Estimating the impact of imported malaria on local transmission in a near elimination setting: a case study from Bhutan

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Summary

Background Bhutan has achieved a substantial reduction in both malaria morbidity and mortality over the last two decades and is aiming for malaria elimination certification in 2025. However, a significant percentage of malaria cases in Bhutan are imported (acquired in another country). The aim of the study was to understand how importation drives local malaria transmission in Bhutan.

Methods Information on geo-located individual-level laboratory-confirmed malaria cases between 2016 and 2020 was obtained from the Bhutan Vector-borne Disease Control Program. Records included the date of diagnosis and treatment, type of cases classified as indigenous or imported, and malaria species. Hawkes Processes were used to study the role of imported malaria in local transmission in Bhutan. We imposed 15 days delay for a mosquito to become infectious in the model.

Findings There were 285 cases during the study period and 58.6% (159) were imported malaria. 71.1% (113) of these imported cases were *Plasmodium vivax* and 73.6% (117) were from India. The model suggested that a person remains infectious for 8 days for *Plasmodium falciparum* malaria but over 19 days for *P. vivax*. The background intensity from imported malaria cases was much greater for *P. vivax* cases (maximum 0.17) resulting in more importations than *P. falciparum* cases (maximum 0.06). However, model fitting suggested that local *P. falciparum* transmission was mainly driven by importations but additional factors such as relapse played a role for *P. vivax*.

Interpretation Imported malaria cases are key drivers of transmission within Bhutan, with most cases since 2016 being *P. vivax*. Control programmes should be devised to target interventions towards the *P. vivax* strain and test those who are more likely to bring in imported malaria cases or acquire it from returning travellers.

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Keywords: Bhutan; Malaria; Elimination; Hawkes processes; Surveillance; Transmission

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Research in context

Evidence before this study

We searched PubMed for articles using the terms "Malaria AND Elimination AND (Importation OR imported) AND role AND transmission AND (local OR indigenous)" without any language restrictions. The search returned 13 published studies on malaria elimination and importation. None of the studies quantified the role of imported malaria on local transmission by malaria species and infectivity period of imported cases.

Added value of this study

This study evaluated the role of imported malaria in driving local cases in Bhutan and measured the infectivity of cases for both *Plasmodium falciparum* and *Plasmodium vivax*. Two high-risk groups of malaria importation were labourers and farmers. Local cases of *P. falciparum* were mostly driven by importation, but cases of *P. vivax* were influenced by other factors (relapse) in addition to imported cases. Imported cases remained infectious for 8 days for *P. falciparum* but over doubled to 19 days for *P. vivax* malaria leading to greater transmissibility. Further, importation was much greater for *P. vivax* cases than for *P. falciparum* cases.

Implications of all the available evidence

The results highlight the role of imported malaria in driving local transmission. They also illustrate the broader impact of importation in elimination efforts. Understanding how local transmission is being driven by importation will help policymakers in devising public health programs including testing and providing preventive measures. Onward transmission can be prevented by more sensitive diagnostics such as PCR and detection of histidine-rich protein 2 (HRP2) antigen (using rapid diagnostic test).

Introduction

The WHO developed the *Global Technical Strategy for Malaria 2016–2030* (GTS), which set a vision to reduce malaria incidence by 45% and 75% by 2020 and 2025, compared to 2015.[1] The WHO strategy is complemented by the Roll Back Malaria advocacy plan, *Action and Investment to Defeat Malaria 2016–2030* (AIM).[2] GTS and AIM set an ambitious global target of eliminating malaria in at least 21 countries by 2020, known as E–2020 countries and 35 countries by 2030.[2,3] However, global targets have been missed in 2022 since there were 249 million cases in 2020 compared to 212 million in 2015.[3] This was attributed to the COVID-19 pandemic.[4] Notwithstanding this hiccup in the global trend, total malaria cases in the 21 E–2020 countries reduced by 79% from 2010 to 2019.[4]

In Bhutan, the focus of this study, a substantial reduction in both malaria morbidity and mortality has been achieved over the last two decades.[5,6] The number of malaria cases has declined by over 99% in 2020 (54 cases) compared to 2000 (5935 cases), although its elimination as per the national plan has not yet succeeded.[7] All malaria cases in Bhutan are classified as either indigenous or local (no history of travel to malaria endemic areas in last two weeks) or imported cases (history of travel to endemic areas two weeks prior to diagnosis of malaria) or introduced (a clear link to an imported case).[8] Imported malaria among Bhutanese are those individuals returning from malaria endemic countries or international migrants. Travellers entering Bhutan, defined as staying overnight, from malaria endemic countries undergo mandatory tests for malaria. In addition, active blood testing is done in targeted high-risk groups such as long-term migrant workers to Bhutan. In the elimination phase when total numbers of malaria cases are declining, transmission tends to occur sporadically within distinct foci.[9–12] These distinct foci are often hard-to-reach areas, including international border and forested areas, where transmission can be at least partly driven by imported malaria cases rather than sustained transmission within the country,[13–20] and Bhutan is no exception to this pattern.[21]

Malaria surveillance systems need to be robust so they can identify the role imported cases versus local transmission is playing in malaria receptive areas.[22,23] However, there are limited methods to identify if cases were driven by imported cases. Traditionally, travel surveys can be used to work out if malaria cases are driven by imported cases, but these are often incomplete. Genetic sequencing of the parasite can be done to determine the transmission patterns; however, this is expensive. Another suggested method is to use Hawkes Processes, which does not require any information about travel history or genetics.[24]

Hawkes Processes[25] are a type of mathematically well-founded point process that have been applied in different areas such as earthquakes[26] and finance.[27] More recently they have been used to model infectious disease transmission including Ebola in the Democratic Republic of Congo,[28] malaria transmission in China and Eswatini,[24] dengue in Australia,[29] invasive meningococcal diseases in Germany[30] and COVID-19 in the United States of America.[31] We think of them as semi-mechanistic because the self-exciting nature of the process captures the disease transmission mechanisms well, whilst enabling the user to encode disease specifics such as the shape of how infectious a person remains through time (similar to serial interval) and the time varying contributions from the importations. Hawkes Processes are uniquely suited to model the spread of disease in areas close to elimination because they use case data rather than prevalence information, which is

hard to estimate in areas of low transmission. These methods have also been found to be robust in circumstances with up to 10% underreporting,[24] which can be a particular issue with malaria, due to asymptomatic transmission and low rates of seeking care. Therefore, the aim of this study was to present a descriptive analysis of malaria transmission in Bhutan and understand the role of importations in driving local malaria transmission using semi-mechanistic Hawes Processes.

Methods

Study area

Bhutan is located in the Eastern Himalayas, bordering China in the north and India in the east, south and west. The country is divided administratively into 20 districts and 205 sub-districts. In 2017, the total population of Bhutan was 681,720.[32] Historically, malaria transmission has occurred in 82 sub-districts of seven districts,[33] with 209,090 people living in these districts (Fig. 1) and the study area comprised mainly in these 82 sub-districts, but some areas within Bhutan.

Data source

In this study, nationwide data on malaria cases were obtained from 2016 to 2020 from the national malaria surveillance system, hosted by the Bhutan Vector-borne Disease Control Program (VDCP). These data contain laboratory-confirmed malaria cases (defined as clinically diagnosed cases with either malaria parasite presence confirmed by microscopy or a positive rapid diagnostic test [RDT] result). The infections were categorised by species: *Plasmodium falciparum* and *Plasmodium vivax*. The malaria cases were defined either as local, introduced or imported: (i) Local cases were defined as having no history of travel to endemic areas in the past 6 months. (ii) Introduced cases were those with a clear link to an imported case (in other words, a secondary infection arising from an imported case in the country). (iii) Imported cases were those with a history of travel to a malaria endemic area up to 6 weeks prior to the current episode of malaria. In the descriptive analysis, local and introduced were classified as local malaria because transmission originated in Bhutan. Information available for the study included: malaria case numbers by sub-district from 2016 to 2020, including introduced and imported cases, and complete information on the date of diagnosis and species. Where information about a case was missing, such as missing location of diagnosis, missing date of onset of fever, and missing date of diagnosis, the case was excluded from the descriptive analysis but imputed in the Hawkes Process analysis.

Population estimates used in this study were from publications from the National Statistical Bureau and the Office of the Census Commissioner of Bhutan.[32] An electronic map of district boundaries in shapefile format was obtained from the DIVA-GIS Areas database (https://www.diva-gis.org/). Adminstrative approval was

Fig. 1: **Imported and local malaria cases in Bhutan, 2015–2020.**

approved vide letter number PPD/admin. CV/(9)/2020-21/172 dated Sept 22, 2021. Ethical approval for this study was obtained from the Research Ethical Board of Health, Bhutan Ministry of Health.

Hawkes Process analysis

Following Unwin and colleagues,[24] we used a Hawkes Processes through the *epiHawkes* R package to model malaria transmission in Bhutan from all the 70 *P. falciparum* cases and 220 *P. vivax* cases that were diagnosed between 2016 and 2020. Our time range was chosen because the proportion of missing data between 2016 and 2020 was 5% while those before 2016 were 44%. Instead of directly estimating the number of infected cases, our model was used to estimate the intensity or force of infection, $\lambda(t)$, through time. The intensity function is a positive function that characterizes the rate at which events happen at a specific point in time. For example, if $\lambda(t)$ was a constant (λ), then the number of infections would follow a Poisson process which is homogenous in time. However, a constant λ is unrealistic, and we paramaterise our $\lambda(t)$ as a self exciting process, where there is a mean changing rate over time which also self excites. Our model was defined as:

$$\lambda(t) = \mu(t) + \sum_{t > t_i + \beta} \alpha * (t - (t_i + \beta)) \exp\left(-\frac{\delta * (t - (t_i + \beta))^2}{2}\right)$$

where $\mu(t)$ is the background intensity from imported malaria cases at time t, $\beta = 15$ is the delay between a mosquito biting an infected human and becoming infectious derived from literature,[34] α controls the intensity from local transmission, δ controls the duration of the infectious period, and i is the case index. Following Unwin and colleagues[24] the background intensity was further specified as a trigonometric function:

$$\mu(t) = \max\left(A + Bt + M\cos\left(\frac{2\pi t}{p}\right) + N\sin\left(\frac{2\pi t}{p}\right), 0\right),$$

where $p = 365.25$ days (the length of a year) and A, B, M and N are constants to be fitted using maximum likelihood estimation.[25] A and B describe a linear trend that control if and how fast the imported malaria cases are declining over time and M and N describe the seasonal fluctuations that occur in this setting.

We fitted temporal models for *P. falciparum* and *P. vivax* separately to the date of onset variables using Maximum Likelihood Estimation, since there was an analytic likelihood.[24] We imputed symptoms onset for cases where no date was recorded assuming a constant fixed delay between date of symptoms onset and date of diagnosis from the complete data. Since Hawkes Processes require unique event times, we uniformly distributed events throughout the day they occurred if there was more than one event on a given day. We initialised the optimisation routine in the *optimx* R package from 10 different start points and selected our final parameters to be the ones with the minimum negative of the log-likelihood where $\alpha > 0$ and $\delta > 0$.

We use goodness of fit tests to evaluate how well the Hawkes Process models fitted the data. First, we considered how the integral of the intensity between 0 and t_i varied with the index of the event, i. Second, we used the time–rescaling theorem that states that the differences in the integrals of the intensity between two subsequent events are independent exponential random variables with mean 1. We used Kolmogorov–Smirnov (KS) tests and quantile–quantile (Q–Q) plots to assess how well our model fits the data. If the data can be represented by a Hawkes Process, the quantiles plotted against the empirical quantiles or cumulative distribution function should closely align within a 45-degree line, ideally within the confidence bounds (as explained by Brown and colleagues[35]).

We then use a thining based simulation method to further evaluate model fit and to estimate the proportion of new cases that were imported.[24] We sampled 10,000 observations from both the full Hawkes Process and just the background intensity (assuming no person-to-person transmission) for both *P. falciparum* and *P. vivax* models. The case reproduction number (R_c), or the number of secondary cases from a primary case, can be estimated using the branching factor of the Hawkes Process

$$R_c = \frac{\alpha}{\delta}.$$

Role of the funding source

There was no funding source for this study.

Results

Descriptive analysis

During the study period (2016–2020), there were 285 malaria cases (both species) and 55.8% (159) were imported cases. Males made up 76.1% (217) of total cases. The age composition of malaria cases was: <13 years (7.4%, 21 cases), 13–18 (6.3%, 18), 19–25 (20.7%, 59), 26–35 (28.1%, 80), 36–45 (14.7%, 42), and >45 (22.8%, 65). The mean age of malaria patients was 33.8 years (SD = 16.8). The two most common occupations were farmers (35.0%, 136) and labourers (32.9%, 128). *P. vivax* constituted 75.4% (215) of cases and 58.6% (167) cases were in Bhutanese nationals (Table 1).

There were 159 (58.6%) imported cases of malaria during the study period. Eighty-seven percent (139) of cases were in men and more than 60% of cases were reported in the age groups of 19–25 years (32.1%, 51) and 26–35 years (30.8%, 49), respectively. The mean age of malaria patients was 30.6 years (SD = 13.2). Labourers

Characteristics	Total (N = 285)		Imported (N = 159)	
	Number	%	Number	%
Sex				
Female	68	23.9	20	12.6
Male	217	76.1	139	87.4
Age: Mean (SD)	33.8 (16.8)		30.6 (13.2)	
Age group (years)				
<13	21	7.4	7	4.4
13–18	18	6.3	9	5.7
19–25	59	20.7	51	32.1
26–35	80	28.1	49	30.8
36–45	42	14.7	21	13.2
>45	65	22.8	22	13.8
Occupation				
Labourers	90	31.6	90	56.6
Farmers	106	37.2	30	18.9
Students	31	10.9	11	6.9
Public servants	10	3.5	6	3.8
Others	48	16.8	22	13.8
Malaria species				
PV	215	75.4	113	71.1
PF	65	22.8	42	26.4
Mixed	5	1.8	4	2.5
Country of origin				
Bhutan	167	58.6	42	26.4
India	118	41.4	117	73.6

PV, *Plasmodium vivax*; PF, *Plasmodium falciparum*.

***Table 1*: Socio-demo characteristics of malaria cases in Bhutan, 2016–2020.**

made up more than 56.6% (90) of the imported cases followed by farmers (17.5%, 30). Again, *P. vivax* was the dominant species 71.1% (113) in imported cases and 73.6% (117) of cases originated from India (Table 1). Imported cases decreased over the years, with the highest number of cases in 2016 with 56 cases and the lowest number (only nine cases) in 2020 (Fig. 1). Both species of malaria had more imported than local cases, except for 2020 (Fig. 2).

The spatial distribution of imported and local malaria cases is shown in Fig. 3. Imported cases were distributed throughout Bhutan, whereas local cases were confined to the southern districts bordering India. This reflects the presence of suitable climatic and environmental conditions for malaria vectors in the southern border districts.

Hawkes Process analysis

The shape of the transmission kernel and the time-varying contribution to the background intensity are shown in Fig. 4. After the imposed 15 days delay for a mosquito to become infectious, our model suggests that a person remains infectious for 8 days for *P. falciparum* malaria (red line) but over double at 19 days for *P. vivax* malaria (blue line) (Fig. 4A). We also found that the background intensity (μ) was much greater for *P. vivax* cases (maximum intensity 0.17, blue line), resulting from more importations than *P. falciparum* cases (maximum intensity 0.06, red line) (Fig. 4B). The case reproduction number for *P. falciparum* malaria was 0.088 whereas it was higher at 0.20 for *P. vivax* malaria.

We see from our Kolmogorov–Smirnov goodness of fit test (Figure S1A) that the fit of the model to the *P. falciparum* data was good and mostly lay within the dashed-line 95% CI, but for *P. vivax* there is a lack of fit for the low quantiles where the points lie outside the confidence bounds (Figure S1B). This pattern is also repeated in the Q–Q plots presented in Figure S1C and D.

From the simulations in Fig. 5A, we see that the *P. falciparum* model fitted the data well because the total case count (red line) from the data lies in the middle of the simulations (black lines). Without fitting to data about whether a case was imported or locally acquired (and just plotting it in the figures), we can see that *P. falciparum* transmission is mainly driven by importations because the blue simulations overlap the black simulations, and the true number of importations (green line) lies within the middle of the simulations. The same trend is also shown in Figures S2A and B, which compares the daily total cases and importations respectively for the *P. falciparum* data (red line) and model simulations (black lines). Although there was good agreement between the *P. vivax* model simulations (black lines) and total case count (red line) in Fig. 5B, the model suggests that a larger proportion of cases was importations (blue lines) than the data suggest (green line). Again, this is seen in the daily cases in Figures S2C and D.

Discussion

In this paper, we use descriptive analysis and semi-mechanistic Hawkes Processes to understand the role of imported malaria cases driving the local transmission in Bhutan. More than half of malaria cases in Bhutan were imported cases during the study period. Model simulations for *P. falciparum* showed agreement between the data and simulations with a low case reproduction number estimate, which suggests that local *P. falciparum* is mainly driven by importation. However, the models did not fit well for *P. vivax*, and there was disagreement between modelled estimates and importation data, which may suggest local cases of *P. vivax* are driven by other factors such as relapse in addition to importation. Relapses would be classified as indigenous transmission because they did not have a travel history but were not caused by new local transmission. The role of relapse in the malaria elimination setting is poorly understood or studied. Therefore, further studies on the relapse phenomenon in the context of local malaria transmission in elimination settings are recommended.

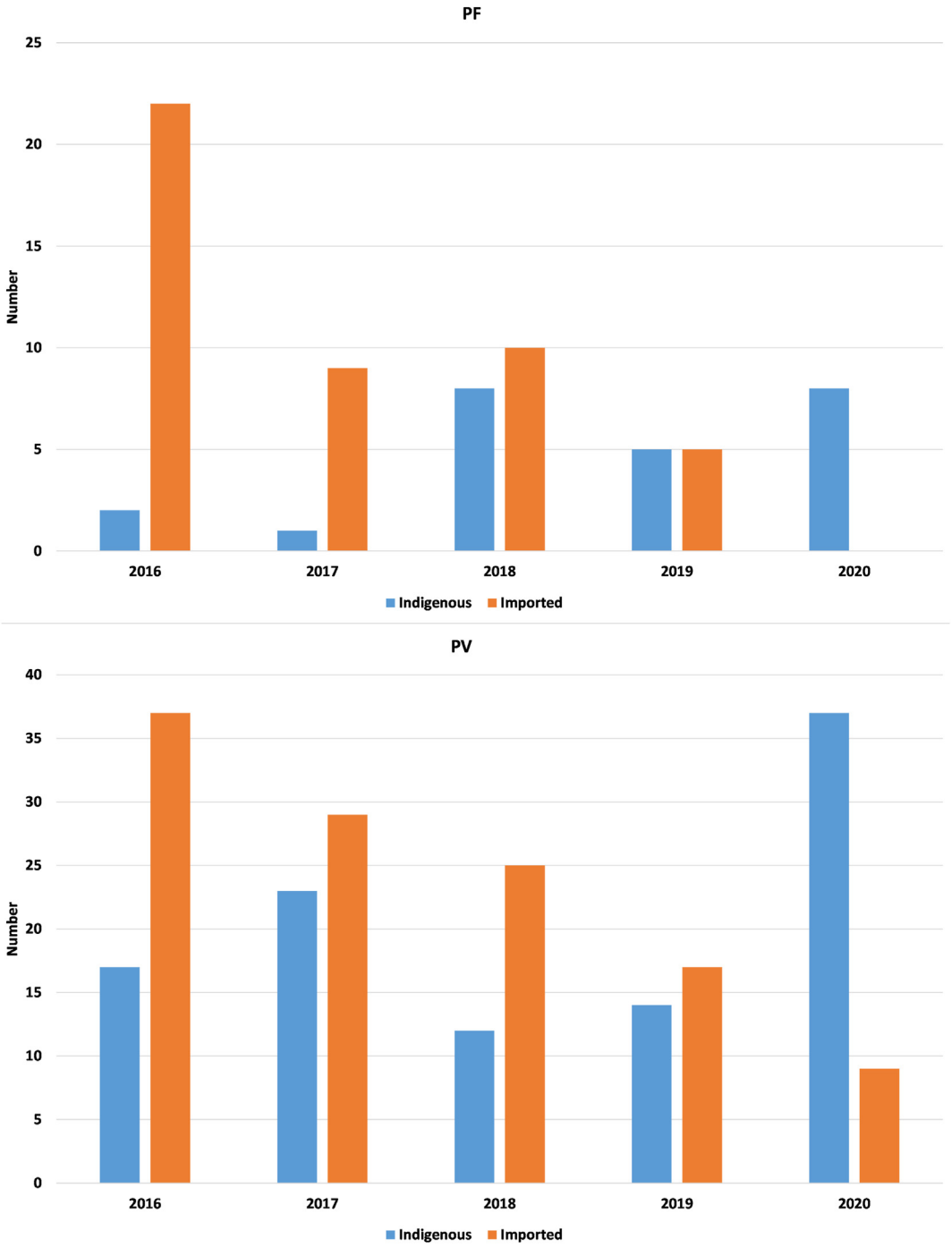

Fig. 2: **Imported and local malaria cases stratified by species, 2015–2020**. PF, *Plasmodium falciparum*; PV, *Plasmodium vivax*.

As the country enters pre-elimination, despite total case numbers decreasing, a significant number of cases are imported cases. This reflects the close historical, economic, and socio-cultural ties with India, with unrestricted movement of people between the two countries across 699 km of international border.[36,37] Migrations from India into Bhutan are of two main categories: (i) long-term migrants, who come to work in development projects for longer periods, and (ii) short term or daily visitors, who enter the country for work or to seek healthcare or recreation and exit on the same day.[38] Each year, 35,000 longer-term workers arrive to

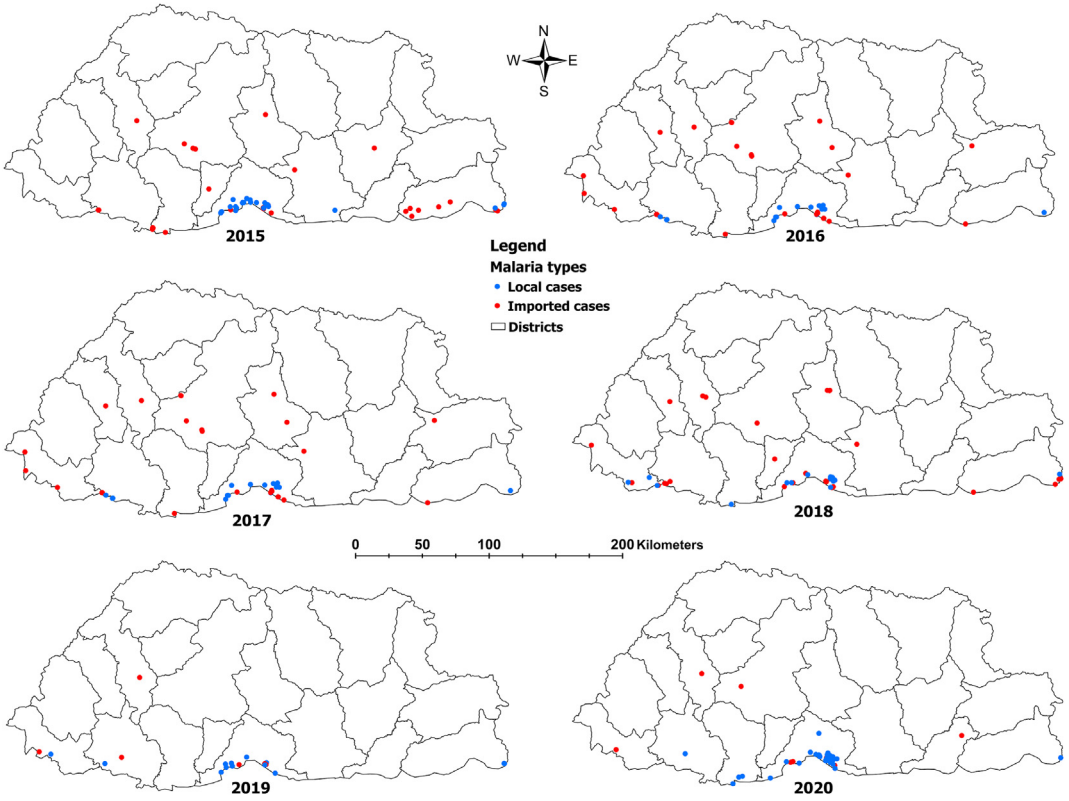

Fig. 3: **Locations of local and imported malaria cases by years in Bhutan, 2015–2020**.

work in Bhutan in major developmental projects while an estimated 1000 daily migrants cross the official southern border towns into Bhutan while over.[8] The latter made up almost 40% of all imported cases during the study period. Daily migrants are currently not screened for malaria and their movement is not properly tracked in the country. Hence appropriate surveillance needs to be designed, including screening and testing to

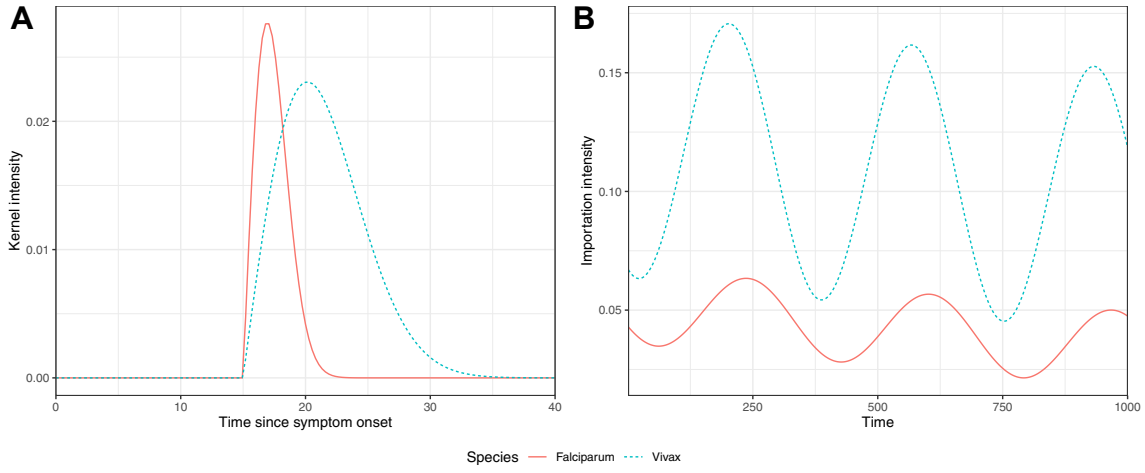

***Fig. 4:* Fitted kernel (A) and background intensity (B) for *Plasmodium falciparum* and *Plasmodium vivax* cases**. The red line shows the terms for the falciparum model with parameters $\alpha = 0.024$, $\delta = 0.27$, $A = 0.052$, $B = -1.8e^{-5}$, $M = -0.0087$ and $N = -0.013$. The blue line shows the terms for the P. vivax model with parameters $\alpha = 0.0074$, $\delta = 0.038$, $A = 0.12$, $B = -2.5e^{-5}$, $M = -0.052$ and $N = -0.020$.

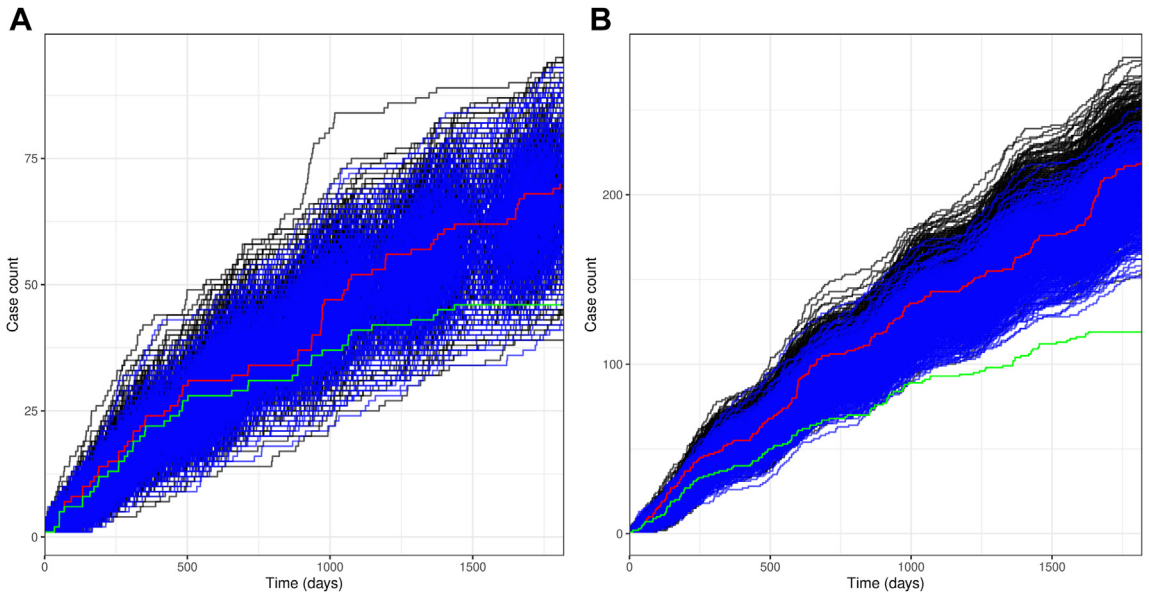

Fig. 5: **Simulated cumulative cases for *Plasmodium falciparum* (A) and *Plasmodium vivax* (B) malaria.** The red line shows all case data, and the green line shows cases that were marked as importations. The black lines show the 10,000 full simulations and the blue lines show simulations for the importations only. Please note a slightly different number of imported malaria cases are shown here compared with Table 1 due to different methodology.

assess the study the risk of malaria importation in this group. The priority for testing should be accorded to those who live across the international border and come to Bhutan for employment.[39,40]

End-game surveillance and control measures are increasingly expensive per case, as a country moves to elimination. Therefore, interventions must be targeted tailored at micro level and subnational level and efficiently to be cost-effective.[41,42] However, local transmission dynamics of malaria, including the role of importation in driving local transmission in the pre-elimination phase, are poorly understood in the absence of expensive genotyping of parasites which is not undertaken routinely. In this context, Hawkes Process models can provide useful insight. Such models can be used to simulate cases over time to show the relative contribution of importation verses local transmission and to run scenario simulations to estimate what might happen in the future under different assumptions. Understanding how local transmission is being driven is important to policy makers so that interventions including testing and providing preventive measures can be targeted towards high-risk groups. For example, current practice does not follow up malaria cases (both *P. falciparum* and *P. vivax* species) once they are treated or discharged from health facilities. The finding from this study suggests *P. vivax* infection are driven by other sources other than imported cases, possibly due to relapse. Therefore, *P. vivax* cases should be followed up for longer period to study clearance of parasites.

The main strength of this study was using national data over 5 years at a fine resolution with accurate information on the date of onset of symptoms and date of diagnosis to model. This is the first study in Bhutan and in the South Asia to quantify the association of importation and local transmission. Further, detail modelling was undertaken by malaria species. Therefore, this method could be adopted by countries in near elimination to understand the role of importation in the local transmission of malaria.

However, there are some limitations that are worth noting. First, one of the major limitations of using surveillance data is the completeness of such data, which if systematic could bias our estimates of model parameters.[24] Previous research has shown that this method is robust up to 10% underreporting. Second, model misspecification, especially in the background intensity, may have biased our parameter estimation. Third, individuals with sub-microscopic parasitaemia could have been missed because malaria diagnosis was done through conventional light microscopy and it has a detection limit of 5–50 parasites/μL.[43] This could also impact model fits as these cases would not be in the line list. Fourth, the imposed 15 days delay for a mosquito to become infectious was based on the literature. However, local micro-climatic conditions can influence and make this period variable. Fifth, with intensity-based simulation trajectories from the full simulation are independent of those from the background simulation so the proportion of imported cases cannot be calculated. This could be done if cluster-based simulation was used

instead. Sixth, we use a unimodal kernel for our intensity which cannot account for relapse. We suggest that investigating using a bimodal kernel would be a good avenue for future research.

In conclusion, local malaria transmission in Bhutan is largely driven by the importation of *P. falciparum* malaria cases and control programmes should be targeted to limit local transmission that results from these importations. For example, regular testing of those people who travel regularly or targeting interventions to these migrant workers could be fruitful. While *P. vivax* local cases are not completely driven by imported cases so longer follow up of cases would be required to determine the parasite clearance. Finally, Hawkes Processes can be a useful tool for countries embarking on malaria elimination to evaluate the role of malaria importation in driving local transmission for initiating relevant and most cost-effective prevention and control measures.

Contributors

KW, HJTU, SB and PG: conceived the study; KW, HJTU, and SB: undertook analysis, interpretation of the results and drafted manuscript; KP and Tobgyal: involved in data acquisition; AC, DG, MK, TT, SB and PG: critical review of manuscript.

Data sharing statement

The R-codes and data are available at https://github.com/MLGlobalHealth/bhutan_hawkes.

Editor note

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Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2024.100497.

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