2020. Non-highlighted shehias were not identified as hotspot during the study period as per G_i^* local spatial clustering test. The maps show Zanzibar's major islands: Pemba (northern island) and Unguja (southern island).

likely to be only deployed for academic purposes, rather than routinely on a large scale to allow ZAMEP to make programmatic decisions that are timely and responsive to seasonal changes in malaria epidemiology. In the absence of a reliable, timely and sustainable approach to differentiate autochthonous from imported infections, self-reported travel history to a malaria-endemic area is a next best, but imperfect, proxy indicator, which is information that is currently collected by ZAMEP during follow-up of passively detected index cases. At present, for ZAMEP's programmatic purposes, identifying clusters of cases (ie, hotspots) is a priority, regardless of whether cases are autochthonous or imported. This represents the first step in allowing ZAMEP to allocate finite resources where they are most needed, effective, and most likely maximise interventions' impact on malaria transmission and burden, from ensuring enough commodities are available to diagnose and test cases, mobilising DMSOs for case follow-up, to possibly deploying shehia-level interventions. Future analyses with ZAMEP will build on the analyses presented here and will further analyse specific characteristics of stable and unstable hotspots, how travel varies spatially and temporally, how much travel-associated cases are truly imported cases, and how much imported cases contribute to secondary cases and, thus, local transmission.

Studies analysing the spatiotemporal distribution of malaria have traditionally relied on surveys of well-defined at-risk populations,[25–29] but increasingly—as countries' health management information systems have been strengthened—studies have used routine passive case detection[25 26 28–33] to define clusters of malaria risk. These studies reported variable patterns of spatiotemporal clustering. Thus, some studies reported the existence of consistent hotspots,[32 34] while others suggest greater variability.[25 26 28 29] For example, in Ouagadougou, Burkina Faso, the location of clusters identified as high risk varied little across three transmission periods.[32] In contrast, in Kilifi county, Kenya, only two temporally stable hotspots were identified over the 1-year study period, comprising 2.7% of all study households and contributing to 10.8% of all malaria cases confirmed by RDT.[35]

Using passive case detection, our findings support the hypothesis that—in an elimination setting such as Zanzibar—malaria tends to significantly cluster within certain hotspot geographical units.[25 28 29 36–38] Across

Zanzibar's shehias, 79 (20.4%) were identified as a hotspot in any given year, with malaria observed to significantly cluster spatially and temporally. These hotspot shehias contributed disproportionally to the number of reported malaria index cases, with 52% of all index cases during the study period being reported from there. Similarly, in the 12 stable hotspot shehias (ie, 3.1% of all shehias), 14.5% of all index cases were reported. Depending on whether spatial analyses include or exclude travel, the distribution of hotspots does vary (figures 5–7). Thus, northern Pemba shehias were only hotspots when index cases without a travel history were included in the analyses, implying that transmission there was largely autochthonous. Similarly, hotspots in southern Unguja were identified in all spatial analyses, implying that reported malaria cases may be both due to cases associated with travel and autochthonous transmission; whether cases are due to travel-associated cases seeding autochthonous transmission needs further investigation. ZAMEP is currently discussing with the Zanzibar Malaria Elimination Advisory Committee how interventions should differ in hotspot shehias depending on the proportion of cases having a travel history or not.

The use of routinely collected case data through the MCN system does offer the opportunity to detect malaria case clusters down to the shehia, village and household levels at an affordable cost. Interventions tailored and targeted to hotspots have been hypothesised to be highly efficient method in reducing malaria transmission not only inside these hotspots, but also in adjacent geographical areas.[10] While biologically plausible, so far there has been mixed evidence to support this conceptual approach. For example, in Rufiji District on mainland Tanzania, locally tailored and targeted interventions contributed to reduce malaria transmission in hotspot villages.[33] Similarly, on Sabang island, Indonesia, an intensified application of malaria diagnosis, ACTs, LLINs and IRS in hotspot areas contributed to a 30-fold reduction in malaria incidence from 3.18 to 0.13 per 1000 population.[39] In contrast, a trial in western Kenya targeting hotspots with intensified interventions—larviciding, LLINs, IRS and mass drug administration—failed to result in any sustained reduction in malaria transmission in targeted hotspots and failed to impact malaria transmission outside of targeted areas.[40]

For Zanzibar, a number of more aggressive programmatic approaches to reduce malaria transmission in hotspot shehias could be envisaged, including screen and treat strategies, potentially using a more highly sensitive diagnostic test,[41–43] or targeted mass/focal drug administration.[44 45] Since travel-associated malaria represents a large proportion of detected cases, in order to realistically achieve elimination additional interventions targeting travellers, especially prior to high transmission seasons, should be considered, including chemoprophylaxis for anyone travelling from Zanzibar to mainland Tanzania, and mass screening and treatment or presumptive treatment of anyone arriving from the mainland to Zanzibar.[9 46–48] Not addressing travel-associated malaria and reducing its contribution to Zanzibar's malaria burden will prevent Zanzibar to achieve elimination—a conclusion also made by a recent study modelling different malaria intervention scenarios for Zanzibar.[49]

Limitations

A number of potential caveats of our analyses should be highlighted, most of which are due to the fact that we used routinely collected programmatic data from ZAMEP in our analyses and not data from a carefully controlled academic research study. First, malaria testing to identify cases is RDT based, which in the context of Zanzibar is known to have—depending on infections' parasite densities—low to moderate sensitivity[50 51]; consequently, it is likely that low parasitaemia, asymptomatic infections were missed. It is unlikely, however, that such infections would have clustered in a specific spatiotemporal pattern that is different from the findings we report here, and, thus, would unlikely change our findings and conclusions. Second, while we show that almost half of the reported cases are associated with travel, we cannot truly state that these are imported due to the long time period covered by the self-reporting (ie, 30 days prior to being diagnosed with malaria) and the possibility of these cases having been infected locally. Local transmission of malaria does still occur in Zanzibar, as shown by the association of case counts with rainfall, as well as a continued high number of cases in early 2020, when travel volume to mainland Tanzania substantially decreased due to the emerging COVID-19 pandemic. Such phenomenon is not unique to Zanzibar, and has been observed in other malaria island elimination settings, such as Bioko island.[52] To ascertain whether cases with a travel history are truly imported, more advanced approaches such as whole-of-genome sequencing[24] would have to be used, which, however, due to infrastructure requirements and costs is not feasible to do routinely on a large scale. Currently, ZAMEP is not yet differentiating autochthonous from travel-associated (or imported) cases, as discussions on what interventions could be effective in reducing imported malaria are still ongoing. Third, depending on the week, month and year, a range (eg, between 65.6% and 80.7% for any given year) of index cases were followed up and investigated. Most often such variability in case follow-up and investigation is due to DMSO bandwidth availability resulting from a high incidence of malaria cases—the more index cases are detected and reported at health facilities, the more probable it is that DMSO will not be able to follow up all index cases and visit their households. Fourth, we delineated our hotspots to the shehia boundaries, rather than a defined area size (eg, 1 km^2). This was done because shehias are the lowest administrative unit that plan, implement and monitor malaria programming in Zanzibar; any response to an increase in cases would occur at shehia or—depending on the size of the increase—district level. Finally, spatial analyses performed using arbitrary spatial divisions such as shehia

administrative boundaries can be affected by the modifiable areal unit problem.[53 54] For example, cases that were reported at a health facility in a given shehia could stem from households in a different shehia, and therefore, bias shehia-level malaria trends and the identification of hotspots. We mitigated for this specific bias, by assigning primary index cases to a shehia based on the case's household geo-tag rather than the facility where they had been diagnosed. Certainly, the possibility remains, however, that cases got infected outside of their shehia (eg, during travel). We, therefore, are careful to emphasise that identified hotspots represent clusters of reported cases rather than necessarily hotspots of transmission.

CONCLUSION

The scale-up of malaria interventions has greatly reduced malaria transmission in Zanzibar since 2006, with mean annual shehia incidence being 3.8 cases per 1000 over the 2015–2020 study period. In our analyses, we identified 79 (20.5%) of Zanzibar's shehias as malaria hotspots in any given year between 2015 and 2020; 12 of these shehias were considered temporally stable.

The findings presented here demonstrate that data collected through routing testing of febrile patients for malaria, as well as case follow-up and RACD, can help describe malaria epidemiology at small spatial scales. From a programmatic perspective, we recommend that malaria efforts in Zanzibar should progress from an approach that is based on universal coverage of interventions to an approach that is more tailored and nuanced, with resources prioritised and allocated to a select number of geographical units, that is, hotspot shehias. Continued, annual analysis of the MCN data should be able to assess the temporal stability of the hotspots so that—if needed—changes in such prioritised programming can be made; additionally, once adjustment is made for cases that have a reported travel history outside of Zanzibar, hotspots of residual transmission can be identified. Future analyses with ZAMEP will build on the analyses presented here and allow a microstratification of Zanzibar's malaria risk, so that interventions could be tailored to each of the hotspots' characteristics, including travel. Thus, in those shehia hotpots, where the proportion of cases with a history of travel represent most of the reported cases, interventions related to travel (such as social behaviour change communication, chemoprevention, screening people at ports of entry) should be deployed, since they would be more effective than shehia-wide IRS or LLIN distribution. Only then will Zanzibar be able to achieve malaria elimination.

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