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# Evaluation Of Malaria Surveillance In Bhutan, 2006-2012

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## **Evaluation of Malaria Surveillance in Bhutan, 2006-2012**

**ABSTRACT**

Bhutan is embarking on elimination over the course of the next decade. The purpose of this evaluation is to assess the ability of the current surveillance system to meet the objectives of the Vector-borne Disease Control Programme (VDCP), to highlight the priorities of the surveillance system as the nation transitions into an era of elimination, and to identify areas that require attention for this goal to be achieved. An evaluation of the national malaria surveillance system of Bhutan from 2006 to 2012 was conducted using the CDC updated guidelines for evaluation.<sup>1</sup> National malaria surveillance data, written VDCP protocols, and informal interviews were assessed. Cases and deaths decreased over the time period, and program indicators surpassed WHO milestones for the transition to elimination. Overall, the malaria surveillance system is strong and produces data that is useful and of good quality, but the pivot to elimination will require system function enhancement through increased and more accurate blood screens, active case finding and investigation, focally-targeted response measures, and solutions to the challenges of funding re-introductions of infections.

### **Acknowledgements**

I would like to thank the individuals at the VDCP for their openness, generosity, and excellent instruction during my time in Gelephu and for graciously sharing the surveillance data, without which this project would not have been possible. I would also like to thank Professor Kaveh Khoshnood and the Royal Institute of Health Sciences of Bhutan whose cooperation facilitated my internship, as well as the Bhutan Foundation and the Yale South Asian Studies Council for generously providing funding. Finally, I would like to thank Dr. Amanda Durante and Dr. Sunil Parikh for their invaluable insight and guidance throughout this project.

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## INTRODUCTION

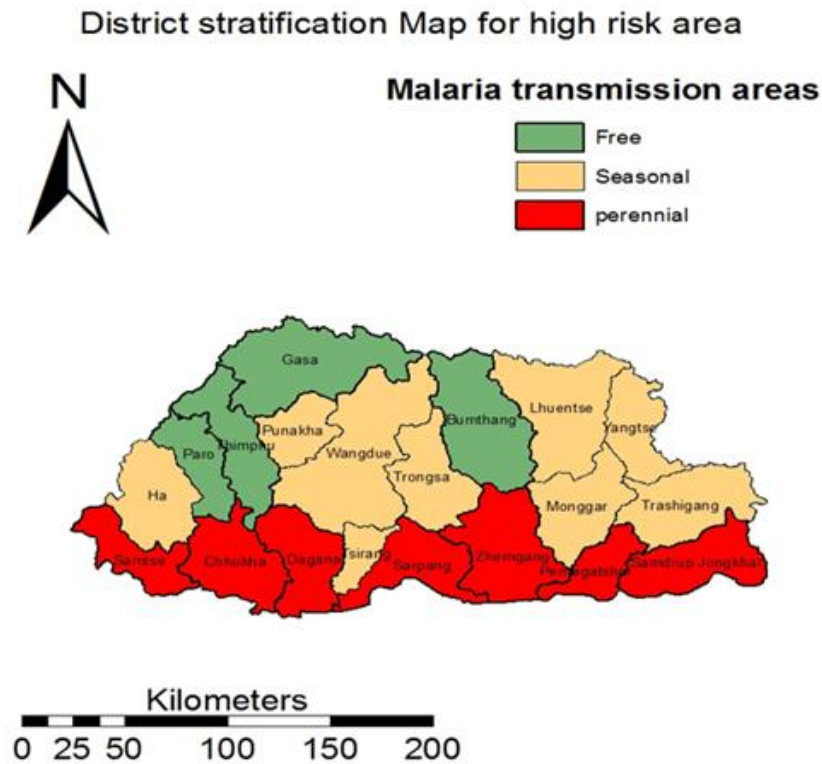
The past decade has been a period of greatly intensified efforts to prevent and control malaria on a global scale. The offensive has been supported by an abundance of publicity and funding, as well as leadership from the WHO, the Bill & Melinda Gates Foundation, and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).<sup>2,3</sup> Global malaria deaths decreased 26% over the period of 2000 to 2010, and incidence dropped by 17%, according to WHO estimates.<sup>4,5</sup> The aggressive control efforts have permitted many countries to begin the transition to (pre-)elimination activities, and the Roll Back Malaria initiative plans for more nations to join the list over the coming decade.<sup>4,6</sup>

Elimination is an ambitious goal, defined by the WHO as “reduction to zero of the incidence of infection caused by a specified agent in a defined geographical area as a result of deliberate efforts.”<sup>7</sup> Elimination initiatives entail a conceit of their own; in contrast to programs of malaria control, which aim broadly to reduce to the number of cases and deaths “to a locally acceptable level,”<sup>8</sup> elimination strategies specifically seek to interrupt local transmission. With an increasingly finer focus, programs concentrate their attentions from the national scale to the residual foci of active transmission, and finally to individual cases.<sup>7,9</sup> While the decision to move from a strategy of control to one of elimination depends on the nature of endemicity within the country, the capacity of the medical and public health sectors, and political will, the WHO has suggested the potential epidemiologic milestones for transition: a blood slide positivity rate (SPR) of less than 5% for suspected malaria cases to move from a control program to pre-elimination, and an annual parasite index (API) of less than one case per thousand population at risk per year to transition from a pre-elimination to an elimination program.<sup>7</sup> Considerable evidence must be amassed to prove the absence of any locally acquired infections for a minimum

of three consecutive years required for WHO certification of malaria elimination.<sup>7,8</sup> Following the successful interruption of local transmission, continuing vigilance is required to prevent malaria resurgence.<sup>7,10</sup>

The Himalayan nation of Bhutan (population 683,407 in 2009) has long struggled with malaria.<sup>11</sup> Distribution of malaria transmission in Bhutan is limited by its topography and climate. Four northern districts experience no malaria transmission as a result of their elevation; any malaria cases are likely imported. Nine districts experience seasonal transmission during the summer months, while perennial transmission occurs in the seven southern districts bordering India (Figure 1).<sup>12,13</sup> Nationally, most cases occur in August and September, following the rainy season, with a secondary peak in April. Two thirds of all cases occur among males, and farmers are definitively the occupational group most at risk, followed by students and laborers.<sup>11</sup> This mirrors a global trend of malaria becoming increasingly associated with males and with specific occupational risk groups.<sup>4</sup>





**Figure 1** Malaria transmission in Bhutan (map courtesy of the VDCP)<sup>14</sup>

The *Plasmodium* species endemic to Bhutan are *P. falciparum* and *P. vivax*.<sup>13, 15</sup> The most serious disease sequelae, including cerebral malaria and death, are caused by *P. falciparum*, making it the necessary target for any interventions to reduce mortality.<sup>16</sup> *P. vivax* has the potential to form hypnozoites, a life stage that can lie dormant in liver cells for a period of weeks to a year or more before causing clinical relapse.<sup>17</sup> Hypnozoites represent a major challenge to elimination efforts, functioning as an asymptomatic reservoir of infection (even in the absence of new mosquito bites), and are impervious to standard antimalarial therapies which target the blood stage of infection.<sup>16, 17</sup> Primaquine uniquely targets both blood stage gametocytes and hypnozoites, making it a critical tool for elimination.<sup>18</sup> However, its widespread use is

challenged by its propensity to cause hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency.<sup>17, 18</sup>

Since 2006, Bhutanese patients infected with *P. falciparum* are required to stay in the treating health care facility for the three-day treatment course of Coartem, an artemisinin-based combination therapy (ACT) of artemether and lumefantrine. Starting in 2011, a single dose of primaquine administered immediately before discharge was added to the treatment protocol as a part of clinical pro-elimination efforts. Malaria cases caused by *P. vivax* are treated with a combination of chloroquine and primaquine (pregnant women only receive chloroquine).<sup>19</sup> No surveys have been conducted to determine the prevalence of G6PD deficiency in Bhutan. In a geostatistical model of malaria endemic countries, Howes et al. (2012) estimated G6PD deficiency prevalence in Bhutan to be 5.9% (interquartile range 3.6-9.6%), but without survey data, the uncertainty associated with this prediction is great.<sup>18</sup> In addition, a drug resistance study has been established at six sentinel sites, and thus far has not identified any resistant cases. Although in its nascent stages, monitoring the efficacy of drug treatments is a critical component of the overall elimination strategy in Bhutan to ensure radical cures in all patients.<sup>14</sup>

Bhutan's proximity to India remains a major challenge to control as porous borders and a large population of foreign workers are constant sources for new infections. Bhutan is surrounded by states with some of the highest slide positivity rates for *P. falciparum* in India, and many of the foreign laborers come from the highly prevalent state of Orissa.<sup>20</sup> The number of migrant workers is expected to increase over the coming years as several major hydropower projects are planned—most of them in regions with seasonal transmission.<sup>21</sup>

An additional challenge is the absence of definitive characterization of the primary vector species responsible for malaria transmission in Bhutan. In nearby Indian states,

*Anopheles minimus*, *An. fluviatilis*, and *An. dirus* have been confirmed as primary vectors of malaria transmission, with *An. philippinensis-nivipes* also contributing.<sup>22</sup> Studies in Assam, the Indian state that is contiguous with the majority of Bhutan's southern border, have found *An. philippinensis-nivipes* and *An. annularis* to be among the most common Anopheline species, but *An. dirus* and *An. minimus* to be extremely anthropophilic (>90%).<sup>23, 24</sup> It is thought that *An. dirus* is primarily responsible for the maintenance of persistent malaria in forest and forest fringe areas of Assam.<sup>25</sup> The landscape, topology, and climate of southern Bhutan are continuous with that of Assam, so it may be that these Anopheline species are similarly active in the malaria-endemic region of Bhutan. Vector surveys conducted in Bhutan have confirmed the presence of the potential vector species *Anopheles dirus*, *Anopheles pseudowillmori*, *Anopheles willmori*, *Anopheles maculatus*, *Anopheles fluviatilis*, and *Anopheles vagus*.<sup>13</sup> *An. culicifacies*, *An. pseudowillmori*, and *An. willmori* are the species that have been most commonly found indoors in vector studies and are therefore suspected to play a role in malaria transmission in Bhutan.<sup>11</sup>

All vector-borne disease-related activities in Bhutan—including surveillance, prevention, and outbreak control—are consolidated under the Vector-borne Disease Control Programme (VDCP), a division of the Department of Public Health, Ministry of Health of Bhutan. Since surveillance was initiated in 1965, reported cases reached at peak in 1994 with 39,852 malaria cases.<sup>15</sup> Since then, the VDCP launched an aggressive malaria control strategy, strengthening and expanding earlier efforts. In the Basic Health Units (BHUs) and district hospitals, there was a re-emphasis on early patient diagnosis and treatment. Starting in 2006, long lasting insecticidal nets (LLINs) were rolled out to replace the earlier insecticide-treated bed nets (ITBNs) that required regular re-impregnation. By 2010, the VDCP had achieved

90% household LLIN coverage in areas with perennial and seasonal transmission and ITBNs were phased out.<sup>12</sup> Environmental larviciding had previously been a component of vector control strategies, but was determined to be ineffective due to washout by summer monsoon rains. The practice was discontinued in 2010. Focal IRS is conducted twice per year in areas of perennial transmission districts with a recent history of cases.<sup>12</sup> Three sentinel sites for IRS and LLIN efficacy in the district of Sarpang have yet to find any evidence of insecticide resistance in Anopheline mosquitoes.<sup>14</sup>

Following these efforts, malaria incidence in Bhutan has drastically reduced. The VDCP had targeted for a 75% reduction in malaria morbidity and mortality by 2013, as compared to the 2005 baseline.<sup>11</sup> Malaria dropped from the 16<sup>th</sup> leading cause of years of life lost in 1990 to the 46<sup>th</sup> in 2010.<sup>26</sup> Bhutan now has reached the pre-elimination stage and is gearing up for concerted efforts over the coming years to be certified by the WHO as malaria-free.<sup>2</sup>

Elimination rests on a country's ability to interrupt transmission of malaria within its borders. This requires the rapid identification and radical cure of all individuals infected with *Plasmodium* parasites to reduce on-going transmission, as well as targeted vector control activities to decrease human-mosquito contact and vectorial capacity. A strong public health surveillance system is a critical component of any elimination strategy, both to ensure highly sensitive case-finding and to inform and direct the increasingly focal vector control activities conducted in this stage. Surveillance systems also provide the three years' worth of evidence needed to receive the WHO malaria-free certification. Finally, vigilant surveillance remains important even after a country is malaria-free to prevent resurgence.<sup>6-8</sup>

While surveillance is lauded as a keystone for malaria elimination, the details of this role are often unspecified, perhaps due in part to the necessity of tailoring surveillance to the specific

epidemiology, public health capacity, and disease control strategy of a given country. In the case of Bhutan, the clinical protocols and vector control activities of the VDCP have been reported previously, but the capacity of the surveillance system to aid in national elimination aspirations has not been specifically explored.<sup>13, 15</sup> Furthermore, this is the first study to consider the sensitivity of the system through an examination the internal quality assurance mechanism of blood slide cross-checking. The purpose of this evaluation is to assess the ability of the current malaria surveillance system in Bhutan to meet the objectives of the VDCP's malaria strategic plan: (1) reduce the number of malaria-related deaths to zero by 2016, (2) achieve zero local malaria transmission by 2016, and (3) obtain WHO malaria-free certification by 2020.<sup>14</sup> The aim is to highlight the priorities of the surveillance system as the nation transitions into an era of elimination, and to identify areas that require attention for this goal to be achieved.

## **METHODS**

An evaluation of the national malaria surveillance system of Bhutan was conducted using the CDC updated guidelines for evaluation.<sup>1</sup> National malaria surveillance data from 2006 to 2012 were analyzed to determine numbers of blood slides collected and numbers of malaria cases by *Plasmodium sp.* and by district among residents and non-residents for each year during the study period. Written VDCP protocols were reviewed and interviews were conducted with health workers, malaria technicians, district health officials and VDCP personnel. The period of 2006 onwards was chosen for evaluation because it aligns with the transition to the use of LLITNs and electronic record-keeping on the part of the VDCP, and to achieve a finer focus on the pre-elimination years.

An in-depth analysis of the blood slide cross-check data for 2011 was conducted. Proportions meeting standards of preparation were calculated. Percent agreement was calculated based on the results of the initial health center slide reading and the results from the VDCP cross-check. All data were analyzed using SAS 9.3 and Microsoft Excel.

## **SYSTEM EVALUATION**

### **Description of the system**

Malaria surveillance is orchestrated by the VDCP. The Public Health Laboratory is responsible for the nascent Notifiable Disease surveillance program (first established in 2010, moved to online, electronic reporting February 2012), which includes malaria and other vector-borne diseases among its notifiable list. At this point, the VDCP maintains control of malaria surveillance, although there is hope for improved data sharing in the future. The designated targets of the VDCP that are relevant to the project of surveillance are: to reduce to zero malaria-related deaths and to transition to an elimination phase over the next ten years<sup>27</sup>.

Malaria surveillance is conducted year-round across the entire population of Bhutan. All health care in the country is provided by the government, so any individual seeking formal care is covered by the surveillance system. Any febrile patient reporting to a health center is screened for malaria. Diagnosis is made exclusively by Giemsa-stained blood slide examination for parasite presence and species via light microscopy according to WHO guidelines for malaria diagnosis.<sup>28</sup> Rapid diagnostic tests (RDTs) are not widely available or used. Where they are employed, RDTs are considered superfluous as blood slide microscopy is always conducted and it is those results that are reported. A case is defined as anyone with *Plasmodium spp.* parasites in his or her blood, regardless of parasite density.

All health center records and surveillance reports are completed on paper and are delivered by post or by car to the VDCP. Health centers send in reports to the VDCP every month, except for those in the seven endemic districts which report weekly by phone.<sup>12</sup> Reports for a given month are to be received by the VDCP by the beginning of the second week of the following month, although some reports are received up to two months after this due to distance and difficulties of travel. All data is received by the Information Unit of the VDCP and since 2006 has been entered into EpiInfo. The data collected by the surveillance system is used to inform the planning of control and prevention activities, including targeted IRS and heightened efforts of community outreach, environmental management, and vector studies. The village-level criteria currently used by the VDCP to determine where to conduct the twice-yearly (March and September) focal IRS are: (1) Presence of malaria cases during the three preceding years, (2) API above four cases per 1,000 population for three preceding years, (3) SPR above 2% for preceding three years, (4) Having a direct border with India, and (5) Presence of suspected vectors. The 2012 guidelines included the addition of focal IRS following a malaria index case, if that area did not qualify for IRS under the above criteria.<sup>14</sup> Quarterly reports are sent from the VDCP to health centers and a formal annual report is prepared for a review of the previous year with Ministry of Health officials.

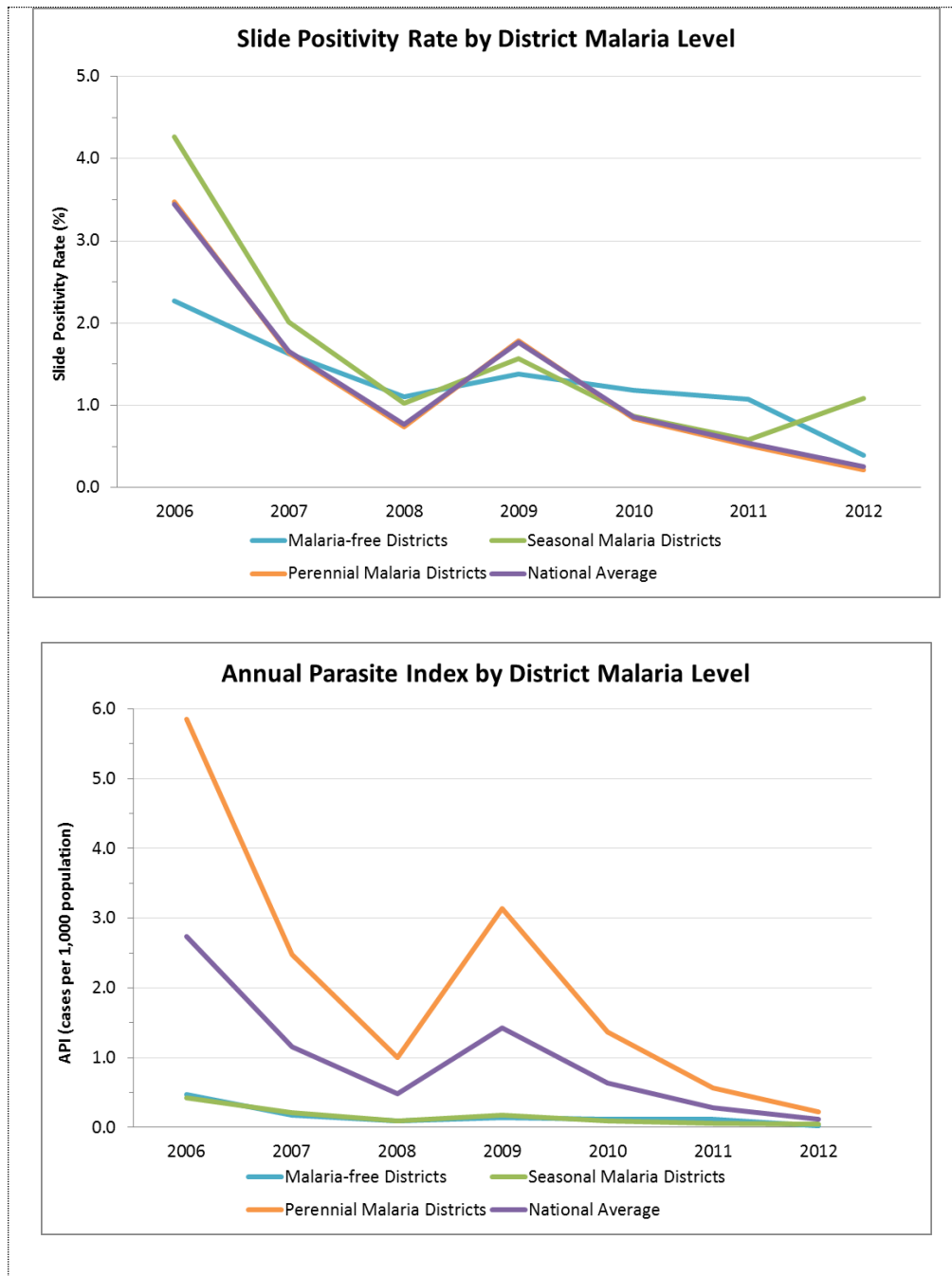
In addition, the surveillance system contains an internal quality assurance mechanism: All health centers that treated febrile patients within the last month are required to send a portion of blood slides they collected to the VDCP for cross-checking by a trained professional. Health centers with fewer than 50 fever patients are required to send in all of their slides, while those with 50 or more are required to send all of their positive slides and 10% of their negative slides for cross-checking. Slides are reviewed by an official at the VDCP with more advanced

parasitology training to assess accuracy in initial diagnosis. The official is blinded to the initial result while slides are examined for the presence and species of parasites. The size, evenness, staining, and cleanliness are recorded (dichotomously, acceptable or not), as well as whether the slide includes both thick and thin smears as required by VDCP protocols.<sup>12</sup>

### **Malaria surveillance results**

Overall, total malaria cases (including cases among both residents and non-residents of Bhutan) declined from 2,276 in 2006 to 106 in 2012 (Figure 3). The exception was 2009 when there was a single-year increase to 1,098 cases, up from 361 in 2008; in 2010 cases dropped again to 465. Health workers and VDCP officials suspected this was due to waning efficacy of LLINs as the increase was not localized, but was rather seen across the country. Additional LLINs were distributed in early 2010. The district of Sarpang (in the region of perennial transmission) consistently had high numbers of cases, and accounted for the majority of cases from 2009 on (See Appendix 1). Over the seven year period, 15 malaria-attributable deaths occurred, decreasing from four in 2006 to a single death in 2012, suggesting that the VDCP's zero-mortality goal may be achievable.



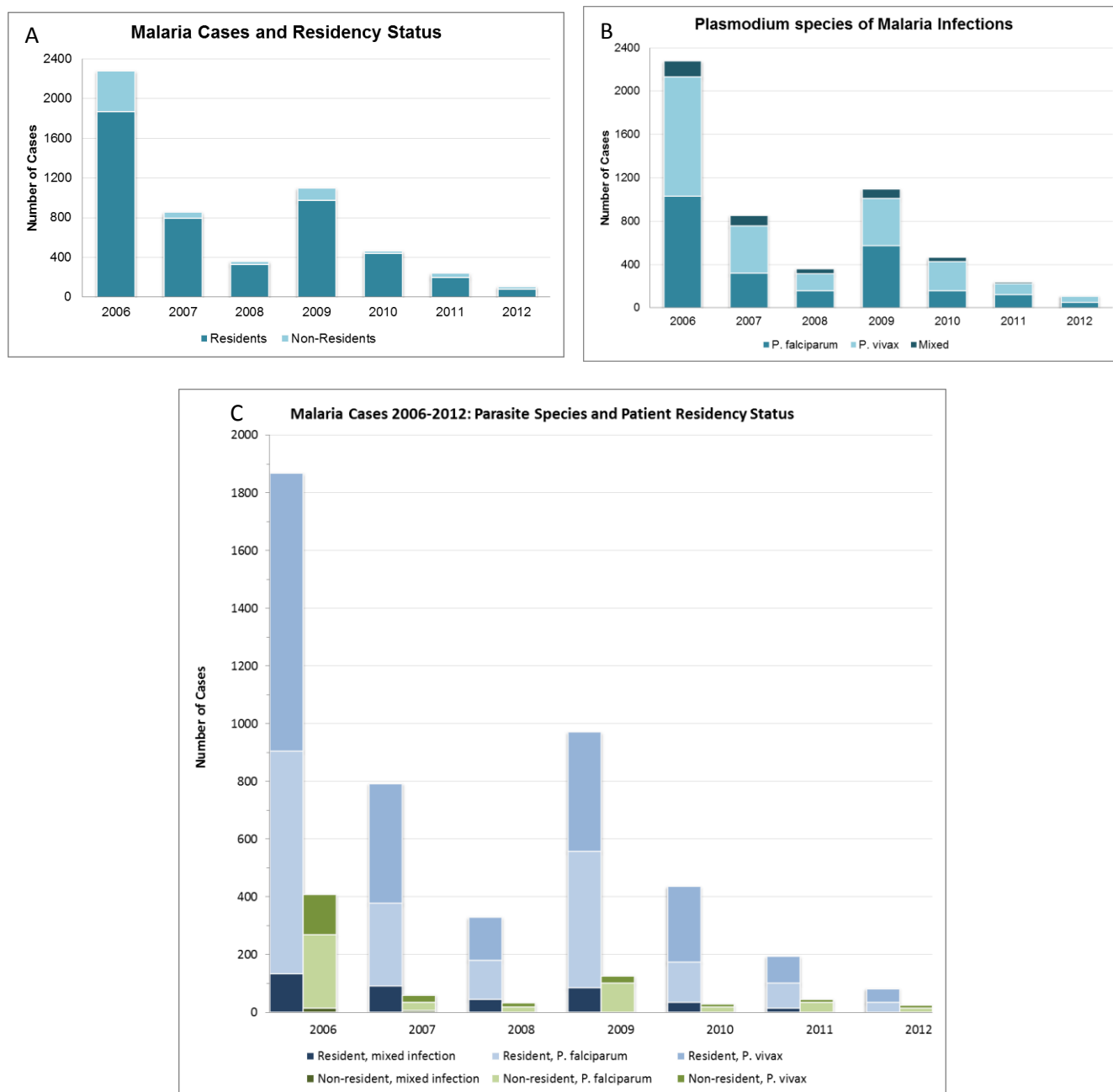


**Figure 2** Indicators of program progress: SPR and API

Slide positivity rate and annual parasite index both decreased over this period, surpassing WHO milestones for program transition to pre-elimination and elimination (Figure 2).<sup>7</sup> The SPR was below 5% for all three levels of regional transmission for the duration of the seven-year

period, with the national average decreasing from 3.4% in 2006 to 0.3% in 2012. API fell below one case per thousand population in districts with perennial transmission in 2011, while API for regions of seasonal and no malaria transmission was less than 0.5 throughout.

### Malaria Cases in Bhutan 2006-2012



**Figure 3 Malaria cases in Bhutan 2006-2012** by (a) case residency status, (b) *Plasmodium* species of infection, and (c) species of infection among residents and non-residents.

Nationally, non-residents comprised between 6.2% (in 2010) and 22.6% (in 2012) of all cases (Figure 3). However, these cases were not evenly distributed across all districts; rather, there were more transient, localized effects in particular districts, changing from year to year. In 2011, every foreign case in the country came from Sarpang, where they accounted for 45 of 148 total cases (30.4%). In 2012, cases among non-residents were only reported in Wangdue and Sarpang; they accounted for 7 of 15 (46.7%) of cases in Wangdue and 17 of 67 (25.4%) of cases in Sarpang.

Proportions of infections by species (*P. falciparum*, *P. vivax*, or mixed infection) did not vary significantly over time. From 2006-2012, *P. vivax* accounted for nearly two thirds of all infections in seasonal transmission and malaria-free districts, while an additional 22.3-25.0% were due to *P. falciparum* and 12.3-13.0% were mixed. In the perennial transmission districts, infections were more evenly split between *P. falciparum* and *P. vivax* (43.1% and 48.6%, respectively; 8.3% mixed), perhaps due to the high burden of *P. falciparum* in neighboring Assam.<sup>29, 30</sup>

### **Blood slide cross-check**

Of 2,514 blood slides analyzed during the 2011 cross-check process, 1160 (46.14%) were of excellent quality, free from any staining problems or blemishes and containing both thin and thick smears; over half were sub-optimal in at least one characteristic (the blood smears for 90.97% were of a normal size, 88.11% were even, 93.04% were clean, and 93.24% were stained satisfactorily). The greatest deficit was in the proportion of slides prepared with thick and thin blood smears: only 56.01% of slides examined were prepared according to protocol with both thick and thin blood smears, while 38.15% of slides were prepared with only thick smears and

2.94% with only thin smears. Additionally, sixty slides (2.37%) arrived broken at the VDCP and could not be read.

Where slide readings from both the original health worker and the VDCP professional during cross-check could be compared, agreement of parasite presence or absence between the two was >97% for districts of all three transmission levels (Table 1). Errors were not evenly distributed, with two health centers responsible for 12 of 19 false positives (all of which were identified as *P. vivax* infections) discovered in 2011.

Malaria-free Districts				Seasonal Transmission Districts			
		VDCP Cross-check				VDCP Cross-check	
		Positive	Negative			Positive	Negative
Health Worker	Positive	3	1	Health Worker	Positive	6	9
	Negative	1	88		Negative	0	377
Agreement = 97.9%				Agreement = 97.7%			
Perennial Transmission Districts				Malaria-free Districts			
		VDCP Cross-check				VDCP Cross-check	
		Positive	Negative			Positive	Negative
Health Worker	Positive	98	9	Health Worker	Positive	107	19
	Negative	13	1910		Negative	14	2375
Agreement = 98.9%				Agreement = 98.8%			

**Table 1** Agreement of slide readings during cross-check

### System Usefulness and Attributes

The national malaria surveillance system of Bhutan successfully produces useful data which health workers at the VDCP are able to use to direct entomological control measures, to evaluate the success of interventions, and to plan future initiatives targeting critical areas. The system alerted VDCP officials to the 2009 outbreak—leading to the distribution of additional

LLINs in 2010—and has tracked the more local trends, such as the reduction in incidence in Samdrupjonkar, which had formerly had rates comparable to those of Sarpang. Sarpang can now be identified as the major contributor of cases, and thus presents itself as a target for additional control efforts.

Because data is collected at the village level, an even finer scale can be used for analysis and the identification of transmission hotspots. The ability to address local heterogeneities in transmission via village-level data will be a valuable asset to the VDCP as it begins to categorize and target foci of transmission for its elimination effort.<sup>31, 32</sup> The system has been instrumental to the great progress made in malaria control thus far, but the full potential of the data collected has not been realized due to very limited statistical or spatial analyses performed. For the malaria surveillance system to facilitate Bhutan's progression towards indigenous malaria elimination, the most important of the CDC attributes are data quality, sensitivity, timeliness, and flexibility, and it is these that must be improved.

#### *Data Quality*

The quality of data generated by the national malaria surveillance system of Bhutan is quite high. Surveillance is complete across the country and includes zero reporting. The inclusion of the blood slide cross-checking process allows for evaluation of the validity of diagnoses. At present, false positives and false negatives are counted, but no percentages or measures of agreement are computed; doing so would make comparisons more feasible. In its guidelines for malaria microscopy quality assurance, the WHO recommends calculating percent agreement between health worker and validator reading for the presence of any parasites (regardless of species) and for the presence of *P. falciparum*.<sup>33</sup> Given the preponderance of slides misidentified as containing *P. vivax*, an additional measure of agreement for this species

identification could be added as well. The quality of blood slide preparation and the accuracy with which they are read by local health workers is certainly an area for improvement.

Agreement between health workers and the validator at the VDCP has been sufficient for the control stage, but must be improved going forward if Bhutan is to achieve elimination when every case must be identified and treated. This will require additional training for local health workers, more rigorous attention to individual worker performance, and remedial measures when required.

### *Sensitivity*

The sensitivity of the system is determined by two factors: patients' health care-seeking behavior and the ability of health workers to identify parasites in blood slides (as discussed above). In informal interviews, some health workers expressed concern that some rural and uneducated individuals may still seek care from traditional healers during times of illness. According to the 2009 national Malaria Indicator Survey and Bed Net Knowledge, Attitude, and Practice Study (MIS & KAP) of 796 households, 745 (93.6%) knew what malaria was and 663 (83.3%) identified fever (the criteria for blood screening in health centers) as a major symptom. Regarding treatment, 739 (92.8%) respondents said that malaria could effectively be treated by visiting a health center, while only 3 (0.4%) said treatment could be achieved by visiting a traditional healer or astrologer.<sup>34</sup> Increasing public awareness and encouraging individuals to go to health care centers when they experience a fever has been a focus of the VDCP's malaria control strategy and they have continued to address gaps in knowledge since this survey was conducted.

The sensitivity of the system has been sufficiently high to enable many of the gains in malaria control—such as IRS spraying in response to outbreaks—and reductions in mortality

through prompt and effective patient treatment and follow-up. Still, if elimination of malaria-related deaths and ultimately all indigenous transmission is to be achieved, sensitivity will have to be driven higher still with the addition of active case detection components to the system. Reactive case detection has successfully been used to focally increase sensitivity by requiring active blood screens of household members and other residents within a defined radius of any newly identified malaria case.<sup>35,36</sup> This form of intensified case detection will be necessary to progress from control to elimination.<sup>6,21</sup>

### *Timeliness*

If any new autochthonous cases do arise, it will be critical to identify them as soon as possible, both for optimal treatment and follow-up for that patient, and for the initiation of local control measures such as IRS and bed net checks to prevent transmission. Again, patient care-seeking behavior influences the timeliness of the system. The VDCP has made concerted efforts to raise awareness and encourage individuals to visit health care centers, and in the MIS & KAP survey, 83.5% of respondents reported seeking health care within 24 hours of a fever.<sup>34</sup> It is possible that individuals may have been inclined to over-report health center attendance, and as malaria incidence continues to decline, the presence of a fever may become less worrisome over time if the perceived risk of malaria is small. The WHO has suggested using the proportion of *P. falciparum* infections with gametocytes present as a timeliness indicator. Because treatment of *P. falciparum* infections within the first six days from the onset of symptoms is typically sufficient to prevent the development of gametocytes, this proportion serves as a proxy indicator for the timeliness of patient diagnosis and treatment.<sup>8</sup> The VDCP therefore may consider incorporating this measure into its protocols. Ideally, the presence of gametocytes and resulting proportion could be recorded and calculated at the point of care, but it may be more feasible

given the degree of parasitology training for most health workers to restrict this computation to the blood slide cross-check process.

Most health centers are able to submit their reports on time, but the regular delay of others—either due to the seclusion of the particular BHU or seasonally-disrupted terrain—is suboptimal. While electronic reporting would theoretically solve this problem, there are neither the funds to provide computers to health centers, nor the technical expertise among most health workers to operate such a system. To improve timeliness, telephone reporting, which is already regularly practiced with success in the southern districts, could be expanded to the seasonal transmission districts, potentially as a transient feature activated during the high case season.

### *Flexibility*

The flexibility of this system remains untested, but to support improvements in timeliness and case detection, system agility will be critical. Structurally, it seems able to accommodate new components such as telephone reporting and reactive case detection. If resources could be mustered and partnerships established, genetic analysis of parasites can be used to determine whether infections were locally acquired or imported;<sup>37</sup> such an addition would not seem to substantially challenge the structure of the current system. Critically, elimination efforts will require on-going review of the progress of the program and evaluation of the performance of the surveillance system. To this end, the system must be flexible enough to adapt to the results of such reviews. In addition, there is the potential for the malaria surveillance system to demonstrate its flexibility in other ways, such as the expansion to include surveillance for other diseases. A logical addition to this system would be the inclusion of dengue reporting.



*Positive Predictive Value*

A relatively small number of false positives have somewhat deflated positive predictive values as the total number of malaria cases have dwindled. As the numbers of true incident infections continue to decline over the coming years, the PPV will only continue to decline. The blood slide cross-check system monitors this too, although PPV is not explicitly calculated as it should be in the future. Improving health worker microscopy abilities should help to improve this and ensure that resources are being allocated correctly. However, what may be even more important than PPV in this context is negative predictive value. False negatives present the threat of severe disease sequelae and the potential for onward transmission. Again, on-going health worker training will be critical to maximizing the predictive power of negative results.

*Representativeness*

Unlike other countries with private health care sectors, all patients in Bhutan attend government health care centers, all of which report to the VDCP. Although structurally consistent throughout the country, the system may not be completely uniform in its quality of coverage, with BHUs in the endemic districts having higher numbers of blood slides collected. However, due to the climate of Bhutan and the ecological restriction of the mosquito vector to the southern districts, imperfect representativeness is not detrimental. The priority is and must be the functioning of the surveillance system in endemic districts.

*Simplicity*

The system as it currently stands is quite simple. As a result of the VDCP's functional autonomy, there are no intervening entities between the point of diagnosis and the center of data receipt and analysis. As the national Public Health Laboratory begins to establish its own system

of nationally reportable diseases, the degree of complexity may increase, but this remains to be seen.

### *Acceptability*

In informal interviews, health workers spoke positively of the means of surveillance and did not complain about monthly reporting protocols. However, lower than expected numbers of blood slides sent in for confirmation suggest a lack of acceptability in this portion of the process. It may be that declining numbers of malaria cases have lessened the sense of urgency of this endeavor. VDCP personnel suggested BHU workers may be keeping the limited number of positive slides for reference purposes. To achieve optimal standards of case detection, district health centers must be encouraged to continue to send in the required number of blood slides as the blood slide cross-checking process is the only means by which the VDCP can assess the sensitivity and specificity of diagnoses. This is especially important for achieving the goal of eliminating malaria-attributed deaths. Health care workers must particularly identify every *P. falciparum* infection, the principal species contributing to malaria-associated deaths, and the cross-check process is the only in-built mechanism to assess their ability to do so.

### *Stability*

In many ways, the simplicity and low reliance on technology renders the malaria surveillance system quite structurally stable and resilient in the face of obstacles such as power outages. The main challenge to stability will be how to sustain high quality surveillance and aggressive control efforts as funding decreases. Studies of malaria resurgence had found that nearly all instances of resurgence are due to the slackening of control efforts, which are themselves primarily due to insufficient resources.<sup>10, 38</sup> In the absence of any external reduction

in regional transmission potential, the activities used to achieve malaria control or elimination must be maintained.<sup>39</sup> The VDCP and its malaria control activities are funded by the Royal Government of Bhutan, the Government of India, the WHO, and the Global Fund (GFATM).<sup>21</sup> International funding has suffered as a result of the global financial crisis.<sup>3</sup> Bhutan in particular may be a victim of its own success as the donors who have provided substantial support in the past begin to turn their attention elsewhere to countries still experiencing high rates of malaria transmission. The current Global Fund grant is about to expire and if these funds are not replaced by another source, the efficacy of control actions and the progress made thus far in Bhutan may be threatened, as well as the future of elimination.

## **DISCUSSION**

Overall, the malaria surveillance system of Bhutan is strong and produces data that is useful and of good quality. The performance of the system thus far has been critical to the major reductions to malaria morbidity and mortality in Bhutan. However, the pivot to elimination will require system function to ratchet up even further.

First, to attack remaining reservoirs of infection and to prevent onward transmission, diagnostic accuracy is paramount. The predictive power of negative results is of particular significance because every false negative represents a missed opportunity to treat malaria case, preventing harmful sequelae in that individual and addressing a potential source for future infections in others. The existence of a quality assurance component is a great strength of the structure of this surveillance system, but it is only of value if the results are utilized. Health worker accountability is lacking. At present, health centers that have repeated errors identified through the cross-check process are invited to send health workers to refresher trainings at the

VDCP, but often do not. Health workers must be held to a higher standard, with formalized expectations for performance.<sup>33</sup> The WHO recommends a system of on-going training and assessment of microscopists for competency in slide preparation and reading of both parasite presence and species, coupled with a clear protocol for remedial measures if expectations are not met.<sup>33</sup> As the managing agency, the VDCP will be responsible for more actively acknowledging those that have performed well and requiring additional trainings for those who have not. The VDCP could consider adding cross-check results to the quarterly surveillance reports distributed to health centers as a way to establish public accountability.

Second, targeted response to cases can interrupt transmission. In-depth investigations of cases are required to better assess the source of infection.<sup>38</sup> For instance, although travel history (both within-country to endemic districts and outside of Bhutan) is obtained from individuals, cases are still ascribed to the health center of diagnosis, not to the area of (suspected) acquisition. Similarly, the reporting scheme should consider a more nuanced categorization for non-residents as their length of stay in Bhutan could reveal whether the infection likely occurred locally or was imported. The results of these case investigations then must be mined at the program level to attack foci of transmission and to implement targeted measures addressing populations identified as having the greatest risk, due to geographic location or occupational hazard.<sup>4,31</sup> Zooming in to the village level will the VDCP to spatially target transmission hotspots and intensify vector control activities there. Reactive case detection should be added to better identify infected individuals. Innovative means of exposure reduction will have to be developed to prevent infection in at-risk groups such as farmers, which are not protected by the primary vector control activities of IRS and LLIN use. In this case, the malaria surveillance system has been successful

in identifying an at-risk population, but this information has not been translated into public health action. Elimination rests on the ability of the VDCP to bridge this gap.

Third, more sophisticated data management and analysis are required. The malaria surveillance system in Bhutan collects much more information than is utilized, and harnessing this information more effectively could aid in pro-elimination efforts. Nationally, human resources represent a significant challenge in Bhutan as there is little training in statistics and epidemiology for all but a few individuals. Nevertheless, those involved in data analysis and the slide cross-check process should consider adding basic figures, such as slide reader agreement to their standard analysis of the data. Similarly, slide positivity rate is only calculated by the VDCP at the end of the year; having health workers calculate monthly SPRs for their BHUs may help them to better understand the local transmission as compared to the raw case counts currently used. These relatively simple calculations can provide a way to compare districts and the national average, to assess progress over time, and to meaningfully communicate with outside entities concerned with public health. Sensitivity in particular must regularly be calculated for the blood slide cross check data and must lead more directly and rapidly to supplemental microscopy training for health workers when it is required. Data must be disaggregated to compare to WHO targets for elimination. For instance, slide positivity rates must not exceed 5% per month, even during peak season, according to the WHO. The VDCP does not regularly calculate slide positivity rates, but data is aggregated to the yearly level. These practices have not hampered control efforts in the past, but if Bhutan is to achieve its goal of indigenous malaria elimination and the WHO certification, these issues must be addressed.

Fourth, timeliness of reporting is an area for improvement, and could be addressed through telephone reporting. During the rainy season in particular, travel is slowed by muddied

roads or arrested entirely by roadblocks due to landslides or river flooding. Although always a priority, timeliness will be critical as Bhutan progresses on its elimination agenda. Rapid reporting to the VDCP is a precondition to any agency-level response to interrupt transmission. It is VDCP policy that emergency IRS be carried out across a 1 km radius from any indigenous case.<sup>12</sup> Telephone reporting would improve timeliness of reporting and is the only feasible technological improvement as fax machines and computers are out of the question due to cost and the training that would be required for health workers to use them. Technological improvements at the program level may be more feasible, and could also facilitate improved data sharing between the VDCP and PHL, although the two entities must negotiate reporting standards first.

There have been preliminary discussions of adding a GIS component to malaria tracking in Bhutan, using GPS data collected over smart phones. If collaborations between the WHO and VDCP are successful and phones are provided to health workers, telephone reporting could be standardized as a piece of that project. The expansion of technological capacity via mobile phones also creates the opportunity for the design of innovative surveillance features and reporting methods. Several countries have successfully established SMS reporting systems, including Sri Lanka in 2009.<sup>2, 35, 40</sup> Any such initiatives in Bhutan would be contingent not only on funding, but on system design, and the accessibility and acceptability to local health workers.

Going forward, the surveillance system will also have to expand and tighten its coverage of non-residents in Bhutan. A major obstacle for the elimination of malaria in Bhutan will be ongoing reintroductions of malaria through porous borders and migrant laborers. Nearly half of all cases in Wangdue district in 2012 were non-residents. Wangdue is the site of a major hydropower project which has been contracted to an Indian construction company. Currently,

when a worker at one of these sites is found to be infected with *Plasmodium spp.* parasites, the VDCP attempts to carry out mass blood screenings of all the workers at the site. However, this only occurs if the VDCP is notified in the first place and if a mass screening can be negotiated with the project manager. Foreign laborers will be a particularly difficult population to monitor; there is a high degree of cycling as workers come to Bhutan for a few months before returning home, allowing for multiple re-introductions of infections. Demanding work schedules and fear of losing ability to work may decrease care-seeking behavior. There are plans to institute blood screens as a prerequisite for foreign workers, which has the potential to drastically decrease the number of malaria cases in Bhutan. However, there is the possibility that it could make foreign workers less likely to seek care if they become sick if they believe that this may result in the loss of their work privileges.

The Roll Back Malaria initiative suggests that countries with highly malarious borders may choose to postpone elimination efforts until neighboring countries are able to control their high incidence levels.<sup>6</sup> Waiting for India would mean a substantial delay for Bhutan which is anxious to be free of malaria, but without significant improvements in malaria control across the border the future of elimination in Bhutan seems uncertain, and the 2020 timeline especially so. In the absence of effective surveillance and health service delivery in Assam, this state and its neighbors will continue to act as a source for re-introduction of infections in southern Bhutan.<sup>41</sup> Cross-border collaborations have been limited until now, but they will have to be a priority for both countries to see case reductions in this area. The Asia Pacific Malaria Elimination Network represents the collective interests of the region and could therefore act as a mediator to broker collaborations and facilitate joint applications for cross-border funding.<sup>41, 42</sup>

Finally, and more broadly, the successes of the VDCP and the malaria surveillance system can be leveraged in the control of emerging vector-borne diseases in Bhutan such as dengue, leishmaniasis, and chikungunya. Integrated vector management strategies can be used to progress towards elimination even as the spread of these other diseases is controlled, and the surveillance apparatus for malaria could be expanded to fill the present void of systematic surveillance of other vector-borne diseases.

### **Priority Actions:**

**More sophisticated data management and analysis.** The surveillance system utilizes just a fraction of the information which is collected, and harnessing this information more effectively could aid in pro-elimination efforts. Human resources are a challenge, but even the addition of relatively simple calculations such as percent agreement of slide readings can provide a way to compare districts and the national average, to assess progress over time, and to meaningfully communicate with outside public health entities.

**Optimize diagnostic capacity.** Additional immediate training for local health workers is a necessity, as well as a more rigorous attention to individual worker performance. Routine refresher training should be required. Competency will be difficult to maintain in an era of elimination, so rapid diagnostic tests may need to be added to diagnostic algorithms, if field performance improves.

**Improved timeliness.** Standardizing telephone reporting is one avenue. The VDCP may consider incorporating the proportion of *P. falciparum* infections with gametocytes present as an indicator of timeliness of patient diagnosis for use during the cross-check process. Timeliness will likely improve with expansion of digital access and potential SMS based reporting...

**Active case-finding when risk is high.** This should include active blood screenings in the vicinity of locally acquired infections, as well as a more pro-active approach towards imported infections. There are plans to institute blood screens as a prerequisite for foreign workers, which would be a significant step in the control of cross-border malaria.

**Formalization of cross-border collaboration.** A major obstacle for the elimination of malaria in Bhutan will be ongoing reintroductions of malaria through porous borders and migrant laborers. Unified efforts between India and Bhutan are required.

**Expansion of surveillance apparatus to include other diseases.** The successes of the malaria surveillance system can be leveraged in the control of emerging vector-borne diseases in Bhutan, such as dengue, leishmaniasis, and chikungunya.

**Additional studies into G6PD prevalence and vector ecology.** G6PD prevalence must be determined; the hazard of using primaquine as a standard treatment in the absence of this knowledge is great, and monitoring should be conducted adverse reactions. Research into the ecological epidemiology of malaria in Bhutan, including vector incrimination and environmental drivers of transmission, would allow targeted vector control as well as forward-looking risk assessment for challenges such as climate change.



Bhutan has seen major reductions in malaria morbidity and mortality since the 1994 peak of cases, and a substantial dwindling from 2006-2012. Surveillance has played an important role in the ability of the VDCP to provide high quality, targeted control services to the foci of transmission during this period. Bhutan is now aligning itself in the pre-elimination stage, but higher rates of case detection through increased and more accurate blood screens will be required. Despite significant challenges of funding and the potential of re-introductions of infections, elimination in Bhutan may be possible if top-tier surveillance is conducted and vector control activities are conducted with vigor.

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Appendix 1

Malaysia Level	District	2006			2007			2008			2009			2010			2011			2012				
		Population	BSE	SPR	API	BSE	SPR	API	BSE	SPR	API	BSE	SPR	API	BSE	SPR	API	BSE	SPR	API	BSE	SPR	API	
No Malaria	Bumihang	17,257	184	1.1%	0.12	0.29	0.00	0.00	0.8%	0.06	0.00	0.00	0.0%	0.00	0.00	0.00	0.0%	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Gas	3,346	0	0.0%	0.00	0.00	0.00	0.00	0.0%	0.00	0.00	0.00	0.0%	0.00	0.00	0.00	0.0%	0.00	0.00	0.00	0.00	0.00	0.00	
	Pano	39,118	442	2.5%	0.28	0.70	1.5%	0.10	0.4%	0.03	0.00	0.00	0.0%	0.00	0.00	0.00	0.0%	0.00	0.00	0.00	0.00	0.00	0.00	
	Thimphu	101,883	2,722	2.3%	0.62	1,568	1.5%	0.20	1,096	1.3%	0.14	1,307	1.5%	0.20	1,440	1.1%	0.16	1,354	1.0%	0.14	873	0.3%	0.03	0.03
	<b>TOTAL</b>	<b>161,604</b>	<b>3,348</b>	<b>2.3%</b>	<b>0.47</b>	<b>1,782</b>	<b>1.6%</b>	<b>0.18</b>	<b>1,452</b>	<b>1.3%</b>	<b>0.10</b>	<b>1,599</b>	<b>1.4%</b>	<b>0.14</b>	<b>1,608</b>	<b>1.2%</b>	<b>0.12</b>	<b>1,674</b>	<b>1.1%</b>	<b>0.11</b>	<b>1,024</b>	<b>0.4%</b>	<b>0.02</b>	<b>0.02</b>
Seasonal	Lhunte	16,301	30	3.3%	0.06	50	6.0%	0.18	88	0.9%	0.00	25	0.0%	0.00	66	0.0%	0.00	9	0.0%	0.00	0	0.00	0.00	0.00
	Monggar	39,922	455	4.2%	0.48	409	2.4%	0.25	218	0.9%	0.05	158	3.8%	0.15	446	1.1%	0.13	518	0.4%	0.05	259	0.0%	0.00	0.00
	Punakha	25,204	417	0.5%	0.08	616	0.6%	0.16	291	1.7%	0.20	134	0.0%	0.00	0	0.0%	0.00	14	0.0%	0.00	34	0.0%	0.00	0.00
	Wangdue	33,668	435	2.1%	0.27	146	4.1%	0.18	65	1.5%	0.03	404	2.0%	0.24	407	0.7%	0.09	698	0.6%	0.12	480	3.1%	0.24	0.24
	Trashigang	51,781	113	4.4%	0.10	198	4.5%	0.17	110	0.9%	0.02	94	3.2%	0.06	48	2.1%	0.02	35	0.0%	0.00	64	0.0%	0.00	0.00
	Trashyungtse	18,995	1	0.0%	0.00	95	3.2%	0.16	3	0.0%	0.00	3	0.0%	0.00	1	0.0%	0.00	61	1.6%	0.05	33	0.0%	0.00	0.00
	Haa	12,397	0	0.0%	0.00	23	0.0%	0.00	58	0.0%	0.00	37	0.0%	0.00	8	0.0%	0.00	21	0.0%	0.00	39	0.0%	0.00	0.00
	Tongsa	14,448	34	11.8%	0.28	44	2.3%	0.07	17	17.6%	0.21	0	0.0%	0.00	32	0.0%	0.00	27	0.0%	0.00	11	9.1%	0.07	0.15
	Tsimgo	19,932	834	7.1%	2.96	855	1.5%	0.65	1293	0.8%	0.50	1819	1.4%	1.25	1667	0.9%	0.70	872	0.7%	0.30	836	0.4%	0.15	0.15
	<b>TOTAL</b>	<b>232,648</b>	<b>2,319</b>	<b>4.3%</b>	<b>0.43</b>	<b>2,434</b>	<b>2.0%</b>	<b>0.21</b>	<b>2,143</b>	<b>1.0%</b>	<b>0.09</b>	<b>2,674</b>	<b>1.6%</b>	<b>0.18</b>	<b>2,655</b>	<b>0.9%</b>	<b>0.10</b>	<b>2,255</b>	<b>0.6%</b>	<b>0.06</b>	<b>1,756</b>	<b>1.1%</b>	<b>0.05</b>	<b>0.05</b>
Perennial	Chukha	79,943	830	2.5%	2.49	575	1.0%	0.69	6377	0.4%	0.31	10037	0.6%	0.74	6188	0.3%	0.21	5570	0.2%	0.13	6478	0.0%	0.01	0.01
	Dagana	24,579	104	7.7%	0.33	381	1.3%	0.59	2533	0.5%	0.45	2923	2.1%	2.52	2741	1.2%	1.34	1748	0.5%	0.33	1907	0.1%	0.04	0.04
	Pemagatshel	23,478	183	6.0%	0.47	1734	1.7%	1.24	1634	0.8%	0.51	2120	0.5%	0.38	2304	0.7%	0.64	2302	0.3%	0.26	2218	0.2%	0.21	0.21
	Sandrupingkhur	36,608	1493	4.4%	1.68	7904	4.0%	7.65	6888	1.4%	2.35	7600	1.2%	2.49	6706	0.7%	1.15	5208	0.3%	0.44	5600	0.1%	0.16	0.16
	Santse	64,313	21027	2.3%	3.86	10952	0.6%	0.92	9638	0.2%	0.26	10654	0.6%	1.06	9591	0.3%	0.45	5652	0.2%	0.20	3888	0.0%	0.00	0.00
	Surpung	40,456	2145	3.8%	1.40	1976	1.6%	0.18	1372	1.9%	0.36	2216	3.3%	3.06	2148	0.3%	0.16	3652	0.8%	0.35	3888	0.0%	0.00	0.00
	Zharpang	14,457	165	1.1%	0.07	137	0.9%	0.04	103	0.7%	0.04	103	0.7%	0.04	103	0.7%	0.04	103	0.7%	0.04	103	0.7%	0.04	0.04
	<b>TOTAL</b>	<b>289,155</b>	<b>60112</b>	<b>3.5%</b>	<b>5.85</b>	<b>47230</b>	<b>1.6%</b>	<b>2.47</b>	<b>43673</b>	<b>0.7%</b>	<b>1.01</b>	<b>58069</b>	<b>1.8%</b>	<b>3.14</b>	<b>50353</b>	<b>0.8%</b>	<b>1.36</b>	<b>40552</b>	<b>0.5%</b>	<b>0.56</b>	<b>39732</b>	<b>0.2%</b>	<b>0.23</b>	<b>0.23</b>
	<b>NATIONAL TOTAL</b>	<b>683,407</b>	<b>66079</b>	<b>3.4%</b>	<b>2.73</b>	<b>51446</b>	<b>1.7%</b>	<b>1.16</b>	<b>47268</b>	<b>0.8%</b>	<b>0.48</b>	<b>62342</b>	<b>1.8%</b>	<b>1.42</b>	<b>54616</b>	<b>0.9%</b>	<b>0.64</b>	<b>44481</b>	<b>0.5%</b>	<b>0.28</b>	<b>42512</b>	<b>0.2%</b>	<b>0.12</b>	<b>0.12</b>