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1 **Title**

2 Spatial clustering of drug-resistant tuberculosis in Hlabisa sub-district, KwaZulu-Natal, 2011-  
3 2015

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21 **Running head**

22 Spatial clusters of tuberculosis in KwaZulu-Natal

23 **Summary** 199 words

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25 **References:** 34

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27 **Figures:** 3

28 **Keywords**

29 Geographical information systems, disease clustering, HIV infections

30 **SUMMARY**

31 *Setting*

32 Incidence rates of tuberculosis in South Africa are amongst the highest in the world, and  
33 drug-resistance is a major concern. Understanding geographic variation in disease may  
34 guide targeted interventions.

35 *Objective*

36 We aimed to characterise the spatial distribution of drug-resistant tuberculosis (DRTB) in a  
37 rural area of KwaZulu-Natal, South Africa, and test for clustering.

38 *Design*

39 This was a cross-sectional analysis of DRTB patients managed at a rural district hospital  
40 from 2011-2015. We mapped all patients in hospital data to local areas; and linked to a  
41 population-based demographic surveillance system to map patients to individual  
42 homesteads. We used kernel density estimation to visualise the distribution of disease and  
43 tested for clustering using spatial scan statistics.

44 *Results*

45 There were 489 patients with DRTB in the sub-district; 111 lived in the smaller demographic  
46 surveillance area. Spatial clustering analysis identified a high-risk cluster (relative risk of  
47 DRTB within cluster compared to outside: 3.0,  $p < 0.001$ ) in the south-east, a region  
48 characterised by high population density and high HIV prevalence.

49 *Conclusion*

50 We have demonstrated evidence of a geographic high risk cluster of DRTB. This suggests  
51 that targeting interventions to spatial areas of highest risk, where transmission may be  
52 ongoing, could be effective.

53

## 54 INTRODUCTION

55 Incidence rates of tuberculosis (TB) in South Africa are amongst the highest in the world.<sup>1</sup> In  
56 2015 there were an estimated 454,000 new diagnoses, a rate of 834 per 100,000  
57 population, and it is the leading natural cause of death in the country.<sup>1, 2</sup> Rates of TB are  
58 particularly high in the province of KwaZulu-Natal, largely driven by the high prevalence of  
59 human immunodeficiency virus (HIV) and complicated by TB drug resistance.<sup>3, 4</sup>

60 Understanding the spatial distribution of disease is important for effective control. Spatial  
61 analyses can be used to identify the worst affected areas, generate hypotheses about  
62 transmission, and guide interventions.<sup>5</sup> Tests of spatial clustering can be used to identify  
63 groups of patients that occur closer together in space than would be expected by chance.  
64 These analyses have been used to identify areas of likely TB transmission.<sup>6-14</sup> Visualisation  
65 of spatial data on maps also provides a powerful means of communicating information about  
66 the disease to policy makers and the public.

67 The Africa Health Research Institute (AHRI) in the Hlabisa sub-district of KwaZulu-Natal,  
68 South Africa, maintains a large health and demographic surveillance system. This includes  
69 individual residential locations mapped to an accuracy of less than two metres, and routine  
70 linkage to public sector records.<sup>15, 16</sup> The aim of this study was to characterise the spatial  
71 distribution of drug-resistant TB (DRTB) in the sub-district, test for spatial clustering, and  
72 discuss implications for prevention and care.

73

## 74 STUDY POPULATION AND METHODS

### 75 *Study area*

76 Hlabisa health sub-district is an area of approximately 1,450km<sup>2</sup> and 247,350 residents in  
77 uMkhanyakude district, northern KwaZulu-Natal, South Africa (Figure 1A). It is characterised  
78 by high prevalence of HIV with high rates of associated TB (577 recorded TB cases per  
79 100,000 population in uMkhanyakude in 2015; 64.3% HIV positive).<sup>3, 17</sup> The AHRI  
80 demographic surveillance area is located within the Hlabisa sub-district (Figure 1B). This a  
81 region of 435km<sup>2</sup>, with approximately 11,000 homesteads and 60,000 residents, in which  
82 AHRI has undertaken population-based demographic surveillance since 2000.<sup>15</sup>

### 83 *Data sources and identification of DRTB patients*

84 This was a cross-sectional analysis of patients diagnosed with DRTB between 2011 and  
85 2015 who were resident in the Hlabisa health sub-district. Since 2011, all patients with DRTB  
86 aged 12 years and older were admitted to the TB ward at Hlabisa hospital for at least the

87 first month of treatment. Since July 2013, individuals in the sub-district with DRTB have been  
88 identified through Xpert MTB/RIF testing at one of 17 primary health care clinics. Prior to  
89 that, most patients were identified through culture-based methods, apart from a small  
90 number of patients diagnosed using Xpert MTB/RIF tests at a clinical trial site.<sup>18</sup>

91 We identified patients with DRTB using ICD-10 discharge codes in the Hlabisa hospital  
92 information system. We defined DRTB based on South African coding standards,  
93 incorporating codes for rifampicin mono-resistant, multidrug-resistant (MDR) and extensively  
94 drug-resistant (XDR) TB.<sup>19</sup> We calculated the proportion of patients in the hospital  
95 admissions data who had DRTB, and described characteristics of patients. Data from the  
96 hospital information system are routinely linked to the AHRI demographic surveillance data  
97 using the South African identification number or through a standard probabilistic matching  
98 algorithm.<sup>15</sup> We used linked data to identify individual homestead locations.

99 The research was approved by the Biomedical Research Ethics Committee of the University  
100 of KwaZulu-Natal (ref. BE290/16), the Ethics Committee of the London School of Hygiene  
101 and Tropical Medicine (ref. 11814), and the Health Research Committee of the KwaZulu-  
102 Natal Department of Health (ref. 378/16). These committees waived the requirement for  
103 individual informed consent to use the hospital admissions data, as the data were routinely  
104 collected from hospital records and there was no direct interaction with individual patients.

### 105 *Spatial analysis*

106 We conducted two spatial analyses which derived patient geographic locations using  
107 different methods: a local area analysis which covered the entire Hlabisa sub-district; and a  
108 micro-geographic analysis using the precise locations of patient homesteads within the  
109 smaller AHRI demographic surveillance area.

110 In the local area analysis, we compared the spatial distribution of DRTB patients with all  
111 other hospital admissions. Local areas are informal regions used by local populations to  
112 describe the sub-district, and have been mapped by AHRI (315 local areas in the Hlabisa  
113 sub-district in total, Figure 1B). We extracted patient-reported local areas of residence from a  
114 free text field in the hospital data, and matched them to mapped names of local areas.

115 In the micro-geographic analysis, we compared point residential locations for patients with  
116 DRTB to the spatial distribution of the general population. We used residential locations from  
117 the AHRI demographic surveillance data. For DRTB patients, we identified the exact  
118 homestead of residence which was recorded in the surveillance system closest in time to the  
119 patient's date of admission to Hlabisa hospital. The distribution of the general population was

120 derived by calculating total person years of residence in each homestead over the study  
121 period.

122 We tested for spatial clustering of DRTB in both the local area and micro-geographic  
123 analyses. We used spatial scan statistics, implemented in the SaTScan software,<sup>20</sup> to test  
124 the hypothesis that DRTB patients were closer together in space than the underlying  
125 population distribution. Scan statistics are used to compare the observed number of cases  
126 within spatial windows of various sizes with those that would be expected, in this case, under  
127 a random Poisson distribution. A likelihood ratio is calculated for each window which  
128 compares the observed and expected numbers of cases inside and outside the window.  
129 Monte Carlo simulations are then used to generate random distributions of cases under the  
130 Poisson distribution, which are compared to the observed data to calculate a p-value. We set  
131 the maximum cluster size to 3 km, because spatial dependencies have previously been  
132 reported for HIV within this distance in this study area.<sup>21</sup>

133 We also plotted the locations of clusters on a smoothed map of the relative proportion of  
134 DRTB patients compared to the underlying distribution in continuous geographical space.  
135 These maps were produced using kernel density estimation with a standard Gaussian kernel  
136 of 3km radius.

137 Analyses were performed using R v 3.2.3, using the packages *spatstat* and *rsatscan*.<sup>22, 23</sup>

138

## 139 **RESULTS**

140 Between 2011 and 2015, there were 19,408 individuals admitted to Hlabisa hospital who  
141 could be allocated to a local area in the Hlabisa sub-district. Of these, 489 (2.5%) had an  
142 ICD-10 hospital discharge code indicating DRTB, among whom the majority (478, 98%) had  
143 MDR disease.

144 Characteristics of patients with DRTB are shown in Table 1. Approximately half (250, 51%)  
145 the patients were female, and the modal age group was 25-34 years. There were 340 (70%)  
146 HIV positive DRTB patients, among whom 202 (60%) were on antiretroviral therapy at the  
147 time of admission. One in six (78, 16%) DRTB patients died prior to discharge, and five  
148 absconded from hospital.

### 149 *Local area analysis of DRTB in the Hlabisa sub-district*

150 We used the distribution of all 19,408 patients admitted to Hlabisa hospital across the local  
151 areas in the sub-district as a denominator for analyses of spatial clustering amongst the 489  
152 DRTB patients.

153 There was one high relative risk cluster, located in the south-east of the sub-district  
154 ( $p < 0.001$ ). This cluster had a radius of 1.9 km, comprised four local areas with a total of 79  
155 DRTB patients compared to 29 that would be expected by chance, and had a relative risk of  
156 3.0. There was some evidence of a low relative risk cluster in the west of the sub-district,  
157 close to the hospital ( $p = 0.08$ ). This cluster had a radius of 2.1 km; comprised four local areas  
158 with six patients compared to 19 expected, and a relative risk of 0.3. Locations of these two  
159 clusters, overlaid on a smoothed map of the relative proportion of DRTB patients compared  
160 to all hospital admissions are displayed in Figure 2.

#### 161 *Micro-geographic analysis of DRTB in the AHRI demographic surveillance area*

162 There were 144 DRTB patients whose hospital data could be linked to the AHRI population  
163 surveillance data. Of these, 111 had a recorded homestead location during the study period  
164 and were included in the analysis (94 patients had a residential location recorded in the  
165 same year as their admission date; 16 of the remaining patients had a residence recorded  
166 before their admission date, and one had a residence location recorded the year after their  
167 admission date). The remaining 33 patients were excluded from this analysis because they  
168 did not have a homestead of residence recorded during the period of this study (2011-2015).

169 The 111 patients with DRTB resided at 106 unique homestead locations; 10 patients shared  
170 homesteads with another patient. The most likely high relative risk cluster ( $p = 0.057$ ) had a  
171 radius of 2.8 km. The cluster comprised 55 patients compared to 31 that would be expected  
172 by chance, had a relative risk of 2.5, and all the homesteads with more than one patient  
173 were in this area. It was in a similar region to the high-risk cluster resulting from the local  
174 area-level analysis of the entire Hlabisa sub-district, in the south-east of the demographic  
175 surveillance area. This is the area around a township and is characterised by high population  
176 density and HIV prevalence compared to the rest of the demographic surveillance area.<sup>21</sup>  
177 There were no low relative risk clusters identified in this analysis.

178

## 179 **DISCUSSION**

180 In this study, we have described the spatial distribution of DRTB in the Hlabisa sub-district of  
181 KwaZulu-Natal for the first time. DRTB was highly prevalent in this region, with 489 (2.5%) of  
182 inpatients at Hlabisa hospital affected over a five-year period. Almost all had MDR disease  
183 and 16% died in hospital. There was clear evidence of a geographic high risk cluster of  
184 DRTB in the south-east of the region. This area is characterised by relatively high population  
185 density and high incidence and prevalence of HIV.<sup>21</sup> This spatial heterogeneity of DRTB in a  
186 high burden, predominantly rural area was consistent with findings from lower HIV

187 prevalence settings, although our analysis was at a more granular level than most previous  
188 studies.<sup>6, 10, 11</sup>

189 Establishing the spatial distribution of disease in rural areas such as the Hlabisa sub-district  
190 is challenging. This is because residential addresses are not recorded routinely in hospital  
191 systems, many people live in informal settlements which are not accurately mapped, and the  
192 population is highly mobile.<sup>24</sup> A strength of our study is that we used precise residential  
193 locations collected in the AHRI demographic surveillance system. We were therefore able to  
194 derive the geographic distribution of DRTB from two different data sources: the self-reported  
195 local area of residence from hospital data, and, for residents of the AHRI demographic  
196 surveillance area, the homestead of residence. High risk clusters of disease were indicated  
197 in the same approximate area using both methods, suggesting that the observed clustering  
198 is genuine.

199 The area of spatial clustering was characterised by high population density, and only 10  
200 (18%) patients in the cluster shared residences with other patients. This implies that  
201 transmission of DRTB in this community may have occurred in public places as well as  
202 within households. Other studies have also indicated the importance of community-based  
203 transmission of TB in similar settings.<sup>12, 25-30</sup> Indoor venues with poor ventilation in which  
204 people come into close contact including healthcare facilities, public transport, churches and  
205 bars have been implicated as possible areas of transmission. An important component of  
206 DRTB prevention is therefore to identify such venues in the community and implement  
207 interventions including active case finding by regular screening; contact tracing; improving  
208 access to treatment, and airborne infection control measures in health facilities.

209 The distinct spatial clustering of the disease suggests that targeting these interventions to  
210 suspected high transmission areas could be effective. However, our findings only reveal  
211 where people with DRTB reside, and uncovering precisely where transmission is occurring  
212 will require more detailed clinical and molecular epidemiology. A prospective cohort of  
213 people with DRTB is now operational in the study area where information is collected about  
214 social contact patterns and use of shared public spaces. This will be integrated with whole  
215 genome sequence data to provide better understanding of transmission.

216 The results of our study also highlight the importance of the interaction between HIV and TB  
217 in this population. Almost three quarters of the patients with DRTB were HIV positive,  
218 compared to a prevalence in the population of approximately one quarter. The area of spatial  
219 clustering of DRTB was characterised by high HIV prevalence, and is in a similar region to a  
220 geographic cluster of HIV positive individuals identified previously.<sup>21</sup> In this study population,  
221 approximately 60% of HIV positive patients were on antiretroviral therapy. Previous studies



222 have suggested that improved coverage of antiretroviral therapy at both the individual and  
223 community levels can contribute to reducing the incidence of TB.<sup>31-33</sup>

224 Our study had several limitations. The analysis was restricted to DRTB patients, because we  
225 were only able to ascertain cases through hospital admissions data. Drug-sensitive TB  
226 patients are only admitted when clinically essential whereas policy at the time of the study  
227 was for all drug-resistant patients to be admitted for at least one month. We were therefore  
228 unable to determine whether the distribution of drug-resistant disease is similar to drug-  
229 sensitive disease. Future studies in this area will integrate additional data from the electronic  
230 TB register (ETR.net) to characterise the distribution of drug-sensitive TB.

231 The hospital information system used in this study also did not contain clinical information  
232 about history of treatment for TB. With the data available we therefore could not make any  
233 inference about the balance of primary and secondary drug resistance in the population.  
234 However, most recent data from high HIV prevalence settings suggest that, regardless of  
235 treatment history, the majority of DRTB cases arise from transmission.<sup>34</sup>

236 Another limitation was the use of hospital discharge codes to define DRTB patients, which is  
237 an underestimate of the true number. We will have missed patients that were not coded in  
238 the hospital data as DRTB; children younger than 12 years who may have been managed  
239 elsewhere; individuals who had DRTB detected but did not go to hospital, and those with  
240 undetected disease. However, we have no reason to suspect that these factors would  
241 operate in a geographically heterogeneous way that would lead to spurious spatial clusters.

242 The spatial analysis of DRTB in the wider Hlabisa sub-district was limited by use of local  
243 areas as opposed to individual addresses. However, results were similar to the analysis of  
244 precise point locations in the demographic surveillance area, which suggests that this  
245 method may be useful for similar analyses in future. We also used a hospital-based  
246 denominator as a proxy for the underlying population in this analysis. This will therefore be  
247 influenced by spatial factors which govern the distribution of conditions relating to other  
248 admissions. Finally, we described the characteristics of individuals using hospital data, but  
249 further information on patients would allow a more detailed analysis of risk factors in this  
250 population.

## 251 **CONCLUSIONS**

252 Our study shows concerning evidence of possible ongoing transmission of DRTB in this area  
253 of high prevalence. This suggests that targeting interventions to spatial areas of highest risk  
254 could be effective in supporting progress towards the WHO's End TB strategy for a 90%  
255 reduction in new cases by 2035.<sup>35</sup>

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261 manuscript. FT, RL and CMS designed the study. KH oversaw collection of hospital data. All  
262 authors contributed to and approved the final manuscript. We have no conflicts of interest to  
263 declare.

264

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359 **TABLES**360 *Table 1: Characteristics of drug-resistant tuberculosis patients, Hlabisa hospital (2011-2015)*

Characteristic	N	%
<b>Sex</b>		
Male	239	48.9
Female	250	51.1
<b>Age group (years)</b>		
5-14	10	2.0
15-24	59	12.1
25-34	166	33.9
35-44	143	29.2
45-54	66	13.5
55-64	27	5.5
65-74	10	2.0
75+	8	1.6
<b>Year of admission</b>		
2011	77	15.7
2012	98	20.0
2013	103	21.1
2014	115	23.5
2015	96	19.6
<b>Drug-resistant tuberculosis type</b>		
MDR	478	97.8
Rifampicin mono-resistant	5	1.0
XDR	6	1.2
<b>Site of disease</b>		
Pulmonary	421	86.1
Extrapulmonary	5	1.0
Missing	63	12.9
<b>HIV/ ART status*</b>		
HIV positive, on ART	202	41.3
HIV positive, not on ART	133	27.2
HIV positive, ART missing	5	1.0
HIV negative	67	13.7
Missing	82	16.8

Discharge status		
Discharged	394	80.6
Transferred	12	2.5
Died	78	16.0
Absconded	5	1.0

361 MDR, multidrug-resistant; XDR, extensively drug-resistant; HIV, human immunodeficiency  
362 virus; ART, antiretroviral therapy.

363 \*at time of hospital admission

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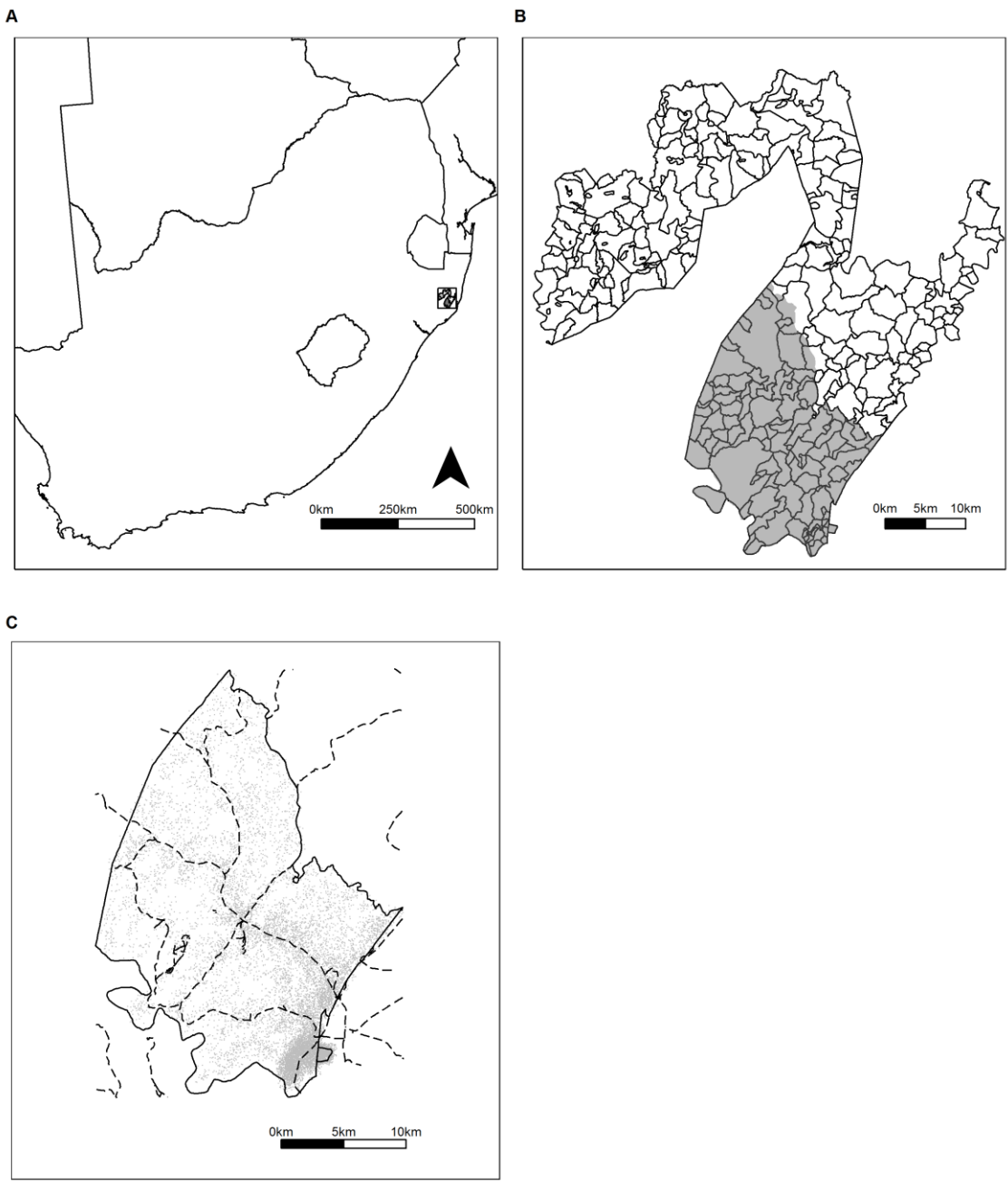
383 **FIGURES**

384 *Figure 1: Study site*

385 A: Location of Hlabisa sub-district within South Africa

386 B: Hlabisa sub-district, showing local areas and Africa Health Research Institute  
387 demographic surveillance area (shaded)

388 C: Africa Health Research Institute demographic surveillance area, with roads and  
389 approximate locations of homesteads (incorporating intentional random error)

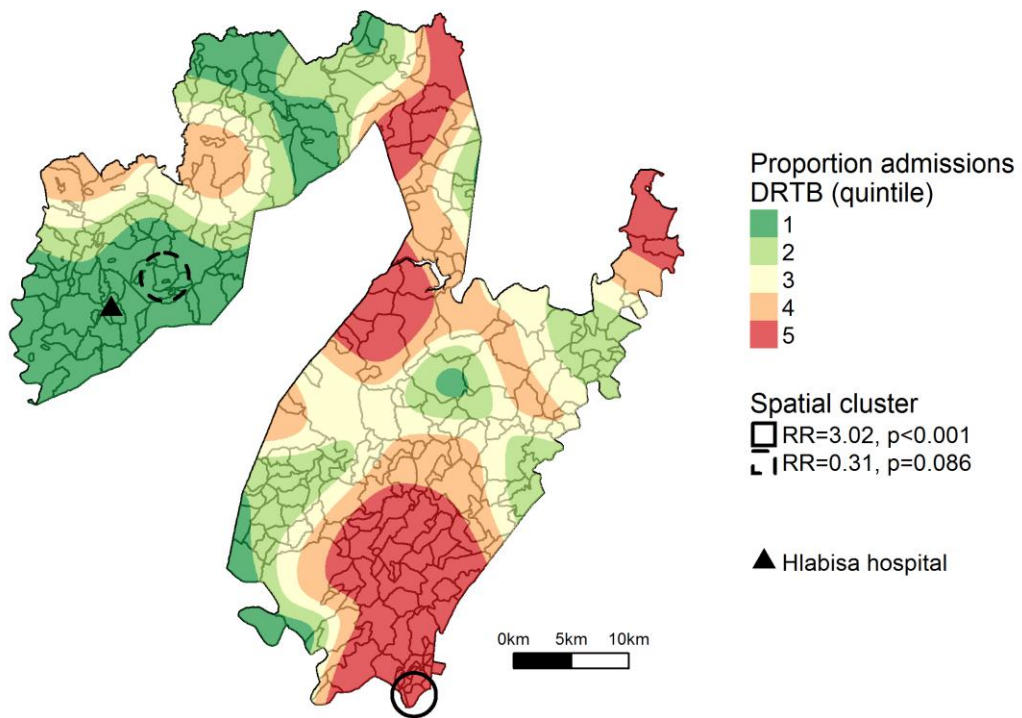


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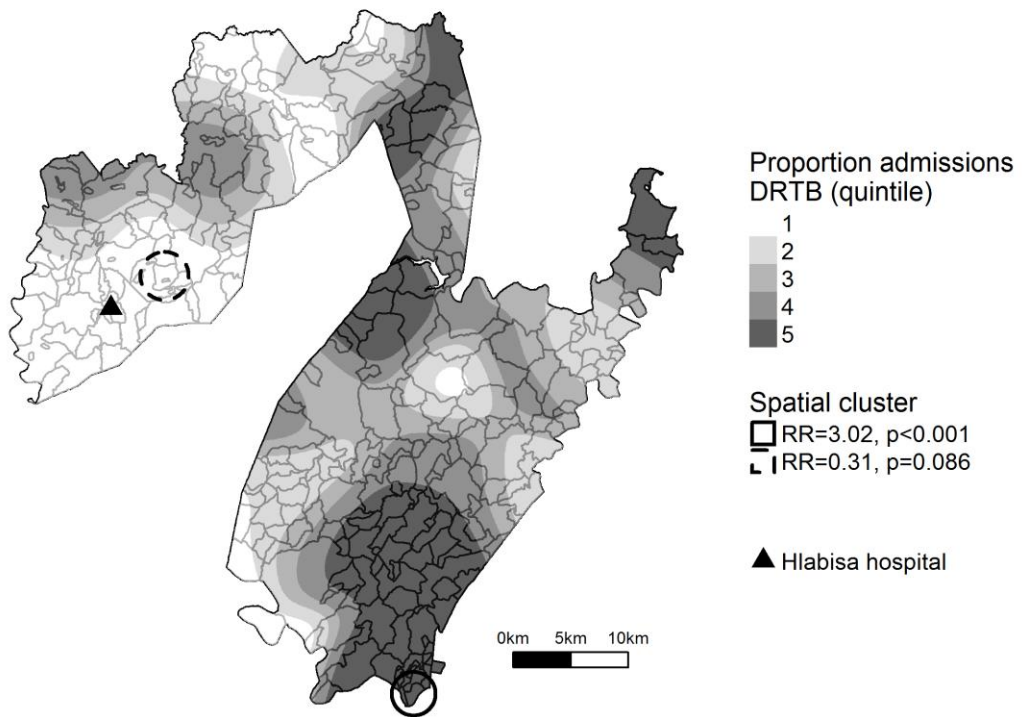
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392 *Figure 2: Spatial clustering of drug-resistant tuberculosis in Hlabisa sub-district, 2011-2015.*

393 *Locations determined using patient-reported local areas in hospital information system.*



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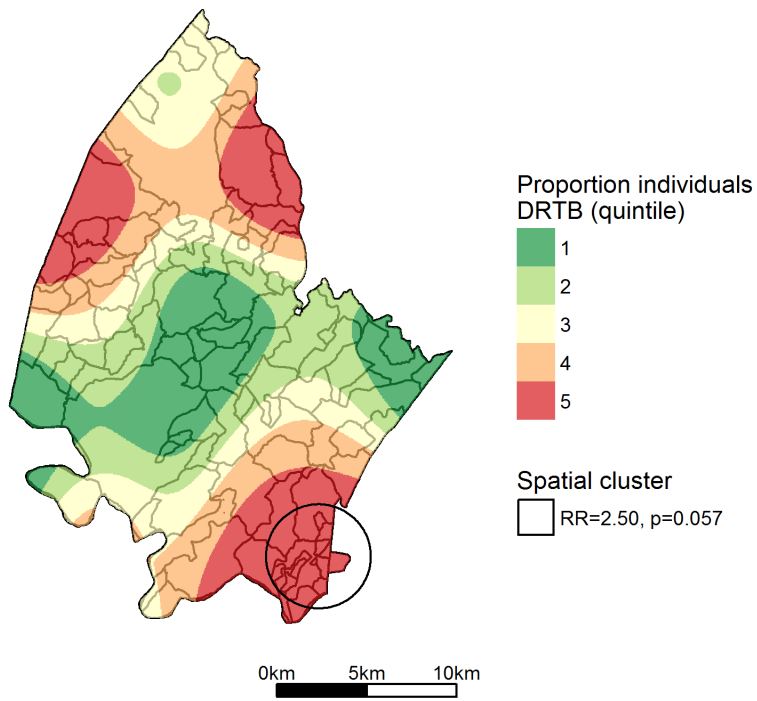


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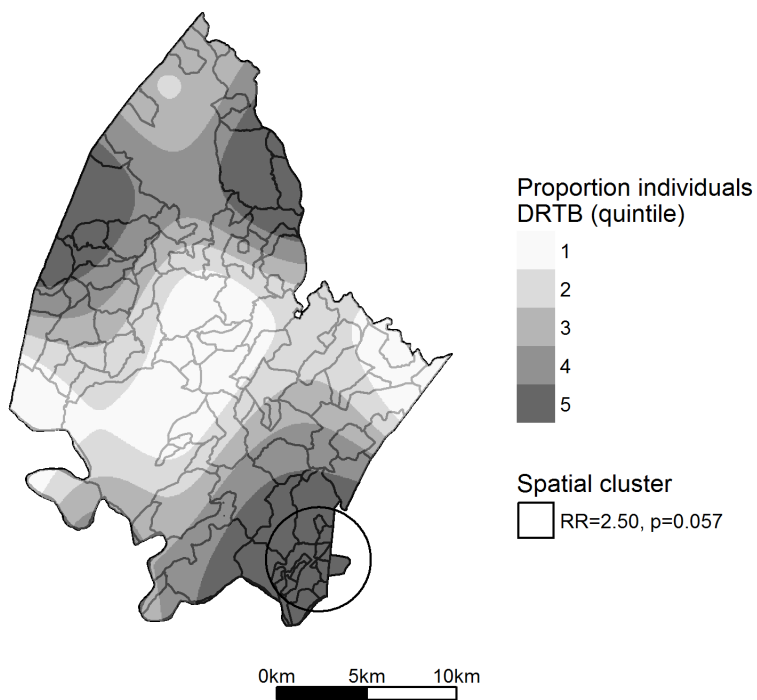
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397 *Figure 3: Spatial clustering of drug-resistant tuberculosis in Africa Health Research Institute*  
398 *demographic surveillance area, 2011-2015. Locations determined by linking hospital data to*  
399 *individual homesteads in demographic surveillance system.*



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