

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

1 **Spatial-temporal clustering analysis of yaws on Lihir Island, Papua New** 2 **Guinea to enhance planning and implementation of eradication programs**

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20 **Abstract**

21 **Background**

22 In the global program for the eradication of yaws, assessments of the prevalence of the disease
23 are used to decide where to initiate mass treatment. However, the smallest administrative unit
24 which should be used as the basis for making decisions is not clear. We investigated spatial and
25 temporal clustering of yaws to help inform the choice of implementation unit.

26 **Methodology/Principal findings**

27 We analyzed 11 years of passive surveillance data on incident yaws cases ($n = 1448$) from Lihir
28 Island, Papua New Guinea. After adjusting for age, sex, and trends in health-seeking, we
29 detected three non-overlapping spatiotemporal clusters ($p < 1 \times 10^{-17}$, $p = 1.4 \times 10^{-14}$, $p = 1.4 \times 10^{-8}$). These lasted from 28 to 47 months in duration and each encompassed between 4 and 6
30 villages. We also assessed spatial clustering of prevalent yaws cases ($n = 532$) that had been
31 detected in 7 biannual active case finding surveys beginning in 2013. We identified 1 statistically
32 significant cluster in each survey. We considered the possibility that schools that serve multiple
33 villages might be loci of transmission, but we found no evidence that incident cases of yaws
34 among 8- to 14-year-olds clustered within primary school attendance areas ($p = 0.684$).

36 **Conclusions/Significance**

37 These clusters likely reflect transmission of yaws across village boundaries; villages may be
38 epidemiologically linked to a degree such that mass drug administration may be more effectively
39 implemented at a spatial scale larger than the individual village.

40 **Author Summary**

41 The World Health Organization aims to eradicate yaws using mass drug administration (MDA),
42 which consists of treating everyone in an administrative unit with antibiotics. The administrative

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43 unit in a country which is used as the basis for making decisions about implementing MDA is
44 called the implementation unit. Prevalence assessments are used to identify endemic
45 communities for mass treatment programs, but the spatial scale (e.g. village, sub-district, district,
46 or province) at which mass treatment should be implemented is currently unclear. The choice of
47 implementation unit depends on many factors; one of these is the underlying transmission
48 patterns of the disease. Using data from Lihir Island, Papua New Guinea, we found that
49 geographic clusters of yaws often spanned multiple villages. These clusters likely reflect
50 transmission of the infectious disease across village boundaries and suggest that it may be best to
51 implement MDA at a spatial scale larger than the individual village, for example at sub-district
52 level.

53 **Introduction**

54 Yaws, a bacterial disease caused by *Treponema pallidum* subspecies *pertenue*, causes skin
55 lesions and arthralgia, most commonly in school-age children [1]. Yaws spreads via direct skin-
56 to-skin contact. While yaws was widespread in tropical areas in the first half of the twentieth
57 century, the disease currently persists primarily in Melanesia and parts of west and central Africa
58 [2]. The discovery that oral azithromycin treats yaws as effectively as injectable penicillin
59 sparked renewed interest in eradicating this neglected tropical disease [3,4]. Yaws often enters a
60 latent stage during which patients are no longer infectious or symptomatic, but still infected and
61 at risk of the disease reactivating and once again being infectious. Eradicating yaws necessarily
62 requires treating all infections, including latent ones. The World Health Organization (WHO)
63 yaws eradication strategy calls for 1 or more rounds of mass drug administration (MDA) in all
64 yaws-endemic areas; that is, treating with azithromycin nearly everyone in these areas, regardless

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65 of individuals' disease status. MDA aims to cure yaws even in latently infected individuals,
66 thereby preventing them from later becoming infectious.

67 Before implementing yaws elimination programs, public health officials need to decide the
68 spatial scale at which to conduct MDA. They refer to the geographic level (e.g. province, district,
69 sub-district or village) with respect to which they decide to start and stop MDA as the
70 "implementation unit" [5]. The WHO initially recommended that the village or community
71 should be the implementation unit [4]. This recommendation was informed, in part, by research
72 concluding that village-level yaws prevalence is a stronger risk factor for yaws than household-
73 level prevalence [6,7]. A more recent review argued that conducting yaws prevalence surveys at
74 the village level is impractical and that the implementation unit for the initial round of MDA
75 should instead be a unit with a population of 100,000 to 250,000 people and that for subsequent
76 treatment rounds the implementation unit could be lowered to the village [8]. The choice of
77 implementation unit is an unresolved challenge in formulating yaws eradication strategy and
78 reflects a lack of research on the spatial epidemiology of yaws. Understanding yaws transmission
79 and clustering not only helps inform the choice of implementation unit, but also is needed to
80 design statistically rigorous assessments of yaws prevalence within each implementation unit.

81 Because clustering of an infectious disease can occur at multiple spatial scales simultaneously
82 [9], research is needed on yaws spatial epidemiology at multiple scales. In this study we assess
83 whether clusters (i.e. areas of disproportionately high prevalence or incidence) of yaws extend
84 across neighboring villages. Spatial-temporal clusters of disease extending across villages may
85 indicate that appreciable levels of disease transmission occur between villages. While most yaws
86 studies have relied on cross-sectional data, we leverage more than a decade of clinical records to
87 include a temporal component in our analysis. Finally, given that yaws is predominantly a

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88 disease of school children and might be expected to be spread at schools, we investigate whether
89 primary school attendance areas help explain the spatial distribution of yaws.

90 Methods

91 Study setting

92 We conducted this study on Lihir Island, a 200 km² tropical island in New Ireland Province,
93 Papua New Guinea. Fig 1 shows that the island's mountainous interior is largely uninhabited and
94 the population of approximately 12 500 Lihirians lives in coastal villages linked by a road that
95 encircles the island. Even the most geographically distant pair of villages are only 35.2 km apart
96 by road. Approximately 4680 migrants live on the island. The island houses a large-scale gold
97 mine. A network of government-run aid posts, a clinic at a Catholic mission station, and the Lihir
98 Medical Centre (LMC) (a hospital that serves both mine personnel and the public) deliver health
99 care services. Yaws has long been endemic in the region; Dr. Robert Koch visited Lihir in 1900
100 and subsequently reported that he observed yaws throughout the Bismarck Archipelago, the
101 group of islands that comprise the northeastern part of present-day Papua New Guinea [10,11].

102 Spatial-temporal clusters of incident yaws from outpatient records

103 We queried the LMC electronic medical record to identify all outpatients who had been
104 diagnosed with yaws between early April 2005 and 29 May 2016. We included only those
105 patients whose reported place of residence was a Lihir village. LMC typically recorded migrants
106 to Lihir (even those living there indefinitely) as being from their place of origin, not the Lihirian
107 village where they currently live.

108 To be considered an incident yaws case at the LMC, patients must present with a skin lesion
109 consistent with yaws and have positive results on both the *Treponema pallidum*
110 hemagglutination assay (TPHA) and the rapid plasma reagin (RPR) test. The TPHA is a highly

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111 specific biomarker that provides definitive diagnosis of prior or current treponemal infection,
112 while RPR, despite being less specific, indicates current disease activity [14].
113 We defined a cluster as a set of 1 or more villages where we observed more incident yaws cases
114 in a time period than expected, given the spatial and temporal distribution of all outpatient visits
115 to the LMC by Lihir village residents and the age and sex distribution of these patients. To detect
116 statistically significant non-spatially overlapping clusters of outpatient yaws diagnoses, we
117 conducted a retrospective space-time analysis in SaTScan version 9.4.4 using the discrete
118 Poisson model [15–17]. We defined the spatial relationships between villages by the road
119 distances between village centroids. Following standard practice for using SaTScan, we set the
120 maximum allowed cluster duration to be half the duration of the study period. Similarly, we
121 constrained the maximum spatial size of a cluster to encompass villages accounting for no more
122 than half the outpatient visits over the course of the study period.

123 **Spatial clusters of prevalent yaws from active surveys**

124 Starting in April 2013, we implemented a round of mass drug administration with azithromycin
125 on Lihir to demonstrate the feasibility of eliminating yaws [18]. All people older than 2 months
126 were offered treatment regardless of symptoms. At the same we administered azithromycin, we
127 examined the participants to identify all suspected yaws cases. We subsequently screened the
128 population every 6 months to identify and treat symptomatic yaws cases and their contacts. In
129 this study, we analyze data through the seventh survey of active case finding, which took place in
130 April and May 2016. We collected venous blood samples from consenting individuals suspected
131 of having yaws and performed TPHA and RPR testing on these samples. We swabbed the ulcers
132 of all suspected yaws cases in surveys 3 through 7. Polymerase chain reaction (PCR) tests were

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133 performed on these swabs. The test consists of amplifying three *T. pallidum* gene targets: *tp0548*,
134 *tpN47* (*tp0574*), and a *pertenuie*-specific region of the *tprL* (*tp1031*) gene [19].

135 In contrast to individuals in the outpatient data from the LMC, we categorized screened
136 individuals in the active case finding data by their current village of residence, without regard to
137 migrant status. We also included as a village in this analysis an informal migrant settlement. We
138 excluded from the analysis cases in villages during surveys where the number of individuals
139 screened was missing for that village.

140 To assess spatial clusters based on data from active case finding with serological confirmation,
141 we analyzed data from each survey separately using the spatial-only discrete Poisson model in
142 SaTScan. Clusters were villages or groups of villages where the proportion of screened
143 individuals who had yaws was greater than expected. We constrained the maximum cluster size
144 such that no cluster contains more than half of the screened population.

145 **Clustering of incident yaws cases within primary school attendance areas**

146 Using data on the village of residence of students at each Lihir primary school in 2013, we
147 defined primary school attendance areas based on the most frequent primary school affiliation of
148 primary school-enrolled children from each village.

149 In this analysis, we restricted the outpatient visit data to 8-to 14-year-olds. We calculated for
150 each village the number of incident yaws cases divided by the total number of outpatient visits.
151 Next, we calculated the F-statistic from weighted analysis of variance (ANOVA) to quantify the
152 degree to which primary school attendance areas account for between-village differences in the
153 number of yaws cases per outpatient visit. We weighted each proportion by the inverse of its
154 variance. Because the inverse of the variance is not defined when there are no yaws cases among

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155 8- to 14-year-olds from a given village in a given year, we added 2 yaws cases and 4 outpatient
156 visits to every village only when calculating weights [20].

157 Finally, to test whether clustering of yaws cases in primary school attendance areas deviated
158 from the null hypothesis (that clustered cases in villages served by a given primary school result
159 from their spatial clustering rather than attendance at the same school), we permuted the primary
160 school attendance area assignments while maintaining the condition that each primary school
161 serves a sequential set of villages along the circumference of the island and calculated the F-
162 statistic for each permutation using weighted ANOVA , thereby constructing an empirical
163 distribution from which we calculated p-values [21]. Analyses were conducted in R version 3.4.2
164 [22].

165 **Ethics approval and informed consent**

166 The protocol was approved by the National Medical Research Advisory Committee of the Papua
167 New Guinea National Department of Health (MRAC no. 12.36).

168 **Results**

169 **Passive case detection and spatial-temporal clusters of incident yaws cases**

170 From 11 years of routinely collected clinical data on residents of Lihir villages, we identified
171 2365 distinct symptomatic yaws cases but excluded 917. Our main analysis is based on 1448
172 cases of yaws among 1271 patients (Fig 2A). During this period, Lihirians made a total of
173 288 729 outpatient visits to the LMC (Fig 2B; S1 Fig). The median age at diagnosis of the yaws
174 cases was 9 years (interquartile range: 6 – 13). The cumulative number of yaws patients per
175 village varied widely, ranging from 4 yaws cases out of 1390 outpatient visits from Huniho and 4
176 out of 3156 from Lienbil to 234 out of 32859 from Kunaye 1.

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177 We detected 3 statistically significant spatial-temporal clusters (Fig 3, S2 Fig). The most
178 statistically significant cluster ($p < 1 \times 10^{-17}$) lasted from July 2009 into March 2012 and
179 encompassed 6 villages at the southern tip of Lihir (cluster 1); the most distant pair of villages in
180 that cluster are 10.7 km apart by road. The next most statistically significant cluster ($p = 1.4 \times 10^{-14}$)
181 lasted from the beginning of the study period (April 2005) until the beginning of March 2009
182 and occurred in 4 villages located along the east coast of Lihir (cluster 2) and spanned over a
183 road distance of 5.1 km. Finally, the third statistically significant cluster ($p = 1.4 \times 10^{-8}$) lasted
184 from January 2014 through the end of the study period in May 2016. It comprised 4 villages
185 located in the northeast corner of Lihir (cluster 3) which are at most 7.4 kilometers apart by road.
186 Our analysis of spatial-temporal clustering incident yaws cases was robust to a range of
187 assumptions, including restricting only to yaws cases for which a positive RPR result was
188 recorded in the medical record (S1 Table), not adjusting for age and sex (S2 Table), and using
189 SaTScan's case-only space-time permutation method instead of the discrete Poisson method [23]
190 (S3 Table and S4 Table). While the exact timing and duration of clusters varied somewhat
191 between the different analyses, all found evidence of 3 high statistically significant spatial-
192 temporal clusters, and the temporal order and general locations of those clusters were unchanged.

193 **Active case finding and spatial clustering of prevalent yaws cases**

194 Out of 95 353 screenings during the 7 biannual active case finding surveys (mean of 13 622
195 individuals screened per survey), we identified 568 serologically confirmed yaws cases, of which
196 36 were excluded (Fig 4). More than half of all serologically confirmed cases were identified
197 during the first (pre-MDA) round of screening. Before exclusions, the median age of the
198 serologically confirmed cases was 12 years (interquartile range: 8 – 14). We detected 1

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199 statistically significant cluster in each survey, at the $\alpha = 0.05$ level of significance (Fig 5). The
200 number of villages in each cluster varied widely from 1 to 16.
201 In a supporting analysis we repeated our active-case finding analysis using PCR-confirmed cases
202 only. S3 Fig lists 116 PCR-confirmed cases and 11 exclusions by survey, and results for PCR-
203 confirmed cases are shown in S4 Fig. The results from PCR-confirmed and serologically
204 confirmed yaws cases are broadly similar in that most clusters of serologically-confirmed cases
205 overlapped with a cluster of PCR-confirmed cases, but fewer of the clusters detected in the PCR-
206 based analysis were statistically significant. Unlike in the analysis of serologically confirmed
207 cases, there were no statistically significant clusters of PCR-confirmed yaws in the third or fifth
208 surveys.

209 **Primary school attendance areas and yaws**

210 We categorized each village into 1 of 7 primary school attendance areas. Four of the primary
211 school attendance areas consisted of 4 villages, while the remaining 3 areas consisted of 1, 3, and
212 6 villages apiece (Fig 6A). We identified a total of 643 incident cases of serologically confirmed
213 yaws among 8- to 14-year-olds, out of 32 202 visits by outpatients age 8 to 14. We did not find
214 evidence for clustering of incident yaws cases among 8- to 14-year-olds within primary school
215 attendance areas in individual years 2006 through 2015 (p-values ranged from 0.0687 in 2006 to
216 0.9881 in 2009), nor in the combined data ($p = 0.6846$) (Fig 6 and S5 Table).

217 **Discussion**

218 We found highly statistically significant spatial-temporal clusters of incident yaws cases, which
219 stretched over multiple years and multiple villages. These clusters likely reflect transmission of
220 yaws across village boundaries. The overall incidence of yaws can be viewed as the sum of an
221 endemic and an epidemic component. The transmission dynamics of yaws on Lihir may consist

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222 of repeated and overlapping “outbreaks” of yaws that, when aggregated at the scale of the entire
223 island, create the appearance of a persistently high-level endemic disease. The results of our
224 analysis of purely spatial clusters (based on data from biannual surveys of active case finding)
225 correspond in some respects to the results of our analysis of spatial-temporal clusters. For
226 example, in the period January 2014 to May 2016 we identified a spatial-temporal cluster in
227 northeastern Lihir that coincided with purely spatial clusters identified in May and October 2014
228 in the same area. More generally, our analysis of active case finding data found multi-village
229 clusters of yaws in nearly all 7 surveys. This provides further evidence that at least some of the
230 mechanisms that govern the spatial and temporal distribution of yaws operate at a scale larger
231 than the village level. We did not find evidence for clustering of yaws within primary school
232 attendance areas. While yaws transmission could be rare in an absolute sense within primary
233 schools, a plausible alternative is that outside-of-school transmission simply overwhelms any
234 signal from within-school transmission.

235 Our study has implications for yaws elimination: If spatial-temporal clusters are an inherent part
236 of the transmission dynamics of yaws, then this suggests that even if interventions are
237 implemented consistently, the path to elimination is unlikely to be smooth and clusters of yaws
238 may still occur. If the background prevalence of yaws is lower, presumably any clusters would
239 be more apparent. Also, our analysis suggests that the persistence of yaws following MDA
240 cannot be attributed purely to a lack of control in a single location nor to reintroduction of yaws
241 at just 1 location. Indeed, our findings are compatible with the fact that many of the cases of
242 yaws that occurred following MDA were in people who were not treated during MDA [24].
243 Finally, if the observed clustering is due to appreciable inter-village yaws transmission, we
244 suggest that villages may be epidemiologically linked to such a degree that they may not

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245 effectively serve as implementation units. If the recommended implementation unit size were
246 20 000 to 50 000 people, then Lihir in its entirety would be treated as a single IU and all the
247 clusters identified in this analysis would be subsumed into the same IU.
248 Little prior research has addressed the spatial-temporal epidemiology of yaws, and, to our
249 knowledge, no prior research focuses on the spatial scale that is the focus of our analysis. A
250 recent study from the Solomon Islands sampled villages and then households within villages to
251 assess the prevalence of yaws and identify risk factors. The study found that yaws clusters in
252 villages more so than in households but did not address spatial patterns at the scale of multiple
253 neighboring villages [6]. Earlier work on yaws suggests that geographically heterogeneous
254 environmental factors such as humidity influence the prevalence of yaws [25]. Environmental or
255 social factors may lead to consistently higher levels of yaws in some locations: Public health
256 staff on Lihir anecdotally described Tumbuapil—a village at the southern tip of Lihir as having a
257 consistently high burden of yaws. Notably, Tumbuapil was part of statistically significant
258 clusters in more active case surveys (4 of 7) than any other village and was part of the spatial-
259 temporal cluster with the highest observed-to-expected ratio. We lack village-level data on risk
260 factors, so we cannot assess what, if any, factors may contribute to higher prevalence in some
261 villages rather than others.
262 Our study has several limitations: First, our results could reflect patterns in health-care seeking
263 specific to yaws. While our analyses account for trends in the total number of outpatient visits
264 from each village and condition on age and sex, spatially and temporally localized interest in
265 seeking care for skin lesions could, in principle, generate such clusters but we think this is
266 improbable. Second, an environmental or social risk factor for the transmissibility of yaws or
267 people's susceptibility to yaws could underpin the spatial-temporal clusters we observed. Multi-

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268 village spatial-temporal clusters in theory could form even in the absence of transmission
269 between villages, but we are unaware of any risk factors that vary not only at the relevant spatial
270 scale but also at the relevant temporal scale. Third, the number of outpatient visits varied greatly
271 by village, with fewer visits from villages that are farther from LMC; we may have lacked power
272 in our spatial-temporal analysis to detect yaws clusters in areas such as the northwest part of
273 Lihir where we identified a spatial-only cluster in the seventh survey. Fourth, directly comparing
274 the spatial-temporal and spatial-only clustering results is difficult in part because the analyses
275 focus on somewhat different underlying populations: We had to include migrants in the spatial-
276 only clustering analysis but could not include them in the spatial-temporal analysis. Additionally,
277 our primary school attendance area clustering analysis associated each village with a single
278 primary school and does not account for the fact that students from a single village may attend
279 different primary schools. We used school attendance records from a single year to define
280 primary school attendance areas; our analysis would not capture changing school attendance
281 patterns. Finally, our findings may not be generalizable to other yaws-endemic areas. Elsewhere,
282 villages may differ substantially from those on Lihir in terms of population size, density,
283 proximity to other villages, and other factors. Conducting research on the spatial epidemiology
284 of yaws in numerous settings would help identify phenomena that are contingent on a particular
285 geography versus those that reflect general characteristics of yaws epidemiology.

286 Operational research in support of yaws eradication will need to continue to investigate the
287 disease's spatial epidemiology: Designing prevalence surveys that employ cluster sampling
288 requires understanding the extent of spatial clustering of yaws. Moreover, a mechanistic
289 understanding of the spatial and temporal scales at which yaws spreads and the extent to which
290 transmission occurs in different settings (e.g. schools versus households) can help inform

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291 intervention strategies, particularly contact tracing. Earlier generations of yaws epidemiologists
292 did not have access to molecular epidemiology tools or to remotely sensed data on environmental
293 risk factors. These approaches may advance our understanding of the spatial epidemiology of
294 yaws but will not replace the ongoing need for high-quality and high-spatial-resolution
295 descriptive epidemiological data collected in both research and programmatic settings.

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308 **Author Contributions**

309 Conceptualization: EQM OM MBM.

310 Data Curation: EQM OM.

311 Formal analysis: EQM.

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320 Writing - review & editing: EQM OM MBM.

321 **Data Availability**

322 The data and code necessary to replicate the analyses are available in the Harvard Dataverse at

323 <https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/NZIVED>.

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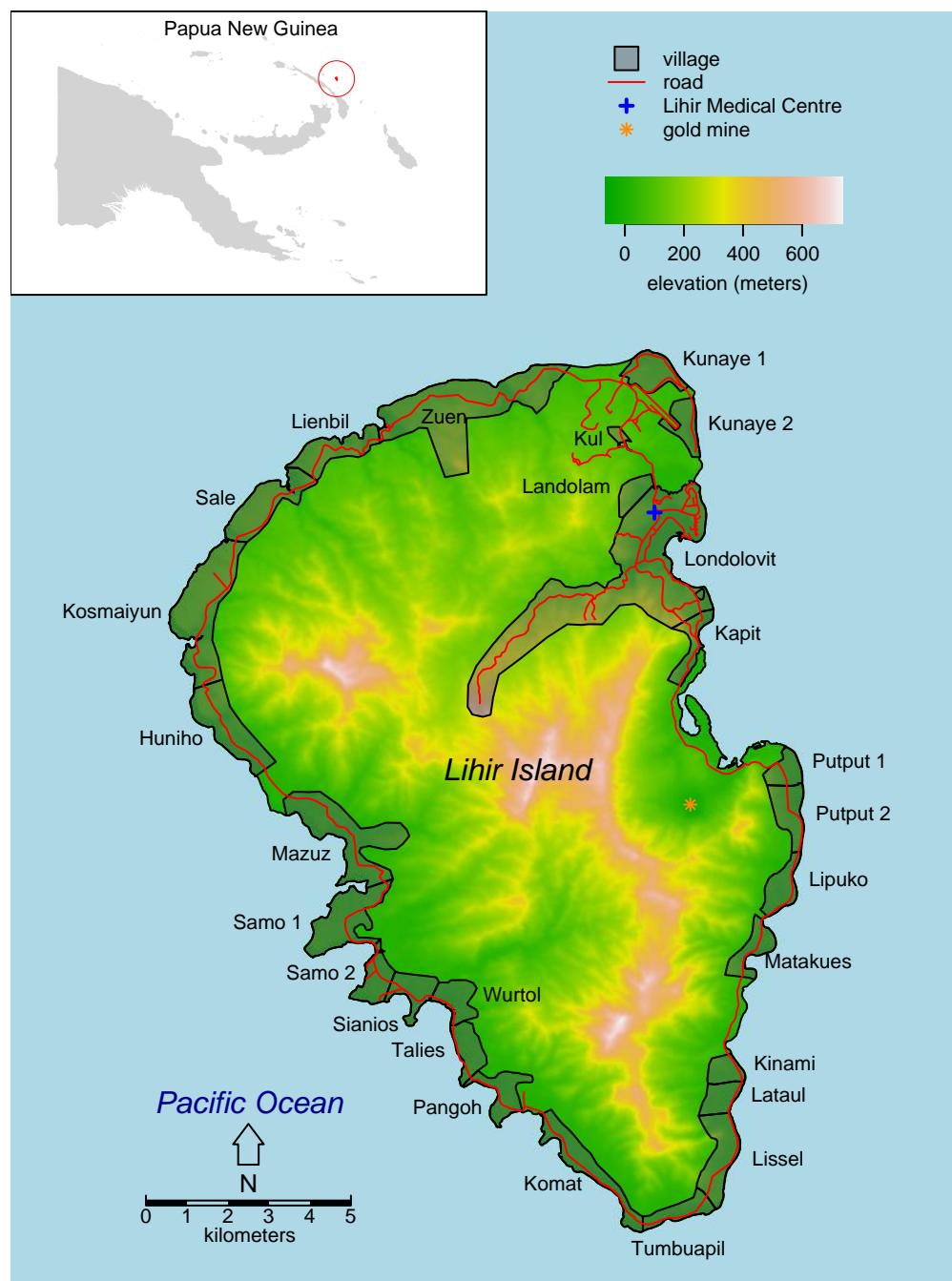
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Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

384 Figures

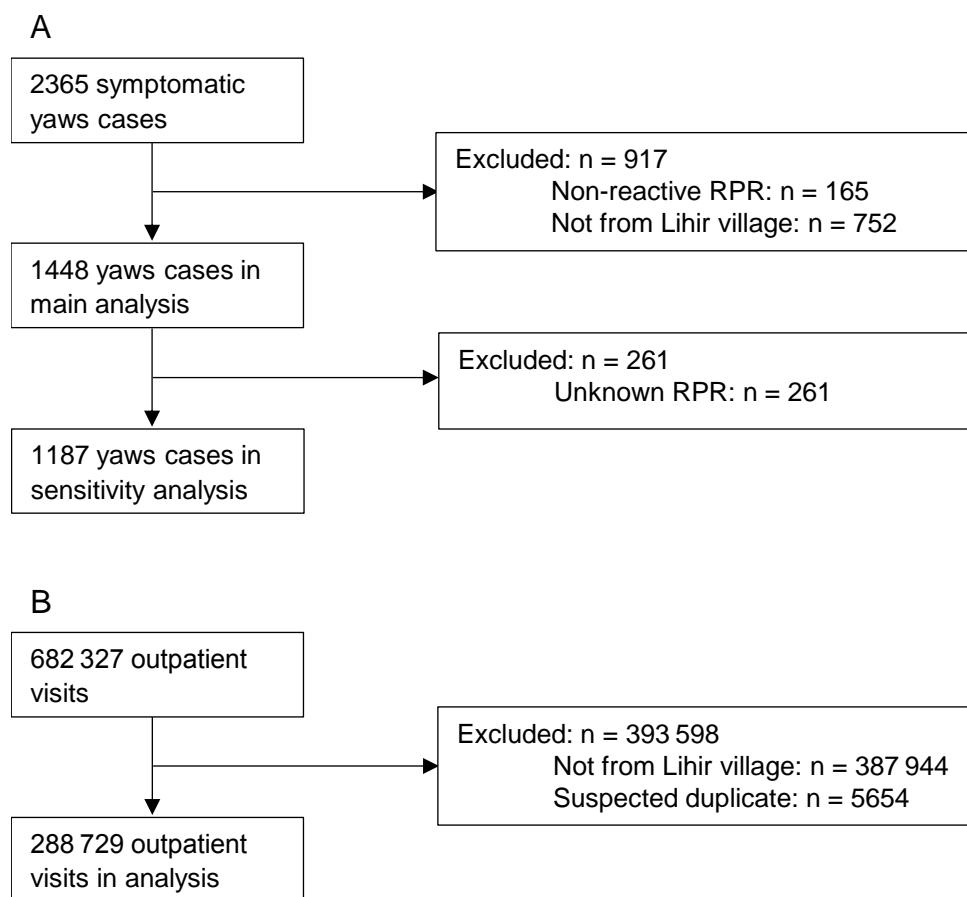


385

386 **Fig 1. Map of Lihir Island.** The top right inset shows the location of Lihir in Papua New
387 Guinea. Note that Landolam is technically not a village but rather an informal migrant
388 settlement. Elevation data was obtained from the Shuttle Radar Topography Mission [12]. The
389 Papua New Guinea map was obtained from GADM database [13].

390

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

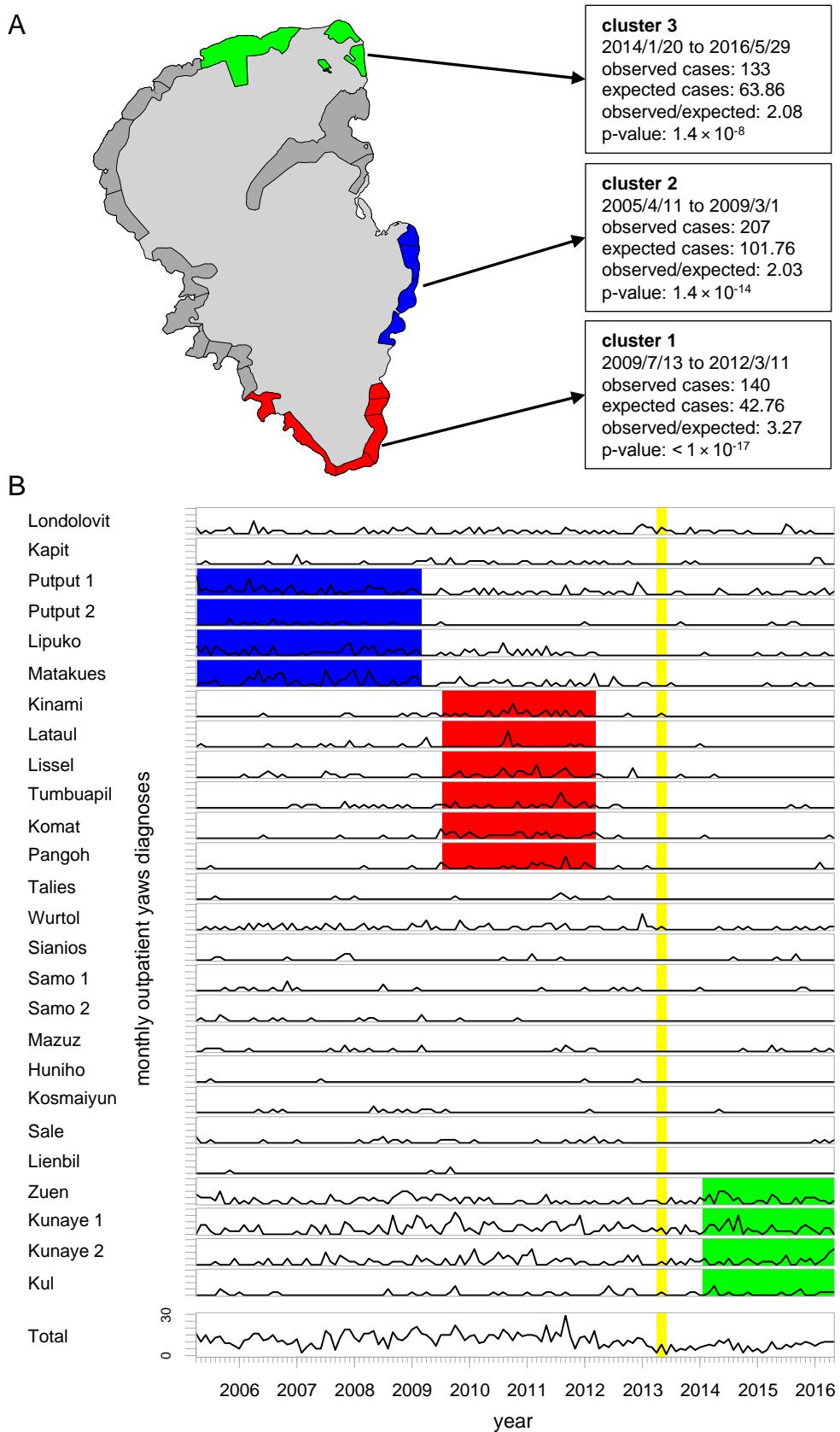


391

392 **Fig 2. Flow diagrams for data in analysis of passively detected yaws.** (A) Exclusions of
393 outpatient passively detected yaws cases and (B) exclusions of all outpatient visits at Lihir
394 Medical Centre.

395

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

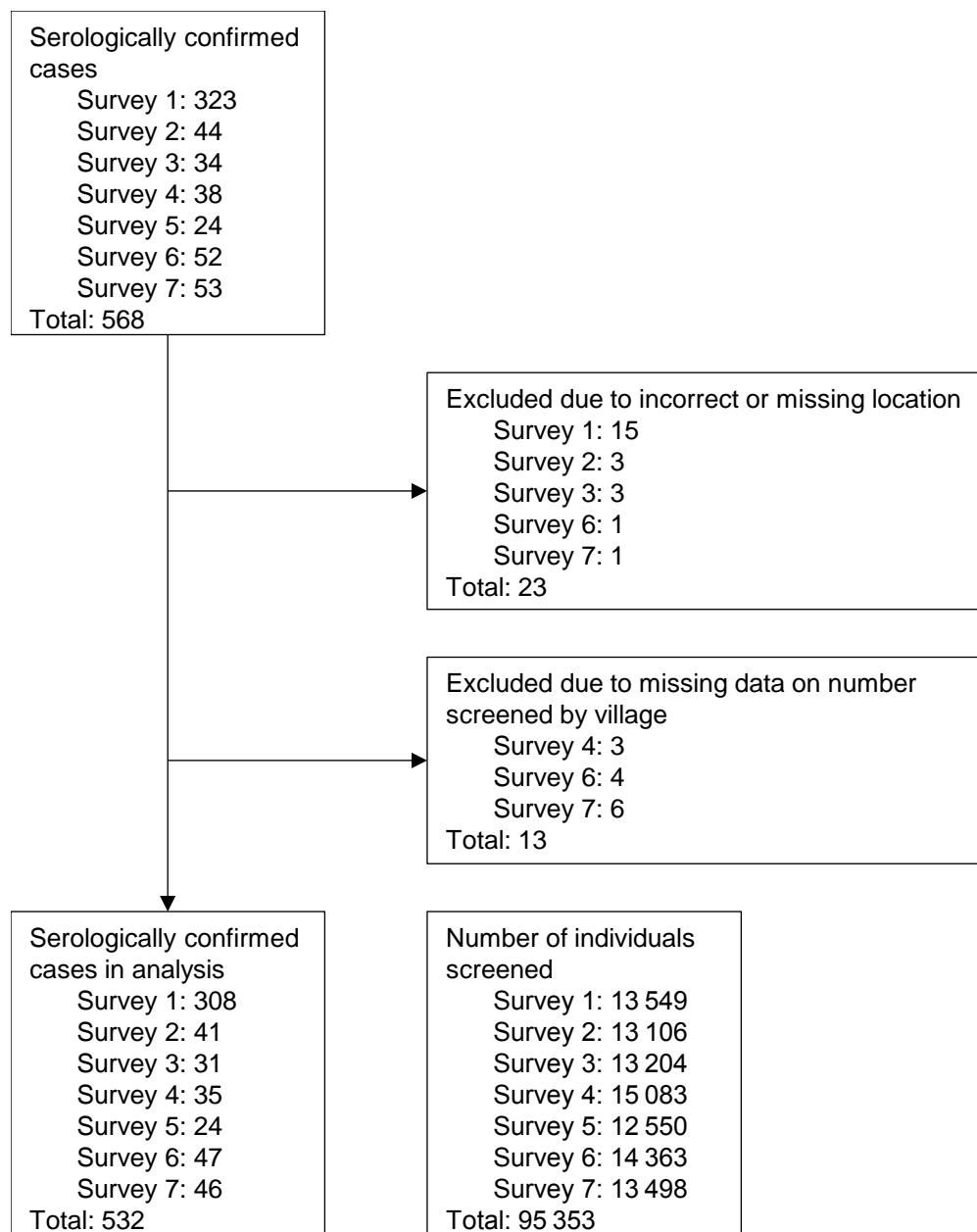


Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

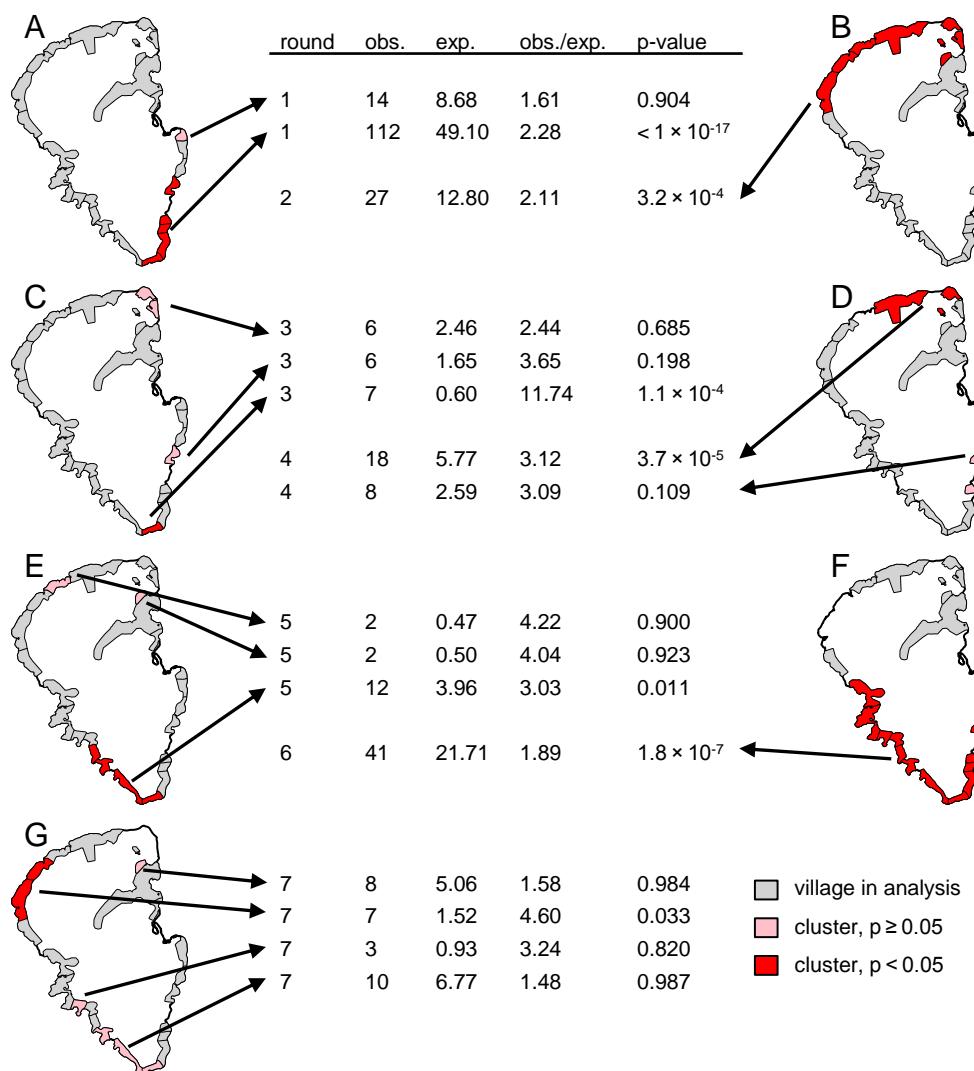
397 **Fig 3. Spatial-temporal clusters of passively detected yaws cases.** (A) Map of results of
398 spatial-temporal Poisson SaTScan analysis of serologically confirmed incident yaws cases,
399 adjusted for age and sex. (B) Times series of outpatient yaws cases aggregated by month by
400 village and for all villages combined. The y-axes for the village-specific time series range from 0
401 to 8. The villages are ordered to match their sequential order around the circumference of Lihir.
402 Red, blue, and green rectangles correspond to spatial-temporal clusters 1, 2, and 3, respectively.
403 The vertical yellow bar corresponds to when mass drug administration was implemented on
404 Lihir.

405

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Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea



411

412 **Fig 5. Spatial clusters of actively detected serologically confirmed yaws cases.** Results of
413 spatial-only discrete Poisson SaTScan analysis for serologically confirmed prevalent yaws cases
414 identified via active case finding for each survey 1 through 7 (A – G, respectively). Villages that
415 are part of statistically significant spatial clusters are shaded in red and not statistically
416 significant clusters are shaded in pink. Villages are shaded gray if they were part of the analysis
417 in the corresponding survey (but not identified as part of a cluster). Villages are excluded from
418 the map for each survey where the number of individuals screened in that survey in that village is
419 unknown. The arrows point from each cluster to details describing the number of observed yaws

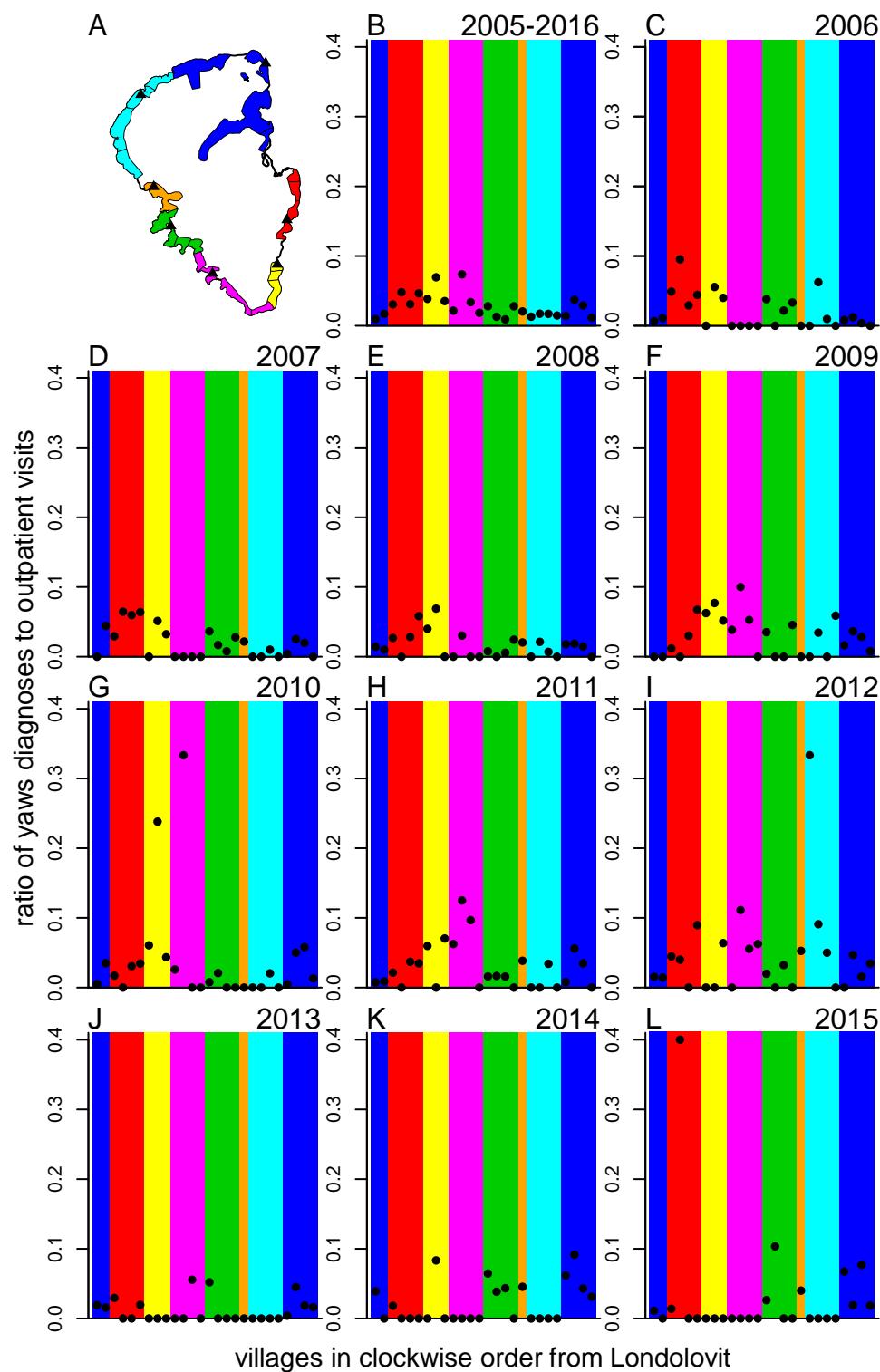
Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

420 cases in that cluster, the number of expected yaws cases, the ratio of observed to expected, and p-

421 value for that cluster.

422

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea



423

424 **Fig 6. Passively detected yaws cases by primary school attendance area and year.** (A) Map
425 of Lihir villages with the colors corresponding to empirically derived primary school attendance

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

426 areas. Each solid black triangle marks the location of a primary school. (B – L) Yaws diagnoses
427 among 8- to 14-year-olds as a proportion of outpatient visits for the entire study period (B) and
428 each year 2006 to 2015 (C – L, respectively). Each data point corresponds to a village and the
429 background colors in each plot correspond to the primary school attendance areas illustrated in
430 (A). The data points ordered left-to-right correspond to the clockwise sequences of villages
431 around Lihir arbitrarily starting from Londolovit, the large village in the northeast quadrant of
432 the island.

433

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

434 Supporting Information

435 S1 Table. Discrete Poisson analysis adjusted for age and sex, confirmed RPR-positive.

ID	Start date	End date	Number of villages	Village IDs	Observed cases	Expected cases	p-value
1	2010/8/2	2012/4/29	6	Tumbuapil, Lissel, Komat, Lataul, Kinami, Pangoh	97	21.56	$<1 \times 10^{-17}$
2	2005/4/11	2009/3/1	4	Putput_1, Putput_2, Lipuko, Matakues	171	83.53	1.0×10^{-11}
3	2014/1/20	2016/5/29	4	Kunaye_1, Kunaye_2, Kul, Zuen	116	52.12	9.4×10^{-9}

436

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

437 **S2 Table. Discrete Poisson analysis (unadjusted).**

ID	Start date	End date	Number of villages	Village IDs	Observed cases	Expected cases	p-value
1	2010/8/2	2012/3/11	6	Tumbuapil, Lissel, Komat, Lataul, Kinami, Pangoh	104	28.90	$<1 \times 10^{-17}$
2	2005/4/11	2008/6/8	4	Lipuko, Putput_2, Matakues, Putput_1	178	79.79	1.2×10^{-14}
3	2009/8/17	2014/12/14	2	Kunaye_1, Kunaye_2	214	119.75	2.7×10^{-9}

438

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

439 **S3 Table. Space-time permutation analysis adjusted for age and sex.**

ID	Start date	End date	Number of villages	Village IDs	Observed cases	Expected cases	p-value
1	2010/8/2	2012/3/11	6	Tumbuapil, Lissel, Komat, Lataul, Kinami, Pangoh	104	44.14	9.0×10^{-13}
2	2005/4/11	2008/6/1	4	Lipuko, Putput_2, Matakues, Putput_1	177	103.80	5.3×10^{-9}
3	2012/5/7	2016/5/29	5	Kul, Kunaye_1, Kunaye_2, Londolovit, Zuen	240	159.64	2.5×10^{-7}

440

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

441 **S4 Table. Space-time permutation analysis (unadjusted).**

ID	Start date	End date	Number of villages	Village IDs	Observed cases	Expected cases	p-value
1	2010/8/2	2012/3/11	6	Tumbuapil, Lissel, Komat, Lataul, Kinami, Pangoh	104	43.21	3.0×10^{-12}
2	2005/4/11	2008/6/1	4	Lipuko, Putput_2, Matakues, Putput_1	177	102.24	9.4×10^{-9}
3	2012/5/7	2016/5/29	5	Kul, Kunaye_1, Kunaye_2, Londolovit, Zuen	240	157.44	3.0×10^{-7}

442

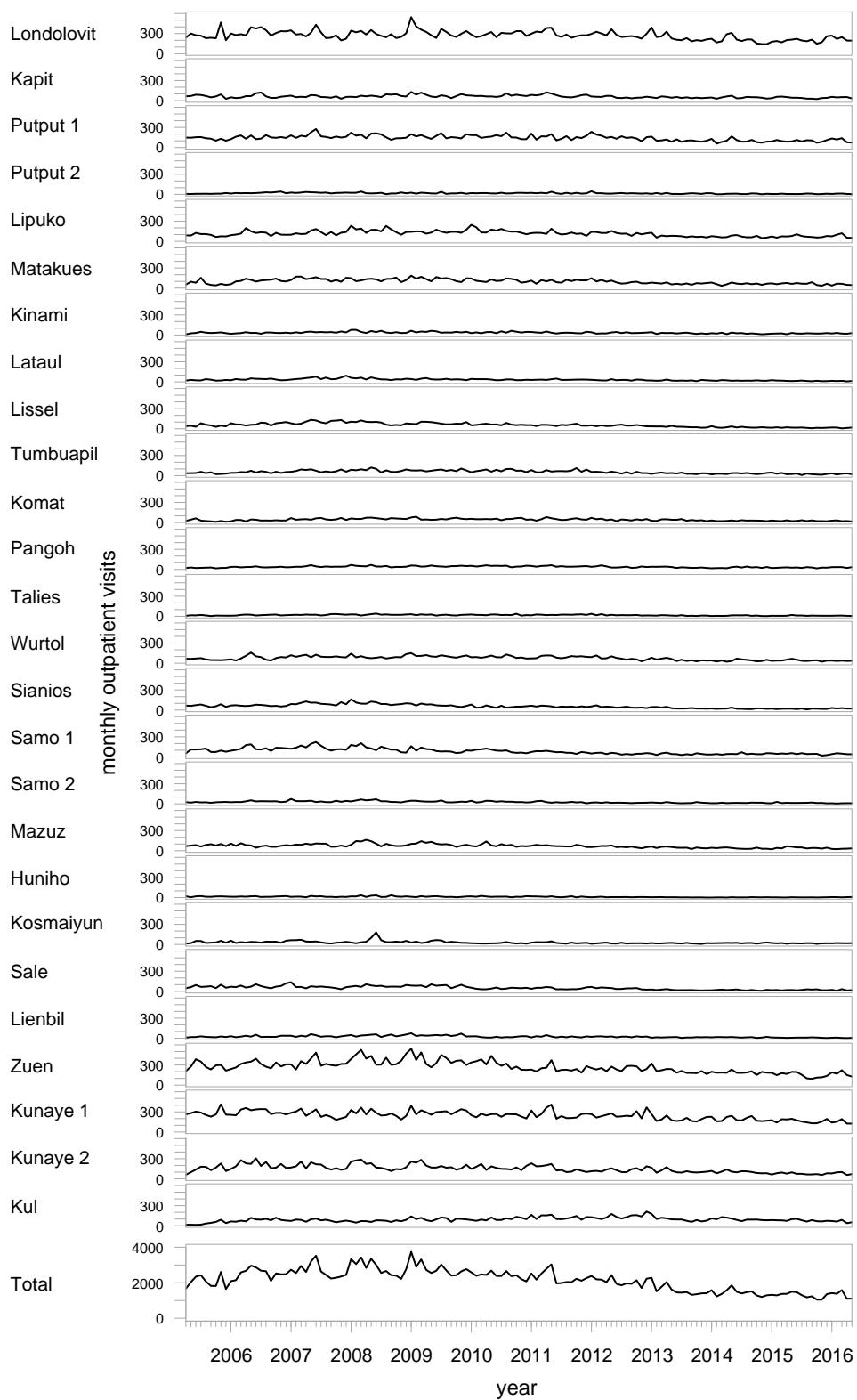
Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

443 **S5 Table. P-values for primary school attendance area analysis.** These p-values result from
444 the permutation test used to assess clustering of yaws in 8- to 14-year-olds by primary school
445 attendance area for each year from 2006 through 2015 and for the entire study period.

446

year	p-value
2006	0.0687
2007	0.4778
2008	0.4068
2009	0.9881
2010	0.6705
2011	0.5949
2012	0.9315
2013	0.9808
2014	0.6875
2015	0.9795
entire study period	0.6846

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

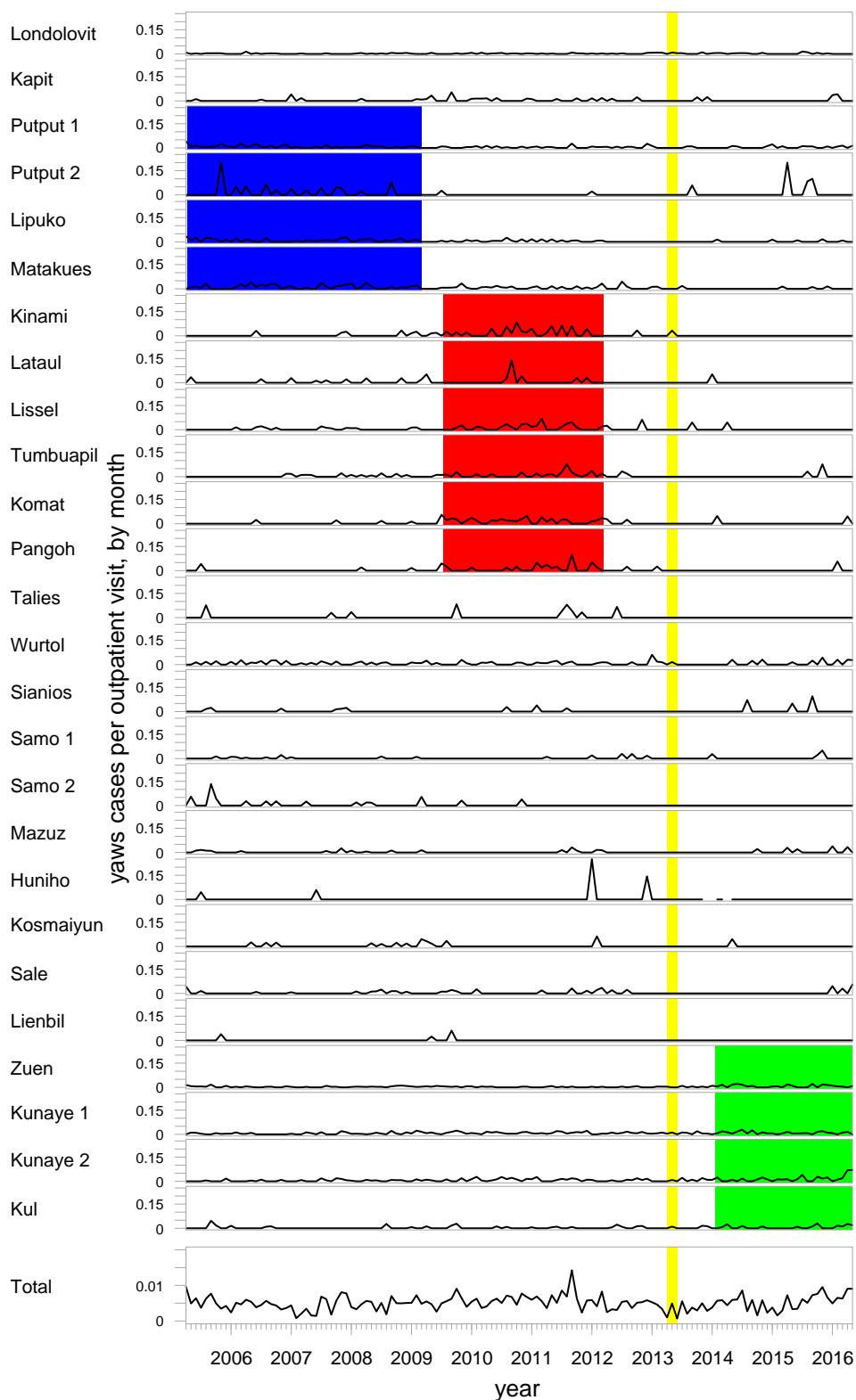


Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

448 **S1 Fig. Outpatient visits to LMC.** Time series of outpatient visits (any diagnosis) aggregated
449 by month by village and for all villages combined. The villages are ordered to match their
450 sequential order around the circumference of Lihir.

451

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea



452

453 **S2 Fig. Passively detected yaws cases as a proportion of outpatient visits.** The time series

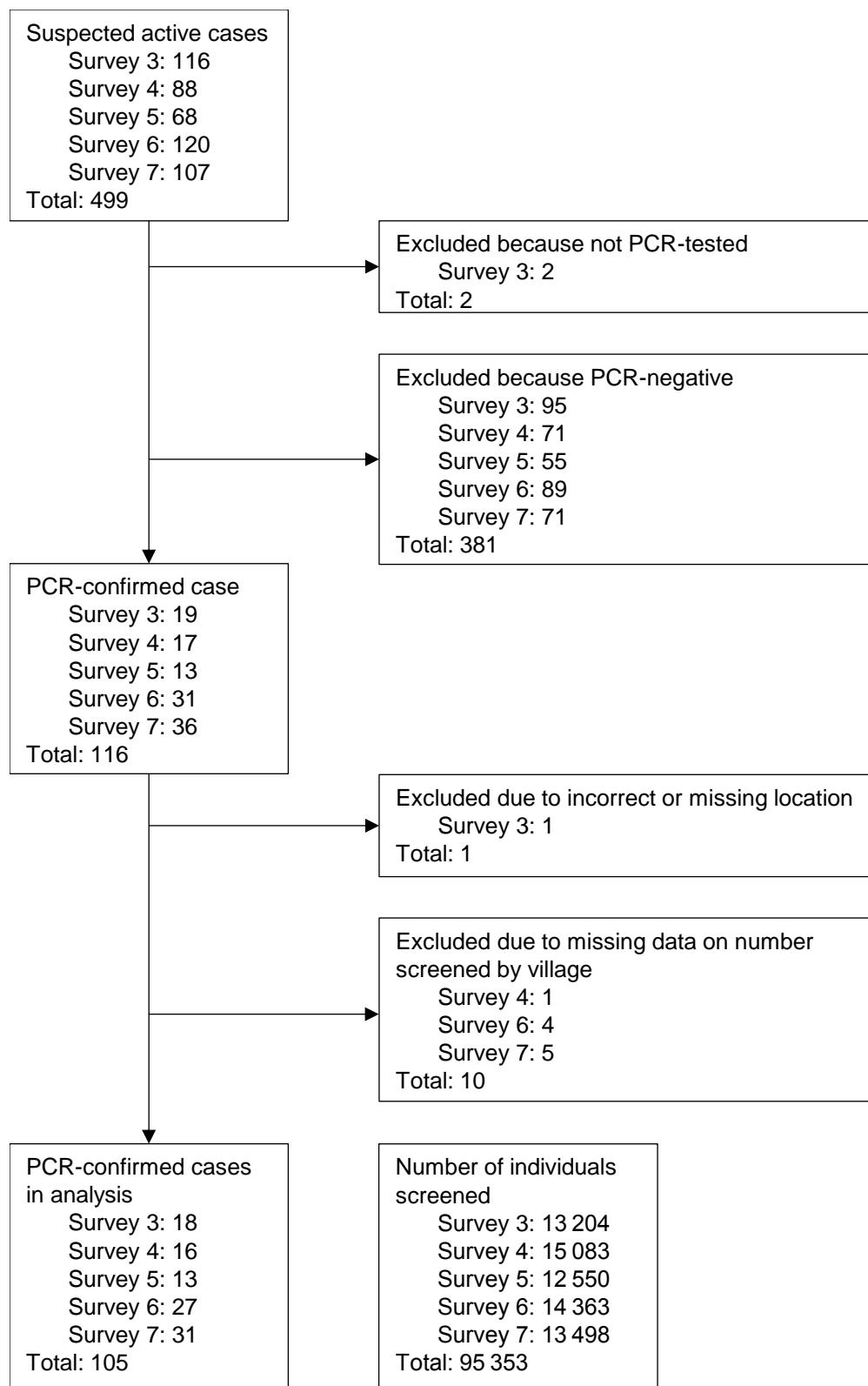
454 show the proportion of outpatient yaws diagnoses as a fraction of all outpatient visits at LMC

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

455 aggregated by month by village and for all villages combined. The villages are ordered to match
456 their sequential order around the circumference of Lihir. Red, blue, and green rectangles
457 correspond to spatial-temporal clusters 1, 2, and 3, respectively, from Fig 3. The vertical yellow
458 bar corresponds to when mass drug administration was implemented on Lihir.

459

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea



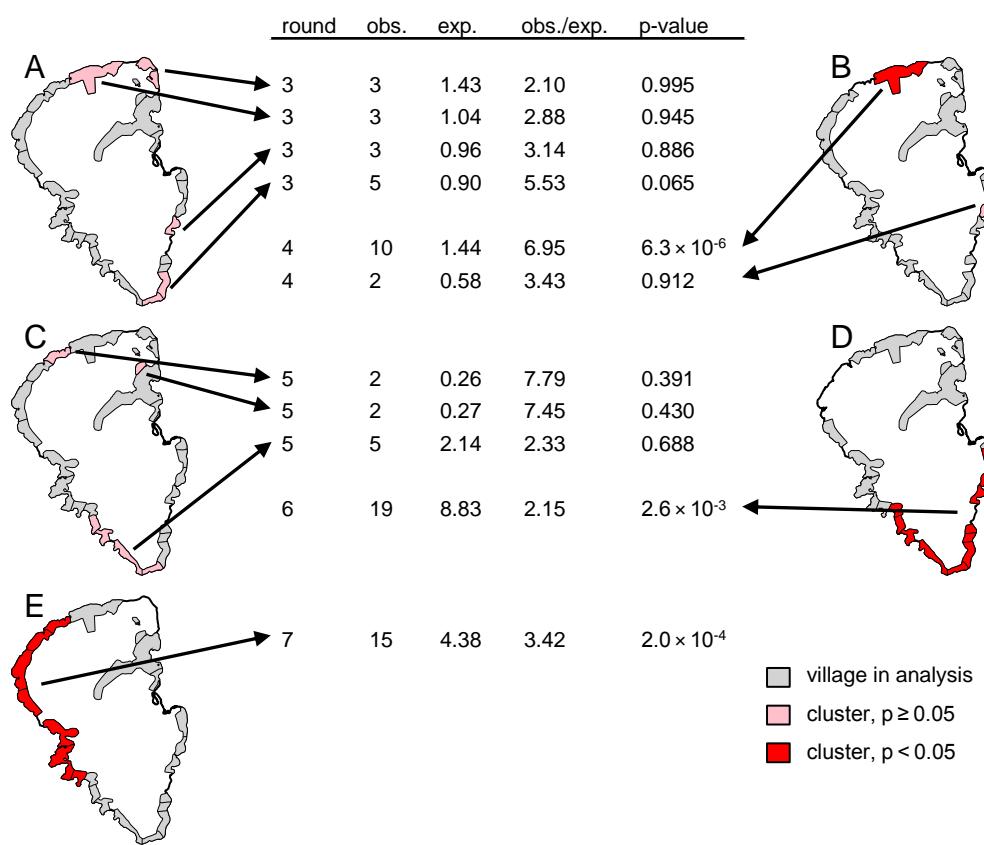
Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea

463 cases, excluded cases, PCR-confirmed cases in the final analysis, and number of individuals

464 screened.

465

Spatial-temporal clustering of yaws on Lihir Island, Papua New Guinea



466

467 **S4 Fig. Spatial clusters of actively detected PCR-confirmed yaws cases.** Results of spatial-
468 only discrete Poisson SaTScan analysis for PCR-confirmed prevalent yaws cases identified via
469 active case finding for each survey 3 through 7 (A – E, respectively). Villages that are part of
470 statistically significant spatial clusters are shaded in red and not statistically significant clusters
471 are shaded in pink. Villages are shaded gray if they were part of the analysis in the corresponding
472 survey (but not identified as part of a cluster). Villages are excluded from the map for each
473 survey where the number of individuals screened in that survey in that village is unknown. The
474 arrows point from each cluster to details describing the number of observed yaws cases in that
475 cluster, the number of expected yaws cases, the ratio of observed to expected, and p-value for
476 that cluster.

477