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Early detection of malaria foci for targeted interventions in endemic southern Zambia

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Background

While *Plasmodium falciparum* is endemic throughout Zambia, the country has documented significant reductions in the burden of malaria[1,2] through the scale-up of malaria control interventions advocated by the World Health Organization's (WHO's) Roll Back Malaria (RBM) Partnership[3] and Zambia's National Malaria Control Program[4]. Zambia's implementation of the "scale-up for impact" approach has included ambitious goals that go beyond the RBM principles, calling for 80% population coverage rates for interventions including insecticide-treated mosquito nets (ITNs) or indoor residual spraying (IRS), intermittent preventive treatment during pregnancy (IPTp) and ITNs, and prompt, effective treatment of cases diagnosed by microscopy or rapid diagnostic tests (RDTs)[4]. A 2010 review of the impact of Zambia's control program found substantial progress toward achieving these goals and concluded "As the infection and disease become more focal, community techniques to map malaria cases and transmission and an approach of testing and treating the remaining infected population will be required"[2].

To this end, efforts are already underway at a cluster of 13 rural health centers (RHCs) in the Choma and Namwala districts in Zambia's Southern Province (see Figure 1). Since August of 2008, a surveillance system has been established based on RDTs, for rapid and accurate diagnoses, and mobile telephones to transmit weekly data by SMS text message from the RHCs to the Malaria Institute at Macha (MIAM), located centrally. The information transmitted includes the name of the RHC, name of the transmitting nurse, number of RDTs used during the week, and the number of positive RDT diagnoses. This data is compiled, monitored for abnormalities, and periodically cross-referenced back to the original clinic records. A more detailed description of the methods has been published previously[5].

The 13 RHCs serve a total population that reached approximately 158,281 people in 2010. The region is characterized as Miombo woodland, with a tropical climate consisting of three seasons: a cool, dry winter (April-August); a hot, dry season (August-November); and one hot, rainy season lasting from approximately November to April each year[6]. Although the elevation gradient is modest (See Figure 1 and Table 1), the RHC sites in the north are in or near a floodplain where the water table depth during normal seasons is only about 2-5m below the ground[5]. The RHC sites farther south are at slightly higher elevations, away from the floodplain, and the water table is generally about 10-40m below the ground[5]. *Anopheles arabiensis* is the predominate vector[6,7]. The discrepancy in the water table impacts the nocturnal humidity and the permanence of surface water, important for the *Anopheles* breeding and blood feeding behaviors[6,8].

The incidence of RDT diagnosed malaria reflects the impact of these geographic and seasonal conditions (See Figure 2). A high transmission season is observed from week 47 through week 22. This is corresponds only approximately with the November to April rainy season. The weeks of elevated incidence start slightly later than the beginning of the rainy season and end slightly later than the end of the rainy season. This lag may be attributed to the *Plasmodium falciparum* incubation delay, a diagnostic delay, the persistence of surface water in the weeks after the rainy season and the *Anopheles* behavior (the vectors gradually increase in number during the rainy season, with the development of breeding habitats, and peak in March and April[6]).

Stratification of the rural health centers by locality and elevation reveals different incidence patterns (See Figure 2 and Table 1). Chitongo is located in the floodplain and incident malaria cases are regularly diagnosed throughout the year. Four RHCs near the floodplain, and serving some homesteads in the floodplain, have minimal incidence during the low transmission season (weeks 23-46). Incident cases are rare during the low transmission season at the eight RHCs in the southern zone that has been termed the "Macha Heartland"[5]. The incidence of diagnosed malaria rises more rapidly at the RHCs in the transitional zone between the floodplain and the heartland as compared to those sites within the heartland. During the 10 weeks at the beginning of the high transmission season (weeks 47-4), the mean

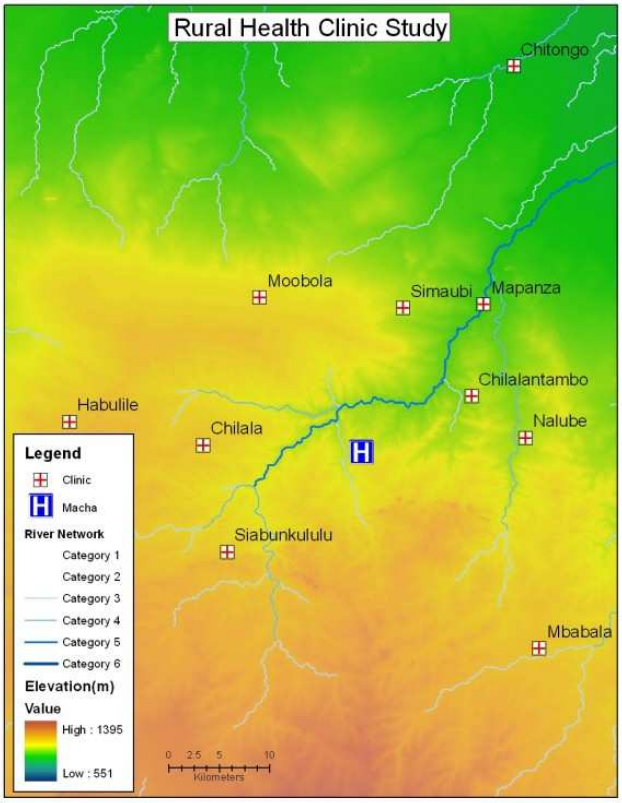

Figure 1: Elevation/Contour map of the Rural Health Center Study Area in Choma/Namwala Districts, Southern Province, Zambia. Rural Health Centers collaborating are named and indicated. Drainage lines and river systems are indicated in ordinal categories. Category 1 is a simple drainage line that flows during and shortly after rain, Category 6 is a permanent large river[5]

incidence of malaria diagnoses is 1.58 (1.10, 2.06) per 10,000 people at sites in the transitional zone, while it is only 0.70 (0.41, 0.99) per 10,000 people at sites in the heartland. However, the overall high transmission season mean incidence is comparable in all three zones (See Table 1).

During periods when mosquito populations are minimal, asymptomatic infection serves as a reservoir for the parasite population and a source of transmission when mosquito populations expand[9,10]. Efforts to move beyond the advances of the scale-up phase of the Zambia malaria control program, ultimately with an eye toward elimination, will need to target these asymptomatic infections. The transition from burden reduction to transmission interruption requires active methods to supplement passive case detection for identification and elimination of malaria foci[11]. Planning for such a program requires a realistic accounting of logistic, and financial feasibility. "Proactive" or "aggressive active case detection" is resource intensive. Each positive diagnosis in a proactive control strategy implemented in the Brazilian Yanomami area was estimated to cost 2.3 times more than a passive diagnosis[12]. Population mobility and testing fatigue are also concerns[11]. Such a program is likely infeasible in Zambia, given the constrained resources and the commitment required to sustain current gains and advance toward the "scaling-up for impact" 80% coverage goal[4]. "Reactive" case detection, in contrast, is a more modest undertaking, triggered when a case is identified by passive case detection, and involves screening around the index case. Surveillance is a vital component of this strategy.

The program in southern Zambia, making use of RDTs and mobile phones, facilitates timely and accurate dissemination of local surveillance data that could be used for reactive case detection. A small pilot study at four of the RHCs (Nalube, Chilalantambo, Mapanza, and Chitongo) supported the feasibility of reactive case detection methods to identify asymptomatic infections during the dry season. It was hypothesized that "targeting malaria during period of low transmission when it is most vulnerable to elimination" could supplement the scaling up efforts to achieve better malaria control[13]. All of the malaria diagnoses from June to August of 2009 at these 4 RHCs were followed up with a visit to their homestead. All consenting residents completed a questionnaire, were tested for malaria, and those testing positive by RDT received treatment. Prevalence, as determined by PCR diagnosis, was statistically significantly higher (p=0.006) among homesteads identified through passive case detection (8.0%) as compared to a control group of randomly selected households (0.7%). 2.3% of RDTs were positive among the case population as compared to 0.7% among the controls, but this difference was not statistically significant (p=0.56). A

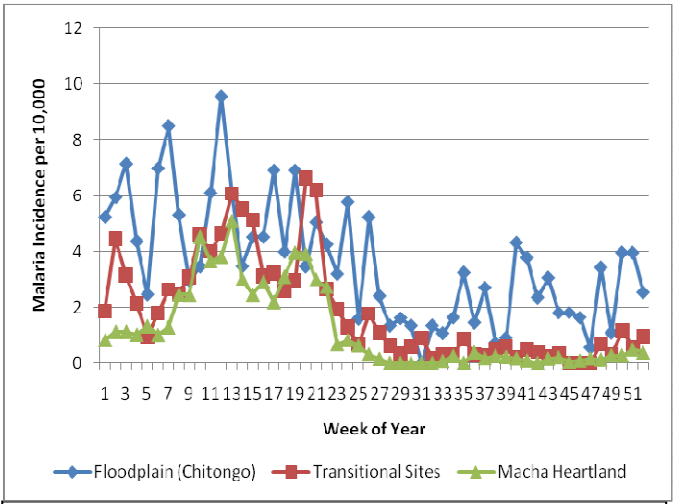

Figure 2: Graph showing the mean weakly incidence of diagnosed Malaria throughout a year at rural health centers in the Choma and Namwala Districts in Southern Province, Zambia. *The centers were separated into three zones based on locality and elevation (See Figure 1).

larger sample size and data from multiple seasons could further validate this approach to identify asymptomatic malaria foci.

In seasonally endemic regions like southern Zambia, the term "epidemic" is essentially used to describe any occurrence of malaria cases in excess of normal[14]. However, there is a lack of precision regarding what should be expected as "normal" on any given week at any specific RHC in an environment with such seasonal and geographically driven incidence variability. An early detection system to identify and target foci of aberrant case burdens (especially during the transitional weeks 47-4) before they spread to adjacent communities could build on the success observed during the dry season when acute exacerbations of incidence are more apparent.

The WHO RBM program supports the establishment of surveillance and early detection systems to prevent or contain malaria epidemics: "Timely detection of cases of illness in a community or region, above the normally expected level, is vital to ensure that health authorities and policy-makers are aware of the serious and immediate threat before them and to help them make decisions on effective control measures"[15]. A RBM framework for public health workers in Africa suggests a variety of simple methods to develop early warnings system thresholds in resource-constrained settings[15].

One very basic method advocated by the WHO[16] does not require access to a computer. An alert threshold is set at the upper third quartile of the previous five years of monthly case numbers for a given location (ie the second highest value for each month among the five years). A method proposed by Cullen et al[17] uses the previous five years of data to determine the monthly mean number of cases and sets the epidemic threshold at the mean plus two standard deviations. Because abnormal years have a greater influence on this method than the WHO technique, "epidemic" years are arbitrarily excluded. The Centers for Disease Control developed the cumulative sum (c-sum) method[18] to increase the historical sample size and reduce the impact of aberrant months on the threshold calculation. The historical baseline is calculated as the average of the reported number of cases for the preceding month, the corresponding month and the following month, for the previous five years. The mean plus two times the standard deviation of these 15 correlated observations is used to calculate a threshold value.

The Cullen et al technique (using the five-year historic monthly mean plus two standard deviations) was applied to cases of *Plasmodium vivax* in northern Thailand during the 1980s[17]. A 2006 paper out of the Thailand Ministry of Public Health Bureau of Vector Borne Disease responded to the Cullen method suggesting "this reporting mechanism is not timely enough to detect the occurrence of a malaria epidemic which usually occurs at the district level over a short period of time"[19]. As an alternative, they propose and test an early detection method employing a *Poisson* distribution in the malaria endemic Kanchanaburi Province. The Province is divided in two zones with different transmission patterns. Following a detection system described by Delacollette in 2001[20], separate alert thresholds were calculated by determining a 95% confidence interval around the weekly mean case numbers during the two years of 2000 and 2001 at nine Vector Borne Disease Control Units divided between the two transmission zones[19]. Validating the threshold levels

against a historic "epidemic year" and prospectively testing the threshold for the year of 2002, the authors conclude that the Poisson distribution offers "an effective alternative method for the development of an early detection system"[19].

Here we will apply this Poisson technique to the Southern Province Zambia surveillance data, calculating weekly thresholds for each of the three zones (floodplain, transitional sites, and Macha heartland) and validate the system against the 2010 data at the RHC level.

Methods

An early detection threshold was developed for 13 RHCs in Southern Province, Zambia. The weekly number of RDT diagnosed malaria cases were obtained from each of the 13 sites for 129 weeks beginning in August, 2008. The data includes many lacunae (See Table 1) due to occasional RDT stock depletion, staff shortages or delayed SMS reporting to the central register at MIAM. Population estimates from a 2001 census for the catchment area of each of the RHCs[5], adjusted with an estimated 3.0% annual growth rate[4] were used as the weekly person-time of exposure.

The 13 RHCs were separated into three zones based on elevation, locality and observed incidence pattern (See Table 1). Aggregating the data from RHCs within the same zone, a Poisson distribution was used to calculate an expected mean weekly incidence and a 95% confidence interval for each zone. The upper limit of this confidence interval was considered the alert threshold for early detection. Weeks where data was missing were excluded from the mean and confidence interval calculations. Line graphs of the weekly means and the upper 95% confidence interval limits for each of the three zones were constructed (See Figures 3, 4 and 5).

Because the majority of RHCs had fewer missing weeks during the 2010 year than in previous years (see Table 1), the zone threshold levels were validated against the 2010 data. The weekly incidence for all available weeks during the 2010 year at each of the 13 RHCs was compared to the zone threshold levels. Of those weeks with data available, the percent which exceeded the threshold level was calculated (See Table 2). In an effort to determine if a

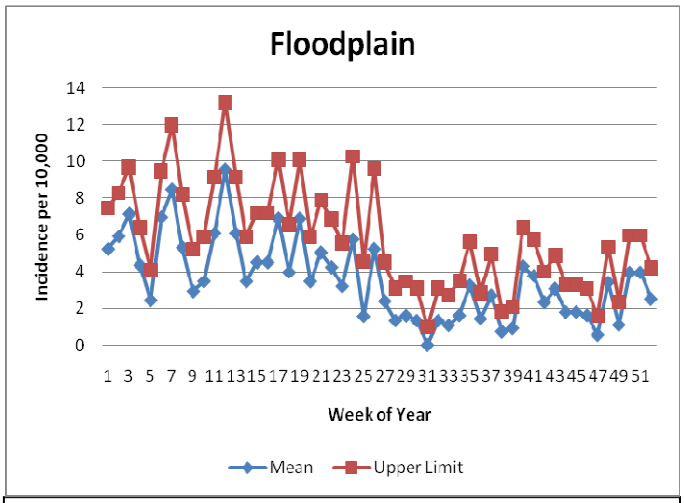

Figure 3: The Poisson distribution of the mean weekly incidence of malaria diagnosis in the flood plain

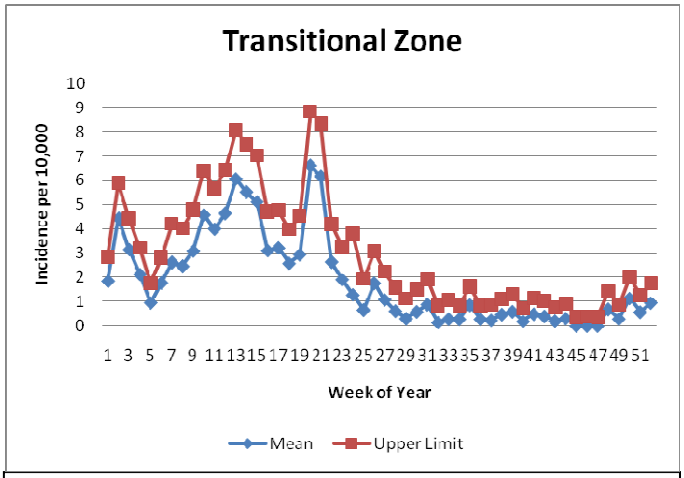

Figure 4: The Poisson distribution of the mean weekly incidence of malaria diagnosis in the transitional zone

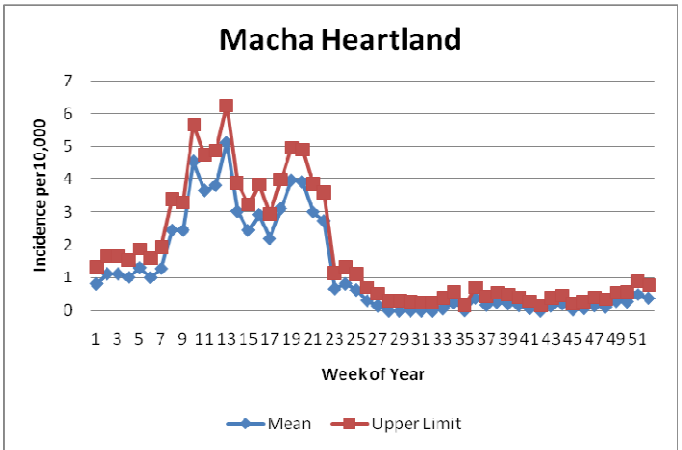

Figure 5: The Poisson distribution of the mean weekly incidence of malaria diagnosis in the Macha Heartland

breach of the threshold was predictive of continued elevated incidence, the percent of those weeks above the threshold which were part of a string of three or more consecutive aberrant weeks was also calculated (See Table 2).

Results

The 2010 data exceed the established thresholds relatively frequently (See Table 2). Many of these

During the low transmission when the threshold is relatively low in the transitional and heartland zones, each incident case could represent a

The percent of those weeks above the threshold value which were part of a consecu

Among the weeks with data available, the percent of those weeks above the threshold level was calculated (see Table 2). A further calculation was performed to determine the percent of those weeks exceeding the threshold value

Each of the 13 RHCs

are shown in Figures 3 and 4.

were used as denominators to calculate weekly incidence of malaria diagnoses. The data includes many lacunae (See Table 1) due to occasional RDT stock depletion, staff shortages or delayed SMS reporting to the central register at MIAM.

The 129 weeks of data span the years 2008 to 2010. A mean weekly incidence of diagnosed malaria cases was calculated for each of the 52 weeks of the year using all years where data was available and aggregating RHCs within the same zone. A Poisson distribution, using the population as the weekly person time of exposure, was calculated

The weekly incidence of diagnosed malaria cases

For each of the 52 weeks of the year, the incidence of diagnosed malaria cases

and test it against the 2010 figures.

Given the success of this Poisson technique and because it does not require five years of historic data,

the development and implementation of appropriate early warning systems

Discussion:
In addition to reactive testing and treating family members of passively identified cases, the communities involved could be reviewed for shortfalls in the scaling-up intervention coverage and the need for additional ITNs or IRS.

The Poisson technique was selected based on the reported successful implementation in Thailand, because it recognizes the importance of granular weekly and local level thresholds to allow for an agile public health response, and because it does not require the 5 years of historic data.

reflecting the granular local and weekly levels

with granular

During the low transmission when the threshold is relatively low in the transitional and heartland zones, each incident case could represent a

but also because it did not require the five years of historic data necessary for the other methods described above.

Applicability of poisson assumptions

Eventually could make individual graphs for each RHC as more years of data become available and other methods could be tried and compared with this method.

Table 1: Patterns of Malaria Rapid Diagnostic Test Diagnoses at 13 Rural Health Centers in Southern Province, Zambia

Health Center	Elevation (m)	Distance from Chitongo (m)	Estimated 2010 Population	Mean Weekly Incidence per 10,000 (95% CI)			Overall % weeks missing data	2010 % weeks missing data
				Low Transmission Season: Weeks 23-46	First 10 Weeks (47-4) of High Transmission Season	High Transmission Season: Weeks 47-22		
Flood Plain:								
Chitongo	1,013	0	19,136	2.15 (1.61, 2.69)	3.87 (2.17, 5.57)	4.63 (3.56, 5.71)	4.65	0.00
Transitional Sites:				0.96 (0.66, 1.26)	1.58 (1.10, 2.06)	2.80 (2.29, 3.31)		
Mapanza	1,059	23,842.15	22,710	0.32 (0.20, 0.44)	1.36 (0.23, 2.50)	2.56 (1.71, 3.41)	3.10	3.85
Simaubi	1,117	26,414.26	9,794	0.14 (0.00, 0.28)	2.41 (1.15, 3.67)	3.57 (2.48, 4.67)	33.33	3.85
Chilalantambo	1,100	33,062.07	3,411	1.99 (1.20, 2.79)	1.22 (0.40, 2.05)	3.03 (1.69, 4.37)	11.63	3.85
Nalube	1,110	36,943.90	3,411	1.18 (0.44, 1.92)	1.57 (0.77, 2.36)	2.25 (1.44, 3.05)	12.40	17.31
Macha Heartland:				0.22 (0.14, 0.29)	0.70 (0.41, 0.99)	3.25 (2.53, 3.98)		
Mangunza	1,087	36,868.70	12,729	0.35 (0.04, 0.66)	0.41 (0.16, 0.66)	2.36 (1.45, 3.27)	22.48	7.69
Moobola	1,165	34,127.33	18,731	0.09 (0.02, 0.15)	0.51 (0.22, 0.80)	1.02 (0.72, 1.32)	23.26	5.77
Macha	1,136	41,245.03	19,950	0.25 (0.11, 0.39)	0.80 (0.30, 1.30)	1.68 (1.17, 2.18)	6.98	5.77
Chilala	1,187	48,677.06	12,565	0.08 (-0.02, 0.18)	0.14 (-0.15, 0.42)	1.47 (0.78, 2.17)	24.03	23.08
Siabunkululu	1,190	56,024.10	12,064	0.25 (0.08, 0.42)	0.07 (-0.03, 0.16)	2.86 (1.65, 4.07)	21.71	25
Habulile	1,210	56,465.00	9,424	0.34 (0.08, 0.60)	1.24 (0.14, 2.35)	3.88 (2.67, 5.09)	6.20	13.46
Mbabala	1,204	57,940.70	13,023	0.01 (-0.01, 0.04)	0.25 (-0.06, 0.55)	0.56 (0.20, 0.92)	7.75	5.77
Kamwanu	1,273	59,384.41	1,333	0.48 (-0.20, 1.15)	2.25 (-0.05, 4.53)	13.12 (7.89, 18.35)	35.66	19.24

Table 2: 2010 weeks exceeding threshold levels

Rural health Center	Low transmission season % weeks above threshold	High transmission season % weeks above threshold	Overall % weeks above threshold	Overall % of aberrant weeks part of a 3+ consecutive week period of incidence above threshold
Chitongo				
Mapanza				
Simaubi				
Chilalantambo				
Nalube				
Mangunza				
Moobola				
Macha				
Chilala				
Siabunkululu				
Habulile				
Mbabala				
Kamwanu				

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