

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in Endemic Area of Northeast Brazil

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023420
Article Type:	Research
Date Submitted by the Author:	08-Apr-2018
Complete List of Authors:	Santos, Márcio; Universidade Federal de Sergipe, Health Education; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Santos, Allan; Universidade Federal de Sergipe, Nursing Barreto, Aline; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Souza, Mariana; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Goes, Marco; Universidade Federal de Sergipe, Medicine Barreto Alves, Jose Antonio; Universidade Federal de Sergipe, Nursing Barreto, Ikaro; Universidade Federal Rural de Pernambuco, Programa de Pos-Graduacao em Biometria e Estatistica Aplicada Silva, José-Rodrigo; Universidade Federal de Sergipe, Statistics and Actuarial Sciences Oliveira, Daniela; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Araújo, Karina; Universidade Federal de Sergipe, Morphology Duthie, Malcolm; Infectious Diseases Research Institute Jesus, Amélia; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology; Universidade Federal de Sergipe, Medicine
Keywords:	Leprosy, Children, Epidemiology < INFECTIOUS DISEASES, Spatial analysis

SCHOLARONE™  
Manuscripts

# Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy

## Cases in Patients Under 15 Years Old in Endemic Area of Northeast Brazil

Márcio B Santos<sup>1,2</sup>, Allan D dos Santos<sup>3</sup>, Aline S Barreto<sup>2</sup>, Mariana do R Souza<sup>2</sup>, Marco A de O Goes<sup>4</sup>, José-Antônio A Barreto<sup>3</sup>, Íkaro D C Barreto<sup>5</sup>, José-Rodrigo S Silva<sup>6</sup>, Daniela T de Oliveira<sup>3</sup>, Karina G de Araujo<sup>7</sup>, Malcolm S Duthie<sup>8</sup>, Amélia R de Jesus<sup>2,9,10</sup>.

<sup>1</sup>Departament of Health Education, Universidade Federal de Sergipe, Brazil; <sup>2</sup>Laboratory of Immunology and Molecular Biology, Universidade Federal de Sergipe, Brazil; <sup>3</sup>Departament of Nursing, Universidade Federal de Sergipe, Brazil; <sup>4</sup>Departament of Medicine, Universidade Federal de Sergipe, Brazil; <sup>5</sup>Mestre, Universidade Federal Rural de Pernambuco (UFPE), Programa de Pos-Graduacao em Biometria e Estatística Aplicada; <sup>6</sup>Doutor, Professor Adjunto do Departamento de Estatística e Ciências Atuariais da Universidade Federal de Sergipe (UFS); <sup>7</sup>Departament of Morphology, Universidade Federal de Sergipe, Aracaju; <sup>8</sup>Infectious Diseases Research Institute (IDRI), Seattle, USA. <sup>9</sup>Departament of Medicine, Universidade Federal de Sergipe, Aracaju. <sup>10</sup>Instituto de Investigação em Imunologia, INCT, CNPq.

### Corresponding Author

Márcio B. Santos

Department of Health Science, Federal University of Sergipe

Av. Gov. Marcelo Déda - São José, Lagarto - SE, Brazil

Postal Code 49400-000

E-mail: bio\_marcio2006@hotmail.com

1  
2  
3 23 **ABSTRACT**

4  
5 24 **Objective:** This study aimed to analyze the clinical and epidemiological indicators and  
6  
7 25 the spatial distribution of leprosy in patients under 15 years old in an endemic area of  
8  
9 26 Northeast Brazil.

10  
11  
12 27 **Design:** Regional surveillance study of all reported cases.

13  
14 28 **Setting:** State of Sergipe, endemic area of Northeast Brazil.

15  
16 29 **Methods:** An ecological and time series study was conducted, based on secondary  
17  
18 30 data reported by the Brazilian Information System on Notifiable Diseases (SINAN) for  
19  
20 31 leprosy cases diagnosed in Sergipe state (2002-2015). We performed spatial analysis  
21  
22 32 by Kernel estimator and Moran index.

23  
24 33 **Results:** The incidence rate was reduced from 6.29 to 3.78 cases per 100,000  
25  
26 34 inhabitants in 2002 and 2015, respectively. However, Sergipe was still classified as  
27  
28 35 highly endemicity in 2015. The mean number of household contacts (HHC) examined  
29  
30 36 was significantly lower than those registered. Clinical data indicated that 21.4% of the  
31  
32 37 patients developed leprosy reactions, and 31.3% presented with some physical  
33  
34 38 disability in the multibacillary (MB) groups. Patients diagnosed by exam within the HHC  
35  
36 39 presented better indicators, such as lower percentage of leprosy reaction and physical  
37  
38 40 disability. Spatial analysis showed the most risk areas distributed on the northeast and  
39  
40 41 cities around the capital, Aracaju.

41  
42 42 **Conclusion:** The data indicate that there is a persistence of active *M. leprae*  
43  
44 43 transmission and a delay in disease detection, following a pattern of high endemicity in  
45  
46 44 many municipalities. The early detection by household contacts examination is  
47  
48 45 important not only to stop transmission but also to detect the cases in a less severe  
49  
50 46 state.

1  
2  
3 47 **Keywords:** Leprosy; Children; Epidemiology; Spatial analysis.  
4  
5  
6  
7

### 8 **Strengths and limitations of this study**

- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60
- 61
- 62
- 63
- 64
- 65
- 66
- 67
- 68
- 69
- 70
- 71
- 72
- 73
- 74
- 75
- 76
- 77
- 78
- 79
- 80
- 81
- 82
- 83
- 84
- 85
- 86
- 87
- 88
- 89
- 90
- 91
- 92
- 93
- 94
- 95
- 96
- 97
- 98
- 99
- 100
- 101
- 102
- 103
- 104
- 105
- 106
- 107
- 108
- 109
- 110
- 111
- 112
- 113
- 114
- 115
- 116
- 117
- 118
- 119
- 120
- 121
- 122
- 123
- 124
- 125
- 126
- 127
- 128
- 129
- 130
- 131
- 132
- 133
- 134
- 135
- 136
- 137
- 138
- 139
- 140
- 141
- 142
- 143
- 144
- 145
- 146
- 147
- 148
- 149
- 150
- 151
- 152
- 153
- 154
- 155
- 156
- 157
- 158
- 159
- 160
- 161
- 162
- 163
- 164
- 165
- 166
- 167
- 168
- 169
- 170
- 171
- 172
- 173
- 174
- 175
- 176
- 177
- 178
- 179
- 180
- 181
- 182
- 183
- 184
- 185
- 186
- 187
- 188
- 189
- 190
- 191
- 192
- 193
- 194
- 195
- 196
- 197
- 198
- 199
- 200
- 201
- 202
- 203
- 204
- 205
- 206
- 207
- 208
- 209
- 210
- 211
- 212
- 213
- 214
- 215
- 216
- 217
- 218
- 219
- 220
- 221
- 222
- 223
- 224
- 225
- 226
- 227
- 228
- 229
- 230
- 231
- 232
- 233
- 234
- 235
- 236
- 237
- 238
- 239
- 240
- 241
- 242
- 243
- 244
- 245
- 246
- 247
- 248
- 249
- 250
- 251
- 252
- 253
- 254
- 255
- 256
- 257
- 258
- 259
- 260
- 261
- 262
- 263
- 264
- 265
- 266
- 267
- 268
- 269
- 270
- 271
- 272
- 273
- 274
- 275
- 276
- 277
- 278
- 279
- 280
- 281
- 282
- 283
- 284
- 285
- 286
- 287
- 288
- 289
- 290
- 291
- 292
- 293
- 294
- 295
- 296
- 297
- 298
- 299
- 300
- 301
- 302
- 303
- 304
- 305
- 306
- 307
- 308
- 309
- 310
- 311
- 312
- 313
- 314
- 315
- 316
- 317
- 318
- 319
- 320
- 321
- 322
- 323
- 324
- 325
- 326
- 327
- 328
- 329
- 330
- 331
- 332
- 333
- 334
- 335
- 336
- 337
- 338
- 339
- 340
- 341
- 342
- 343
- 344
- 345
- 346
- 347
- 348
- 349
- 350
- 351
- 352
- 353
- 354
- 355
- 356
- 357
- 358
- 359
- 360
- 361
- 362
- 363
- 364
- 365
- 366
- 367
- 368
- 369
- 370
- 371
- 372
- 373
- 374
- 375
- 376
- 377
- 378
- 379
- 380
- 381
- 382
- 383
- 384
- 385
- 386
- 387
- 388
- 389
- 390
- 391
- 392
- 393
- 394
- 395
- 396
- 397
- 398
- 399
- 400
- 401
- 402
- 403
- 404
- 405
- 406
- 407
- 408
- 409
- 410
- 411
- 412
- 413
- 414
- 415
- 416
- 417
- 418
- 419
- 420
- 421
- 422
- 423
- 424
- 425
- 426
- 427
- 428
- 429
- 430
- 431
- 432
- 433
- 434
- 435
- 436
- 437
- 438
- 439
- 440
- 441
- 442
- 443
- 444
- 445
- 446
- 447
- 448
- 449
- 450
- 451
- 452
- 453
- 454
- 455
- 456
- 457
- 458
- 459
- 460
- 461
- 462
- 463
- 464
- 465
- 466
- 467
- 468
- 469
- 470
- 471
- 472
- 473
- 474
- 475
- 476
- 477
- 478
- 479
- 480
- 481
- 482
- 483
- 484
- 485
- 486
- 487
- 488
- 489
- 490
- 491
- 492
- 493
- 494
- 495
- 496
- 497
- 498
- 499
- 500
- 501
- 502
- 503
- 504
- 505
- 506
- 507
- 508
- 509
- 510
- 511
- 512
- 513
- 514
- 515
- 516
- 517
- 518
- 519
- 520
- 521
- 522
- 523
- 524
- 525
- 526
- 527
- 528
- 529
- 530
- 531
- 532
- 533
- 534
- 535
- 536
- 537
- 538
- 539
- 540
- 541
- 542
- 543
- 544
- 545
- 546
- 547
- 548
- 549
- 550
- 551
- 552
- 553
- 554
- 555
- 556
- 557
- 558
- 559
- 560
- 561
- 562
- 563
- 564
- 565
- 566
- 567
- 568
- 569
- 570
- 571
- 572
- 573
- 574
- 575
- 576
- 577
- 578
- 579
- 580
- 581
- 582
- 583
- 584
- 585
- 586
- 587
- 588
- 589
- 590
- 591
- 592
- 593
- 594
- 595
- 596
- 597
- 598
- 599
- 600
- 601
- 602
- 603
- 604
- 605
- 606
- 607
- 608
- 609
- 610
- 611
- 612
- 613
- 614
- 615
- 616
- 617
- 618
- 619
- 620
- 621
- 622
- 623
- 624
- 625
- 626
- 627
- 628
- 629
- 630
- 631
- 632
- 633
- 634
- 635
- 636
- 637
- 638
- 639
- 640
- 641
- 642
- 643
- 644
- 645
- 646
- 647
- 648
- 649
- 650
- 651
- 652
- 653
- 654
- 655
- 656
- 657
- 658
- 659
- 660
- 661
- 662
- 663
- 664
- 665
- 666
- 667
- 668
- 669
- 670
- 671
- 672
- 673
- 674
- 675
- 676
- 677
- 678
- 679
- 680
- 681
- 682
- 683
- 684
- 685
- 686
- 687
- 688
- 689
- 690
- 691
- 692
- 693
- 694
- 695
- 696
- 697
- 698
- 699
- 700
- 701
- 702
- 703
- 704
- 705
- 706
- 707
- 708
- 709
- 710
- 711
- 712
- 713
- 714
- 715
- 716
- 717
- 718
- 719
- 720
- 721
- 722
- 723
- 724
- 725
- 726
- 727
- 728
- 729
- 730
- 731
- 732
- 733
- 734
- 735
- 736
- 737
- 738
- 739
- 740
- 741
- 742
- 743
- 744
- 745
- 746
- 747
- 748
- 749
- 750
- 751
- 752
- 753
- 754
- 755
- 756
- 757
- 758
- 759
- 760
- 761
- 762
- 763
- 764
- 765
- 766
- 767
- 768
- 769
- 770
- 771
- 772
- 773
- 774
- 775
- 776
- 777
- 778
- 779
- 780
- 781
- 782
- 783
- 784
- 785
- 786
- 787
- 788
- 789
- 790
- 791
- 792
- 793
- 794
- 795
- 796
- 797
- 798
- 799
- 800
- 801
- 802
- 803
- 804
- 805
- 806
- 807
- 808
- 809
- 810
- 811
- 812
- 813
- 814
- 815
- 816
- 817
- 818
- 819
- 820
- 821
- 822
- 823
- 824
- 825
- 826
- 827
- 828
- 829
- 830
- 831
- 832
- 833
- 834
- 835
- 836
- 837
- 838
- 839
- 840
- 841
- 842
- 843
- 844
- 845
- 846
- 847
- 848
- 849
- 850
- 851
- 852
- 853
- 854
- 855
- 856
- 857
- 858
- 859
- 860
- 861
- 862
- 863
- 864
- 865
- 866
- 867
- 868
- 869
- 870
- 871
- 872
- 873
- 874
- 875
- 876
- 877
- 878
- 879
- 880
- 881
- 882
- 883
- 884
- 885
- 886
- 887
- 888
- 889
- 890
- 891
- 892
- 893
- 894
- 895
- 896
- 897
- 898
- 899
- 900
- 901
- 902
- 903
- 904
- 905
- 906
- 907
- 908
- 909
- 910
- 911
- 912
- 913
- 914
- 915
- 916
- 917
- 918
- 919
- 920
- 921
- 922
- 923
- 924
- 925
- 926
- 927
- 928
- 929
- 930
- 931
- 932
- 933
- 934
- 935
- 936
- 937
- 938
- 939
- 940
- 941
- 942
- 943
- 944
- 945
- 946
- 947
- 948
- 949
- 950
- 951
- 952
- 953
- 954
- 955
- 956
- 957
- 958
- 959
- 960
- 961
- 962
- 963
- 964
- 965
- 966
- 967
- 968
- 969
- 970
- 971
- 972
- 973
- 974
- 975
- 976
- 977
- 978
- 979
- 980
- 981
- 982
- 983
- 984
- 985
- 986
- 987
- 988
- 989
- 990
- 991
- 992
- 993
- 994
- 995
- 996
- 997
- 998
- 999
- 1000

48

## 49 INTRODUCTION

50 Leprosy is a chronic infectious disease caused by infection with *Mycobacterium leprae*  
51 [1]. This pathogen exhibits tissue tropism for phagocytes in the skin and Schwann cells  
52 within peripheral nerves and it presents a long incubation time (from 2 to 7 years)  
53 [2,3]. The disease can manifest across a broad spectrum of symptoms and the  
54 diagnosis is made based on the clinical signs (cutaneous lesions with altered sensitivity  
55 and neurological lesions). Patients are then classified as multibacillary (MB) and  
56 paucibacillary (PB) for treatment purposes, according to criteria accepted by Brazilian  
57 Ministry of Health (BMH) and International Leprosy Association (ILA) [1,2,4–7].

58  
59 Despite control efforts including the widespread use of multidrug therapy (MDT), and  
60 the stabilization of the reported new case detection rate in the last few years, leprosy  
61 remains endemic in many developing countries [3–6,8–11]. In 2014, the World Health  
62 Organization (WHO) reported 213.899 new leprosy cases in 121 countries or territories  
63 [4]. Brazil ranks as the second most burdened country in the world concerning number  
64 of new cases (31,064 in 2014) and has by far the highest number of cases reported in  
65 Americas [4,12,13]. Within Brazil, the highest prevalence has been reported in the  
66 North, Northeast and Midwest regions [8,9]. In 2013, 2,439 new cases were diagnosed  
67 in children under 15 years old in Brazil, yielding a detection rate of 5.03 per 100,000  
68 inhabitants [4].

69  
70 Studies have demonstrated that leprosy presents higher incidence in population with:  
71 low educational degree, precarious health services and domiciliary infrastructure  
72 settlements, and reduced investment in prevention and control [14–16]. Moreover,

1  
2  
3 73 the high incidence rate in children under 15 years is important to indicate there is  
4  
5 74 early exposure of the population to the bacillus, that is associated to elevated  
6  
7 75 prevalence in general population, being a good indicator of a high transmission and  
8  
9 76 bad quality of the control programs [10,12,17–20].  
10  
11  
12 77

13  
14 78 Recently, studies mapping the occurrence of infectious diseases according to their  
15  
16 79 spatial distribution using “Geographic Information Systems (GIS)” have provided  
17  
18 80 important information for public health programs, revealing areas of priority for  
19  
20 81 interventions programs to more efficiently plan and implement control measures  
21  
22 82 [2,9,16,21–23]. The use of GIS in leprosy may allow the identification of spatial-  
23  
24 83 temporal distributions and profile of incidence in defined geographical areas, this  
25  
26 84 potentially contributing to the effectiveness of interventions.  
27  
28  
29

30  
31 85  
32  
33 86 Despite breakthroughs in the epidemiological of leprosy, further improvements in  
34  
35 87 understanding of the disease dynamics in different regions is important for the support  
36  
37 88 of health services as a means for leprosy control. Spatial analyzes studies can provide  
38  
39 89 important understanding of the transmission patterns of *M. leprae* and allow the  
40  
41 90 identification of risk factors [21,23]. The aim of this study was to describe the various  
42  
43 91 clinical and epidemiological indicators, as well as to analyze the spatial distribution, of  
44  
45 92 leprosy cases in patients under 15 years old in an endemic area of Northeast Brazil.  
46  
47  
48

49 93  
50  
51 94  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 95 **METHODS**

4  
5 96 **Patient and Public Involvement and Study Design**

6  
7 97 An ecological and time series epidemiological study was conducted, based on data  
8  
9 98 reported by SINAN (Information System on Notifiable Diseases), database of the  
10  
11 99 Secretariat of Health, Sergipe. Sergipe is located on the coast of Northeast Brazil. The  
12  
13 100 State has 75 municipalities and the capital is Aracaju. It has a population of 2,068,017  
14  
15 101 inhabitants and an area of 21,910,354km<sup>2</sup>, equivalent to 0.26% of the national  
16  
17 102 territory [16]. Population data were obtained from the IBGE (Brazilian Institute of  
18  
19 103 Geography and Statistics), based on population estimates for the intercensus years  
20  
21 104 (2002 - 2015). The historical (from 2002 to 2015) reporting of leprosy cases in children  
22  
23 105 under 15 years old was analyzed. The incidence of leprosy (referred as the new case  
24  
25 106 detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8].  
26  
27  
28  
29

30  
31 107  
32  
33 108 The clinical and epidemiologic indicators collected by Investigation and Notification  
34  
35 109 Form, as recommended by SINAN, were: gender, age, ethnicity, operational  
36  
37 110 classification (PB and MB), clinical form [according to the more refined Ridley-Jopling  
38  
39 111 classification [24,25], based on histopathological analyses: indeterminate leprosy (IL),  
40  
41 112 true tuberculoid (TT), borderline leprosy (BL) and lepromatous leprosy (LL)], leprosy  
42  
43 113 reaction (LR), number of affected nerves, degree of physical disabilities, number of  
44  
45 114 household contacts (HHC) registered and examined, and the patient detection mode.  
46  
47  
48

49 115  
50  
51 116 The parameters adopted by BMH and ILA were followed for interpreting the incidence  
52  
53 117 rate of leprosy in patients under 15 years old. As such, this is classified as: low (<0.50  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 118 cases per 100,000 inhabitants); medium (0.50 to 2.49); high (2.50 to 4.99); very high  
4  
5 119 (5.00 to 9.99) and hyperendemic ( $\geq 10.00$ ) [4].  
6  
7 120

8  
9  
10 121 **Spatial analysis**

11  
12 122 Thematic maps were constructed in each municipality for the period examined  
13  
14 123 according to the leprosy incidence rate in patients under 15 years old and in general  
15  
16 124 population, and for patients presenting with physical disability (incapacity degree 1 or  
17  
18 125 2). The kernel intensity estimator was used by smoothing the statistically generated  
19  
20 126 surface density for the visual detection of hot spots, indicating cases agglomeration in  
21  
22 127 a spatial distribution and a continuous surface from point data [16,21].  
23  
24  
25  
26 128

27  
28 129 We performed either spatial autocorrelation analysis between disease detection rates  
29  
30 130 for each group. The Moran Global Index (MGI)[26] was calculated to identify clusters  
31  
32 131 with risks for disease occurrence. We construct a spatial proximity matrix obtained by  
33  
34 132 the contiguity of autocorrelation. The MGI was calculated as follows:  
35  
36

37 133 (Moran Global Index Mathematical Equation 1)

$$I = \frac{[(n \sum_i \sum_j \omega_{ij} (y_i - \bar{y}) (y_j - \bar{y}))]}{[\sum_i (y_i - \bar{y})^2 \sum_i \sum_j \omega_{ij}]}$$

38  
39  
40  
41 135  
42  
43  
44 136  $\omega_{ij}$  is a contiguity matrix element ( $\omega$ );  $Y_i$  is the incidence rate of municipality  $i$ ;  $Y_j$  is the  
45  
46 137 incidence rate of municipality  $j$ ;  $\bar{Y}$  is the mean of sample and the symbol  $n$  represents  
47  
48 138 the total number of municipalities [26].  
49  
50

51 139  
52  
53 140 The MGI provides a general grouping measure and it is possible to know if there are  
54  
55 141 significant differences between the analyzed areas. However, it does not indicate the  
56  
57  
58  
59  
60

1  
2  
3 142 clusters localization. To do that, we performed the Moran Local Index diagram [26] to  
4  
5 143 build maps and identify the areas with spatial dependence (Local Index of Spatial  
6  
7 144 Association - LISA) of the annual detection means, as follows:

9  
10 145 (Local Index of Spatial Association Mathematical Equation 2)

11  
12 146

$$I = \frac{n[(Z_i \sum_j \omega_{ij} Z_j)]}{(\sum_j Z_j^2)}$$

13  
14  
15  
16 148

17  
18  
19 149  $Z_i = y_i - \bar{y}$ ;  $Z_j = y_j - \bar{y}$ ;  $\omega_{ij}$  is a contiguous matrix element  $\omega$ ;  $Y_i$  is the incidence rate of  
20  
21 150 municipality  $i$ ;  $Y_j$  is the incidence rate of municipality  $j$ ;  $\bar{Y}$  is the sample mean and the  
22  
23 151 symbol  $n$  represents the total number of cities [26]. The Moran Map was used to  
24  
25 152 indicate the clusters and their relation with the neighbors. This analysis verifies the  
26  
27 153 existence of spatial dependence and risk patterns: Q1 (high/high) and Q2 (Low/Low),  
28  
29 154 which indicate municipalities with similar values between their neighbors and Q3  
30  
31 155 (high/low) and Q4 (low/high) for municipalities with different values between their  
32  
33 156 neighbors and no spatial association [26]. Both Moran Index and Kernel maps were  
34  
35 157 constructed using TerraView software 4.2.2.

36  
37  
38  
39 158

### 40 41 42 159 **Statistical analysis**

43  
44 160 Demographic and clinical data were compared across the different subgroups and  
45  
46 161 according to operational classification and the patient detection mode. Percentage,  
47  
48 162 mean and standard deviation of the groups were calculated. D'Agostino and Pearson  
49  
50 163 tests were applied to analyze the normal distribution of data. Statistical differences  
51  
52 164 between the groups were determined by Mann-Whitney and Kruskal-Wallis tests. All  
53  
54 165 analysis was performed using SPSS Statistics, version 24.0. We assessed also the

1  
2  
3 166 tendency analyze by linear regression, where  $y$  (leprosy annual detection) =  $\alpha +$   
4  
5 167  $\beta_1(\text{year})$ . Results were considered statistically different when  $p$ -values < 0.05 were  
6  
7 168 obtained.  
8  
9

10 169

## 11 170 **Ethical Considerations**

12  
13  
14 171 For conducting this study, authorization was previously requested from Coordination  
15  
16 172 of Epidemiological Surveillance, Sergipe state. This project involved research on human  
17  
18 173 subjects and was approved by the Ethics and Research Committee of the Federal  
19  
20 174 University of Sergipe, CAAE 0152.0.107.000-07.  
21  
22

23 175

24 176

## 25 177 **RESULTS**

### 26 178 **Trends in reported leprosy incidence among children**

27  
28 179 The leprosy incidence rate in the general population of Sergipe decreased from 23.08  
29  
30 180 cases to 16.99 per 100,000 inhabitants between 2002 and 2015 (**Figure 1A**). The  
31  
32 181 occurrence of degree 2 physical disability, however, increased in this period (0.76 in  
33  
34 182 2002 to 1.2 in 2015, respectively). The incidence of leprosy in children under 15 years  
35  
36 183 old fluctuated, increasing from 2002 (6.29 cases per 100,000 inhabitants) to 2005  
37  
38 184 (9.82) but then showing a decline to 3.78 in 2015. There was an overall decrease in  
39  
40 185 leprosy incidence in the less than 15 year old group from 2002 to 2015 ( $p$ -value =  
41  
42 186 0.002; **Figure 1B**). The composition of leprosy cases according to the operational  
43  
44 187 classification (PB and MB) was relatively stable across this period, with the majority of  
45  
46 188 cases presenting as PB (**Figure 2A**). We also observed the mean number of HHC  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 189 registered ( $4.65 \pm 2.79$ ) was slightly, but significantly, higher than the number  
4  
5 190 examined ( $3.66 \pm 3.14$ ;  $p$ -value  $< 0.0001$ ; **Figure 2B**).

6  
7 191

### 8 9 192 **Demographics of childhood leprosy cases**

10  
11 193 Next, we evaluated the association among clinical and epidemiological variables  
12  
13 194 according to the leprosy operational classification (patients presenting as PB and MB).  
14  
15 195 Patients presenting as MB or PB were in similar age to ( $10.5 \pm 2.81$  and  $10.07 \pm 3.38$ ,  
16  
17 196 respectively). Despite the extended incubation period of *M. leprae*/leprosy, six cases  
18  
19 197 (1.11%) were reported in children less than one year of age. Of the 538 leprosy cases  
20  
21 198 identified among children under 15 years old the majority were PB [407 (75.7%) PB  
22  
23 199 and 131 (24.3%) MB; **Table 1**]. When stratified on gender, however, the proportion of  
24  
25 200 boys presenting with MB (63.4%) was significantly higher than presenting with PB  
26  
27 201 (48.4%;  $p$ -value = 0.003). An interesting difference was observed when we calculated  
28  
29 202 the ratio (PM/MB) according the ethnic groups. Among those identified as black, the  
30  
31 203 ratio (43/24) was 1.79. Conversely, the ratio of white was higher 4.88 (88/18;  $p$ -value =  
32  
33 204 0.02).

34  
35  
36  
37  
38  
39 205

40  
41 206 As expected, the occurrence of leprosy reactions was significantly higher in MB (21.4%)  
42  
43 207 than PB (4.9%;  $p$ -value  $< 0.0001$ ) patients. The occurrence of degree 2 of physical  
44  
45 208 disability was also higher in MB (4.6%), than in PB patients (0.74%;  $p$ -value = 0.0001).  
46  
47 209 Consistent with this, we observed that the mean of number of affected nerves was  
48  
49 210 higher in MB ( $0.5 \pm 1.03$ ), than PB ( $0.19 \pm 0.54$ ;  $p$ -value = 0.04).

50  
51  
52  
53 211

### 54 55 212 **Impact of case detection methods on leprosy presentation**

1  
2  
3 213 We also performed analysis of association among clinical and epidemiological variables  
4  
5 214 according to the leprosy patient detection mode. The patients were grouped in:  
6  
7 215 spontaneous demand (SDem: patients that looked for medical assistance by  
8  
9 216 themselves); forwarded (FW: patients that were forwarded from a primary clinic to a  
10  
11 217 leprosy reference center); examined HHC; and other. We observed that patients  
12  
13 218 detected by the examined HHC method presented lower mean age ( $9.6 \pm 3.38$ ) than  
14  
15 219 those detected by either the SDem ( $10.54 \pm 3.28$ ) or FW methods ( $10.02 \pm 3.15$ ;  $p$ -  
16  
17 220 value = 0.04; **Table 2**). Interestingly, the percentage of leprosy reaction among the  
18  
19 221 examined HHC group (2.9%;  $p$ -value = 0.02) was lower than that observed among  
20  
21 222 SDem (7.3%) and FW (13.3%). In addition, degree 2 of physical disability was not  
22  
23 223 observed among patients detected in examined HHC group, while SDem and FW  
24  
25 224 presented 0.43% and 3.8%, respectively ( $p$ -value = 0.04). Furthermore, patients  
26  
27 225 identified among examined HHC presented with lower numbers of lesions ( $2.04 \pm 2.96$ ;  
28  
29 226  $p$ -value = 0.04) than SDem ( $3.64 \pm 6.25$ ) and FW ( $4.09 \pm 8.68$ ). Taken together, these  
30  
31 227 data reinforce the importance of HHC examination for the detection of leprosy  
32  
33 228 patients before advancement to more severe symptoms.  
34  
35  
36  
37  
38  
39  
40  
41

### 42 230 **Spatial analyze data**

43  
44 231 Next, we performed the spatial analysis of leprosy cases in the general population, in  
45  
46 232 patients under 15 years old, and in patients presenting with physical disability (both  
47  
48 233 degree 1 and 2). Moran maps have showed higher risk clusters (Q1 - in red; **Figure 3A-**  
49  
50 234 **C**) in similar areas when comparing the maps regarding leprosy cases in children under  
51  
52 235 15 years old, in general population, and patients presenting some physical disability  
53  
54 236 (degree 1 and 2). The higher risk clusters (Q1) were localized in Sergipe state center  
55  
56  
57  
58  
59  
60

1  
2  
3 237 and in the metropolitan area around the capital of State. The municipalities with no  
4  
5 238 spatial association (Q3 - in blue) were localized in the Semiarid region, in the northwest  
6  
7 239 area and in the south region.  
8

9  
10 240

11  
12 241 Similarly, The Kernel estimator, through data interpolation, showed densities (hot  
13  
14 242 spots) of the highest incidence rates located at the northeast and east center regions  
15  
16 243 and in the counties around the state capital (Aracaju city; **Figure 3D-F**). Lower intensity  
17  
18 244 was observed on the western region. Municipalities with intermediate to high  
19  
20 245 incidence values are seen in yellow and red tones of each subfigure. Low incidence  
21  
22 246 areas were reported on west coast municipalities, mostly in smaller counties with  
23  
24 247 small populations.  
25  
26  
27

28 248

## 29 30 249 **DISCUSSION**

31  
32 250 Previous studies have demonstrated that the high leprosy cases detection in patients  
33  
34 251 under 15 years old is a bad parameter for leprosy control program, because it indicates  
35  
36 252 early bacillus transmission from undiagnosed cases [18]. Some authors have  
37  
38 253 speculated either about the risk of vertical/transplacental transmission or through  
39  
40 254 breastfeeding [12].  
41  
42  
43

44 255

45  
46 256 In Brazil, the highest leprosy incidence rate in children was reported in the North area  
47  
48 257 (11.91 cases per 100,000 inhabitants), followed by Northeast (8.12) [12]. We observed  
49  
50 258 the leprosy incidence rate was reduced in children under 15 years old from 2002 to  
51  
52 259 2015 in Sergipe state, however considering the parameters adopted by BMH, the state  
53  
54 260 was classified as very high endemicity in 2002, and still as high endemicity in 2015. It  
55  
56  
57  
58  
59  
60

1  
2  
3 261 remains also with elevated incidence rate and stationary tendency of degree 2 of  
4  
5 262 physical disability. Those data reinforce either that the transmission is intense at early  
6  
7 263 age, there is lack of an effective public health and the disease control is focused in the  
8  
9 264 MDT [12,18]. A similar study performed at Fortaleza city (Brazil), reported also that  
10  
11 265 although a decreasing has been observed on overall detection rate, the number of new  
12  
13  
14 266 cases in those under 15 years old remains stable [13].  
15

16  
17 267  
18  
19 268 Leprosy reactions and physical disability are the most severe leprosy clinical  
20  
21 269 complications [8,27,28]. In addition, the increase or stability of the prevalence of  
22  
23 270 degree 2 of physical disability indicates persisting late diagnosis [13,28]. The early  
24  
25 271 diagnosis of leprosy is essential to the prevention of deformities, whose repercussions  
26  
27 272 are still more catastrophic in children and adolescents [27]. Our data reported 21.4%  
28  
29 273 children with leprosy reaction (LR) and 31.3% with some physical disability in the MB  
30  
31 274 groups. Furthermore, MB patients presented higher mean of affected nerves.  
32  
33 275 Generally, patients under 15 years old do not use to present LR, but studies have  
34  
35 276 reported a low frequency of LR, varying between 1.36% and 8.33% [27]. Those data  
36  
37 277 reinforce that, although there is a decreasing incidence in leprosy, patients have been  
38  
39 278 exposed to bacillus early in life and diagnosed belatedly and hence they have been also  
40  
41 279 developing into some clinical complications.  
42  
43  
44  
45

46 280  
47  
48 281 We have observed either that the mean of HHC examined was significantly lower than  
49  
50 282 those registered by SINAN. Moreover, leprosy patients detected by exam in HHC  
51  
52 283 presented lower mean of age, affected nerves, number of lesions, occurrence of LR  
53  
54 284 and no physical disability, when compared with those identified by spontaneous  
55  
56  
57  
58  
59  
60

1  
2  
3 285 demand or forwarded by others. On the other hand, mostly of patients presenting as  
4  
5 286 degree 2 of physical disability were identified into those forwarded to a leprosy  
6  
7 287 reference center, probably because they started presenting some physical disability.  
8  
9 288 HHC and neighbors are the most important *M. leprae* active sources. The risk of a  
10  
11 289 person developing leprosy is nine times greater among HHC and up to four times  
12  
13 290 greater among contacts with neighbors [12]. Therefore, our data reinforce the  
14  
15 291 importance of leprosy early diagnosis by exam in patients and their household  
16  
17 292 contacts. Besides that, the treatment and the home visits by public health programs,  
18  
19 293 and an efficient health program in schools could represent important actions for the  
20  
21 294 early diagnosis and the reduction of leprosy clinical complications, especially in  
22  
23 295 children.  
24  
25  
26  
27  
28  
29

30 297 Spatial analysis of health events aim to identify geographical patterns by maps of risk  
31  
32 298 and to point out areas of higher severity and to facilitate the planning of public health  
33  
34 299 interventions [9]. The Kernel maps showed the spatial dynamic of leprosy, with a  
35  
36 300 heterogeneous geographical pattern and the highest risk areas for leprosy infection.  
37  
38 301 The highest incidence on counties around the Capital can be due there was a  
39  
40 302 leprosarium at the Nossa Senhora do Socorro (a city of the metropolitan area of  
41  
42 303 Aracaju), that has presented elevated detection rate in mostly evaluated years.  
43  
44 304 Moreover, that area presents reference center to leprosy diagnosis and treatment and  
45  
46 305 hence they have several patients forwarded to these leprosy clinics. It can be also  
47  
48 306 associated with weather featuring such as humidity, considering either that counties  
49  
50 307 near to São Francisco River presented also elevated incidence. In the Malawian  
51  
52 308 Karonga district, a positive relationship between the proximity of water and leprosy  
53  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 309 incidence was previously reported [5]. Some authors have hypothesized that *M. leprae*  
4  
5 310 survives longer outside of human body in humid compared to dry atmospheres [9,13].  
6

7 311

8  
9 312 Interestingly, higher risk clusters were identified in similar areas when we analyzed the  
10  
11 313 occurrence of leprosy cases in children, in general population and patients presenting  
12  
13  
14 314 physical disability. It corroborates the hypothesis that the early transmission of *M.*  
15  
16 315 *leprae* and the occurrence of leprosy in children under 15 years old is directly related  
17  
18 316 to the late diagnosis, which explains the occurrence of patients with degree 2 of  
19  
20  
21 317 physical disability in the same geographic distribution [27].  
22

23 318

24  
25 319 In summary, our study demonstrated that the leprosy incidence rate has decreased in  
26  
27 320 Sergipe state. However, it is still classified as high endemicity considering the WHO  
28  
29 321 proposed ratios for children under 15 years. Patients detected by exam in collectivity  
30  
31 322 or HHC presented better indicators. Altogether, the epidemiological data and spatial  
32  
33 323 analysis indicate that there is persistence of active transmission of *M. leprae* and later  
34  
35 324 case detection in Sergipe state, increasing the risk of transmission in children. In  
36  
37 325 addition, the spatial analysis brings new advantages to comprehend the leprosy  
38  
39 326 dynamic, and reinforce the superimposed regions of high occurrence areas of patients  
40  
41 327 presenting degree 2 of physical disability and cases in children lower than 15 years,  
42  
43 328 and highlights the need to strengthen effective disease control measures, mainly in  
44  
45 329 primary health care.  
46  
47  
48  
49

50 330

51 331

52 332

1  
2  
3 333 **Acknowledgments** The authors would like to thank the Manager of the Nucleus of  
4  
5 334 endemic/Division of Epidemiological Surveillance - [Divisão de Vigilância  
6  
7 335 Epidemiológica (DIVEP)]/ Secretariat of Health of the Sergipe state (SES) for providing  
8  
9 336 information.

11 337 **Funding** This research received no specific grant from any funding agency in the public,  
13  
14 338 commercial or not-for-profit sectors.

16 339 **Contributors** The project was suggested by MS, AS and AJ. The manuscript was written  
17  
18 340 by MS. All authors contributed to refining the idea, analyzing the data, revising the  
19  
20 341 manuscript and have agreed the final version.

22 342 **Competing interests** The authors declare that they have no conflicts of interest.

24 343 **Provenance and peer review** Not commissioned; externally peer reviewed.

26 344 **Data sharing statement** No additional data are available.

28 345

30 346

32 347

348 **References**

349

- 350 1 Simon M, Scherlock J, Duthie MS, *et al*. Clinical, immunological, and genetic  
351 aspects in leprosy. *Drug Dev Res* 2011;**72**:509–27. doi:10.1002/ddr.20457
- 352 2 Duarte-Cunha M, Marcelo da Cunha G, Souza-Santos R. Geographical  
353 heterogeneity in the analysis of factors associated with leprosy in an endemic  
354 area of Brazil: are we eliminating the disease? *BMC Infect Dis* 2015;**15**:196.  
355 doi:10.1186/s12879-015-0924-x
- 356 3 Fulton N, Anderson LF, Watson JM, *et al*. Leprosy in England and Wales 1953-  
357 2012: Surveillance and challenges in low incidence countries. *BMJ Open*  
358 2016;**6**:15–8. doi:10.1136/bmjopen-2015-010608
- 359 4 Freitas LRS, Duarte EC, Garcia LP, *et al*. Trends of main indicators of leprosy in  
360 Brazilian municipalities with high risk of leprosy transmission, 2001–2012. *BMC*  
361 *Infect Dis* 2016;**16**:472. doi:10.1186/s12879-016-1798-2
- 362 5 Duthie MS, Saunderson P, Reed SG. The potential for vaccination in leprosy  
363 elimination: New tools for targeted interventions. *Mem Inst Oswaldo Cruz*  
364 2012;**107**:190–6. doi:10.1590/S0074-02762012000900027
- 365 6 Duthie MS, Gillis TP, Reed SG. Advances and hurdles on the way toward a  
366 leprosy vaccine. *Hum Vaccin* 2011;**7**:1172–83. doi:10.4161/hv.7.11.16848
- 367 7 Kumar A, Girdhar A, Girdhar BK. Six months fixed duration multidrug therapy in  
368 paucibacillary leprosy: Risk of relapse and disability in Agra PB cohort study. *BMJ*  
369 *Open* 2012;**2**:1–6. doi:10.1136/bmjopen-2012-001403

- 1  
2  
3 370 8 de Oliveira DT, Bezerra MM, de Almeida JAP, *et al.* Neurological disability in  
4  
5 371 leprosy: Incidence and gender association in Sergipe, Brazil. *Geospat Health*  
6  
7 372 2012;**6**. doi:10.4081/gh.2012.130  
8  
9  
10 373 9 Alencar CH, Ramos AN, dos Santos ES, *et al.* Clusters of leprosy transmission and  
11  
12 374 of late diagnosis in a highly endemic area in Brazil: Focus on different spatial  
13  
14 375 analysis approaches. *Trop Med Int Heal* 2012;**17**:518–25. doi:10.1111/j.1365-  
15  
16 376 3156.2011.02945.x  
17  
18  
19  
20 377 10 Durrheim DN, Speare R. Global leprosy elimination: Time to change more than  
21  
22 378 the elimination target date. *J Epidemiol Community Health* 2003;**57**:316–7.  
23  
24 379 doi:10.1136/jech.57.5.316  
25  
26  
27  
28 380 11 Barth-Jaeggi T, Steinmann P, Mieras L, *et al.* Leprosy Post-Exposure Prophylaxis  
29  
30 381 (LPEP) programme: Study protocol for evaluating the feasibility and impact on  
31  
32 382 case detection rates of contact tracing and single dose rifampicin. *BMJ Open*  
33  
34 383 2016;**6**. doi:10.1136/bmjopen-2016-013633  
35  
36  
37  
38 384 12 Santos SD, Penna GO, Costa M da CN, *et al.* Leprosy in children and adolescents  
39  
40 385 under 15 years old in an urban centre in Brazil. *Mem Inst Oswaldo Cruz*  
41  
42 386 2016;**111**:359–64. doi:10.1590/0074-02760160002  
43  
44  
45  
46 387 13 Brito AL, Monteiro LD, Ramos Junior AN, *et al.* Tendência temporal da  
47  
48 388 hanseníase em uma capital do Nordeste do Brasil: epidemiologia e análise por  
49  
50 389 pontos de inflexão, 2001 a 2012. *Rev Bras Epidemiol* 2016;**19**:194–204.  
51  
52 390 doi:10.1590/1980-5497201600010017  
53  
54  
55  
56 391 14 Vieira GDD, Aragoso I, Carvalho RMB, *et al.* Hanseníase em Rondônia: incidência  
57  
58  
59  
60

- 1  
2  
3 392 e características dos casos notificados, 2001 a 2012. *Epidemiol e Serviços Saúde*  
4  
5 393 2014;**23**:269–75. doi:10.5123/S1679-49742014000200008  
6  
7  
8 394 15 Queir??s MI, Ramos AN, Alencar CHM, *et al.* Clinical and epidemiological profile  
9  
10 395 of leprosy patients attended at Cear??, 2007-2011. *An Bras Dermatol*  
11  
12 396 2016;**91**:311–7. doi:10.1590/abd1806-4841.20164102  
13  
14  
15  
16 397 16 dos Santos AD, Lima ACR, Santos MB, *et al.* Spatial analysis for the identification  
17  
18 398 of risk areas for schistosomiasis mansoni in the state of Sergipe, Brazil, 2005-  
19  
20 399 2014. *Rev Soc Bras Med Trop* 2016;**49**:608–15. doi:10.1590/0037-8682-0137-  
21  
22 400 2016  
23  
24  
25  
26 401 17 Alencar CHM De, Barbosa JC, Ramos Jr AN, *et al.* Hanseníase no município de  
27  
28 402 Fortaleza, CE, Brasil: aspectos epidemiológicos e operacionais em menores de  
29  
30 403 15 anos (1995-2006). *Rev Bras Enferm* 2008;**61**:694–700. doi:10.1590/S0034-  
31  
32 404 71672008000700007  
33  
34  
35  
36 405 18 Pires CAA, Malcher CMSR, Abreu JMC, *et al.* Hanseníase em menores de 15  
37  
38 406 anos: A importância do exame de contato. *Rev Paul Pediatr* 2012;**30**:292–5.  
39  
40 407 doi:10.1590/S0103-05822012000200022  
41  
42  
43  
44 408 19 Carlos F, Lana F, Amaral EP, *et al.* Hanseníase em menores de 15 anos no Vale  
45  
46 409 do Jequitinhonha, Minas Gerais, Brasil. *Rev Bras Enferm* 2007;**60**:696–700.  
47  
48 410 doi:10.1590/S0034-71672007000600014  
49  
50  
51 411 20 Fernandes C, Gonçalves HS, Cabral PB, *et al.* Increased frequency of CD4 and  
52  
53 412 CD8 regulatory T cells in individuals under 15 years with multibacillary leprosy.  
54  
55 413 *PLoS One* 2013;**8**. doi:10.1371/journal.pone.0079072  
56  
57  
58  
59  
60

- 1  
2  
3 414 21 Barreto AS, Alves B. ORIGINAL ARTICLE SPATIAL ANALYSIS AND  
4  
5 415 EPIDEMIOLOGICAL CHARACTERISTICS OF CASES OF LEPROSY IN AN ENDEMIC  
6  
7 416 AREA. *J Nurs UFPE* 2016;**10**. doi:10.5205/reuol.9881-87554-1-EDSM1011201604  
8  
9  
10 417 22 Khan O, Davenhall W, Ali M, *et al*. Geographical information systems and  
11  
12 418 tropical medicine. *Ann Trop Med Parasitol* 2010;**104**:303–18.  
13  
14 419 doi:10.1179/136485910X12743554759867.Geographical  
15  
16  
17  
18 420 23 Fischer E, Pahan D, Chowdhury S, *et al*. The spatial distribution of leprosy in four  
19  
20 421 villages in Bangladesh: an observational study. *BMC Infect Dis* 2008;**8**:125.  
21  
22 422 doi:10.1186/1471-2334-8-125  
23  
24  
25  
26 423 24 Ridley DS JW. Classification of leprosy according to immunity. A five-group  
27  
28 424 system. *Int J Lepr Other Mycobact Dis* 1966;**34**:255–73.  
29  
30 425 doi:10.1126/science.1238286  
31  
32  
33  
34 426 25 Lockwood DNJ, Sarno E, Smith WC. Classifying leprosy patients--searching for  
35  
36 427 the perfect solution. *Lepr Rev* 2007;**78**:317–20.  
37  
38  
39 428 26 Chen Y. New Approaches for Calculating Moran's Index of Spatial  
40  
41 429 Autocorrelation. *PLoS One* 2013;**8**. doi:10.1371/journal.pone.0068336  
42  
43  
44 430 27 de Oliveira MBB, Diniz LM. Leprosy among children under 15 years of age:  
45  
46 431 Literature review. *An Bras Dermatol* 2016;**91**:196–203. doi:10.1590/abd1806-  
47  
48 432 4841.20163661  
49  
50  
51  
52 433 28 Kumar A, Girdhar A, Kumar Girdhar B. Risk of developing disability in pre and  
53  
54 434 post-multidrug therapy treatment among multibacillary leprosy: Agra MB  
55  
56 435 Cohort study. *BMJ Open* 2012;**2**:1–7. doi:10.1136/bmjopen-2011-000361  
57  
58  
59  
60

436 **Table 1. Association of demographic and clinical data according to the operational**  
 437 **classification of leprosy (PB and MB) in children under 15 years in Sergipe state,**  
 438 **Brazil (2002-2015).**

Variables	Operational Classification		p-value
	PB (n = 407)	MB (n = 131)	
<b>Age mean ± SD</b>	10.07 ± 3.38	10.5 ± 2.81	*0.46
<b>Gender n (%)</b>			
Male	197 (48.4)	83 (63.4)	+0.003
<b>Ethnicity n (%)</b>			
White	88 (21.6)	18 (13.7)	#0.02
Black	43 (10.5)	24 (18.3)	
Brown	251 (61.7)	78 (59.5)	
Indian	4 (0.9)	3 (2.3)	
<b>Leprosy reaction n (%)</b>	20 (4.9)	28 (21.4)	+<0.0001
<b>Physical Disability</b>			
<b>Degree n (%)</b>			
0	337 (82.8)	90 (68.7)	#0.0001
1	26 (6.4)	18 (13.7)	
2	3 (0.74)	6 (4.6)	
<b>Number of affected nerves (mean ± SD)</b>	0.19 ± 0.54	0.5 ± 1.03	*0.04
<b>Number of Lesions (mean ± SD)</b>	1.61 ± 1.14	9.92 ± 12.03	*<0.0001
<b>HHC registered (mean ± SD)</b>	4.6 ± 2.71	4.85 ± 3.04	*0.14
<b>HHC examined (mean ± SD)</b>	3.54 ± 3.04	4.05 ± 3.44	

439 \*Mann-Whitney test; +Fisher's exact test; #Chi-square test. SD = Standard Deviation. We missed data in  
 440 some variables.

441

442 **Table 2. Demographic and clinical aspects accordingly to the detection mode of**  
 443 **leprosy cases in children under 15 years in Sergipe state, Brazil (2002-2015).**

444

Variables	Patient detection mode				p-value
	Spontaneous demand (n = 234)	Forwarding (n = 210)	Examined HHC (n = 69)	Other (n = 25)	
Age mean $\pm$ SD	10.54 $\pm$ 3.28	10.02 $\pm$ 3.15	9.6 $\pm$ 3.38	9.6 $\pm$ 3.22	*0.04
Gender n (%)					
Male	123 (52.6)	110 (52.4)	38 (55.1)	09 (36)	#0.41
Leprosy reaction n (%)	17 (7.3)	28 (13.3)	2 (2.9)	1 (4.0)	#0.02
Physical disability degree n (%)					
0	199 (85.1)	150 (71.4)	55 (79.7)	18 (72)	#0.04
1	17 (7.3)	21 (10)	5 (7.2)	1 (4.0)	
2	1 (0.43)	08 (3.8)	0 (0.0)	0 (0.0)	
Number of affected nerves (mean $\pm$ SD)	0.24 $\pm$ 0.67	0.34 $\pm$ 0.81	0.06 $\pm$ 0.25	0.25 $\pm$ 0.5	*0.48
Number of lesion (mean $\pm$ SD)	3.64 $\pm$ 6.25	4.09 $\pm$ 8.68	2.04 $\pm$ 2.96	4 $\pm$ 5.2	*0.04
HHC registered (mean $\pm$ SD)	4.57 $\pm$ 2.53	4.59 $\pm$ 2.74	5.57 $\pm$ 3.81	3.45 $\pm$ 1.96	*0.04
HHC examined (mean $\pm$ SD)	3.71 $\pm$ 3.02	3.02 $\pm$ 2.98	4.64 $\pm$ 4.06	2.04 $\pm$ 1.77	*0.01

445 \*Kruskal-Wallis test; #Chi-square test. SD = Standard Deviation. We missed data in some variables.

446



1  
2  
3 447 **Figure 1. Leprosy incidence rates in state of Sergipe, Northeast Brazil, 2002-2015.** A)  
4  
5 448 Leprosy incidence rate (per 100,000 inhabitants) in general population (▲), in patients  
6  
7 449 under 15 years old (■), degree 2 of physical disability (◆) and the tendency line. B)  
8  
9  
10 450 Tendency analyzes description. Data were considered statistically different when p-  
11  
12 451 value < 0.05. CI: Confidence Interval.

13  
14 452  
15  
16  
17 453 **Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state**  
18  
19  
20 454 **of Sergipe, Brazil, 2002-2015.** A) Proportion of leprosy cases according to the clinical  
21  
22 455 operational classification (Paucibacillary - PB (■) and Multibacillary – MB (◆) forms). B)  
23  
24 456 Mean and standard deviation (mean ± SD) of the number of household contacts (HHC)  
25  
26 457 that were registered and examined for leprosy diagnosis. Data were considered  
27  
28 458 statistically different when p-value < 0.05. \* Mann-Whitney test.

29  
30  
31 459  
32  
33 460 **Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were**  
34  
35  
36 461 **constructed by TerraView Software 4.2.2.** The Moran Global Index (\*MGI) was  
37  
38 462 calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of  
39  
40 463 leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy  
41  
42 464 cases in the general population. Moran (E) and Kernel (F) maps of occurrence of  
43  
44 465 incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 – 2015).

46  
47 466  
48  
49  
50 467

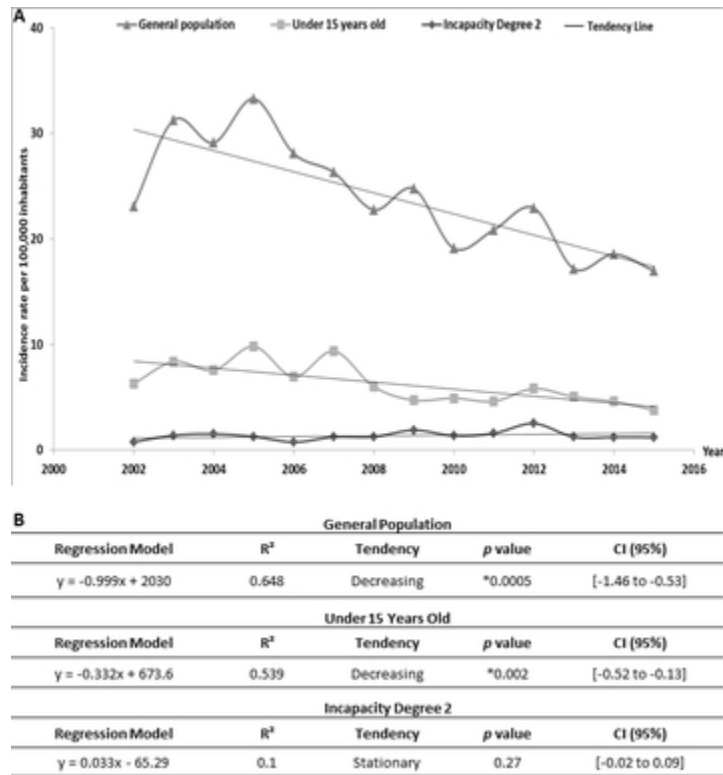


Figure 1. Leprosy incidence rates in state of Sergipe, Northeast Brazil, 2002-2015. A) Leprosy incidence rate (per 100,000 inhabitants) in general population (▲), in patients under 15 years old (□), degree 2 of physical disability (●) and the tendency line. B) Tendency analyzes description. Data were considered statistically different when p-value < 0.05. CI: Confidence Interval.

30x32mm (300 x 300 DPI)

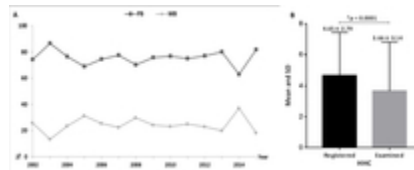


Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Proportion of leprosy cases according to the clinical operational classification (Paucibacillary - PB (□) and Multibacillary - MB (□) forms). B) Mean and standard deviation (mean  $\pm$  SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. \* Mann-Whitney test.

17x7mm (300 x 300 DPI)

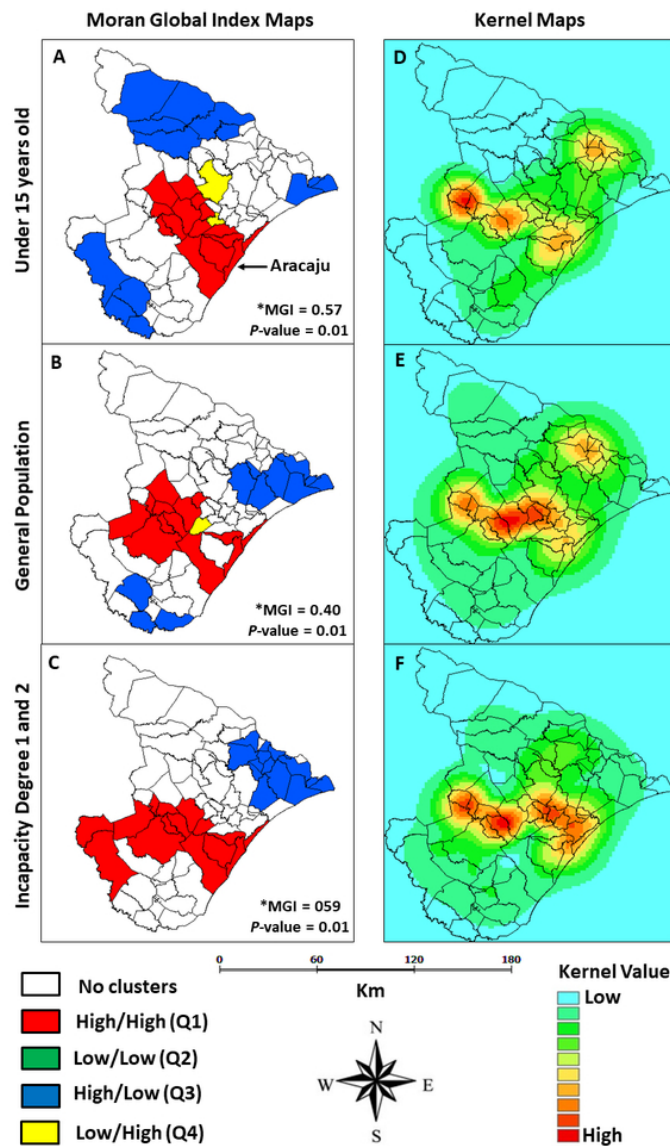


Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were constructed by TerraView Software 4.2.2. The Moran Global Index (\*MGI) was calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy cases in the general population. Moran (E) and Kernel (F) maps of occurrence of incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 - 2015).

64x85mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	01
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	02
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	04-05
Objectives	3	State specific objectives, including any prespecified hypotheses	05
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	06
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	06
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	06
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	06
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	06-07
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	06
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	06-08
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	08-09
		(b) Describe any methods used to examine subgroups and interactions	08-09
		(c) Explain how missing data were addressed	08-09
		(d) If applicable, describe analytical methods taking account of sampling strategy	08-09
		(e) Describe any sensitivity analyses	08-09
<b>Results</b>			08-09

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	09
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	09-10
		(b) Indicate number of participants with missing data for each variable of interest	--
Outcome data	15*	Report numbers of outcome events or summary measures	09-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(b) Report category boundaries when continuous variables were categorized	--
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	09-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in an Endemic Area of Northeast Brazil: an ecological and time series study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023420.R1
Article Type:	Research
Date Submitted by the Author:	06-Feb-2019
Complete List of Authors:	Santos, Márcio; Universidade Federal de Sergipe, Health Education; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Santos, Allan; Universidade Federal de Sergipe, Nursing Barreto, Aline; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Souza, Mariana; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Goes, Marco; Universidade Federal de Sergipe, Medicine Barreto Alves, Jose Antonio; Universidade Federal de Sergipe, Nursing Barreto, Ikaro; Universidade Federal Rural de Pernambuco, Programa de Pos-Graduacao em Biometria e Estatistica Aplicada Silva, José-Rodrigo; Universidade Federal de Sergipe, Statistics and Actuarial Sciences Oliveira, Daniela; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Araújo, Karina; Universidade Federal de Sergipe, Morphology Duthie, Malcolm; Infectious Diseases Research Institute Jesus, Amélia; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology; Universidade Federal de Sergipe, Medicine
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Public health
Keywords:	Leprosy, Children, Epidemiology < INFECTIOUS DISEASES, Spatial analysis

SCHOLARONE™  
Manuscripts

1  
2  
3 **1 Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy**  
4  
5  
6 **2 Cases in Patients Under 15 Years Old in an Endemic Area of Northeast**  
7  
8  
9 **3 Brazil: an ecological and time series study**  
10  
11  
12 **4**

13  
14 5 Márcio B Santos<sup>1,2</sup>, Allan D dos Santos<sup>3</sup>, Aline S Barreto<sup>2</sup>, Mariana do R Souza<sup>2</sup>, Marco A  
15  
16 6 de O Goes<sup>4</sup>, José-Antônio A Barreto<sup>3</sup>, Íkaro D C Barreto<sup>5</sup>, José-Rodrigo S Silva<sup>6</sup>, Daniela  
17  
18 7 T de Oliveira<sup>3</sup>, Karina G de Araujo<sup>7</sup>, Malcolm S Duthie<sup>8</sup>, Amélia R de Jesus<sup>2,9,10</sup>.  
19  
20  
21 8

22  
23  
24 9 <sup>1</sup>Departament of Health Education, Universidade Federal de Sergipe, Brazil; <sup>2</sup>Laboratory of Immunology  
25  
26 10 and Molecular Biology, Universidade Federal de Sergipe, Brazil; <sup>3</sup>Departament of Nursing, Universidade  
27  
28 11 Federal de Sergipe, Brazil; <sup>4</sup>Departament of Medicine, Universidade Federal de Sergipe, Brazil; <sup>5</sup>Mestre,  
29  
30 12 Universidade Federal Rural de Pernambuco (UFPE), Programa de Pos-Graduacao em Biometria e  
31  
32 13 Estatística Aplicada; <sup>6</sup>Doutor, Professor Adjunto do Departamento de Estatística e Ciências Atuariais da  
33  
34 14 Universidade Federal de Sergipe (UFS); <sup>7</sup>Departament of Morphology, Universidade Federal de Sergipe,  
35  
36 15 Aracaju; <sup>8</sup>Infectious Diseases Research Institute (IDRI), Seattle, USA. <sup>9</sup>Departament of Medicine,  
37  
38 16 Universidade Federal de Sergipe, Aracaju. <sup>10</sup>Instituto de Investigação em Imunologia, INCT, CNPq.  
39  
40  
41  
42

43 **18 Corresponding Author**

44  
45 19 Márcio B. Santos

46  
47 20 Department of Health Science, Federal University of Sergipe

48  
49 21 Av. Gov. Marcelo Déda - São José, Lagarto - SE, Brazil

50  
51  
52 22 Postal Code 49400-000

53  
54 23 E-mail: bio\_marcio2006@hotmail.com  
55  
56  
57  
58  
59  
60



1  
2  
3 24 **ABSTRACT**  
4

5 25 **Objective:** This study aimed to analyze the clinical and epidemiological indicators,  
6  
7  
8 26 temporal trends and the spatial distribution of leprosy in patients under 15 years old in  
9  
10 27 an endemic area of Northeast Brazil.

11  
12  
13 28 **Design:** Regional surveillance study of all reported cases.

14  
15 29 **Setting:** State of Sergipe, endemic area of Northeast Brazil.

16  
17  
18 30 **Methods:** An ecological and time series study was conducted, based on secondary  
19  
20 31 data reported by the Brazilian Information System on Notifiable Diseases (SINAN) for  
21  
22 32 leprosy cases diagnosed in Sergipe state (2002-2015). The analysis of temporal trends  
23  
24 33 was performed using the Joinpoint Regression Program through Poisson regression.  
25  
26 34 We performed spatial analysis by Kernel estimator and Moran index.

27  
28  
29 35 **Results:** The incidence rate was reduced from 6.29 to 3.78 cases per 100,000  
30  
31 36 inhabitants in 2002 and 2015, respectively. However, Sergipe was still classified as  
32  
33 37 highly endemicity in 2015. The mean number of household contacts (HHC) examined  
34  
35 38 was significantly lower than those registered. Clinical data indicated that 21.4% of the  
36  
37 39 patients developed leprosy reactions, and 31.3% presented with some physical  
38  
39 40 disability in the multibacillary (MB) groups. Patients diagnosed by exam within the HHC  
40  
41 41 presented better indicators, such as lower percentage of leprosy reaction and physical  
42  
43 42 disability. Spatial analysis showed the most risk areas distributed on the northeast and  
44  
45 43 cities around the capital, Aracaju.

46  
47  
48 44 **Conclusion:** The data indicate that there is a persistence of active *M. leprae*  
49  
50 45 transmission and a delay in disease detection, following a pattern of high endemicity in  
51  
52 46 many municipalities. The early detection by household contacts examination is  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 47 important not only to stop transmission but also to detect the cases in a less severe  
4  
5 48 state.

6  
7  
8 49 **Keywords:** Leprosy; Children; Epidemiology; Spatial analysis.  
9  
10  
11  
12

### Strengths and limitations of this study

- This is a surveillance study that includes all notified cases of leprosy, in a State of Brazil with moderate prevalence of the disease.
- This is the first summary of leprosy cases in patients under 15 years old in Sergipe state, Northeast Brazil.
- This study was conducted using secondary data reported by SINAN and this source of data may have datasets missing.
- We also mapped the leprosy cases and physical disability in children under 15 years in areas of higher prevalence of leprosy in the general population, using geoprocessing tools.
- We compared the leprosy patient detection mode and how it affects the disease severity at diagnosis and the occurrence of leprosy reactions and physical disabilities.

13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33 50  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 51 INTRODUCTION

52 Leprosy is a chronic infectious disease caused by infection with *Mycobacterium leprae*  
53 [1]. This pathogen exhibits tissue tropism for phagocytes in the skin and Schwann cells  
54 within peripheral nerves and it presents a long incubation time (from 2 to 7 years)  
55 [2,3]. The disease can manifest across a broad spectrum of symptoms and the  
56 diagnosis is made based on the clinical signs (cutaneous lesions with altered sensitivity  
57 and neurological lesions). Patients are then classified as multibacillary (MB) and  
58 paucibacillary (PB) for treatment purposes, according to criteria accepted by Brazilian  
59 Ministry of Health (BMH) and International Leprosy Association (ILA) [1,2,4–7].

60  
61 Despite control efforts including the widespread use of multidrug therapy (MDT), and  
62 the stabilization of the reported new case detection rate in the last few years, leprosy  
63 remains endemic in many developing countries [3–6,8–11]. In 2014, the World Health  
64 Organization (WHO) reported 213,899 new leprosy cases in 121 countries or territories  
65 [4]. Brazil ranks as the second most burdened country in the world concerning number  
66 of new cases (31,064 in 2014) and has by far the highest number of cases reported in  
67 Americas [4,12,13]. Within Brazil, the highest prevalence has been reported in the  
68 North, Northeast and Midwest regions [8,9]. The incidence of leprosy (referred as the  
69 new case detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8]. In 2013, 2,439  
70 new cases were diagnosed in children under 15 years old in Brazil, yielding a detection  
71 rate of 5.03 per 100,000 inhabitants [4].

72  
73 Studies have demonstrated that leprosy presents higher incidence in population with:  
74 low educational degree, precarious health services and domiciliary infrastructure

1  
2  
3 75 settlements, and reduced investment in prevention and control [14–16]. Moreover,  
4  
5 76 the high incidence rate in children under 15 years is important to indicate there is  
6  
7  
8 77 early exposure of the population to the bacillus, that is associated to elevated  
9  
10  
11 78 prevalence in general population, being a good indicator of a high transmission and  
12  
13 79 bad quality of the control programs [10,12,17–20]. There is no study reporting the  
14  
15 80 incidence of leprosy in children under 15 years in Sergipe state.  
16  
17

18 81  
19  
20 82 Recently, studies mapping the occurrence of infectious diseases according to their  
21  
22 83 spatial distribution using “Geographic Information Systems (GIS)” have provided  
23  
24 84 important information for public health programs, revealing areas of priority for  
25  
26 85 interventions programs to more efficiently plan and implement control measures  
27  
28 86 [2,9,16,21–23]. The use of GIS in leprosy may allow the identification of spatial-  
29  
30  
31 87 temporal distributions and profile of incidence in defined geographical areas, this  
32  
33 88 potentially contributing to the effectiveness of interventions.  
34  
35  
36 89

37  
38  
39 90 Despite breakthroughs in the epidemiological of leprosy, further improvements in  
40  
41 91 understanding of the disease dynamics in different regions is important for the support  
42  
43 92 of health services as a means for leprosy control. Spatial analyzes studies can provide  
44  
45 93 important understanding of the transmission patterns of *M. leprae* and allow the  
46  
47 94 identification of risk factors [21,23]. The aim of this study was to describe the 1)  
48  
49 95 various clinical and epidemiological indicators of leprosy; to analyze 2) temporal trends  
50  
51 96 and 3) the spatial distribution of leprosy cases in patients under 15 years old in an  
52  
53 97 endemic area of Northeast Brazil.  
54  
55  
56 98

## 99 **METHODS**

### 100 **Study Design**

101 The source of all data from this study was the leprosy cases and the information of  
102 each individual case notified by the health centers of the municipalities to the SINAN  
103 (Information System on Notifiable Diseases) from the State of Sergipe, Brazil. This is an  
104 important database of the Secretariat of Health of all States of Brazil, to report  
105 information about sociodemographic, clinical features and the address of notifiable  
106 diseases. Leprosy is a notifiable disease in Brazil, and as a legislative requirement, all  
107 leprosy cases have to be notified to the SINAN, including information about social and  
108 demographic features, clinical forms and follow-up of each patient. Sergipe is located  
109 on the coast of Northeast Brazil. The State has 75 municipalities and the capital is  
110 Aracaju. It has a population of 2,068,017 inhabitants and an area of 21,910,354km<sup>2</sup>,  
111 equivalent to 0.26% of the national territory. The median population per county was  
112 27,573.56 in 2015 [16]. Population data were obtained from the IBGE (Brazilian  
113 Institute of Geography and Statistics), based on population estimates for the  
114 intercensus years (2002 - 2015). An ecological and time series epidemiological study  
115 was conducted, based on the leprosy cases reported by SINAN. The historical (from  
116 2002 to 2015) reporting of leprosy cases in children under 15 years old was analyzed.  
117 We also compared those data with data in all ages and with the occurrence of physical  
118 disability. The incidence of leprosy (referred as the new case detection rate) in Sergipe  
119 in 2010 was 18.4 per 100,000 [8].

120

121 The clinical and epidemiologic indicators collected by Investigation and Notification  
122 Form from SINAN, were: gender, age, ethnicity, address, operational classification (PB

1  
2  
3 123 and MB), clinical form [according to the more refined Ridley-Jopling classification  
4  
5 124 [24,25], based on histopathological analyses: indeterminate leprosy (IL), true  
6  
7  
8 125 tuberculoid (TT), borderline leprosy (BL) and lepromatous leprosy (LL)], leprosy  
9  
10 126 reaction (LR), number of affected nerves, degree of physical disabilities, number of  
11  
12  
13 127 household contacts (HHC) registered and examined, and the patient detection mode.  
14

15 128

17  
18 129 The parameters adopted by BMH and ILA were followed for interpreting the incidence  
19  
20 130 rate of leprosy in patients under 15 years old. As such, this is classified as: low (<0.50  
21  
22 131 cases per 100,000 inhabitants); medium (0.50 to 2.49); high (2.50 to 4.99); very high  
23  
24 132 (5.00 to 9.99) and hyperendemic ( $\geq 10.00$ ) [4].  
25  
26  
27

28 133

### 30 134 **Spatial analysis**

31  
32 135 Thematic maps were constructed in each municipality for the period examined  
33  
34 136 according to the leprosy incidence rate in patients under 15 years old and in general  
35  
36 137 population, and for patients presenting with physical disability (incapacity degree 1 or  
37  
38 138 2). The kernel technique was applied to identify the intensity of the distribution of  
39  
40 139 leprosy cases in the state of Sergipe. This technique shows the statistically generated  
41  
42 140 surface density for the visual detection of hot spots, that indicates agglomeration of  
43  
44 141 cases in a spatial distribution. This is an appropriate data interpolation for application  
45  
46 142 in point location data. The point distribution was transformed into a smoothed surface  
47  
48 143 and presented as a continuous map, representing different levels of case intensity. The  
49  
50 144 amount of smoothing, that is, the width of the radius of influence was defined as 3,000  
51  
52 145 meters, since this value generated an adequate representation of the distribution of  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 146 the leprosy cases in the municipalities, minimizing the overlapping bias or the  
4  
5  
6 147 occurrence of sub distribution patterns smoothed [16,21].  
7

8 148

9  
10 149 We performed either spatial autocorrelation analysis between disease detection rates  
11  
12  
13 150 for each group. The Moran Global Index (MGI)[26] was calculated to identify clusters  
14  
15 151 with risks for disease occurrence. We construct a spatial proximity matrix obtained by  
16  
17  
18 152 the contiguity of spatial correlation. The MGI was calculated as follows:

19  
20 153 (Moran Global Index Mathematical Equation 1)

21  
22  
23 154 
$$I = \frac{[(n \sum_i \sum_j \omega_{ij} (\gamma_i - \bar{\gamma}) (\gamma_j - \bar{\gamma}))]}{[\sum_i (\gamma_i - \bar{\gamma})^2 \sum_i \sum_j \omega_{ij}]}$$
  
24 155  
25 156  
26 157

27  
28  
29 158  $\omega_{ij}$  is a contiguity matrix element ( $\omega$ );  $\gamma_i$  is the incidence rate of municipality  $i$ ;  $\gamma_j$  is the  
30  
31 159 incidence rate of municipality  $j$ ;  $\bar{\gamma}$  is the mean of sample and the symbol  $n$  represents  
32  
33 160 the total number of municipalities [26].  
34  
35  
36 161

37  
38  
39 162 The MGI provides a general grouping measure and it is possible to know if there are  
40  
41 163 significant differences between the analyzed areas. However, it does not indicate the  
42  
43  
44 164 clusters localization. To do that, we performed the Moran Local Index diagram [26] to  
45  
46 165 build maps and identify the areas with spatial dependence (Local Index of Spatial  
47  
48 166 Association - LISA) of the annual detection means, as follows:

49  
50  
51 167 (Local Index of Spatial Association Mathematical Equation 2)

52  
53 168

54  
55  
56 169 
$$I = \frac{n[(Z_i \sum_j \omega_{ij} Z_j)]}{(\sum_j Z_j^2)}$$
  
57 170  
58 171  
59 172

173

174  $Z_i = y_i - \bar{y}$ ;  $Z_i = y_i - \bar{y}$ ;  $\Omega_{ij}$  is a contiguous matrix element  $\omega$ ;  $y_i$  is the incidence rate of  
175 municipality  $i$ ;  $y_j$  is the incidence rate of municipality  $j$ ;  $\bar{y}$  is the sample mean and the  
176 symbol  $n$  represents the total number of cities [26]. The Moran Map was used to  
177 indicate the clusters and their relationship with the neighbors. This analysis verifies the  
178 existence of spatial dependence and risk patterns: Q1 (high/high) and Q2 (Low/Low),  
179 which indicate municipalities with similar values between their neighbors and Q3  
180 (high/low) and Q4 (low/high) for municipalities with different values between their  
181 neighbors and no spatial association. A spatial proximity matrix obtained by the  
182 contiguity criterion was adopted. The level of significance was 5% and the Moran  
183 Global Index ( $I$ ) varying between -1 and +1, representing the spatial autocorrelation of  
184 leprosy detection rate in the geographic space analyzed to identify spatial clusters and  
185 risk areas. Values between 0 and +1 indicate positive spatial autocorrelation (Q1 and  
186 Q2) and between -1 and 0 negative spatial autocorrelation (Q3 and Q4) [26,27]. Both  
187 Moran Index and Kernel maps were constructed using TerraView software 4.2.2.

188

### 189 **Statistical analysis**

190 Demographic and clinical data were compared across the different subgroups and  
191 according to operational classification and the patient detection mode. Percentage,  
192 mean and standard deviation of the groups were calculated. For groups' comparison,  
193 we first analyze if the data followed normal distribution by the D'Agostino and Pearson  
194 normality test, and statistical differences between the groups were determined by  
195 Mann-Whitney and Kruskal-Wallis tests. All analysis was performed using SPSS



1  
2  
3 196 Statistics, version 24.0. Results were considered statistically different when  $p$ -values <  
4  
5 197 0.05 were obtained.  
6  
7

8 198  
9  
10 199 In order to enable trend analysis, annual incidence of leprosy was calculated as  
11  
12 200 dependent variables ( $y$ ), and the years of the study period as the independent  
13  
14 201 variables ( $x$ ). Initially, trend analysis was performed with the Joinpoint program,  
15  
16 202 version 4.0.4 (Surveillance Research, National Cancer Institute, USA). This program  
17  
18 203 estimates the Annual Percentage Change (APC) of a segmented linear regression  
19  
20 204 (Jointpont regression) and identifies inflection points. Each inflection point reflects  
21  
22 205 changes in the increase or decline of le rates [27]. Poisson regression is used to  
23  
24 206 determine the number of segments required to adequately explain the relationship  
25  
26 207 between two variables [27]. We considered the points of trend change that presented  
27  
28 208  $p$ -value < 0.05.  
29  
30  
31  
32  
33  
34  
35  
36  
37

38 209

### 210 **Ethical Considerations**

211 For conducting this study, authorization was previously requested from Coordination  
212 of Epidemiological Surveillance, Sergipe state. This project involved research on human  
213 subjects and was approved by the Ethics and Research Committee of the Federal  
214 University of Sergipe, CAAE 0152.0.107.000-07.

215

### 216 **Patient and Public Involvement statement**

217 There was no patient and public involvement in this study. The study was based on  
218 secondary data.  
219

## 220 RESULTS

### 221 Trends in reported leprosy incidence among children

222 The incidence of leprosy in children under 15 years old fluctuated, increasing from  
223 2002 (6.29 cases per 100,000 inhabitants) to 2005 (9.82) but then showing a decline to  
224 3.78 in 2015. There was an overall decrease trend in leprosy incidence in children  
225 from 2002 to 2015, by Joinpoint regression analyzes (APC = -5.3 and  $p$ -value < 0.05;  
226 **Figure 1A and B**). Similarly, the leprosy incidence rate in the general population of  
227 Sergipe decreased from 23.08 cases to 16.99 per 100,000 inhabitants between 2002  
228 and 2015 (**Figure 1A and C**). The occurrence of degree 2 physical disability, however,  
229 increased in this period (0.76 in 2002 to 1.2 in 2015, respectively), however there is no  
230 significant reduction (APC = 2.6 and  $p$ -value = 0.20; **Figure 1A and D**). The composition  
231 of leprosy cases according to the operational classification (PB and MB) was relatively  
232 stable across this period, with majority of cases presenting as PB (**Figure 2A**). We also  
233 observed the mean number of HHC registered ( $4.65 \pm 2.79$ ) was slightly, but  
234 significantly, higher than the number examined ( $3.66 \pm 3.14$ ;  $p$ -value < 0.0001; **Figure**  
235 **2B**).

### 237 Demographics of childhood leprosy cases

238 Next, we evaluated the association among clinical and epidemiological variables  
239 according to the leprosy operational classification (patients presenting as PB and MB).  
240 Patients presenting as MB or PB were in similar age to ( $10.5 \pm 2.81$  and  $10.07 \pm 3.38$ ,  
241 respectively). Despite the extended incubation period of *M. leprae*/leprosy, six cases  
242 (1.11%) were reported in children less than one year of age. Of the 538 leprosy cases  
243 identified among children under 15 years old the majority were PB [407 (75.7%) PB

1  
2  
3 244 and 131 (24.3%) MB; **Table 1**]. When stratified on gender, however, the proportion of  
4  
5 245 boys presenting with MB (63.4%) was significantly higher than presenting with PB  
6  
7  
8 246 (48.4%;  $p$ -value = 0.003). An interesting difference was observed when we calculated  
9  
10 247 the ratio (PB/MB) according the ethnic groups. Among those identified as black, the  
11  
12 248 ratio (43/24) was 1.79. Conversely, the ratio of white was higher 4.88 (88/18;  $p$ -value =  
13  
14  
15 249 0.02).

16  
17  
18 250

19  
20 251 As expected, the occurrence of leprosy reactions was significantly higher in MB (21.4%)  
21  
22 252 than PB (4.9%;  $p$ -value < 0.0001) patients. The occurrence of degree 2 of physical  
23  
24 253 disability was also higher in MB (4.6%), than in PB patients (0.74%;  $p$ -value = 0.0001).  
25  
26  
27 254 Consistent with this, we observed that the mean of number of affected nerves was  
28  
29 255 higher in MB ( $0.5 \pm 1.03$ ), than PB ( $0.19 \pm 0.54$ ;  $p$ -value = 0.04).  
30  
31

32  
33  
34 256

### 35 257 **Impact of case detection methods on leprosy presentation**

36  
37 258 We also performed analysis of association among clinical and epidemiological variables  
38  
39 259 according to the leprosy patient detection mode. The patients were grouped in:  
40  
41 260 spontaneous demand (SDem: patients that looked for medical assistance by  
42  
43 261 themselves); forwarded (FW: patients that were forwarded from a primary clinic to a  
44  
45 262 leprosy reference center); examined HHC; and other. We observed that patients  
46  
47 263 detected by the examined HHC method presented lower mean age ( $9.6 \pm 3.38$ ) than  
48  
49 264 those detected by either the SDem ( $10.54 \pm 3.28$ ) or FW methods ( $10.02 \pm 3.15$ ;  $p$ -  
50  
51 265 value = 0.04; **Table 2**). Interestingly, the percentage of leprosy reaction among the  
52  
53 266 examined HHC group (2.9%;  $p$ -value = 0.02) was lower than that observed among  
54  
55 267 SDem (7.3%) and FW (13.3%). In addition, degree 2 of physical disability was not  
56  
57  
58  
59  
60

1  
2  
3 268 observed among patients detected in examined HHC group, while SDem and FW  
4  
5 269 presented 0.43% and 3.8%, respectively ( $p$ -value = 0.04). Furthermore, patients  
6  
7  
8 270 identified among examined HHC presented with lower numbers of lesions ( $2.04 \pm 2.96$ ;  
9  
10 271  $p$ -value = 0.04) than SDem ( $3.64 \pm 6.25$ ) and FW ( $4.09 \pm 8.68$ ). Taken together, these  
11  
12 272 data reinforce the importance of HHC examination for the detection of leprosy  
13  
14  
15 273 patients before advancement to more severe symptoms.  
16  
17  
18 274

### 20 275 **Spatial analyze data**

22 276 Next, we performed the spatial analysis of leprosy cases in the general population, in  
23  
24 277 patients under 15 years old, and in patients presenting with physical disability (both  
25  
26 278 degree 1 and 2). Moran maps have showed higher risk clusters (Q1 - in red; **Figure 3A-**  
27  
28 279 **C**) in similar areas when comparing the maps regarding leprosy cases in children under  
29  
30 280 15 years old, in general population, and patients presenting some physical disability  
31  
32 281 (degree 1 and 2). The higher risk clusters (Q1) were localized in Sergipe state center  
33  
34 282 and in the metropolitan area around the capital of State. The municipalities with no  
35  
36 283 spatial association (Q3 - in blue) were localized in the Semiarid region, in the northwest  
37  
38 284 area and in the south region.  
39  
40  
41  
42  
43  
44  
45 285

46  
47 286 Similarly, The Kernel estimator, through data interpolation, showed densities (hot  
48  
49 287 spots) of the highest incidence rates located at the northeast and east center regions  
50  
51 288 and in the counties around the state capital (Aracaju city; **Figure 3D-F**). Lower intensity  
52  
53 289 was observed on the western region. Municipalities with intermediate to high  
54  
55 290 incidence values are seen in yellow and red tones of each subfigure. Low incidence  
56  
57  
58  
59  
60

1  
2  
3 291 areas were reported on west coast municipalities, mostly in smaller counties with  
4  
5 292 small populations.  
6  
7

8 293

9  
10 294 **DISCUSSION**

11  
12 295 Previous studies have demonstrated that the high leprosy cases detection in patients  
13  
14 296 under 15 years old is a bad parameter for leprosy control program, because it indicates  
15  
16 297 early bacillus transmission from undiagnosed cases [18]. Some authors have  
17  
18 298 speculated either about the risk of vertical/transplacental transmission or through  
19  
20 299 breastfeeding [12].  
21  
22  
23  
24

25 300

26  
27 301 In Brazil, the highest leprosy incidence rate in children was reported in the North area  
28  
29 302 (11.91 cases per 100,000 inhabitants), followed by Northeast (8.12) [12]. We observed  
30  
31 303 the leprosy incidence rate was reduced in children under 15 years old from 2002 to  
32  
33 304 2015 in Sergipe state, however considering the parameters adopted by BMH, the state  
34  
35 305 was classified as very high endemicity in 2002, and still as high endemicity in 2015. It  
36  
37 306 remains also with elevated incidence rate and stationary tendency of degree 2 of  
38  
39 307 physical disability. Those data reinforce either that the transmission is intense at early  
40  
41 308 age, there is lack of an effective public health and the disease control is focused in the  
42  
43 309 MDT [12,18]. A similar study performed at Fortaleza city (Brazil), reported also that  
44  
45 310 although a decreasing has been observed on overall detection rate, the number of new  
46  
47 311 cases in those under 15 years old remains stable [13].  
48  
49  
50  
51  
52

53 312

54  
55 313 Leprosy reactions and physical disability are the most severe leprosy clinical  
56  
57 314 complications [8,28,29]. In addition, the increase or stability of the prevalence of  
58  
59  
60

1  
2  
3 315 degree 2 of physical disability indicates persisting late diagnosis [13,29]. The early  
4  
5 316 diagnosis of leprosy is essential to the prevention of deformities, whose repercussions  
6  
7  
8 317 are still more catastrophic in children and adolescents [28]. Our data reported 21.4%  
9  
10 318 children with leprosy reaction (LR) and 31.3% with some physical disability in the MB  
11  
12  
13 319 groups. Furthermore, MB patients presented higher mean of affected nerves.  
14  
15 320 Generally, patients under 15 years old do not use to present LR, but studies have  
16  
17 321 reported a low frequency of LR, varying between 1.36% and 8.33% [28]. Those data  
18  
19 322 reinforce that, although there is a decreasing incidence in leprosy, patients have been  
20  
21 323 exposed to bacillus early in life and diagnosed belatedly and hence they have been also  
22  
23 324 developing into some clinical complications.  
24  
25  
26  
27  
28  
29

30 326 We have observed either that the mean of HHC examined was significantly lower than  
31  
32 327 those registered by SINAN. Moreover, leprosy patients detected by exam in HHC  
33  
34 328 presented lower mean of age, affected nerves, number of lesions, occurrence of LR  
35  
36 329 and no physical disability, when compared with those identified by spontaneous  
37  
38 330 demand or forwarded by others. On the other hand, mostly of patients presenting as  
39  
40 331 degree 2 of physical disability were identified into those forwarded to a leprosy  
41  
42 332 reference center, probably because they started presenting some physical disability.  
43  
44  
45 333 HHC and neighbors are the most important *M. leprae* active sources. The risk of a  
46  
47 334 person developing leprosy is nine times greater among HHC and up to four times  
48  
49 335 greater among contacts with neighbors [12]. Therefore, our data reinforce the  
50  
51 336 importance of leprosy early diagnosis by exam in patients and their household  
52  
53 337 contacts. Besides that, the treatment and the home visits by public health programs,  
54  
55 338 and an efficient health program in schools could represent important actions for the  
56  
57  
58  
59  
60

1  
2  
3 339 early diagnosis and the reduction of leprosy clinical complications, especially in  
4  
5  
6 340 children.

7  
8 341

9  
10 342 Spatial analysis of health events aim to identify geographical patterns by maps of risk  
11  
12  
13 343 and to point out areas of higher severity and to facilitate the planning of public health  
14  
15 344 interventions [9]. The Kernel maps showed the spatial dynamic of leprosy, with a  
16  
17  
18 345 heterogeneous geographical pattern and the highest risk areas for leprosy infection.  
19  
20 346 The highest incidence on counties around the Capital can be due there was a  
21  
22  
23 347 leprosarium at the Nossa Senhora do Socorro (a city of the metropolitan area of  
24  
25 348 Aracaju), that has presented elevated detection rate in mostly evaluated years.  
26  
27  
28 349 Moreover, that area presents reference center to leprosy diagnosis and treatment and  
29  
30 350 hence they have several patients forwarded to these leprosy clinics. It can be also  
31  
32  
33 351 associated with weather featuring such as humidity, considering either that counties  
34  
35 352 near to São Francisco River presented also elevated incidence. In the Malawian  
36  
37  
38 353 Karonga district, a positive relationship between the proximity of water and leprosy  
39  
40 354 incidence was previously reported [5]. Some authors have hypothesized that *M. leprae*  
41  
42 355 survives longer outside of human body in humid compared to dry atmospheres [9,13].  
43  
44

45 356

46  
47 357 Interestingly, higher risk clusters were identified in similar areas when we analyzed the  
48  
49  
50 358 occurrence of leprosy cases in children, in general population and patients presenting  
51  
52 359 physical disability. It corroborates the hypothesis that the early transmission of *M.*  
53  
54 360 *leprae* and the occurrence of leprosy in children under 15 years old is directly related  
55  
56  
57 361 to the late diagnosis, which explains the occurrence of patients with degree 2 of  
58  
59 362 physical disability in the same geographic distribution [28]. The maps present certain  
60

1  
2  
3 363 disagreements regarding the occurrence of leprosy cases in the state of Sergipe  
4  
5 364 because they use distinct techniques of spatial analysis. The Kernel estimator produces  
6  
7  
8 365 a continuous surface, with densities calculated at all locations, based on total number  
9  
10 366 of cases and no considering the geographical boundaries of the municipalities  
11  
12  
13 367 [27,30,31]. The Kernel technique presents greater advantages to the quick visualization  
14  
15 368 of areas that deserve attention, besides not being affected by political-administrative  
16  
17 369 division, while the Moran technique, constructs maps considering the political-  
18  
19 370 administrative divisions of the state and the clusters are based on the number of cases  
20  
21 371 by the municipalities population rates [27,30].  
22  
23  
24  
25  
26

27 373 Our study had some limitations, particularly because it was conducted using secondary  
28  
29 374 data reported by SINAN. This source of date can present numbers under notification  
30  
31 375 and datasets missing. However, in Brazil we have a specific normative that is an  
32  
33 376 obligation to notify several diseases to SINAN, and leprosy is one of them. SINAN is an  
34  
35 377 important database of the Secretariat of Health of all States of Brazil, to report  
36  
37 378 information about sociodemographic, clinical features and the address of each  
38  
39 379 diagnosed case. This source of data can present under notification because Leprosy is  
40  
41 380 an asymptomatic disease and the active search would be important to detect more  
42  
43 381 cases, but all diagnosed cases are reported to SINAN. The limitation mentioned about  
44  
45 382 missing data is not very important in the case of the disease prevalence, but the  
46  
47 383 complete information about the cases follow-up, such as degree of neurological  
48  
49 384 disability at the end of treatment, leprosy reactions and treatment details, because it is  
50  
51 385 a secondary database that depends on other doctors or nurses from the health care  
52  
53 386 centers to fulfill the information. Despite this, those data reported high endemicity of  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 387 leprosy cases in patients under 15 years old, and this study do not focus on patient  
4  
5 388 follow-up.  
6  
7

8 389

9  
10 390 In summary, our study demonstrated that the leprosy incidence rate has decreased in  
11  
12 391 Sergipe state. However, it is still classified as high endemicity considering the WHO  
13  
14 392 proposed ratios for children under 15 years. Patients detected by exam in collectivity  
15  
16 393 or HHC presented better indicators. Altogether, the epidemiological data and spatial  
17  
18 394 analysis indicate that there is persistence of active transmission of *M. leprae* and later  
19  
20 395 case detection in Sergipe state, increasing the risk of transmission in children. In  
21  
22 396 addition, the spatial analysis brings new advantages to comprehend the leprosy  
23  
24 397 dynamic, and reinforce the superimposed regions of high occurrence areas of patients  
25  
26 398 presenting degree 2 of physical disability and cases in children lower than 15 years,  
27  
28 399 and highlights the need to strengthen effective disease control measures, mainly in  
29  
30 400 primary health care.  
31  
32  
33  
34  
35

36  
37 401 **Acknowledgments** The authors would like to thank the Manager of the Nucleus of  
38  
39 402 endemic/Division of Epidemiological Surveillance - [Divisão de Vigilância  
40  
41 403 Epidemiológica (DIVEP)]/ Secretariat of Health of the Sergipe state (SES) for providing  
42  
43 404 information.  
44  
45  
46  
47

48 405 **Funding** This research received no specific grant from any funding agency in the public,  
49  
50 406 commercial or not-for-profit sectors.  
51

52  
53 407 **Contributors** The project was suggested by MB-S, MA, JB and AS. The statistical  
54  
55 408 analyzes was performed by MB-S, IB, JS and AJ. The spatial analyzes was performed by  
56  
57 409 MS, AS, AB and KA. The manuscript was written by MB-S, AB, DO, MD and AJ. All  
58  
59  
60

1  
2  
3 410 authors contributed to refining the idea, revising the manuscript and have agreed the  
4  
5 411 final version.

6  
7  
8 412 **Competing interests** The authors declare that they have no conflicts of interest.

9  
10 413 **Provenance and peer review** Not commissioned; externally peer reviewed.

11  
12 414 **Data sharing statement** No additional data are available.

13  
14  
15 415

16  
17  
18 416 **References**

19  
20  
21 417

22  
23  
24 418 1 Simon M, Scherlock J, Duthie MS, *et al*. Clinical, immunological, and genetic  
25  
26 419 aspects in leprosy. *Drug Dev Res* 2011;**72**:509–27. doi:10.1002/ddr.20457

27  
28  
29  
30 420 2 Duarte-Cunha M, Marcelo da Cunha G, Souza-Santos R. Geographical  
31  
32 421 heterogeneity in the analysis of factors associated with leprosy in an endemic  
33  
34 422 area of Brazil: are we eliminating the disease? *BMC Infect Dis* 2015;**15**:196.  
35  
36 423 doi:10.1186/s12879-015-0924-x

37  
38  
39  
40 424 3 Fulton N, Anderson LF, Watson JM, *et al*. Leprosy in England and Wales 1953-  
41  
42 425 2012: Surveillance and challenges in low incidence countries. *BMJ Open*  
43  
44 426 2016;**6**:15–8. doi:10.1136/bmjopen-2015-010608

45  
46  
47  
48 427 4 Freitas LRS, Duarte EC, Garcia LP, *et al*. Trends of main indicators of leprosy in  
49  
50 428 Brazilian municipalities with high risk of leprosy transmission, 2001–2012. *BMC*  
51  
52 429 *Infect Dis* 2016;**16**:472. doi:10.1186/s12879-016-1798-2

53  
54  
55  
56  
57 430 5 Duthie MS, Saunderson P, Reed SG. The potential for vaccination in leprosy  
58  
59 431 elimination: New tools for targeted interventions. *Mem Inst Oswaldo Cruz*

- 1  
2  
3 432 2012;**107**:190–6. doi:10.1590/S0074-02762012000900027  
4  
5  
6 433 6 Duthie MS, Gillis TP, Reed SG. Advances and hurdles on the way toward a  
7  
8 434 leprosy vaccine. *Hum Vaccin* 2011;**7**:1172–83. doi:10.4161/hv.7.11.16848  
9  
10  
11  
12 435 7 Kumar A, Girdhar A, Girdhar BK. Six months fixed duration multidrug therapy in  
13  
14 436 paucibacillary leprosy: Risk of relapse and disability in Agra PB cohort study. *BMJ*  
15  
16 437 *Open* 2012;**2**:1–6. doi:10.1136/bmjopen-2012-001403  
17  
18  
19  
20 438 8 de Oliveira DT, Bezerra MM, de Almeida JAP, *et al.* Neurological disability in  
21  
22 439 leprosy: Incidence and gender association in Sergipe, Brazil. *Geospat Health*  
23  
24 440 2012;**6**. doi:10.4081/gh.2012.130  
25  
26  
27  
28 441 9 Alencar CH, Ramos AN, dos Santos ES, *et al.* Clusters of leprosy transmission and  
29  
30 442 of late diagnosis in a highly endemic area in Brazil: Focus on different spatial  
31  
32 443 analysis approaches. *Trop Med Int Heal* 2012;**17**:518–25. doi:10.1111/j.1365-  
33  
34 444 3156.2011.02945.x  
35  
36  
37  
38  
39 445 10 Durrheim DN, Speare R. Global leprosy elimination: Time to change more than  
40  
41 446 the elimination target date. *J Epidemiol Community Health* 2003;**57**:316–7.  
42  
43 447 doi:10.1136/jech.57.5.316  
44  
45  
46  
47 448 11 Barth-Jaeggi T, Steinmann P, Mieras L, *et al.* Leprosy Post-Exposure Prophylaxis  
48  
49 449 (LPEP) programme: Study protocol for evaluating the feasibility and impact on  
50  
51 450 case detection rates of contact tracing and single dose rifampicin. *BMJ Open*  
52  
53 451 2016;**6**. doi:10.1136/bmjopen-2016-013633  
54  
55  
56  
57 452 12 Santos SD, Penna GO, Costa M da CN, *et al.* Leprosy in children and adolescents  
58  
59 453 under 15 years old in an urban centre in Brazil. *Mem Inst Oswaldo Cruz*

- 1  
2  
3 454 2016;**111**:359–64. doi:10.1590/0074-02760160002  
4  
5  
6 455 13 Brito AL, Monteiro LD, Ramos Junior AN, *et al.* Tendência temporal da  
7  
8  
9 456 hanseníase em uma capital do Nordeste do Brasil: epidemiologia e análise por  
10  
11 457 pontos de inflexão, 2001 a 2012. *Rev Bras Epidemiol* 2016;**19**:194–204.  
12  
13 458 doi:10.1590/1980-5497201600010017  
14  
15  
16  
17 459 14 Vieira GDD, Aragoso I, Carvalho RMB, *et al.* Hanseníase em Rondônia: incidência  
18  
19 460 e características dos casos notificados, 2001 a 2012. *Epidemiol e Serviços Saúde*  
20  
21 461 2014;**23**:269–75. doi:10.5123/S1679-49742014000200008  
22  
23  
24  
25 462 15 Queirós MI, Ramos AN, Alencar CHM, *et al.* Clinical and epidemiological profile  
26  
27 463 of leprosy patients attended at Ceará, 2007-2011. *An Bras Dermatol*  
28  
29 464 2016;**91**:311–7. doi:10.1590/abd1806-4841.20164102  
30  
31  
32  
33 465 16 dos Santos AD, Lima ACR, Santos MB, *et al.* Spatial analysis for the identification  
34  
35 466 of risk areas for schistosomiasis mansoni in the state of Sergipe, Brazil, 2005-  
36  
37 467 2014. *Rev Soc Bras Med Trop* 2016;**49**:608–15. doi:10.1590/0037-8682-0137-  
38  
39 468 2016  
40  
41  
42  
43  
44 469 17 Alencar CHM De, Barbosa JC, Ramos Jr AN, *et al.* Hanseníase no município de  
45  
46 470 Fortaleza, CE, Brasil: aspectos epidemiológicos e operacionais em menores de  
47  
48 471 15 anos (1995-2006). *Rev Bras Enferm* 2008;**61**:694–700. doi:10.1590/S0034-  
49  
50 472 71672008000700007  
51  
52  
53  
54 473 18 Pires CAA, Malcher CMSR, Abreu JMC, *et al.* Hanseníase em menores de 15  
55  
56 474 anos: A importância do exame de contato. *Rev Paul Pediatr* 2012;**30**:292–5.  
57  
58 475 doi:10.1590/S0103-05822012000200022  
59  
60

- 1  
2  
3 476 19 Carlos F, Lana F, Amaral EP, *et al.* Hanseníase em menores de 15 anos no Vale  
4  
5 do Jequitinhonha, Minas Gerais, Brasil. *Rev Bras Enferm* 2007;**60**:696–700.  
6 477  
7  
8 478 doi:10.1590/S0034-71672007000600014  
9  
10  
11 479 20 Fernandes C, Gonçalves HS, Cabral PB, *et al.* Increased frequency of CD4 and  
12  
13 CD8 regulatory T cells in individuals under 15 years with multibacillary leprosy.  
14 480  
15  
16 481 *PLoS One* 2013;**8**. doi:10.1371/journal.pone.0079072  
17  
18  
19 482 21 Barreto AS, Alves B. ORIGINAL ARTICLE SPATIAL ANALYSIS AND  
20  
21 EPIDEMIOLOGICAL CHARACTERISTICS OF CASES OF LEPROSY IN AN ENDEMIC  
22 483  
23 AREA. *J Nurs UFPE* 2016;**10**. doi:10.5205/reuol.9881-87554-1-EDSM1011201604  
24 484  
25  
26  
27 485 22 Khan O, Davenhall W, Ali M, *et al.* Geographical information systems and  
28  
29 tropical medicine. *Ann Trop Med Parasitol* 2010;**104**:303–18.  
30 486  
31  
32 487 doi:10.1179/136485910X12743554759867.Geographical  
33  
34  
35  
36 488 23 Fischer E, Pahan D, Chowdhury S, *et al.* The spatial distribution of leprosy in four  
37  
38 villages in Bangladesh: an observational study. *BMC Infect Dis* 2008;**8**:125.  
39 489  
40  
41 490 doi:10.1186/1471-2334-8-125  
42  
43  
44 491 24 Ridley DS JW. Classification of leprosy according to immunity. A five-group  
45  
46 system. *Int J Lepr Other Mycobact Dis* 1966;**34**:255–73.  
47 492  
48  
49 493 doi:10.1126/science.1238286  
50  
51  
52 494 25 Lockwood DNJ, Sarno E, Smith WC. Classifying leprosy patients--searching for  
53  
54 the perfect solution. *Lepr Rev* 2007;**78**:317–20.  
55 495  
56  
57  
58 496 26 Chen Y. New Approaches for Calculating Moran's Index of Spatial  
59  
60 497 Autocorrelation. *PLoS One* 2013;**8**. doi:10.1371/journal.pone.0068336

- 1  
2  
3 498 27 Goes JAP, Souza DDG, Andrade LA, *et al.* Trend and spatial analysis of prostate  
4 cancer mortality in the state of Sergipe, Brazil. *Geospat Health* 2018;**13**.  
5  
6 499  
7  
8 500 doi:10.4081/gh.2018.732  
9  
10  
11 501 28 de Oliveira MBB, Diniz LM. Leprosy among children under 15 years of age:  
12  
13 Literature review. *An Bras Dermatol* 2016;**91**:196–203. doi:10.1590/abd1806-  
14 502  
15 4841.20163661  
16 503  
17  
18  
19 504 29 Kumar A, Girdhar A, Kumar Girdhar B. Risk of developing disability in pre and  
20  
21 post-multidrug therapy treatment among multibacillary leprosy: Agra MB  
22 505  
23 Cohort study. *BMJ Open* 2012;**2**:1–7. doi:10.1136/bmjopen-2011-000361  
24 506  
25  
26  
27 507 30 dos Santos AD, Lima ACR, Santos MB, *et al.* Spatial analysis for the identification  
28  
29 of risk areas for schistosomiasis mansoni in the state of Sergipe, Brazil, 2005-  
30 508  
31 2014. *Rev Soc Bras Med Trop* 2016;**49**. doi:10.1590/0037-8682-0137-2016  
32 509  
33  
34  
35 510 31 Santos MB, dos Santos AD, da Silva PP, *et al.* Spatial analysis of viral hepatitis  
36  
37 and schistosomiasis coinfection in an endemic area in Northeastern Brazil. *Rev*  
38 511  
39 *Soc Bras Med Trop* 2017;**50**. doi:10.1590/0037-8682-0411-2016  
40 512  
41  
42  
43 513  
44  
45  
46  
47 514  
48  
49  
50 515  
51  
52  
53 516  
54  
55  
56  
57 517  
58  
59  
60

518

519

520

521 **Table 1. Association of demographic and clinical data according to the operational**  
 522 **classification of leprosy (PB and MB) in children under 15 years in Sergipe state,**  
 523 **Brazil (2002-2015).**

Variables	Operational Classification		p-value
	PB (n = 407)	MB (n = 131)	
<b>Age mean ± SD</b>	10.07 ± 3.38	10.5 ± 2.81	*0.46
<b>Gender n (%)</b>			
Male	197 (48.4)	83 (63.4)	+0.003
<b>Ethnicity n (%)</b>			
White	88 (21.6)	18 (13.7)	#0.02
Black	43 (10.5)	24 (18.3)	
Brown	251 (61.7)	78 (59.5)	
Indian	4 (0.9)	3 (2.3)	
<b>Leprosy reaction n (%)</b>	20 (4.9)	28 (21.4)	+<0.0001
<b>Physical Disability</b>			
<b>Degree n (%)</b>			
0	337 (82.8)	90 (68.7)	#0.0001
1	26 (6.4)	18 (13.7)	
2	3 (0.74)	6 (4.6)	
<b>Number of affected nerves</b> <b>(mean ± SD)</b>	0.19 ± 0.54	0.5 ± 1.03	*0.04
<b>Number of Lesions (mean ±</b>	1.61 ± 1.14	9.92 ± 12.03	*<0.0001

SD)

HHC registered (mean ± SD) 4.6 ± 2.71 4.85 ± 3.04 \*0.14

HHC examined (mean ± SD) 3.54 ± 3.04 4.05 ± 3.44

524 \*Mann-Whitney test; \*Fisher's exact test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC  
525 = household contacts; SD = Standard Deviation. We missed data in some variables.  
526

For peer review only



527 **Table 2. Demographic and clinical aspects accordingly to the detection mode of**  
 528 **leprosy cases in children under 15 years in Sergipe state, Brazil (2002-2015).**

529

Variables	Patient detection mode				p-value
	Spontaneous demand (n = 234)	Forwarding (n = 210)	Examined HHC (n = 69)	Other (n = 25)	
<b>Age mean ± SD</b>	10.54 ± 3.28	10.02 ± 3.15	9.6 ± 3.38	9.6 ± 3.22	*0.04
<b>Gender n (%)</b>					
Male	123 (52.6)	110 (52.4)	38 (55.1)	09 (36)	#0.41
<b>Leprosy reaction n (%)</b>	17 (7.3)	28 (13.3)	2 (2.9)	1 (4.0)	#0.02
<b>Physical disability degree n (%)</b>					
0	199 (85.1)	150 (71.4)	55 (79.7)	18 (72)	#0.04
1	17 (7.3)	21 (10)	5 (7.2)	1 (4.0)	
2	1 (0.43)	08 (3.8)	0 (0.0)	0 (0.0)	
<b>Number of affected nerves (mean ± SD)</b>	0.24 ± 0.67	0.34 ± 0.81	0.06 ± 0.25	0.25 ± 0.5	*0.48
<b>Number of lesion (mean ± SD)</b>	3.64 ± 6.25	4.09 ± 8.68	2.04 ± 2.96	4 ± 5.2	*0.04
<b>HHC registered (mean ± SD)</b>	4.57 ± 2.53	4.59 ± 2.74	5.57 ± 3.81	3.45 ± 1.96	*0.04
<b>HHC examined (mean ± SD)</b>	3.71 ± 3.02	3.02 ± 2.98	4.64 ± 4.06	2.04 ± 1.77	*0.01

530 \*Kruskal-Wallis test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC = household  
 531 contacts; SD = Standard Deviation. We missed data in some variables.

532

1  
2  
3 533 **Figure 1. Leprosy incidence rates and temporal trend in state of Sergipe, Northeast**  
4  
5 534 **Brazil, 2002-2015.** A) Leprosy incidence rate (per 100,000 inhabitants) in general  
6  
7  
8 535 population (▲), in patients under 15 years old (■), degree 2 of physical disability (◆)  
9  
10 536 and the tendency line. Temporal trend of standardized incidence rates by Joinpoint  
11  
12  
13 537 Regression for B) patients under 15 years old, C) General population and D) incapacity  
14  
15 538 degree. Data were considered statistically different when p-value < 0.05. CI:  
16  
17  
18 539 Confidence Interval.

19  
20  
21 540

22  
23 541 **Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state**  
24  
25 **of Sergipe, Brazil, 2002-2015.** A) Number of leprosy cases according to the clinical  
26  
27 542 operational classification (Paucibacillary - PB (■) and Multibacillary – MB (■) forms). B)  
28  
29 543 Mean and standard deviation (mean ± SD) of the number of household contacts (HHC)  
30  
31 544 that were registered and examined for leprosy diagnosis. Data were considered  
32  
33 545 statistically different when p-value < 0.05. \* Mann-Whitney test.  
34  
35  
36 546

37  
38  
39 547

40  
41 548 **Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were**  
42  
43 549 **constructed by TerraView Software 4.2.2.** The Moran Global Index (\*MGI) was  
44  
45 550 calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of  
46  
47 551 leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy  
48  
49 552 cases in the general population. Moran (E) and Kernel (F) maps of occurrence of  
50  
51 553 incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 – 2015).

52  
53  
54  
55 554

56  
57  
58  
59 555  
60

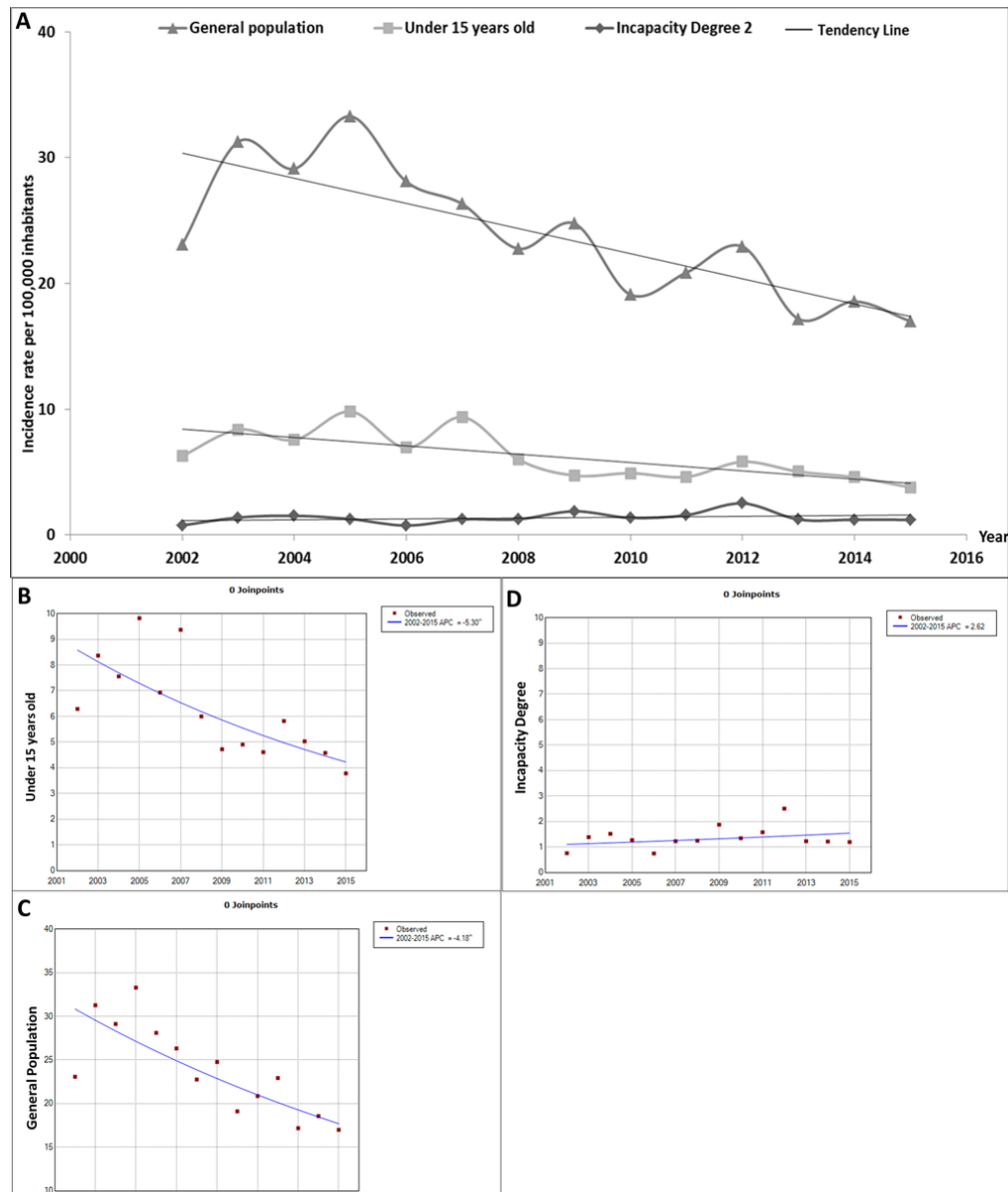


Figure 1. Leprosy incidence rates and temporal trend in state of Sergipe, Northeast Brazil, 2002-2015. A) Leprosy incidence rate (per 100,000 inhabitants) in general population (□), in patients under 15 years old (□), degree 2 of physical disability (□) and the tendency line. Temporal trend of standardized incidence rates by Joinpoint Regression for B) patients under 15 years old, C) General population and D) incapacity degree. Data were considered statistically different when p-value < 0.05. CI: Confidence Interval.

85x101mm (300 x 300 DPI)

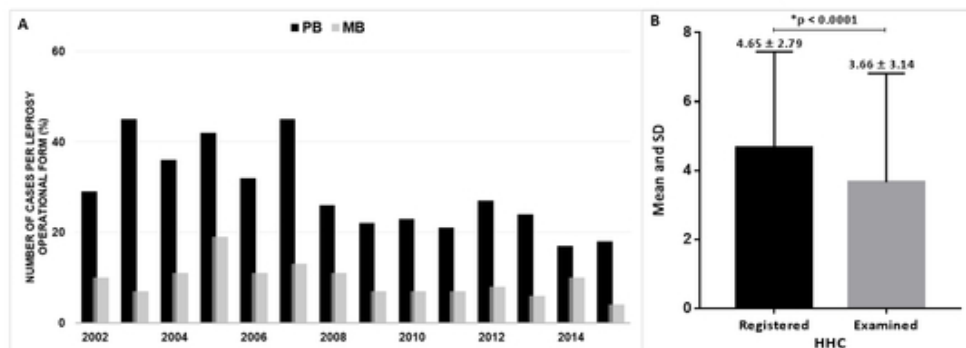


Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Number of leprosy cases according to the clinical operational classification (Paucibacillary - PB (□) and Multibacillary - MB (□) forms). B) Mean and standard deviation (mean ± SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. \* Mann-Whitney test.

46x17mm (300 x 300 DPI)

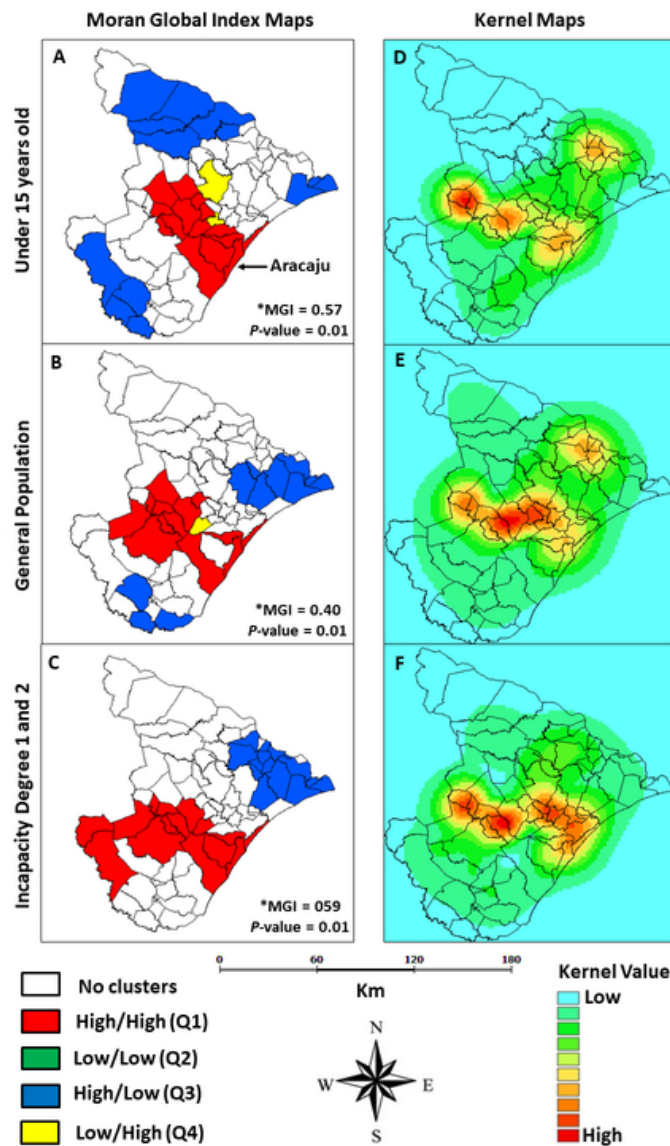


Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were constructed by TerraView Software 4.2.2. The Moran Global Index (\*MGI) was calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy cases in the general population. Moran (E) and Kernel (F) maps of occurrence of incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 - 2015).

48x64mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

Section/Topic	Item #	Recommendation	Reported on page #
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	01
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	02
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	04-05
Objectives	3	State specific objectives, including any prespecified hypotheses	05
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	06
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	06
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	06
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	06
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	06-07
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	06
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	06-08
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	08-09
		(b) Describe any methods used to examine subgroups and interactions	08-09
		(c) Explain how missing data were addressed	08-09
		(d) If applicable, describe analytical methods taking account of sampling strategy	08-09
		(e) Describe any sensitivity analyses	08-09
<b>Results</b>			08-09

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	09
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	09-10
		(b) Indicate number of participants with missing data for each variable of interest	--
Outcome data	15*	Report numbers of outcome events or summary measures	09-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(b) Report category boundaries when continuous variables were categorized	--
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	09-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in an Endemic Area of Northeast Brazil: an ecological and time series study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023420.R2
Article Type:	Research
Date Submitted by the Author:	20-Mar-2019
Complete List of Authors:	Santos, Márcio; Universidade Federal de Sergipe, Health Education; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Santos, Allan; Universidade Federal de Sergipe, Nursing Barreto, Aline; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Souza, Mariana; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Goes, Marco; Universidade Federal de Sergipe, Medicine Barreto Alves, Jose Antonio; Universidade Federal de Sergipe, Nursing Barreto, Ikaro; Universidade Federal Rural de Pernambuco, Programa de Pos-Graduacao em Biometria e Estatistica Aplicada Silva, José-Rodrigo; Universidade Federal de Sergipe, Statistics and Actuarial Sciences Oliveira, Daniela; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Araújo, Karina; Universidade Federal de Sergipe, Morphology Duthie, Malcolm; Infectious Diseases Research Institute Jesus, Amélia; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology; Universidade Federal de Sergipe, Medicine
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Public health
Keywords:	Leprosy, Children, Epidemiology < INFECTIOUS DISEASES, Spatial analysis

SCHOLARONE™  
Manuscripts



1  
2  
3 1 **Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy**  
4  
5  
6 2 **Cases in Patients Under 15 Years Old in an Endemic Area of Northeast**  
7  
8  
9 3 **Brazil: an ecological and time series study**  
10  
11  
12 4

13  
14 5 Márcio B Santos<sup>1,2</sup>, Allan D dos Santos<sup>3</sup>, Aline S Barreto<sup>2</sup>, Mariana do R Souza<sup>2</sup>, Marco A  
15  
16 6 de O Goes<sup>4</sup>, José-Antônio A Barreto<sup>3</sup>, Íkaro D C Barreto<sup>5</sup>, José-Rodrigo S Silva<sup>6</sup>, Daniela T  
17  
18 7 de Oliveira<sup>3</sup>, Karina G de Araujo<sup>7</sup>, Malcolm S Duthie<sup>8</sup>, Amélia R de Jesus<sup>2,9,10</sup>.  
19  
20  
21 8

22  
23  
24 9 <sup>1</sup>Departament of Health Education, Universidade Federal de Sergipe, Brazil; <sup>2</sup>Laboratory of Immunology  
25  
26 10 and Molecular Biology, Universidade Federal de Sergipe, Brazil; <sup>3</sup>Departament of Nursing, Universidade  
27  
28 11 Federal de Sergipe, Brazil; <sup>4</sup>Departament of Medicine, Universidade Federal de Sergipe, Brazil; <sup>5</sup>Mestre,  
29  
30 12 Universidade Federal Rural de Pernambuco (UFPE), Programa de Pos-Graduacao em Biometria e  
31  
32 13 Estatística Aplicada; <sup>6</sup>Doutor, Professor Adjunto do Departamento de Estatística e Ciências Atuariais da  
33  
34 14 Universidade Federal de Sergipe (UFS); <sup>7</sup>Departament of Morphology, Universidade Federal de Sergipe,  
35  
36 15 Aracaju; <sup>8</sup>Infectious Diseases Research Institute (IDRI), Seattle, USA. <sup>9</sup>Departament of Medicine,  
37  
38 16 Universidade Federal de Sergipe, Aracaju. <sup>10</sup>Instituto de Investigação em Imunologia, INCT, CNPq.  
39  
40  
41  
42  
43  
44

45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

18 **Corresponding Author**

19 Márcio B. Santos

20 Department of Health Science, Federal University of Sergipe

21 Av. Gov. Marcelo Déda - São José, Lagarto - SE, Brazil

22 Postal Code 49400-000

23 E-mail: bio\_marcio2006@hotmail.com

1  
2  
3 24 **ABSTRACT**  
4

5 25 **Objective:** This study aimed to analyze the clinical and epidemiological indicators,  
6  
7  
8 26 temporal trends and the spatial distribution of leprosy in patients under 15 years old in  
9  
10 27 an endemic area of Northeast Brazil.

11  
12  
13 28 **Design:** Regional surveillance study of all reported cases.

14  
15 29 **Setting:** State of Sergipe, endemic area of Northeast Brazil.

16  
17 30 **Methods:** An ecological and time series study was conducted, based on secondary data  
18  
19 31 reported by the Brazilian Information System on Notifiable Diseases (SINAN) for leprosy  
20  
21 32 cases diagnosed in Sergipe state (2002-2015). The analysis of temporal trends was  
22  
23 33 performed using the Joinpoint Regression Program through Poisson regression. We  
24  
25 34 performed spatial analysis by Kernel estimator and Moran index.

26  
27 35 **Results:** The incidence rate was reduced from 6.29 to 3.78 cases per 100,000 inhabitants  
28  
29 36 in 2002 and 2015, respectively. However, Sergipe was still classified as highly endemicity  
30  
31 37 in 2015. The mean number of household contacts (HHC) examined was significantly  
32  
33 38 lower than those registered. Clinical data indicated that 21.4% of the patients developed  
34  
35 39 leprosy reactions, and 31.3% presented with some physical disability in the  
36  
37 40 multibacillary (MB) groups. Patients diagnosed by exam within the HHC presented  
38  
39 41 better indicators, such as lower percentage of leprosy reaction and physical disability.  
40  
41 42 Spatial analysis showed the most risk areas distributed on the northeast and cities  
42  
43 43 around the capital, Aracaju.

44  
45 44 **Conclusion:** The data indicate that there is a persistence of active *M. leprae* transmission  
46  
47 45 and a delay in disease detection, following a pattern of high endemicity in many  
48  
49 46 municipalities. The early detection by household contacts examination is important not  
50  
51 47 only to stop transmission but also to detect the cases in a less severe state.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 48 **Keywords:** Leprosy; Children; Epidemiology; Spatial analysis.  
4  
5

6 49  
7  
8

### Strengths and limitations of this study

- This is a surveillance study that includes all notified cases of leprosy, in a State of Brazil with moderate prevalence of the disease.
  - This is the first summary of leprosy cases in patients under 15 years old in Sergipe state, Northeast Brazil.
  - This study was conducted using secondary data reported by SINAN and this source of data may have datasets missing.
  - We also mapped the leprosy cases and physical disability in children under 15 years in areas of higher prevalence of leprosy in the general population, using geoprocessing tools.
  - We compared the leprosy patient detection mode and how it affects the disease severity at diagnosis and the occurrence of leprosy reactions and physical disabilities.
- 9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 50 INTRODUCTION

51 Leprosy is a chronic infectious disease caused by infection with *Mycobacterium leprae*  
52 [1]. This pathogen exhibits tissue tropism for phagocytes in the skin and Schwann cells  
53 within peripheral nerves and it presents a long incubation time (from 2 to 7 years) [2,3].  
54 The disease can manifest across a broad spectrum of symptoms and the diagnosis is  
55 made based on the clinical signs (cutaneous lesions with altered sensitivity and  
56 neurological lesions). Patients are then classified as multibacillary (MB) and  
57 paucibacillary (PB) for treatment purposes, according to criteria accepted by Brazilian  
58 Ministry of Health (BMH) and International Leprosy Association (ILA) [1,2,4–7].

59  
60 Despite control efforts including the widespread use of multidrug therapy (MDT), and  
61 the stabilization of the reported new case detection rate in the last few years, leprosy  
62 remains endemic in many developing countries [3–6,8–11]. In 2014, the World Health  
63 Organization (WHO) reported 213,899 new leprosy cases in 121 countries or territories  
64 [4]. Brazil ranks as the second most burdened country in the world concerning number  
65 of new cases (31,064 in 2014) and has by far the highest number of cases reported in  
66 Americas [4,12,13]. Within Brazil, the highest prevalence has been reported in the  
67 North, Northeast and Midwest regions [8,9]. The incidence of leprosy (referred as the  
68 new case detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8]. In 2013, 2,439 new  
69 cases were diagnosed in children under 15 years old in Brazil, yielding a detection rate  
70 of 5.03 per 100,000 inhabitants [4].

71  
72 Studies have demonstrated that leprosy presents higher incidence in population with:  
73 low educational degree, precarious health services and domiciliary infrastructure

1  
2  
3 74 settlements, and reduced investment in prevention and control [14–16]. Moreover, the  
4  
5 75 high incidence rate in children under 15 years is important to indicate there is early  
6  
7  
8 76 exposure of the population to the bacillus, that is associated to elevated prevalence in  
9  
10  
11 77 general population, being a good indicator of a high transmission and bad quality of the  
12  
13 78 control programs [10,12,17–20]. There is no study reporting the incidence of leprosy in  
14  
15 79 children under 15 years in Sergipe state.  
16  
17  
18 80

19  
20 81 Recently, studies mapping the occurrence of infectious diseases according to their  
21  
22 82 spatial distribution using “Geographic Information Systems (GIS)” have provided  
23  
24 83 important information for public health programs, revealing areas of priority for  
25  
26 84 interventions programs to more efficiently plan and implement control measures  
27  
28 85 [2,9,16,21–23]. The use of GIS in leprosy may allow the identification of spatial-temporal  
29  
30 86 distributions and profile of incidence in defined geographical areas, this potentially  
31  
32 87 contributing to the effectiveness of interventions.  
33  
34  
35 88

36  
37  
38  
39 89 Despite breakthroughs in the epidemiological of leprosy, further improvements in  
40  
41 90 understanding of the disease dynamics in different regions is important for the support  
42  
43 91 of health services as a means for leprosy control. Spatial analyzes studies can provide  
44  
45 92 important understanding of the transmission patterns of *M. leprae* and allow the  
46  
47 93 identification of risk factors [21,23]. The aim of this study was to describe the 1) various  
48  
49 94 clinical and epidemiological indicators of leprosy; to analyze 2) temporal trends and 3)  
50  
51 95 the spatial distribution of leprosy cases in patients under 15 years old in an endemic  
52  
53 96 area of Northeast Brazil.  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 98 **METHODS**  
4

5  
6 99 **Study Design**  
7

8 100 The source of all data from this study was the leprosy cases and the information of each  
9  
10 101 individual case notified by the health centers of the municipalities to the SINAN  
11  
12 102 (Information System on Notifiable Diseases) from the State of Sergipe, Brazil. This is an  
13  
14 103 important database of the Secretariat of Health of all States of Brazil, to report  
15  
16 104 information about sociodemographic, clinical features and the address of notifiable  
17  
18 105 diseases. Leprosy is a notifiable disease in Brazil, and as a legislative requirement, all  
19  
20 106 leprosy cases have to be notified to the SINAN, including information about social and  
21  
22 107 demographic features, clinical forms and follow-up of each patient. Sergipe is located  
23  
24 108 on the coast of Northeast Brazil. The State has 75 municipalities and the capital is  
25  
26 109 Aracaju. It has a population of 2,068,017 inhabitants and an area of 21,910,354km<sup>2</sup>,  
27  
28 110 equivalent to 0.26% of the national territory. The median population per county was  
29  
30 111 27,573.56 in 2015 [16]. Population data were obtained from the IBGE (Brazilian Institute  
31  
32 112 of Geography and Statistics), based on population estimates for the intercensus years  
33  
34 113 (2002 - 2015). An ecological and time series epidemiological study was conducted, based  
35  
36 114 on the leprosy cases reported by SINAN. The historical (from 2002 to 2015) reporting of  
37  
38 115 leprosy cases in children under 15 years old was analyzed. We also compared those data  
39  
40 116 with data in all ages and with the occurrence of physical disability. The incidence of  
41  
42 117 leprosy (referred as the new case detection rate) in Sergipe in 2010 was 18.4 per 100,000  
43  
44 118 [8].  
45  
46  
47  
48  
49  
50  
51  
52  
53

54 119

55  
56  
57 120 The clinical and epidemiologic indicators collected by Investigation and Notification  
58  
59 121 Form from SINAN, were: gender, age, ethnicity, address, operational classification (PB  
60

1  
2  
3 122 and MB), clinical form [according to the more refined Ridley-Jopling classification  
4  
5 123 [24,25], based on histopathological analyses: indeterminate leprosy (IL), true  
6  
7  
8 124 tuberculoid (TT), borderline leprosy (BL) and lepromatous leprosy (LL)], leprosy reaction  
9  
10 125 (LR), number of affected nerves, degree of physical disabilities, number of household  
11  
12  
13 126 contacts (HHC) registered and examined, and the patient detection mode.  
14

15 127

16  
17  
18 128 The parameters adopted by BMH and ILA were followed for interpreting the incidence  
19  
20 129 rate of leprosy in patients under 15 years old. As such, this is classified as: low (<0.50  
21  
22 130 cases per 100,000 inhabitants); medium (0.50 to 2.49); high (2.50 to 4.99); very high  
23  
24 131 (5.00 to 9.99) and hyperendemic ( $\geq 10.00$ ) [4].  
25  
26  
27

28 132

### 29 133 **Spatial analysis**

30  
31  
32 134 Thematic maps were constructed in each municipality for the period examined  
33  
34 135 according to the leprosy incidence rate in patients under 15 years old and in general  
35  
36 136 population, and for patients presenting with physical disability (incapacity degree 1 or  
37  
38 137 2). The kernel technique was applied to identify the intensity of the distribution of  
39  
40 138 leprosy cases in the state of Sergipe. This technique shows the statistically generated  
41  
42 139 surface density for the visual detection of hot spots, that indicates agglomeration of  
43  
44 140 cases in a spatial distribution. This is an appropriate data interpolation for application in  
45  
46 141 point location data. The point distribution was transformed into a smoothed surface and  
47  
48 142 presented as a continuous map, representing different levels of case intensity. The  
49  
50 143 amount of smoothing, that is, the width of the radius of influence was defined as 3,000  
51  
52 144 meters, since this value generated an adequate representation of the distribution of the  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 145 leprosy cases in the municipalities, minimizing the overlapping bias or the occurrence of  
4  
5  
6 146 sub distribution patterns smoothed [16,21].  
7

8 147

9  
10 148 We performed either spatial autocorrelation analysis between disease detection rates  
11  
12  
13 149 for each group. The Moran Global Index (MGI)[26] was calculated to identify clusters  
14  
15  
16 150 with risks for disease occurrence. We construct a spatial proximity matrix obtained by  
17  
18 151 the contiguity of spatial correlation. The MGI was calculated as follows:

19  
20 152 (Moran Global Index Mathematical Equation 1)

21  
22  
23 153 
$$I = \frac{[(n \sum_i \sum_j \omega_{ij} (\gamma_i - \check{y}) (\gamma_j - \check{y}))]}{[\sum_i (\gamma_i - \check{y})^2 \sum_i \sum_j \omega_{ij}]}$$
  
24 154  
25 155  
26 156

27  
28  
29 157  $\omega_{ij}$  is a contiguity matrix element ( $\omega$ );  $\gamma_i$  is the incidence rate of municipality  $i$ ;  $\gamma_j$  is the  
30  
31  
32 158 incidence rate of municipality  $j$ ;  $\check{y}$  is the mean of sample and the symbol  $n$  represents  
33  
34  
35 159 the total number of municipalities [26].  
36

37 160

38  
39 161 The MGI provides a general grouping measure and it is possible to know if there are  
40  
41  
42 162 significant differences between the analyzed areas. However, it does not indicate the  
43  
44  
45 163 clusters localization. To do that, we performed the Moran Local Index diagram [26] to  
46  
47 164 build maps and identify the areas with spatial dependence (Local Index of Spatial  
48  
49 165 Association - LISA) of the annual detection means, as follows:

50  
51 166 (Local Index of Spatial Association Mathematical Equation 2)

52  
53  
54 167

55  
56 168 
$$I = \frac{n[(Z_i \sum_j \omega_{ij} Z_j)]}{(\sum_j Z_j^2)}$$
  
57 169  
58 170  
59  
60



1  
2  
3 1714  
5  
6 1727  
8 173  $Z_i = y_i - \bar{y}$ ;  $Z_j = y_j - \bar{y}$ ;  $\omega_{ij}$  is a contiguous matrix element  $\omega$ ;  $y_i$  is the incidence rate of9  
10 174 municipality  $i$ ;  $y_j$  is the incidence rate of municipality  $j$ ;  $\bar{y}$  is the sample mean and the11  
12 175 symbol  $n$  represents the total number of cities [26]. The Moran Map was used to indicate13  
14 176 the clusters and their relationship with the neighbors. This analysis verifies the existence15  
16 177 of spatial dependence and risk patterns: Q1 (high/high) and Q2 (Low/Low), which17  
18 178 indicate municipalities with similar values between their neighbors and Q3 (high/low)19  
20 179 and Q4 (low/high) for municipalities with different values between their neighbors and21  
22 180 no spatial association. A spatial proximity matrix obtained by the contiguity criterion was23  
24 181 adopted. The level of significance was 5% and the Moran Global Index (I) varying25  
26 182 between -1 and +1, representing the spatial autocorrelation of leprosy detection rate in27  
28 183 the geographic space analyzed to identify spatial clusters and risk areas. Values between29  
30 184 0 and +1 indicate positive spatial autocorrelation (Q1 and Q2) and between -1 and 031  
32 185 negative spatial autocorrelation (Q3 and Q4) [26,27]. Both Moran Index and Kernel33  
34 186 maps were constructed using TerraView software 4.2.2.35  
36 18737  
38 188 **Statistical analysis**39  
40 189 The annual incidence rates were calculated for the general population, according to the41  
42 190 population data from IBGE. For patients younger than 15 years the annual rates were43  
44 191 age-standardised, and the standard population used was the population under 15 years45  
46 192 from IBGE. Demographic and clinical data were compared across the different47  
48 193 subgroups and according to operational classification and the patient detection mode.49  
50 194 Percentage, mean and standard deviation of the groups were calculated. For groups'

1  
2  
3 195 comparison, we first analyze if the data followed normal distribution by the D'Agostino  
4  
5 196 and Pearson normality test, and statistical differences between the groups were  
6  
7  
8 197 determined by Mann-Whitney and Kruskal-Wallis tests. All analysis was performed  
9  
10 198 using SPSS Statistics, version 24.0. Results were considered statistically different when  
11  
12  
13 199  $p$ -values < 0.05 were obtained.

14  
15 200

16  
17 201 In order to enable trend analysis, annual incidence rate of leprosy was calculated as  
18  
19 202 dependent variables (y), and the years of the study period as the independent variables  
20  
21 203 (x). Initially, trend analysis was performed with the Joinpoint program, version 4.0.4  
22  
23 204 (Surveillance Research, National Cancer Institute, USA). This program estimates the  
24  
25 205 Annual Percentage Change (APC) of a segmented linear regression (Joinpoint  
26  
27 206 regression) and identifies inflection points. Each inflection point reflects changes in the  
28  
29 207 increase or decline of leprosy rates [27]. The joinpoint regression provided the  
30  
31 208 adjustment of a series of lines as well as their inflection points on a logarithmic scale by  
32  
33 209 means of the annual trend test. To obtain the adjustment based on the best line of each  
34  
35 210 analyzed segment, the Monte Carlo permutation method was used as a test of  
36  
37 211 significance. From the definition of the follow-ups, the annual percentage change (APC)  
38  
39 212 and the average annual percentage change (AAPC), with their respective 95% confidence  
40  
41 213 intervals, were estimated and tested. If the occurrence of an inflection point with inverted  
42  
43 214 direction was verified, the study periods were analyzed separately. The number of  
44  
45 215 inflections used in the analysis was the result of models defined by the program itself, in  
46  
47 216 order to allow the best representation of the trend, with the lowest number of inflection  
48  
49 217 points. The result showed growth (positive APC values), reduction (APC negative values)  
50  
51 218 or maintenance (APC value equal to zero) of the trend throughout the historical series  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 219 analyzed (2006-2014). Poisson regression is used to determine the number of segments  
4  
5 220 required to adequately explain the relationship between two variables [27]. We  
6  
7  
8 221 considered the points of trend change that presented  $p$ -value  $< 0.05$ .  
9

10  
11 222

### 12 13 223 **Ethical Considerations**

14  
15  
16 224 For conducting this study, authorization was previously requested from Coordination of  
17  
18 225 Epidemiological Surveillance, Sergipe state. This project involved research on human  
19  
20 226 subjects and was approved by the Ethics and Research Committee of the Federal  
21  
22  
23 227 University of Sergipe, CAAE 0152.0.107.000-07.  
24  
25

26 228

### 27 28 229 **Patient and Public Involvement statement**

29  
30 230 There was no patient and public involvement in this study. The study was based on  
31  
32  
33 231 secondary data.  
34  
35

36 232

## 37 38 233 **RESULTS**

### 39 40 234 **Trends in reported leprosy incidence among children**

41  
42 235 The incidence of leprosy in children under 15 years has declined from 6.29 cases per  
43  
44 236 100,000 inhabitants in 2002, to 3.78 in 2015, confirmed by Joinpoint regression analyzes  
45  
46 237 ( $APC = -5.3$  and  $p$ -value  $< 0.05$ ; **Figure 1A and B**). Similarly, the leprosy incidence rate in  
47  
48 238 the general population of Sergipe decreased from 23.08 cases to 16.99 per 100,000  
49  
50 239 inhabitants between 2002 and 2015 (**Figure 1A and C**). The occurrence of degree 2  
51  
52 240 physical disability, however, increased in this period (0.76 in 2002 to 1.2 in 2015,  
53  
54 241 respectively), however it is a non-significant increasing trend ( $APC = 2.6$  and  $p$ -value =  
55  
56 242 0.20; **Figure 1A and D**). The composition of leprosy cases according to the operational

1  
2  
3 243 classification (PB and MB) was relatively stable across this period, with majority of cases  
4  
5 244 presenting as PB (**Figure 2A**). We also observed the mean number of HHC registered  
6  
7  
8 245 ( $4.65 \pm 2.79$ ) was slightly, but significantly, higher than the number examined ( $3.66 \pm$   
9  
10 246  $3.14$ ;  $p$ -value  $< 0.0001$ ; **Figure 2B**).

11  
12  
13 247

#### 14 15 248 **Demographics of childhood leprosy cases**

16  
17 249 Next, we evaluated the association among clinical and epidemiological variables  
18  
19  
20 250 according to the leprosy operational classification (patients presenting as PB and MB).  
21  
22 251 Patients presenting as MB or PB were in similar age to ( $10.5 \pm 2.81$  and  $10.07 \pm 3.38$ ,  
23  
24 252 respectively). Despite the extended incubation period of *M. leprae*/leprosy, six cases  
25  
26 253 ( $1.11\%$ ) were reported in children less than one year of age. Of the 538 leprosy cases  
27  
28 254 identified among children under 15 years old the majority were PB [407 ( $75.7\%$ ) PB and  
29  
30 255 131 ( $24.3\%$ ) MB; **Table 1**]. When stratified on gender, however, the proportion of boys  
31  
32 256 presenting with MB ( $63.4\%$ ) was significantly higher than presenting with PB ( $48.4\%$ ;  $p$ -  
33  
34 257 value =  $0.003$ ). An interesting difference was observed when we calculated the ratio  
35  
36 258 (PB/MB) according the ethnic groups. Among those identified as black, the ratio ( $43/24$ )  
37  
38 259 was  $1.79$ . Conversely, the ratio of white was higher  $4.88$  ( $88/18$ ;  $p$ -value =  $0.02$ ).  
39  
40  
41  
42  
43  
44  
45  
46

47 260

48 261 As expected, the occurrence of leprosy reactions was significantly higher in MB ( $21.4\%$ )  
49  
50 262 than PB ( $4.9\%$ ;  $p$ -value  $< 0.0001$ ) patients. The occurrence of degree 2 of physical  
51  
52 263 disability was also higher in MB ( $4.6\%$ ), than in PB patients ( $0.74\%$ ;  $p$ -value =  $0.0001$ ).  
53  
54 264 Consistent with this, we observed that the mean of number of affected nerves was  
55  
56 265 higher in MB ( $0.5 \pm 1.03$ ), than PB ( $0.19 \pm 0.54$ ;  $p$ -value =  $0.04$ ).  
57  
58  
59  
60

266

## 267 **Impact of case detection methods on leprosy presentation**

268 We also performed analysis of association among clinical and epidemiological variables  
269 according to the leprosy patient detection mode. The patients were grouped in:  
270 spontaneous demand (SDem: patients that looked for medical assistance by  
271 themselves); forwarded (FW: patients that were forwarded from a primary clinic to a  
272 leprosy reference center); examined HHC; and other. We observed that patients  
273 detected by the examined HHC method presented lower mean age ( $9.6 \pm 3.38$ ) than  
274 those detected by either the SDem ( $10.54 \pm 3.28$ ) or FW methods ( $10.02 \pm 3.15$ ;  $p$ -value  
275 = 0.04; **Table 2**). Interestingly, the percentage of leprosy reaction among the examined  
276 HHC group (2.9%;  $p$ -value = 0.02) was lower than that observed among SDem (7.3%) and  
277 FW (13.3%). In addition, degree 2 of physical disability was not observed among patients  
278 detected in examined HHC group, while SDem and FW presented 0.43% and 3.8%,  
279 respectively ( $p$ -value = 0.04). Furthermore, patients identified among examined HHC  
280 presented with lower numbers of lesions ( $2.04 \pm 2.96$ ;  $p$ -value = 0.04) than SDem ( $3.64$   
281  $\pm 6.25$ ) and FW ( $4.09 \pm 8.68$ ). Taken together, these data reinforce the importance of  
282 HHC examination for the detection of leprosy patients before advancement to more  
283 severe symptoms.

284

## 285 **Spatial analyze data**

286 Next, we performed the spatial analysis of leprosy cases in the general population, in  
287 patients under 15 years old, and in patients presenting with physical disability (both  
288 degree 1 and 2). Moran maps have showed higher risk clusters (Q1 - in red; **Figure 3A-**  
289 **C**) in similar areas when comparing the maps regarding leprosy cases in children under  
290 15 years old, in general population, and patients presenting some physical disability

1  
2  
3 291 (degree 1 and 2). The higher risk clusters (Q1) were localized in Sergipe state center and  
4  
5 292 in the metropolitan area around the capital of State. The municipalities with no spatial  
6  
7  
8 293 association (Q3 - in blue) were localized in the Semiarid region, in the northwest area  
9  
10 294 and in the south region.  
11  
12

13 295

15 296 Similarly, The Kernel estimator, through data interpolation, showed densities (hot spots)  
16  
17 297 of the highest incidence rates located at the northeast and east center regions and in  
18  
19 298 the counties around the state capital (Aracaju city; **Figure 3D-F**). Lower intensity was  
20  
21 299 observed on the western region. Municipalities with intermediate to high incidence  
22  
23 300 values are seen in yellow and red tones of each subfigure. Low incidence areas were  
24  
25 301 reported on west coast municipalities, mostly in smaller counties with small  
26  
27 302 populations.  
28  
29  
30  
31

32 303

### 35 304 **DISCUSSION**

37 305 Previous studies have demonstrated that the high leprosy cases detection in patients  
38  
39 306 under 15 years old is a bad parameter for leprosy control program, because it indicates  
40  
41 307 early bacillus transmission from undiagnosed cases [18]. Some authors have speculated  
42  
43 308 either about the risk of vertical/transplacental transmission or through breastfeeding  
44  
45 309 [12].  
46  
47  
48

49 310

51 311 In Brazil, the highest leprosy incidence rate in children was reported in the North area  
52  
53 312 (11.91 cases per 100,000 inhabitants), followed by Northeast (8.12) [12]. We observed  
54  
55 313 the leprosy incidence rate was reduced in children under 15 years old from 2002 to 2015  
56  
57  
58 314 in Sergipe state, however considering the parameters adopted by BMH, the state was  
59  
60

1  
2  
3 315 classified as very high endemicity in 2002, and still as high endemicity in 2015. It remains  
4  
5 316 also with elevated incidence rate and stationary tendency of degree 2 of physical  
6  
7  
8 317 disability. Those data reinforce either that the transmission is intense at early age, there  
9  
10 318 is lack of an effective public health and the disease control is focused in the MDT [12,18].  
11  
12  
13 319 A similar study performed at Fortaleza city (Brazil), reported also that although a  
14  
15 320 decreasing has been observed on overall detection rate, the number of new cases in  
16  
17 321 those under 15 years old remains stable [13].  
18  
19

20 322

21  
22 323 Leprosy reactions and physical disability are the most severe leprosy clinical  
23  
24 324 complications [8,28,29]. In addition, the increase or stability of the prevalence of degree  
25  
26 325 2 of physical disability indicates persisting late diagnosis [13,29]. The early diagnosis of  
27  
28 326 leprosy is essential to the prevention of deformities, whose repercussions are still more  
29  
30 327 catastrophic in children and adolescents [28]. Our data reported 21.4% children with  
31  
32 328 leprosy reaction (LR) and 31.3% with some physical disability in the MB groups.  
33  
34 329 Furthermore, MB patients presented higher mean of affected nerves. Generally,  
35  
36 330 patients under 15 years old do not use to present LR, but studies have reported a low  
37  
38 331 frequency of LR, varying between 1.36% and 8.33% [28]. Those data reinforce that,  
39  
40 332 although there is a decreasing incidence in leprosy, patients have been exposed to  
41  
42 333 bacillus early in life and diagnosed belatedly and hence they have been also developing  
43  
44 334 into some clinical complications.  
45  
46  
47  
48  
49

50 335

51  
52 336 We have observed either that the mean of HHC examined was significantly lower than  
53  
54 337 those registered by SINAN. Moreover, leprosy patients detected by exam in HHC  
55  
56 338 presented lower mean of age, affected nerves, number of lesions, occurrence of LR and  
57  
58  
59  
60

1  
2  
3 339 no physical disability, when compared with those identified by spontaneous demand or  
4  
5  
6 340 forwarded by others. On the other hand, mostly of patients presenting as degree 2 of  
7  
8 341 physical disability were identified into those forwarded to a leprosy reference center,  
9  
10 342 probably because they started presenting some physical disability. HHC and neighbors  
11  
12  
13 343 are the most important *M. leprae* active sources. The risk of a person developing leprosy  
14  
15 344 is nine times greater among HHC and up to four times greater among contacts with  
16  
17  
18 345 neighbors [12]. Therefore, our data reinforce the importance of leprosy early diagnosis  
19  
20 346 by exam in patients and their household contacts. Besides that, the treatment and the  
21  
22  
23 347 home visits by public health programs, and an efficient health program in schools could  
24  
25 348 represent important actions for the early diagnosis and the reduction of leprosy clinical  
26  
27  
28 349 complications, especially in children.

29  
30 350

31  
32 351 Spatial analysis of health events aim to identify geographical patterns by maps of risk  
33  
34  
35 352 and to point out areas of higher severity and to facilitate the planning of public health  
36  
37  
38 353 interventions [9]. The Kernel maps showed the spatial dynamic of leprosy, with a  
39  
40  
41 354 heterogeneous geographical pattern and the highest risk areas for leprosy infection. The  
42  
43  
44 355 highest incidence on counties around the Capital can be due there was a leprosarium at  
45  
46  
47 356 the Nossa Senhora do Socorro (a city of the metropolitan area of Aracaju), that has  
48  
49  
50 357 presented elevated detection rate in mostly evaluated years. Moreover, that area  
51  
52  
53 358 presents reference center to leprosy diagnosis and treatment and hence they have  
54  
55  
56 359 several patients forwarded to these leprosy clinics. It can be also associated with  
57  
58  
59 360 weather featuring such as humidity, considering either that counties near to São  
60  
361 Francisco River presented also elevated incidence. In the Malawian Karonga district, a  
362 positive relationship between the proximity of water and leprosy incidence was



1  
2  
3 363 previously reported [5]. Some authors have hypothesized that *M. leprae* survives longer  
4  
5 364 outside of human body in humid compared to dry atmospheres [9,13].  
6  
7  
8 365

9  
10 366 Interestingly, higher risk clusters were identified in similar areas when we analyzed the  
11  
12  
13 367 occurrence of leprosy cases in children, in general population and patients presenting  
14  
15 368 physical disability. It corroborates the hypothesis that the early transmission of *M.*  
16  
17 369 *leprae* and the occurrence of leprosy in children under 15 years old is directly related to  
18  
19  
20 370 the late diagnosis, which explains the occurrence of patients with degree 2 of physical  
21  
22 371 disability in the same geographic distribution [28]. The maps present certain  
23  
24  
25 372 disagreements regarding the occurrence of leprosy cases in the state of Sergipe because  
26  
27 373 they use distinct techniques of spatial analysis. The Kernel estimator produces a  
28  
29  
30 374 continuous surface, with densities calculated at all locations, based on total number of  
31  
32 375 cases and no considering the geographical boundaries of the municipalities [27,30,31].  
33  
34  
35 376 The Kernel technique presents greater advantages to the quick visualization of areas  
36  
37 377 that deserve attention, besides not being affected by political-administrative division,  
38  
39  
40 378 while the Moran technique, constructs maps considering the political-administrative  
41  
42 379 divisions of the state and the clusters are based on the number of cases divided by the  
43  
44  
45 380 municipalities [27,30].  
46

47 381  
48  
49 382 Our study had some limitations, particularly because it was conducted using secondary  
50  
51 383 data reported by SINAN. This source of data can present numbers under notification and  
52  
53 384 datasets missing. However, in Brazil we have a specific normative that is an obligation  
54  
55 385 to notify several diseases to SINAN, and leprosy is one of them. SINAN is an important  
56  
57 386 database of the Secretariat of Health of all States of Brazil, to report information about  
58  
59  
60

1  
2  
3 387 sociodemographic, clinical features and the address of each diagnosed case. This source  
4  
5 388 of data can present under notification because Leprosy is an asymptomatic disease and  
6  
7  
8 389 the active search would be important to detect more cases, but all diagnosed cases are  
9  
10 390 reported to SINAN. The limitation mentioned about missing data is not very important  
11  
12  
13 391 in the case of the disease prevalence, but the complete information about the cases  
14  
15 392 follow-up, such as degree of neurological disability at the end of treatment, leprosy  
16  
17 393 reactions and treatment details, because it is a secondary database that depends on  
18  
19 394 other doctors or nurses from the health care centers to fulfill the information. Despite  
20  
21 395 this, those data reported high endemicity of leprosy cases in patients under 15 years  
22  
23  
24  
25 396 old, and this study do not focus on patient follow-up.  
26  
27  
28 397

29  
30 398 In summary, our study demonstrated that the leprosy incidence rate has decreased in  
31  
32 399 Sergipe state. However, it is still classified as high endemicity considering the WHO  
33  
34 400 proposed ratios for children under 15 years. Patients detected by exam in collectivity or  
35  
36 401 HHC presented better indicators. Altogether, the epidemiological data and spatial  
37  
38 402 analysis indicate that there is persistence of active transmission of *M. leprae* and later  
39  
40 403 case detection in Sergipe state, increasing the risk of transmission in children. In  
41  
42 404 addition, the spatial analysis brings new advantages to comprehend the leprosy  
43  
44 405 dynamic, and reinforce the superimposed regions of high occurrence areas of patients  
45  
46 406 presenting degree 2 of physical disability and cases in children lower than 15 years, and  
47  
48 407 highlights the need to strengthen effective disease control measures, mainly in primary  
49  
50 408 health care.

51  
52 409 **Acknowledgments** The authors would like to thank the Manager of the Nucleus of  
53  
54 410 endemic/Division of Epidemiological Surveillance - [Divisão de Vigilância  
55  
56  
57  
58  
59  
60

1  
2  
3 411 Epidemiológica (DIVEP)]/ Secretariat of Health of the Sergipe state (SES) for providing  
4  
5 412 information.

6  
7  
8  
9 413 **Funding** This research received no specific grant from any funding agency in the public,  
10  
11 414 commercial or not-for-profit sectors.

12  
13 415 **Contributors** The project was suggested by MB-S, MA, JB and AS. The statistical analyzes  
14  
15 416 was performed by MB-S, IB, JS and AJ. The spatial analyzes was performed by MS, AS,  
16  
17 417 AB and KA. The manuscript was written by MB-S, AB, DO, MD and AJ. All authors  
18  
19 418 contributed to refining the idea, revising the manuscript and have agreed the final  
20  
21 419 version.

22  
23  
24  
25 420 **Competing interests** The authors declare that they have no conflicts of interest.

26  
27 421 **Provenance and peer review** Not commissioned; externally peer reviewed.

28  
29 422 **Data sharing statement** No additional data are available.

30  
31  
32  
33 423

34  
35 424 **References**

36  
37  
38  
39 425

40  
41  
42 426 1 Simon M, Scherlock J, Duthie MS, *et al.* Clinical, immunological, and genetic  
43  
44 427 aspects in leprosy. *Drug Dev Res* 2011;**72**:509–27. doi:10.1002/ddr.20457

45  
46  
47  
48 428 2 Duarte-Cunha M, Marcelo da Cunha G, Souza-Santos R. Geographical  
49  
50 429 heterogeneity in the analysis of factors associated with leprosy in an endemic  
51  
52 430 area of Brazil: are we eliminating the disease? *BMC Infect Dis* 2015;**15**:196.  
53  
54 431 doi:10.1186/s12879-015-0924-x

55  
56  
57  
58 432 3 Fulton N, Anderson LF, Watson JM, *et al.* Leprosy in England and Wales 1953-  
59  
60

- 1  
2  
3 433 2012: Surveillance and challenges in low incidence countries. *BMJ Open*  
4  
5 434 2016;**6**:15–8. doi:10.1136/bmjopen-2015-010608  
6  
7  
8  
9 435 4 Freitas LRS, Duarte EC, Garcia LP, *et al.* Trends of main indicators of leprosy in  
10  
11 436 Brazilian municipalities with high risk of leprosy transmission, 2001–2012. *BMC*  
12  
13 437 *Infect Dis* 2016;**16**:472. doi:10.1186/s12879-016-1798-2  
14  
15  
16  
17 438 5 Duthie MS, Saunderson P, Reed SG. The potential for vaccination in leprosy  
18  
19 439 elimination: New tools for targeted interventions. *Mem Inst Oswaldo Cruz*  
20  
21 440 2012;**107**:190–6. doi:10.1590/S0074-02762012000900027  
22  
23  
24  
25 441 6 Duthie MS, Gillis TP, Reed SG. Advances and hurdles on the way toward a  
26  
27 442 leprosy vaccine. *Hum Vaccin* 2011;**7**:1172–83. doi:10.4161/hv.7.11.16848  
28  
29  
30  
31 443 7 Kumar A, Girdhar A, Girdhar BK. Six months fixed duration multidrug therapy in  
32  
33 444 paucibacillary leprosy: Risk of relapse and disability in Agra PB cohort study. *BMJ*  
34  
35 445 *Open* 2012;**2**:1–6. doi:10.1136/bmjopen-2012-001403  
36  
37  
38  
39 446 8 de Oliveira DT, Bezerra MM, de Almeida JAP, *et al.* Neurological disability in  
40  
41 447 leprosy: Incidence and gender association in Sergipe, Brazil. *Geospat Health*  
42  
43 448 2012;**6**. doi:10.4081/gh.2012.130  
44  
45  
46  
47 449 9 Alencar CH, Ramos AN, dos Santos ES, *et al.* Clusters of leprosy transmission and  
48  
49 450 of late diagnosis in a highly endemic area in Brazil: Focus on different spatial  
50  
51 451 analysis approaches. *Trop Med Int Heal* 2012;**17**:518–25. doi:10.1111/j.1365-  
52  
53 452 3156.2011.02945.x  
54  
55  
56  
57 453 10 Durrheim DN, Speare R. Global leprosy elimination: Time to change more than  
58  
59 454 the elimination target date. *J Epidemiol Community Health* 2003;**57**:316–7.

- 1  
2  
3 455 doi:10.1136/jech.57.5.316  
4  
5  
6 456 11 Barth-Jaeggi T, Steinmann P, Mieras L, *et al.* Leprosy Post-Exposure Prophylaxis  
7  
8  
9 457 (LPEP) programme: Study protocol for evaluating the feasibility and impact on  
10  
11 458 case detection rates of contact tracing and single dose rifampicin. *BMJ Open*  
12  
13 459 2016;**6**. doi:10.1136/bmjopen-2016-013633  
14  
15  
16  
17 460 12 Santos SD, Penna GO, Costa M da CN, *et al.* Leprosy in children and adolescents  
18  
19 461 under 15 years old in an urban centre in Brazil. *Mem Inst Oswaldo Cruz*  
20  
21 462 2016;**111**:359–64. doi:10.1590/0074-02760160002  
22  
23  
24  
25 463 13 Brito AL, Monteiro LD, Ramos Junior AN, *et al.* Tendência temporal da  
26  
27 464 hanseníase em uma capital do Nordeste do Brasil: epidemiologia e análise por  
28  
29 465 pontos de inflexão, 2001 a 2012. *Rev Bras Epidemiol* 2016;**19**:194–204.  
30  
31 466 doi:10.1590/1980-5497201600010017  
32  
33  
34  
35  
36 467 14 Vieira GDD, Aragoso I, Carvalho RMB, *et al.* Hanseníase em Rondônia: incidência  
37  
38 468 e características dos casos notificados, 2001 a 2012. *Epidemiol e Serviços Saúde*  
39  
40 469 2014;**23**:269–75. doi:10.5123/S1679-49742014000200008  
41  
42  
43  
44 470 15 Queir??s MI, Ramos AN, Alencar CHM, *et al.* Clinical and epidemiological profile  
45  
46 471 of leprosy patients attended at Cear??, 2007-2011. *An Bras Dermatol*  
47  
48 472 2016;**91**:311–7. doi:10.1590/abd1806-4841.20164102  
49  
50  
51  
52 473 16 dos Santos AD, Lima ACR, Santos MB, *et al.* Spatial analysis for the identification  
53  
54 474 of risk areas for schistosomiasis mansoni in the state of Sergipe, Brazil, 2005-  
55  
56 475 2014. *Rev Soc Bras Med Trop* 2016;**49**:608–15. doi:10.1590/0037-8682-0137-  
57  
58 476 2016  
59  
60

- 1  
2  
3 477 17 Alencar CHM De, Barbosa JC, Ramos Jr AN, *et al.* Hanseníase no município de  
4  
5 478 Fortaleza, CE, Brasil: aspectos epidemiológicos e operacionais em menores de  
6  
7 479 15 anos (1995-2006). *Rev Bras Enferm* 2008;**61**:694–700. doi:10.1590/S0034-  
8  
9 480 71672008000700007  
10  
11  
12  
13 481 18 Pires CAA, Malcher CMSR, Abreu JMC, *et al.* Hanseníase em menores de 15  
14  
15 482 anos: A importância do exame de contato. *Rev Paul Pediatr* 2012;**30**:292–5.  
16  
17 483 doi:10.1590/S0103-05822012000200022  
18  
19  
20  
21 484 19 Carlos F, Lana F, Amaral EP, *et al.* Hanseníase em menores de 15 anos no Vale  
22  
23 485 do Jequitinhonha, Minas Gerais, Brasil. *Rev Bras Enferm* 2007;**60**:696–700.  
24  
25 486 doi:10.1590/S0034-71672007000600014  
26  
27  
28  
29 487 20 Fernandes C, Gonçalves HS, Cabral PB, *et al.* Increased frequency of CD4 and  
30  
31 488 CD8 regulatory T cells in individuals under 15 years with multibacillary leprosy.  
32  
33 489 *PLoS One* 2013;**8**. doi:10.1371/journal.pone.0079072  
34  
35  
36  
37 490 21 Barreto AS, Alves B. ORIGINAL ARTICLE SPATIAL ANALYSIS AND  
38  
39 491 EPIDEMIOLOGICAL CHARACTERISTICS OF CASES OF LEPROSY IN AN ENDEMIC  
40  
41 492 AREA. *J Nurs UFPE* 2016;**10**. doi:10.5205/reuol.9881-87554-1-EDSM1011201604  
42  
43  
44  
45  
46 493 22 Khan O, Davenhall W, Ali M, *et al.* Geographical information systems and  
47  
48 494 tropical medicine. *Ann Trop Med Parasitol* 2010;**104**:303–18.  
49  
50 495 doi:10.1179/136485910X12743554759867.Geographical  
51  
52  
53  
54 496 23 Fischer E, Pahan D, Chowdhury S, *et al.* The spatial distribution of leprosy in four  
55  
56 497 villages in Bangladesh: an observational study. *BMC Infect Dis* 2008;**8**:125.  
57  
58 498 doi:10.1186/1471-2334-8-125  
59  
60

- 1  
2  
3 499 24 Ridley DS JW. Classification of leprosy according to immunity. A five-group  
4  
5 500 system. *Int J Lepr Other Mycobact Dis* 1966;**34**:255–73.  
6  
7  
8 501 doi:10.1126/science.1238286  
9  
10  
11 502 25 Lockwood DNJ, Sarno E, Smith WC. Classifying leprosy patients--searching for  
12  
13 503 the perfect solution. *Lepr Rev* 2007;**78**:317–20.  
14  
15  
16  
17 504 26 Chen Y. New Approaches for Calculating Moran's Index of Spatial  
18  
19 505 Autocorrelation. *PLoS One* 2013;**8**. doi:10.1371/journal.pone.0068336  
20  
21  
22  
23 506 27 Goes JAP, Souza DDG, Andrade LA, *et al*. Trend and spatial analysis of prostate  
24  
25 507 cancer mortality in the state of Sergipe, Brazil. *Geospat Health* 2018;**13**.  
26  
27 508 doi:10.4081/gh.2018.732  
28  
29  
30  
31 509 28 de Oliveira MBB, Diniz LM. Leprosy among children under 15 years of age:  
32  
33 510 Literature review. *An Bras Dermatol* 2016;**91**:196–203. doi:10.1590/abd1806-  
34  
35 511 4841.20163661  
36  
37  
38  
39 512 29 Kumar A, Girdhar A, Kumar Girdhar B. Risk of developing disability in pre and  
40  
41 513 post-multidrug therapy treatment among multibacillary leprosy: Agra MB  
42  
43 514 Cohort study. *BMJ Open* 2012;**2**:1–7. doi:10.1136/bmjopen-2011-000361  
44  
45  
46  
47 515 30 dos Santos AD, Lima ACR, Santos MB, *et al*. Spatial analysis for the identification  
48  
49 516 of risk areas for schistosomiasis mansoni in the state of Sergipe, Brazil, 2005-  
50  
51 517 2014. *Rev Soc Bras Med Trop* 2016;**49**. doi:10.1590/0037-8682-0137-2016  
52  
53  
54  
55 518 31 Santos MB, dos Santos AD, da Silva PP, *et al*. Spatial analysis of viral hepatitis  
56  
57 519 and schistosomiasis coinfection in an endemic area in Northeastern Brazil. *Rev*  
58  
59 520 *Soc Bras Med Trop* 2017;**50**. doi:10.1590/0037-8682-0411-2016

521 **Table 1. Association of demographic and clinical data according to the operational**  
 522 **classification of leprosy (PB and MB) in children under 15 years in Sergipe state,**  
 523 **Brazil (2002-2015).**

Variables	Operational Classification		p-value
	PB (n = 407)	MB (n = 131)	
<b>Age mean ± SD</b>	10.07 ± 3.38	10.5 ± 2.81	*0.46
<b>Gender n (%)</b>			
Male	197 (48.4)	83 (63.4)	+0.003
<b>Ethnicity n (%)</b>			
White	88 (21.6)	18 (13.7)	#0.02
Black	43 (10.5)	24 (18.3)	
Brown	251 (61.7)	78 (59.5)	
Indian	4 (0.9)	3 (2.3)	
<b>Leprosy reaction n (%)</b>	20 (4.9)	28 (21.4)	+<0.0001
<b>Physical Disability</b>			
<b>Degree n (%)</b>			
0	337 (82.8)	90 (68.7)	#0.0001
1	26 (6.4)	18 (13.7)	
2	3 (0.74)	6 (4.6)	
<b>Number of affected nerves</b> (mean ± SD)	0.19 ± 0.54	0.5 ± 1.03	*0.04
<b>Number of Lesions (mean ±</b> <b>SD)</b>	1.61 ± 1.14	9.92 ± 12.03	*<0.0001
<b>HHC registered (mean ± SD)</b>	4.6 ± 2.71	4.85 ± 3.04	*0.14
<b>HHC examined (mean ± SD)</b>	3.54 ± 3.04	4.05 ± 3.44	

524 \*Mann-Whitney test; +Fisher's exact test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC  
 525 = household contacts; SD = Standard Deviation. We missed data in some variables.

526



527 **Table 2. Demographic and clinical aspects accordingly to the detection mode of leprosy**  
 528 **cases in children under 15 years in Sergipe state, Brazil (2002-2015).**

529

Variables	Patient detection mode				p-value
	Spontaneous demand (n = 234)	Forwarding (n = 210)	Examined HHC (n = 69)	Other (n = 25)	
<b>Age mean ± SD</b>	10.54 ± 3.28	10.02 ± 3.15	9.6 ± 3.38	9.6 ± 3.22	*0.04
<b>Gender n (%)</b>					
Male	123 (52.6)	110 (52.4)	38 (55.1)	09 (36)	#0.41
<b>Leprosy reaction n (%)</b>	17 (7.3)	28 (13.3)	2 (2.9)	1 (4.0)	#0.02
<b>Physical disability degree n (%)</b>					
0	199 (85.1)	150 (71.4)	55 (79.7)	18 (72)	#0.04
1	17 (7.3)	21 (10)	5 (7.2)	1 (4.0)	
2	1 (0.43)	08 (3.8)	0 (0.0)	0 (0.0)	
<b>Number of affected nerves (mean ± SD)</b>	0.24 ± 0.67	0.34 ± 0.81	0.06 ± 0.25	0.25 ± 0.5	*0.48
<b>Number of lesion (mean ± SD)</b>	3.64 ± 6.25	4.09 ± 8.68	2.04 ± 2.96	4 ± 5.2	*0.04
<b>HHC registered (mean ± SD)</b>	4.57 ± 2.53	4.59 ± 2.74	5.57 ± 3.81	3.45 ± 1.96	*0.04
<b>HHC examined (mean ± SD)</b>	3.71 ± 3.02	3.02 ± 2.98	4.64 ± 4.06	2.04 ± 1.77	*0.01

530 \*Kruskal-Wallis test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC = household contacts;

531 SD = Standard Deviation. We missed data in some variables.

532

1  
2  
3 533 **Figure 1. Leprosy incidence rates and temporal trend in state of Sergipe, Northeast**  
4  
5 534 **Brazil, 2002-2015.** A) Leprosy incidence rate (per 100,000 inhabitants) in general  
6  
7 535 population (▲), in patients under 15 years old (■), degree 2 of physical disability (◆)  
8  
9 536 and the tendency line. Temporal trend of standardized incidence rates by Joinpoint  
10  
11 537 Regression for B) patients under 15 years old, C) General population and D) incapacity  
12  
13 538 degree. Data were considered statistically different when p-value < 0.05. CI: Confidence  
14  
15 539 Interval.

16  
17  
18  
19  
20  
21  
22  
23 541 **Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state**  
24  
25 542 **of Sergipe, Brazil, 2002-2015.** A) Number of leprosy cases according to the clinical  
26  
27 543 operational classification (Paucibacillary - PB (■) and Multibacillary – MB (■) forms). B)  
28  
29 544 Mean and standard deviation (mean ± SD) of the number of household contacts (HHC)  
30  
31 545 that were registered and examined for leprosy diagnosis. Data were considered  
32  
33 546 statistically different when p-value < 0.05. \* Mann-Whitney test.

34  
35  
36  
37  
38  
39  
40  
41 548 **Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were**  
42  
43 549 **constructed by TerraView Software 4.2.2.** The Moran Global Index (\*MGI) was  
44  
45 550 calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of  
46  
47 551 leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy  
48  
49 552 cases in the general population. Moran (E) and Kernel (F) maps of occurrence of  
50  
51 553 incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 – 2015).

52  
53  
54  
55 554

56  
57  
58  
59 555  
60

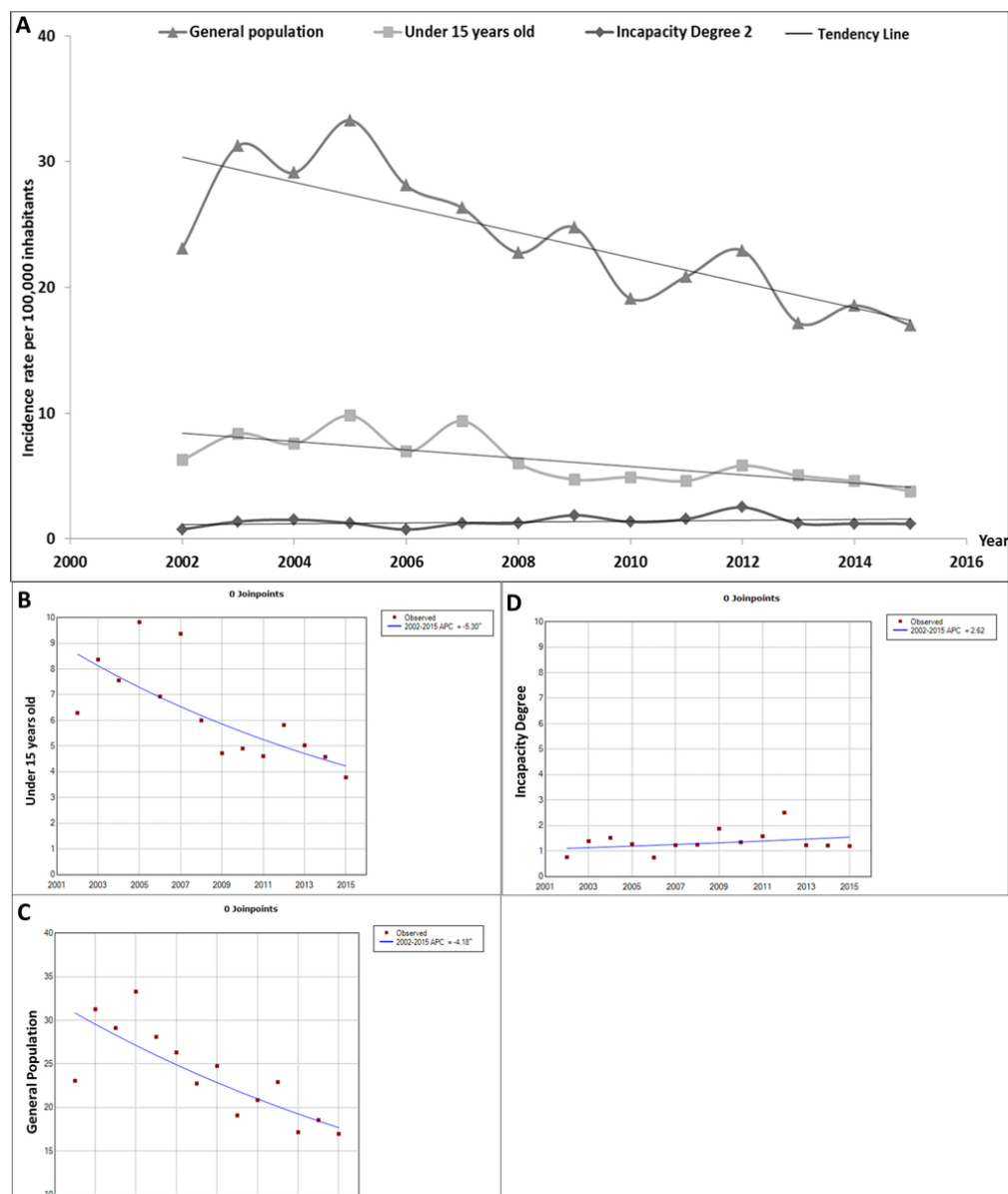


Figure 1. Leprosy incidence rates and temporal trend in state of Sergipe, Northeast Brazil, 2002-2015. A) Leprosy incidence rate (per 100,000 inhabitants) in general population (□), in patients under 15 years old (□), degree 2 of physical disability (□) and the tendency line. Temporal trend of standardized incidence rates by Joinpoint Regression for B) patients under 15 years old, C) General population and D) incapacity degree. Data were considered statistically different when p-value < 0.05. CI: Confidence Interval.

85x101mm (300 x 300 DPI)

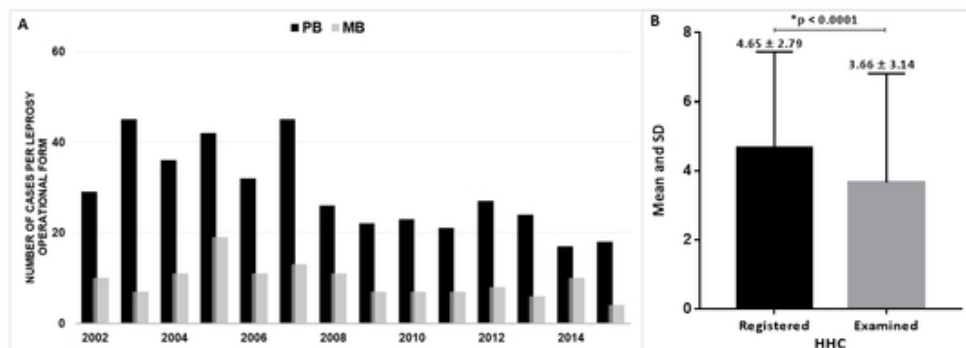


Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Number of leprosy cases according to the clinical operational classification (Paucibacillary - PB (□) and Multibacillary - MB (□) forms). B) Mean and standard deviation (mean ± SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. \* Mann-Whitney test.

46x18mm (300 x 300 DPI)

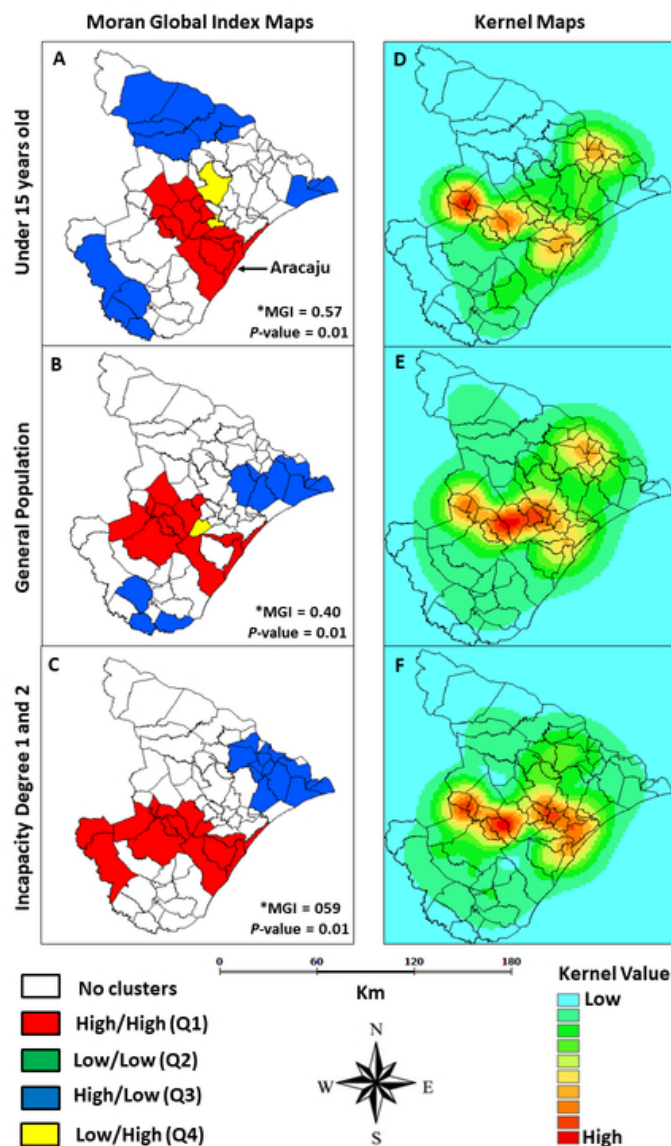


Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were constructed by TerraView Software 4.2.2. The Moran Global Index (\*MGI) was calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy cases in the general population. Moran (E) and Kernel (F) maps of occurrence of incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 - 2015).

48x64mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	01
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	02
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	04-05
Objectives	3	State specific objectives, including any prespecified hypotheses	05
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	06
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	06
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	06
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	06
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	06-07
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	06
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	06-08
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	08-09
		(b) Describe any methods used to examine subgroups and interactions	08-09
		(c) Explain how missing data were addressed	08-09
		(d) If applicable, describe analytical methods taking account of sampling strategy	08-09
		(e) Describe any sensitivity analyses	08-09
<b>Results</b>			08-09

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	09
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	09-10
		(b) Indicate number of participants with missing data for each variable of interest	--
Outcome data	15*	Report numbers of outcome events or summary measures	09-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(b) Report category boundaries when continuous variables were categorized	--
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	09-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in an Endemic Area of Northeast Brazil: an ecological and time series study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023420.R3
Article Type:	Research
Date Submitted by the Author:	27-May-2019
Complete List of Authors:	Santos, Márcio; Universidade Federal de Sergipe, Health Education; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Santos, Allan; Universidade Federal de Sergipe, Nursing Barreto, Aline; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Souza, Mariana; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Goes, Marco; Universidade Federal de Sergipe, Medicine Barreto Alves, Jose Antonio; Universidade Federal de Sergipe, Nursing Barreto, Ikaro; Universidade Federal Rural de Pernambuco, Programa de Pos-Graduacao em Biometria e Estatistica Aplicada Silva, José-Rodrigo; Universidade Federal de Sergipe, Statistics and Actuarial Sciences Oliveira, Daniela; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Araújo, Karina; Universidade Federal de Sergipe, Morphology Duthie, Malcolm; Infectious Diseases Research Institute Jesus, Amélia; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology; Universidade Federal de Sergipe, Medicine
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Public health
Keywords:	Leprosy, Children, Epidemiology < INFECTIOUS DISEASES, Spatial analysis

SCHOLARONE™  
Manuscripts



1  
2  
3 1 **Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy**  
4  
5  
6 2 **Cases in Patients Under 15 Years Old in an Endemic Area of Northeast**  
7  
8  
9 3 **Brazil: an ecological and time series study**  
10  
11  
12 4

13  
14 5 Márcio B Santos<sup>1,2</sup>, Allan D dos Santos<sup>3</sup>, Aline S Barreto<sup>2</sup>, Mariana do R Souza<sup>2</sup>, Marco A  
15  
16 6 de O Goes<sup>4</sup>, José-Antônio A Barreto<sup>3</sup>, Íkaro D C Barreto<sup>5</sup>, José-Rodrigo S Silva<sup>6</sup>, Daniela T  
17  
18 7 de Oliveira<sup>3</sup>, Karina G de Araujo<sup>7</sup>, Malcolm S Duthie<sup>8</sup>, Amélia R de Jesus<sup>2,9,10</sup>.  
19  
20  
21 8

22  
23  
24 9 <sup>1</sup>Departament of Health Education, Universidade Federal de Sergipe, Brazil; <sup>2</sup>Laboratory of Immunology  
25  
26 10 and Molecular Biology, Universidade Federal de Sergipe, Brazil; <sup>3</sup>Departament of Nursing, Universidade  
27  
28 11 Federal de Sergipe, Brazil; <sup>4</sup>Departament of Medicine, Universidade Federal de Sergipe, Brazil; <sup>5</sup>Mestre,  
29  
30 12 Universidade Federal Rural de Pernambuco (UFPE), Programa de Pos-Graduacao em Biometria e  
31  
32 13 Estatística Aplicada; <sup>6</sup>Doutor, Professor Adjunto do Departamento de Estatística e Ciências Atuariais da  
33  
34 14 Universidade Federal de Sergipe (UFS); <sup>7</sup>Departament of Morphology, Universidade Federal de Sergipe,  
35  
36 15 Aracaju; <sup>8</sup>Infectious Diseases Research Institute (IDRI), Seattle, USA. <sup>9</sup>Departament of Medicine,  
37  
38 16 Universidade Federal de Sergipe, Aracaju. <sup>10</sup>Instituto de Investigação em Imunologia, INCT, CNPq.  
39  
40  
41  
42  
43  
44

45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

18 **Corresponding Author**

19 Márcio B. Santos

20 Department of Health Science, Federal University of Sergipe

21 Av. Gov. Marcelo Déda - São José, Lagarto - SE, Brazil

22 Postal Code 49400-000

23 E-mail: bio\_marcio2006@hotmail.com

1  
2  
3 24 **ABSTRACT**  
4

5 25 **Objective:** This study aimed to analyze the clinical and epidemiological indicators,  
6  
7  
8 26 temporal trends and the spatial distribution of leprosy in patients under 15 years old in  
9  
10 27 an endemic area of Northeast Brazil.

11  
12  
13 28 **Design:** Regional surveillance study of all reported cases.

14  
15 29 **Setting:** State of Sergipe, endemic area of Northeast Brazil.

16  
17 30 **Methods:** An ecological and time series study was conducted, based on secondary data  
18  
19 31 reported by the Brazilian Information System on Notifiable Diseases (SINAN) for leprosy  
20  
21 32 cases diagnosed in Sergipe state (2002-2015). The analysis of temporal trends was  
22  
23 33 performed using the Joinpoint Regression Program through Poisson regression. We  
24  
25 34 performed spatial analysis by Kernel estimator and Moran index.

26  
27 35 **Results:** The incidence rate was reduced from 6.29 to 3.78 cases per 100,000 inhabitants  
28  
29 36 in 2002 and 2015, respectively. However, Sergipe was still classified as highly endemicity  
30  
31 37 in 2015. The mean number of household contacts (HHC) examined was significantly  
32  
33 38 lower than those registered. Clinical data indicated that 21.4% of the patients developed  
34  
35 39 leprosy reactions, and 31.3% presented with some physical disability in the  
36  
37 40 multibacillary (MB) groups. Patients diagnosed by exam within the HHC presented  
38  
39 41 better indicators, such as lower percentage of leprosy reaction and physical disability.  
40  
41 42 Spatial analysis showed the most risk areas distributed on the northeast and cities  
42  
43 43 around the capital, Aracaju.

44  
45 44 **Conclusion:** The data indicate that there is a persistence of active *M. leprae* transmission  
46  
47 45 and a delay in disease detection, following a pattern of high endemicity in many  
48  
49 46 municipalities. The early detection by household contacts examination is important not  
50  
51 47 only to stop transmission but also to detect the cases in a less severe state.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 48 **Keywords:** Leprosy; Children; Epidemiology; Spatial analysis.  
4  
5  
6 49

### Strengths and limitations of this study

- This is a surveillance study that includes all notified cases of leprosy, in a State of Brazil with moderate prevalence of the disease.
- This is the first summary of leprosy cases in patients under 15 years old in Sergipe state, Northeast Brazil.
- This study was conducted using secondary data reported by SINAN and this source of data may have datasets missing.
- We also mapped the leprosy cases and physical disability in children under 15 years in areas of higher prevalence of leprosy in the general population, using geoprocessing tools.
- We compared the leprosy patient detection mode and how it affects the disease severity at diagnosis and the occurrence of leprosy reactions and physical disabilities.

## 50 INTRODUCTION

51 Leprosy is a chronic infectious disease caused by infection with *Mycobacterium leprae*  
52 [1]. This pathogen exhibits tissue tropism for phagocytes in the skin and Schwann cells  
53 within peripheral nerves and it presents a long incubation time (from 2 to 7 years) [2,3].  
54 The disease can manifest across a broad spectrum of symptoms and the diagnosis is  
55 made based on the clinical signs (cutaneous lesions with altered sensitivity and  
56 neurological lesions). Patients are then classified as multibacillary (MB) and  
57 paucibacillary (PB) for treatment purposes, according to criteria accepted by Brazilian  
58 Ministry of Health (BMH) and International Leprosy Association (ILA) [1,2,4–7].

59  
60 Despite control efforts including the widespread use of multidrug therapy (MDT), and  
61 the stabilization of the reported new case detection rate in the last few years, leprosy  
62 remains endemic in many developing countries [3–6,8–11]. In 2014, the World Health  
63 Organization (WHO) reported 213,899 new leprosy cases in 121 countries or territories  
64 [4]. Brazil ranks as the second most burdened country in the world concerning number  
65 of new cases (31,064 in 2014) and has by far the highest number of cases reported in  
66 Americas [4,12,13]. Within Brazil, the highest prevalence has been reported in the  
67 North, Northeast and Midwest regions [8,9]. The incidence of leprosy (referred as the  
68 new case detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8]. In 2013, 2,439 new  
69 cases were diagnosed in children under 15 years old in Brazil, yielding a detection rate  
70 of 5.03 per 100,000 inhabitants [4].

71  
72 Studies have demonstrated that leprosy presents higher incidence in population with:  
73 low educational degree, precarious health services and domiciliary infrastructure

1  
2  
3 74 settlements, and reduced investment in prevention and control [14–16]. Moreover, the  
4  
5 75 high incidence rate in children under 15 years is important to indicate there is early  
6  
7  
8 76 exposure of the population to the bacillus, that is associated to elevated prevalence in  
9  
10  
11 77 general population, being a good indicator of a high transmission and bad quality of the  
12  
13 78 control programs [10,12,17–20]. There is no study reporting the incidence of leprosy in  
14  
15 79 children under 15 years in Sergipe state.  
16  
17  
18 80

19  
20 81 Recently, studies mapping the occurrence of infectious diseases according to their  
21  
22 82 spatial distribution using “Geographic Information Systems (GIS)” have provided  
23  
24 83 important information for public health programs, revealing areas of priority for  
25  
26 84 interventions programs to more efficiently plan and implement control measures  
27  
28 85 [2,9,16,21–23]. The use of GIS in leprosy may allow the identification of spatial-temporal  
29  
30  
31 86 distributions and profile of incidence in defined geographical areas, this potentially  
32  
33 87 contributing to the effectiveness of interventions.  
34  
35  
36 88

37  
38  
39 89 Despite breakthroughs in the epidemiological of leprosy, further improvements in  
40  
41 90 understanding of the disease dynamics in different regions is important for the support  
42  
43 91 of health services as a means for leprosy control. Spatial analyzes studies can provide  
44  
45 92 important understanding of the transmission patterns of *M. leprae* and allow the  
46  
47 93 identification of risk factors [21,23]. The aim of this study was to describe the 1) various  
48  
49 94 clinical and epidemiological indicators of leprosy; to analyze 2) temporal trends and 3)  
50  
51 95 the spatial distribution of leprosy cases in patients under 15 years old in an endemic  
52  
53 96 area of Northeast Brazil.  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 98 **METHODS**  
4

5 99 **Study Design**  
6  
7

8 100 The source of all data from this study was the leprosy cases and the information of each  
9  
10 101 individual case notified by the health centers of the municipalities to the SINAN  
11  
12 102 (Information System on Notifiable Diseases) from the State of Sergipe, Brazil. This is an  
13  
14 103 important database of the Secretariat of Health of all States of Brazil, to report  
15  
16 104 information about sociodemographic, clinical features and the address of notifiable  
17  
18 105 diseases. Leprosy is a notifiable disease in Brazil, and as a legislative requirement, all  
19  
20 106 leprosy cases have to be notified to the SINAN, including information about social and  
21  
22 107 demographic features, clinical forms and follow-up of each patient. Sergipe is located  
23  
24 108 on the coast of Northeast Brazil. The State has 75 municipalities and the capital is  
25  
26 109 Aracaju. It has a population of 2,068,017 inhabitants and an area of 21,910,354km<sup>2</sup>,  
27  
28 110 equivalent to 0.26% of the national territory. The median population per county was  
29  
30 111 27,573.56 in 2015 [16]. Population data were obtained from the IBGE (Brazilian Institute  
31  
32 112 of Geography and Statistics), based on population estimates for the intercensus years  
33  
34 113 (2002 - 2015). An ecological and time series epidemiological study was conducted, based  
35  
36 114 on the leprosy cases reported by SINAN. The historical (from 2002 to 2015) reporting of  
37  
38 115 leprosy cases in children under 15 years old was analyzed. We also compared those data  
39  
40 116 with data in all ages and with the occurrence of physical disability. The incidence of  
41  
42 117 leprosy (referred as the new case detection rate) in Sergipe in 2010 was 18.4 per 100,000  
43  
44 118 [8].  
45  
46  
47  
48  
49  
50  
51  
52  
53

54 119

55  
56  
57 120 The clinical and epidemiologic indicators collected by Investigation and Notification  
58  
59 121 Form from SINAN, were: gender, age, ethnicity, address, operational classification (PB  
60

1  
2  
3 122 and MB), clinical form [according to the more refined Ridley-Jopling classification  
4  
5 123 [24,25], based on histopathological analyses: indeterminate leprosy (IL), true  
6  
7  
8 124 tuberculoid (TT), borderline leprosy (BL) and lepromatous leprosy (LL)], leprosy reaction  
9  
10 125 (LR), number of affected nerves, degree of physical disabilities, number of household  
11  
12  
13 126 contacts (HHC) registered and examined, and the patient detection mode.  
14

15 127

16  
17  
18 128 The parameters adopted by BMH and ILA were followed for interpreting the incidence  
19  
20 129 rate of leprosy in patients under 15 years old. As such, this is classified as: low (<0.50  
21  
22 130 cases per 100,000 inhabitants); medium (0.50 to 2.49); high (2.50 to 4.99); very high  
23  
24 131 (5.00 to 9.99) and hyperendemic ( $\geq 10.00$ ) [4].  
25  
26  
27  
28 132

### 29 30 133 **Spatial analysis**

31  
32 134 Thematic maps were constructed in each municipality for the period examined  
33  
34 135 according to the leprosy incidence rate in patients under 15 years old and in general  
35  
36 136 population, and for patients presenting with physical disability (incapacity degree 1 or  
37  
38 137 2). The kernel technique was applied to identify the intensity of the distribution of  
39  
40 138 leprosy cases in the state of Sergipe. This technique shows the statistically generated  
41  
42 139 surface density for the visual detection of hot spots, that indicates agglomeration of  
43  
44 140 cases in a spatial distribution. This is an appropriate data interpolation for application in  
45  
46 141 point location data. The point distribution was transformed into a smoothed surface and  
47  
48 142 presented as a continuous map, representing different levels of case intensity. The  
49  
50 143 amount of smoothing, that is, the width of the radius of influence was defined as 3,000  
51  
52 144 meters, since this value generated an adequate representation of the distribution of the  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 145 leprosy cases in the municipalities, minimizing the overlapping bias or the occurrence of  
4  
5  
6 146 sub distribution patterns smoothed [16,21].  
7

8 147

9  
10 148 We performed either spatial autocorrelation analysis between disease detection rates  
11  
12  
13 149 for each group. The Moran Global Index (MGI)[26] was calculated to identify clusters  
14  
15  
16 150 with risks for disease occurrence. We construct a spatial proximity matrix obtained by  
17  
18 151 the contiguity of spatial correlation. The MGI was calculated as follows:

19  
20 152 (Moran Global Index Mathematical Equation 1)

21  
22  
23 153 
$$I = \frac{[(n \sum_i \sum_j \omega_{ij} (\gamma_i - \check{y}) (\gamma_j - \check{y}))]}{[\sum_i (\gamma_i - \check{y})^2 \sum_i \sum_j \omega_{ij}]}$$
  
24 154  
25 155  
26 156

27  
28  
29 157  $\omega_{ij}$  is a contiguity matrix element ( $\omega$ );  $\gamma_i$  is the incidence rate of municipality  $i$ ;  $\gamma_j$  is the  
30  
31  
32 158 incidence rate of municipality  $j$ ;  $\check{y}$  is the mean of sample and the symbol  $n$  represents  
33  
34  
35 159 the total number of municipalities [26].  
36

37 160

38  
39 161 The MGI provides a general grouping measure and it is possible to know if there are  
40  
41  
42 162 significant differences between the analyzed areas. However, it does not indicate the  
43  
44  
45 163 clusters localization. To do that, we performed the Moran Local Index diagram [26] to  
46  
47 164 build maps and identify the areas with spatial dependence (Local Index of Spatial  
48  
49 165 Association - LISA) of the annual detection means, as follows:

50  
51 166 (Local Index of Spatial Association Mathematical Equation 2)

52  
53  
54 167

55  
56  
57 168 
$$I = \frac{n[(Z_i \sum_j \omega_{ij} Z_j)]}{(\sum_j Z_j^2)}$$
  
58 169  
59 170  
60



1  
2  
3 1714  
5 1726  
7  
8 173  $Z_i = y_i - \bar{y}$ ;  $Z_j = y_j - \bar{y}$ ;  $\omega_{ij}$  is a contiguous matrix element  $\omega$ ;  $y_i$  is the incidence rate of9  
10 174 municipality  $i$ ;  $y_j$  is the incidence rate of municipality  $j$ ;  $\bar{y}$  is the sample mean and the11  
12 175 symbol  $n$  represents the total number of cities [26]. The Moran Map was used to indicate13  
14 176 the clusters and their relationship with the neighbors. This analysis verifies the existence15  
16 177 of spatial dependence and risk patterns: Q1 (high/high) and Q2 (Low/Low), which17  
18 178 indicate municipalities with similar values between their neighbors and Q3 (high/low)19  
20 179 and Q4 (low/high) for municipalities with different values between their neighbors and21  
22 180 no spatial association. A spatial proximity matrix obtained by the contiguity criterion was23  
24 181 adopted. The level of significance was 5% and the Moran Global Index (I) varying25  
26 182 between -1 and +1, representing the spatial autocorrelation of leprosy detection rate in27  
28 183 the geographic space analyzed to identify spatial clusters and risk areas. Values between29  
30 184 0 and +1 indicate positive spatial autocorrelation (Q1 and Q2) and between -1 and 031  
32 185 negative spatial autocorrelation (Q3 and Q4) [26,27]. Both Moran Index and Kernel33  
34 186 maps were constructed using TerraView software 4.2.2.35  
36 18737  
38  
39  
40  
41  
42  
43  
44  
45 188 **Statistical analysis**46  
47 189 The crude annual incidence rates were calculated for the general population, according48  
49 190 to the population data from IBGE. For patients younger than 15 years the annual rates50  
51 191 were age-standardised, and the standard population used was the population under 1552  
53 192 years from IBGE. Demographic and clinical data were compared across the different54  
55 193 subgroups and according to operational classification and the patient detection mode.56  
57 194 Percentage, mean and standard deviation of the groups were calculated. For groups'58  
59  
60

1  
2  
3 195 comparison, we first analyze if the data followed normal distribution by the D'Agostino  
4  
5 196 and Pearson normality test, and statistical differences between the groups were  
6  
7  
8 197 determined by Mann-Whitney and Kruskal-Wallis tests. All analysis was performed  
9  
10 198 using SPSS Statistics, version 24.0. Results were considered statistically different when  
11  
12  
13 199  $p$ -values < 0.05 were obtained.

14  
15 200

16  
17 201 In order to enable trend analysis, annual incidence rate of leprosy was calculated as  
18  
19 202 dependent variables (y), and the years of the study period as the independent variables  
20  
21 203 (x). Initially, trend analysis was performed with the Joinpoint program, version 4.0.4  
22  
23 204 (Surveillance Research, National Cancer Institute, USA). This program estimates the  
24  
25 205 Annual Percentage Change (APC) of a segmented linear regression (Joinpoint  
26  
27 206 regression) and identifies inflection points. Each inflection point reflects changes in the  
28  
29 207 increase or decline of leprosy rates [27]. The joinpoint regression provided the  
30  
31 208 adjustment of a series of lines as well as their inflection points on a logarithmic scale by  
32  
33 209 means of the annual trend test. All the models were run under the same specifications.  
34  
35 210 The minimum number of observations from a joinpoint to either end of the data was 3  
36  
37 211 and the minimum number of observations between two joinpoints was 4. The maximum  
38  
39 212 number of joinpoints allowed was 2. To obtain the adjustment based on the best line of  
40  
41 213 each analyzed segment, the Monte Carlo permutation method was used as a test of  
42  
43 214 significance. From the definition of the follow-ups, the annual percentage change (APC)  
44  
45 215 and the average annual percentage change (AAPC), with their respective 95% confidence  
46  
47 216 intervals, were estimated and tested. If the occurrence of an inflection point with inverted  
48  
49 217 direction was verified, the study periods were analyzed separately. The number of  
50  
51 218 inflections used in the analysis was the result of models defined by the program itself, in  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 219 order to allow the best representation of the trend, with the lowest number of inflection  
4  
5 220 points. The result showed growth (positive APC values), reduction (APC negative values)  
6  
7  
8 221 or maintenance (APC value equal to zero) of the trend throughout the historical series  
9  
10 222 analyzed (2006-2014). Poisson regression is used to determine the number of segments  
11  
12  
13 223 required to adequately explain the relationship between two variables [27]. We  
14  
15 224 considered the points of trend change that presented p-value < 0.05.  
16  
17  
18  
19 225

### 20 21 226 **Ethical Considerations**

22  
23 227 For conducting this study, authorization was previously requested from Coordination of  
24  
25 228 Epidemiological Surveillance, Sergipe state. This project involved research on human  
26  
27  
28 229 subjects and was approved by the Ethics and Research Committee of the Federal  
29  
30 230 University of Sergipe, CAAE 0152.0.107.000-07.  
31  
32

33 231

### 34 35 232 **Patient and Public Involvement statement**

36  
37  
38 233 There was no patient and public involvement in this study. The study was based on  
39  
40 234 secondary data.  
41  
42

43 235

## 44 45 236 **RESULTS**

### 46 47 237 **Trends in reported leprosy incidence among children**

48  
49 238 The incidence of leprosy in children under 15 years has declined from 6.29 cases per  
50  
51 239 100,000 inhabitants in 2002, to 3.78 in 2015, confirmed by Joinpoint regression analyzes  
52  
53 240 (APC = -5.3 and p-value < 0.05; **Figure 1A and B**). Similarly, the leprosy incidence rate in  
54  
55 241 the general population of Sergipe decreased from 23.08 cases to 16.99 per 100,000  
56  
57  
58 242 inhabitants between 2002 and 2015 (**Figure 1A and C**). The occurrence of degree 2  
59  
60

1  
2  
3 243 physical disability, however, increased in this period (0.76 in 2002 to 1.2 in 2015,  
4  
5 244 respectively), however it is a non-significant increasing trend (APC = 2.6 and  $p$ -value =  
6  
7  
8 245 0.20; **Figure 1A and D**). The composition of leprosy cases according to the operational  
9  
10 246 classification (PB and MB) was relatively stable across this period, with majority of cases  
11  
12 247 presenting as PB (**Figure 2A**). We also observed the mean number of HHC registered  
13  
14 248 (4.65  $\pm$  2.79) was slightly, but significantly, higher than the number examined (3.66  $\pm$   
15  
16 249 3.14;  $p$ -value < 0.0001; **Figure 2B**).

250

### 251 **Demographics of childhood leprosy cases**

252 Next, we evaluated the association among clinical and epidemiological variables  
253 according to the leprosy operational classification (patients presenting as PB and MB).  
254 Patients presenting as MB or PB were in similar age to (10.5  $\pm$  2.81 and 10.07  $\pm$  3.38,  
255 respectively). Despite the extended incubation period of *M. leprae*/leprosy, six cases  
256 (1.11%) were reported in children less than one year of age. Of the 538 leprosy cases  
257 identified among children under 15 years old the majority were PB [407 (75.7%) PB and  
258 131 (24.3%) MB; **Table 1**]. When stratified on gender, however, the proportion of boys  
259 presenting with MB (63.4%) was significantly higher than presenting with PB (48.4%;  $p$ -  
260 value = 0.003). An interesting difference was observed when we calculated the ratio  
261 (PB/MB) according the ethnic groups. Among those identified as black, the ratio (43/24)  
262 was 1.79. Conversely, the ratio of white was higher 4.88 (88/18;  $p$ -value = 0.02).

263

264 As expected, the occurrence of leprosy reactions was significantly higher in MB (21.4%)  
265 than PB (4.9%;  $p$ -value < 0.0001) patients. The occurrence of degree 2 of physical  
266 disability was also higher in MB (4.6%), than in PB patients (0.74%;  $p$ -value = 0.0001).

1  
2  
3 267 Consistent with this, we observed that the mean of number of affected nerves was  
4  
5 268 higher in MB ( $0.5 \pm 1.03$ ), than PB ( $0.19 \pm 0.54$ ;  $p$ -value = 0.04).  
6  
7

8 269

### 10 270 **Impact of case detection methods on leprosy presentation**

12  
13 271 We also performed analysis of association among clinical and epidemiological variables  
14  
15 272 according to the leprosy patient detection mode. The patients were grouped in:  
16  
17 273 spontaneous demand (SDem: patients that looked for medical assistance by  
18  
19 274 themselves); forwarded (FW: patients that were forwarded from a primary clinic to a  
20  
21 275 leprosy reference center); examined HHC; and other. We observed that patients  
22  
23 276 detected by the examined HHC method presented lower mean age ( $9.6 \pm 3.38$ ) than  
24  
25 277 those detected by either the SDem ( $10.54 \pm 3.28$ ) or FW methods ( $10.02 \pm 3.15$ ;  $p$ -value  
26  
27 278 = 0.04; **Table 2**). Interestingly, the percentage of leprosy reaction among the examined  
28  
29 279 HHC group (2.9%;  $p$ -value = 0.02) was lower than that observed among SDem (7.3%) and  
30  
31 280 FW (13.3%). In addition, degree 2 of physical disability was not observed among patients  
32  
33 281 detected in examined HHC group, while SDem and FW presented 0.43% and 3.8%,  
34  
35 282 respectively ( $p$ -value = 0.04). Furthermore, patients identified among examined HHC  
36  
37 283 presented with lower numbers of lesions ( $2.04 \pm 2.96$ ;  $p$ -value = 0.04) than SDem ( $3.64$   
38  
39 284  $\pm 6.25$ ) and FW ( $4.09 \pm 8.68$ ). Taken together, these data reinforce the importance of  
40  
41 285 HHC examination for the detection of leprosy patients before advancement to more  
42  
43 286 severe symptoms.  
44  
45  
46  
47  
48  
49  
50

51 287

### 54 288 **Spatial analyze data**

56  
57 289 Next, we performed the spatial analysis of leprosy cases in the general population, in  
58  
59 290 patients under 15 years old, and in patients presenting with physical disability (both  
60

1  
2  
3 291 degree 1 and 2). Moran maps have showed higher risk clusters (Q1 - in red; **Figure 3A-**  
4  
5  
6 292 **C)** in similar areas when comparing the maps regarding leprosy cases in children under  
7  
8 293 15 years old, in general population, and patients presenting some physical disability  
9  
10 294 (degree 1 and 2). The higher risk clusters (Q1) were localized in Sergipe state center and  
11  
12  
13 295 in the metropolitan area around the capital of State. The municipalities with no spatial  
14  
15 296 association (Q3 - in blue) were localized in the Semiarid region, in the northwest area  
16  
17  
18 297 and in the south region.

19  
20 298  
21  
22 299 Similarly, The Kernel estimator, through data interpolation, showed densities (hot spots)  
23  
24  
25 300 of the highest incidence rates located at the northeast and east center regions and in  
26  
27  
28 301 the counties around the state capital (Aracaju city; **Figure 3D-F)**. Lower intensity was  
29  
30 302 observed on the western region. Municipalities with intermediate to high incidence  
31  
32 303 values are seen in yellow and red tones of each subfigure. Low incidence areas were  
33  
34  
35 304 reported on west coast municipalities, mostly in smaller counties with small  
36  
37 305 populations.

38  
39  
40 306

## 41 42 307 **DISCUSSION**

43  
44 308 Previous studies have demonstrated that the high leprosy cases detection in patients  
45  
46  
47 309 under 15 years old is a bad parameter for leprosy control program, because it indicates  
48  
49  
50 310 early bacillus transmission from undiagnosed cases [18]. Some authors have speculated  
51  
52 311 either about the risk of vertical/transplacental transmission or through breastfeeding  
53  
54 312 [12].

55  
56  
57 313  
58  
59  
60

1  
2  
3 314 In Brazil, the highest leprosy incidence rate in children was reported in the North area  
4  
5 315 (11.91 cases per 100,000 inhabitants), followed by Northeast (8.12) [12]. We observed  
6  
7  
8 316 the leprosy incidence rate was reduced in children under 15 years old from 2002 to 2015  
9  
10 317 in Sergipe state, however considering the parameters adopted by BMH, the state was  
11  
12 318 classified as very high endemicity in 2002, and still as high endemicity in 2015. It remains  
13  
14  
15 319 also with elevated incidence rate and stationary tendency of degree 2 of physical  
16  
17 320 disability. Those data reinforce either that the transmission is intense at early age, there  
18  
19 321 is lack of an effective public health and the disease control is focused in the MDT [12,18].  
20  
21  
22 322 A similar study performed at Fortaleza city (Brazil), reported also that although a  
23  
24 323 decreasing has been observed on overall detection rate, the number of new cases in  
25  
26 324 those under 15 years old remains stable [13].  
27  
28  
29 325  
30  
31  
32 326 Leprosy reactions and physical disability are the most severe leprosy clinical  
33  
34 327 complications [8,28,29]. In addition, the increase or stability of the prevalence of degree  
35  
36 328 2 of physical disability indicates persisting late diagnosis [13,29]. The early diagnosis of  
37  
38 329 leprosy is essential to the prevention of deformities, whose repercussions are still more  
39  
40 330 catastrophic in children and adolescents [28]. Our data reported 21.4% children with  
41  
42 331 leprosy reaction (LR) and 31.3% with some physical disability in the MB groups.  
43  
44  
45 332 Furthermore, MB patients presented higher mean of affected nerves. Generally,  
46  
47 333 patients under 15 years old do not use to present LR, but studies have reported a low  
48  
49 334 frequency of LR, varying between 1.36% and 8.33% [28]. Those data reinforce that,  
50  
51 335 although there is a decreasing incidence in leprosy, patients have been exposed to  
52  
53 336 bacillus early in life and diagnosed belatedly and hence they have been also developing  
54  
55  
56 337 into some clinical complications.  
57  
58  
59  
60

1  
2  
3 338  
4

5 339 We have observed either that the mean of HHC examined was significantly lower than  
6  
7  
8 340 those registered by SINAN. Moreover, leprosy patients detected by exam in HHC  
9  
10 341 presented lower mean of age, affected nerves, number of lesions, occurrence of LR and  
11  
12 342 no physical disability, when compared with those identified by spontaneous demand or  
13  
14 343 forwarded by others. On the other hand, mostly of patients presenting as degree 2 of  
15  
16 344 physical disability were identified into those forwarded to a leprosy reference center,  
17  
18 345 probably because they started presenting some physical disability. HHC and neighbors  
19  
20 346 are the most important *M. leprae* active sources. The risk of a person developing leprosy  
21  
22 347 is nine times greater among HHC and up to four times greater among contacts with  
23  
24 348 neighbors [12]. Therefore, our data reinforce the importance of leprosy early diagnosis  
25  
26 349 by exam in patients and their household contacts. Besides that, the treatment and the  
27  
28 350 home visits by public health programs, and an efficient health program in schools could  
29  
30 351 represent important actions for the early diagnosis and the reduction of leprosy clinical  
31  
32 352 complications, especially in children.  
33  
34  
35  
36  
37  
38  
39

40 353

41  
42 354 Spatial analysis of health events aim to identify geographical patterns by maps of risk  
43  
44 355 and to point out areas of higher severity and to facilitate the planning of public health  
45  
46 356 interventions [9]. The Kernel maps showed the spatial dynamic of leprosy, with a  
47  
48 357 heterogeneous geographical pattern and the highest risk areas for leprosy infection. The  
49  
50 358 highest incidence on counties around the Capital can be due there was a leprosarium at  
51  
52 359 the Nossa Senhora do Socorro (a city of the metropolitan area of Aracaju), that has  
53  
54 360 presented elevated detection rate in mostly evaluated years. Moreover, that area  
55  
56 361 presents reference center to leprosy diagnosis and treatment and hence they have  
57  
58  
59  
60



1  
2  
3 362 several patients forwarded to these leprosy clinics. It can be also associated with  
4  
5 363 weather featuring such as humidity, considering either that counties near to São  
6  
7  
8 364 Francisco River presented also elevated incidence. In the Malawian Karonga district, a  
9  
10 365 positive relationship between the proximity of water and leprosy incidence was  
11  
12  
13 366 previously reported [5]. Some authors have hypothesized that *M. leprae* survives longer  
14  
15 367 outside of human body in humid compared to dry atmospheres [9,13].  
16  
17

368

18  
19  
20 369 Interestingly, higher risk clusters were identified in similar areas when we analyzed the  
21  
22  
23 370 occurrence of leprosy cases in children, in general population and patients presenting  
24  
25 371 physical disability. It corroborates the hypothesis that the early transmission of *M.*  
26  
27  
28 372 *leprae* and the occurrence of leprosy in children under 15 years old is directly related to  
29  
30 373 the late diagnosis, which explains the occurrence of patients with degree 2 of physical  
31  
32  
33 374 disability in the same geographic distribution [28]. The maps present certain  
34  
35 375 disagreements regarding the occurrence of leprosy cases in the state of Sergipe because  
36  
37 376 they use distinct techniques of spatial analysis. The Kernel estimator produces a  
38  
39  
40 377 continuous surface, with densities calculated at all locations, based on total number of  
41  
42  
43 378 cases and no considering the geographical boundaries of the municipalities [27,30,31].  
44  
45 379 The Kernel technique presents greater advantages to the quick visualization of areas  
46  
47 380 that deserve attention, besides not being affected by political-administrative division,  
48  
49  
50 381 while the Moran technique, constructs maps considering the political-administrative  
51  
52 382 divisions of the state and the clusters are based on the number of cases divided by the  
53  
54 383 municipalities [27,30].  
55

384

1  
2  
3 385 Our study had some limitations, particularly because it was conducted using secondary  
4  
5 386 data reported by SINAN. This source of data can present numbers under notification and  
6  
7  
8 387 datasets missing. However, in Brazil we have a specific normative that is an obligation  
9  
10 388 to notify several diseases to SINAN, and leprosy is one of them. SINAN is an important  
11  
12 389 database of the Secretariat of Health of all States of Brazil, to report information about  
13  
14 390 sociodemographic, clinical features and the address of each diagnosed case. This source  
15  
16 391 of data can present under notification because Leprosy is an asymptomatic disease and  
17  
18 392 the active search would be important to detect more cases, but all diagnosed cases are  
19  
20 393 reported to SINAN. The limitation mentioned about missing data is not very important  
21  
22 394 in the case of the disease prevalence, but the complete information about the cases  
23  
24 395 follow-up, such as degree of neurological disability at the end of treatment, leprosy  
25  
26 396 reactions and treatment details, because it is a secondary database that depends on  
27  
28 397 other doctors or nurses from the health care centers to fulfill the information. Despite  
29  
30 398 this, those data reported high endemicity of leprosy cases in patients under 15 years  
31  
32 399 old, and this study do not focus on patient follow-up.  
33  
34  
35  
36  
37  
38  
39  
40  
41

400

42 401 In summary, our study demonstrated that the leprosy incidence rate has decreased in  
43  
44 402 Sergipe state. However, it is still classified as high endemicity considering the WHO  
45  
46 403 proposed ratios for children under 15 years. Patients detected by exam in collectivity or  
47  
48 404 HHC presented better indicators. Altogether, the epidemiological data and spatial  
49  
50 405 analysis indicate that there is persistence of active transmission of *M. leprae* and later  
51  
52 406 case detection in Sergipe state, increasing the risk of transmission in children. In  
53  
54 407 addition, the spatial analysis brings new advantages to comprehend the leprosy  
55  
56 408 dynamic, and reinforce the superimposed regions of high occurrence areas of patients  
57  
58  
59  
60

1  
2  
3 409 presenting degree 2 of physical disability and cases in children lower than 15 years, and  
4  
5 410 highlights the need to strengthen effective disease control measures, mainly in primary  
6  
7  
8 411 health care.

9  
10 412 **Acknowledgments** The authors would like to thank the Manager of the Nucleus of  
11  
12  
13 413 endemic/Division of Epidemiological Surveillance - [Divisão de Vigilância  
14  
15 414 Epidemiológica (DIVEP)]/ Secretariat of Health of the Sergipe state (SES) for providing  
16  
17 415 information.

18  
19  
20  
21 416 **Funding** This research received no specific grant from any funding agency in the public,  
22  
23 417 commercial or not-for-profit sectors.

24  
25  
26 418 **Contributors** The project was suggested by MB-S, MA, JB and AS. The statistical analyzes  
27  
28 419 was performed by MB-S, IB, JS and AJ. The spatial analyzes was performed by MS, AS,  
29  
30 420 AB and KA. The manuscript was written by MB-S, AB, DO, MD and AJ. All authors  
31  
32 421 contributed to refining the idea, revising the manuscript and have agreed the final  
33  
34 422 version.

35  
36  
37  
38 423 **Competing interests** The authors declare that they have no conflicts of interest.

39  
40 424 **Provenance and peer review** Not commissioned; externally peer reviewed.

41  
42  
43 425 **Data sharing statement** The source of all data from this study was the leprosy cases and  
44  
45 426 the information of each individual case notified by the health centers of the  
46  
47 427 municipalities to the SINAN (Information System on Notifiable Diseases) from the State  
48  
49 428 of Sergipe, Brazil. SINAN is an important database of the Secretariat of Health of all  
50  
51 429 States of Brazil, to report information about sociodemographic, clinical features and the  
52  
53 430 address of notifiable diseases, such as leprosy.

54  
55  
56  
57 431  
58  
59  
60 432

433

434 **References**

435

- 436 1 Simon M, Scherlock J, Duthie MS, *et al.* Clinical, immunological, and genetic  
437 aspects in leprosy. *Drug Dev Res* 2011;**72**:509–27. doi:10.1002/ddr.20457
- 438 2 Duarte-Cunha M, Marcelo da Cunha G, Souza-Santos R. Geographical  
439 heterogeneity in the analysis of factors associated with leprosy in an endemic  
440 area of Brazil: are we eliminating the disease? *BMC Infect Dis* 2015;**15**:196.  
441 doi:10.1186/s12879-015-0924-x
- 442 3 Fulton N, Anderson LF, Watson JM, *et al.* Leprosy in England and Wales 1953-  
443 2012: Surveillance and challenges in low incidence countries. *BMJ Open*  
444 2016;**6**:15–8. doi:10.1136/bmjopen-2015-010608
- 445 4 Freitas LRS, Duarte EC, Garcia LP, *et al.* Trends of main indicators of leprosy in  
446 Brazilian municipalities with high risk of leprosy transmission, 2001–2012. *BMC*  
447 *Infect Dis* 2016;**16**:472. doi:10.1186/s12879-016-1798-2
- 448 5 Duthie MS, Saunderson P, Reed SG. The potential for vaccination in leprosy  
449 elimination: New tools for targeted interventions. *Mem Inst Oswaldo Cruz*  
450 2012;**107**:190–6. doi:10.1590/S0074-02762012000900027
- 451 6 Duthie MS, Gillis TP, Reed SG. Advances and hurdles on the way toward a  
452 leprosy vaccine. *Hum Vaccin* 2011;**7**:1172–83. doi:10.4161/hv.7.11.16848
- 453 7 Kumar A, Girdhar A, Girdhar BK. Six months fixed duration multidrug therapy in

- 1  
2  
3 454 paucibacillary leprosy: Risk of relapse and disability in Agra PB cohort study. *BMJ*  
4  
5 455 *Open* 2012;**2**:1–6. doi:10.1136/bmjopen-2012-001403  
6  
7  
8  
9 456 8 de Oliveira DT, Bezerra MM, de Almeida JAP, *et al.* Neurological disability in  
10  
11 457 leprosy: Incidence and gender association in Sergipe, Brazil. *Geospat Health*  
12  
13 458 2012;**6**. doi:10.4081/gh.2012.130  
14  
15  
16  
17 459 9 Alencar CH, Ramos AN, dos Santos ES, *et al.* Clusters of leprosy transmission and  
18  
19 460 of late diagnosis in a highly endemic area in Brazil: Focus on different spatial  
20  
21 461 analysis approaches. *Trop Med Int Heal* 2012;**17**:518–25. doi:10.1111/j.1365-  
22  
23 462 3156.2011.02945.x  
24  
25  
26  
27 463 10 Durrheim DN, Speare R. Global leprosy elimination: Time to change more than  
28  
29 464 the elimination target date. *J Epidemiol Community Health* 2003;**57**:316–7.  
30  
31 465 doi:10.1136/jech.57.5.316  
32  
33  
34  
35  
36 466 11 Barth-Jaeggi T, Steinmann P, Mieras L, *et al.* Leprosy Post-Exposure Prophylaxis  
37  
38 467 (LPEP) programme: Study protocol for evaluating the feasibility and impact on  
39  
40 468 case detection rates of contact tracing and single dose rifampicin. *BMJ Open*  
41  
42 469 2016;**6**. doi:10.1136/bmjopen-2016-013633  
43  
44  
45  
46 470 12 Santos SD, Penna GO, Costa M da CN, *et al.* Leprosy in children and adolescents  
47  
48 471 under 15 years old in an urban centre in Brazil. *Mem Inst Oswaldo Cruz*  
49  
50 472 2016;**111**:359–64. doi:10.1590/0074-02760160002  
51  
52  
53  
54 473 13 Brito AL, Monteiro LD, Ramos Junior AN, *et al.* Tendência temporal da  
55  
56 474 hanseníase em uma capital do Nordeste do Brasil: epidemiologia e análise por  
57  
58 475 pontos de inflexão, 2001 a 2012. *Rev Bras Epidemiol* 2016;**19**:194–204.  
59  
60

- 1  
2  
3 476 doi:10.1590/1980-5497201600010017  
4  
5  
6 477 14 Vieira GDD, Aragoso I, Carvalho RMB, *et al.* Hanseníase em Rondônia: incidência  
7  
8 e características dos casos notificados, 2001 a 2012. *Epidemiol e Serviços Saúde*  
9 478  
10 2014;**23**:269–75. doi:10.5123/S1679-49742014000200008  
11 479  
12  
13  
14 480 15 Queir??s MI, Ramos AN, Alencar CHM, *et al.* Clinical and epidemiological profile  
15  
16 of leprosy patients attended at Cear??, 2007-2011. *An Bras Dermatol*  
17 481  
18 2016;**91**:311–7. doi:10.1590/abd1806-4841.20164102  
19 482  
20  
21  
22 483 16 dos Santos AD, Lima ACR, Santos MB, *et al.* Spatial analysis for the identification  
23  
24 of risk areas for schistosomiasis mansoni in the state of Sergipe, Brazil, 2005-  
25 484  
26 2014. *Rev Soc Bras Med Trop* 2016;**49**:608–15. doi:10.1590/0037-8682-0137-  
27 485  
28 2016  
29 486  
30  
31  
32  
33 487 17 Alencar CHM De, Barbosa JC, Ramos Jr AN, *et al.* Hanseníase no município de  
34  
35 Fortaleza, CE, Brasil: aspectos epidemiológicos e operacionais em menores de  
36 488  
37 15 anos (1995-2006). *Rev Bras Enferm* 2008;**61**:694–700. doi:10.1590/S0034-  
38 489  
39 71672008000700007  
40 490  
41  
42  
43  
44 491 18 Pires CAA, Malcher CMSR, Abreu JMC, *et al.* Hanseníase em menores de 15  
45  
46 anos: A importância do exame de contato. *Rev Paul Pediatr* 2012;**30**:292–5.  
47 492  
48 doi:10.1590/S0103-05822012000200022  
49 493  
50  
51  
52 494 19 Carlos F, Lana F, Amaral EP, *et al.* Hanseníase em menores de 15 anos no Vale  
53  
54 do Jequitinhonha, Minas Gerais, Brasil. *Rev Bras Enferm* 2007;**60**:696–700.  
55 495  
56 doi:10.1590/S0034-71672007000600014  
57 496  
58  
59  
60 497 20 Fernandes C, Gonçalves HS, Cabral PB, *et al.* Increased frequency of CD4 and

- 1  
2  
3 498 CD8 regulatory T cells in individuals under 15 years with multibacillary leprosy.  
4  
5 499 *PLoS One* 2013;**8**. doi:10.1371/journal.pone.0079072  
6  
7  
8  
9 500 21 Barreto AS, Alves B. ORIGINAL ARTICLE SPATIAL ANALYSIS AND  
10  
11 501 EPIDEMIOLOGICAL CHARACTERISTICS OF CASES OF LEPROSY IN AN ENDEMIC  
12  
13 502 AREA. *J Nurs UFPE* 2016;**10**. doi:10.5205/reuol.9881-87554-1-EDSM1011201604  
14  
15  
16  
17 503 22 Khan O, Davenhall W, Ali M, *et al*. Geographical information systems and  
18  
19 504 tropical medicine. *Ann Trop Med Parasitol* 2010;**104**:303–18.  
20  
21 505 doi:10.1179/136485910X12743554759867.Geographical  
22  
23  
24  
25 506 23 Fischer E, Pahan D, Chowdhury S, *et al*. The spatial distribution of leprosy in four  
26  
27 507 villages in Bangladesh: an observational study. *BMC Infect Dis* 2008;**8**:125.  
28  
29 508 doi:10.1186/1471-2334-8-125  
30  
31  
32  
33 509 24 Ridley DS JW. Classification of leprosy according to immunity. A five-group  
34  
35 510 system. *Int J Lepr Other Mycobact Dis* 1966;**34**:255–73.  
36  
37 511 doi:10.1126/science.1238286  
38  
39  
40  
41 512 25 Lockwood DNJ, Sarno E, Smith WC. Classifying leprosy patients--searching for  
42  
43 513 the perfect solution. *Lepr Rev* 2007;**78**:317–20.  
44  
45  
46  
47 514 26 Chen Y. New Approaches for Calculating Moran's Index of Spatial  
48  
49 515 Autocorrelation. *PLoS One* 2013;**8**. doi:10.1371/journal.pone.0068336  
50  
51  
52  
53 516 27 Goes JAP, Souza DDG, Andrade LA, *et al*. Trend and spatial analysis of prostate  
54  
55 517 cancer mortality in the state of Sergipe, Brazil. *Geospat Health* 2018;**13**.  
56  
57 518 doi:10.4081/gh.2018.732  
58  
59  
60

- 1  
2  
3 519 28 de Oliveira MBB, Diniz LM. Leprosy among children under 15 years of age:  
4  
5 520 Literature review. *An Bras Dermatol* 2016;**91**:196–203. doi:10.1590/abd1806-  
6  
7 521 4841.20163661  
8  
9  
10  
11 522 29 Kumar A, Girdhar A, Kumar Girdhar B. Risk of developing disability in pre and  
12  
13 523 post-multidrug therapy treatment among multibacillary leprosy: Agra MB  
14  
15 524 Cohort study. *BMJ Open* 2012;**2**:1–7. doi:10.1136/bmjopen-2011-000361  
16  
17  
18  
19 525 30 dos Santos AD, Lima ACR, Santos MB, *et al.* Spatial analysis for the identification  
20  
21 526 of risk areas for schistosomiasis mansoni in the state of Sergipe, Brazil, 2005-  
22  
23 527 2014. *Rev Soc Bras Med Trop* 2016;**49**. doi:10.1590/0037-8682-0137-2016  
24  
25  
26  
27 528 31 Santos MB, dos Santos AD, da Silva PP, *et al.* Spatial analysis of viral hepatitis  
28  
29 529 and schistosomiasis coinfection in an endemic area in Northeastern Brazil. *Rev*  
30  
31 530 *Soc Bras Med Trop* 2017;**50**. doi:10.1590/0037-8682-0411-2016  
32  
33  
34  
35

36 **Table 1. Association of demographic and clinical data according to the operational**  
37 **classification of leprosy (PB and MB) in children under 15 years in Sergipe state,**  
38 **Brazil (2002-2015).**  
39  
40  
41  
42  
43  
44

Variables	Operational Classification		p-value
	PB (n = 407)	MB (n = 131)	
Age mean ± SD	10.07 ± 3.38	10.5 ± 2.81	*0.46
Gender n (%)			
Male	197 (48.4)	83 (63.4)	+0.003
Ethnicity n (%)			
White	88 (21.6)	18 (13.7)	#0.02



Black	43 (10.5)	24 (18.3)	
Brown	251 (61.7)	78 (59.5)	
Indian	4 (0.9)	3 (2.3)	
<b>Leprosy reaction n (%)</b>	20 (4.9)	28 (21.4)	<sup>†</sup> <0.0001
<b>Physical Disability</b>			
<b>Degree n (%)</b>			
0	337 (82.8)	90 (68.7)	<sup>#</sup> 0.0001
1	26 (6.4)	18 (13.7)	
2	3 (0.74)	6 (4.6)	
<b>Number of affected nerves (mean ± SD)</b>	0.19 ± 0.54	0.5 ± 1.03	*0.04
<b>Number of Lesions (mean ± SD)</b>	1.61 ± 1.14	9.92 ± 12.03	*<0.0001
<b>HHC registered (mean ± SD)</b>	4.6 ± 2.71	4.85 ± 3.04	*0.14
<b>HHC examined (mean ± SD)</b>	3.54 ± 3.04	4.05 ± 3.44	

534 \*Mann-Whitney test; <sup>†</sup>Fisher's exact test; <sup>#</sup>Chi-square test. PB = paucibacillary; MB = multibacillary; HHC  
 535 = household contacts; SD = Standard Deviation. We missed data in some variables.

536

537 **Table 2. Demographic and clinical aspects accordingly to the detection mode of leprosy**  
 538 **cases in children under 15 years in Sergipe state, Brazil (2002-2015).**

539

Variables	Patient detection mode				p-value
	Spontaneous demand (n = 234)	Forwarding (n = 210)	Examined HHC (n = 69)	Other (n = 25)	
Age mean ± SD	10.54 ± 3.28	10.02 ± 3.15	9.6 ± 3.38	9.6 ± 3.22	*0.04
Gender n (%)					
Male	123 (52.6)	110 (52.4)	38 (55.1)	09 (36)	#0.41
Leprosy reaction n (%)	17 (7.3)	28 (13.3)	2 (2.9)	1 (4.0)	#0.02
Physical disability degree n (%)					
0	199 (85.1)	150 (71.4)	55 (79.7)	18 (72)	#0.04
1	17 (7.3)	21 (10)	5 (7.2)	1 (4.0)	
2	1 (0.43)	08 (3.8)	0 (0.0)	0 (0.0)	
Number of affected nerves (mean ± SD)	0.24 ± 0.67	0.34 ± 0.81	0.06 ± 0.25	0.25 ± 0.5	*0.48
Number of lesion (mean ± SD)	3.64 ± 6.25	4.09 ± 8.68	2.04 ± 2.96	4 ± 5.2	*0.04
HHC registered (mean ± SD)	4.57 ± 2.53	4.59 ± 2.74	5.57 ± 3.81	3.45 ± 1.96	*0.04
HHC examined (mean ± SD)	3.71 ± 3.02	3.02 ± 2.98	4.64 ± 4.06	2.04 ± 1.77	*0.01

540 \*Kruskal-Wallis test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC = household contacts;

541 SD = Standard Deviation. We missed data in some variables.

542

1  
2  
3 543 **Figure 1. Leprosy incidence rates and temporal trend in state of Sergipe, Northeast**  
4  
5 544 **Brazil, 2002-2015.** A) Leprosy incidence rate (per 100,000 inhabitants) in general  
6  
7 545 population (▲), in patients under 15 years old (■), degree 2 of physical disability (◆)  
8  
9 546 and the tendency line. Temporal trend of standardized incidence rates by Joinpoint  
10  
11 547 Regression for B) patients under 15 years old, C) General population and D) incapacity  
12  
13 548 degree. Data were considered statistically different when p-value < 0.05. CI: Confidence  
14  
15 549 Interval.

16  
17  
18  
19  
20  
21  
22  
23 551 **Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state**  
24  
25 **of Sergipe, Brazil, 2002-2015.** A) Number of leprosy cases according to the clinical  
26  
27 552 operational classification (Paucibacillary - PB (■) and Multibacillary – MB (■) forms). B)  
28  
29 553 Mean and standard deviation (mean ± SD) of the number of household contacts (HHC)  
30  
31 554 that were registered and examined for leprosy diagnosis. Data were considered  
32  
33 555 statistically different when p-value < 0.05. \* Mann-Whitney test.

34  
35  
36  
37  
38  
39  
40  
41 558 **Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were**  
42  
43 559 **constructed by TerraView Software 4.2.2.** The Moran Global Index (\*MGI) was  
44  
45 560 calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of  
46  
47 561 leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy  
48  
49 562 cases in the general population. Moran (E) and Kernel (F) maps of occurrence of  
50  
51 563 incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 – 2015).

52  
53  
54  
55 564

56  
57  
58  
59 565  
60

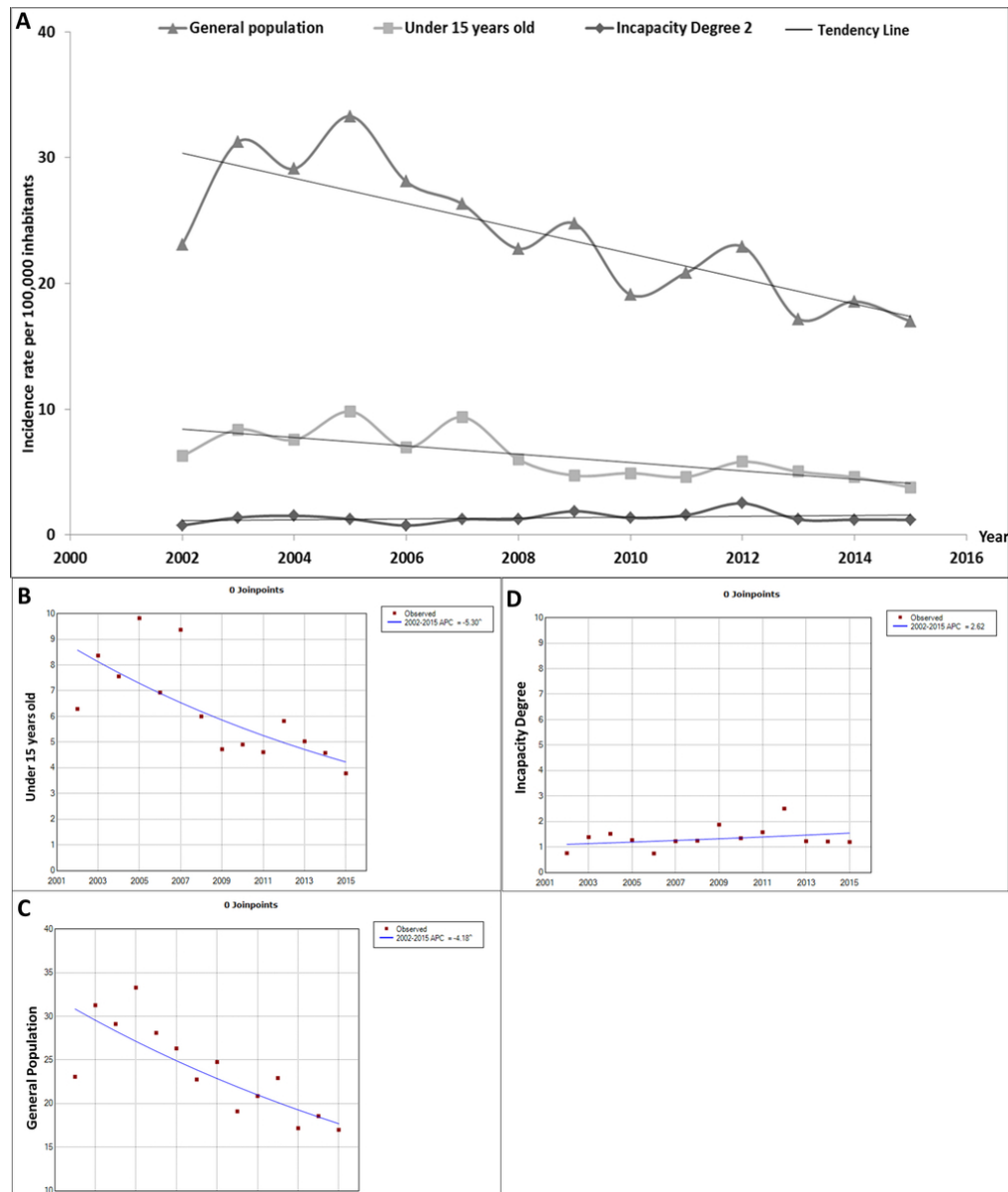


Figure 1. Leprosy incidence rates and temporal trend in state of Sergipe, Northeast Brazil, 2002-2015. A) Leprosy incidence rate (per 100,000 inhabitants) in general population (□), in patients under 15 years old (□), degree 2 of physical disability (□) and the tendency line. Temporal trend of standardized incidence rates by Joinpoint Regression for B) patients under 15 years old, C) General population and D) incapacity degree. Data were considered statistically different when p-value < 0.05. CI: Confidence Interval.

85x101mm (300 x 300 DPI)

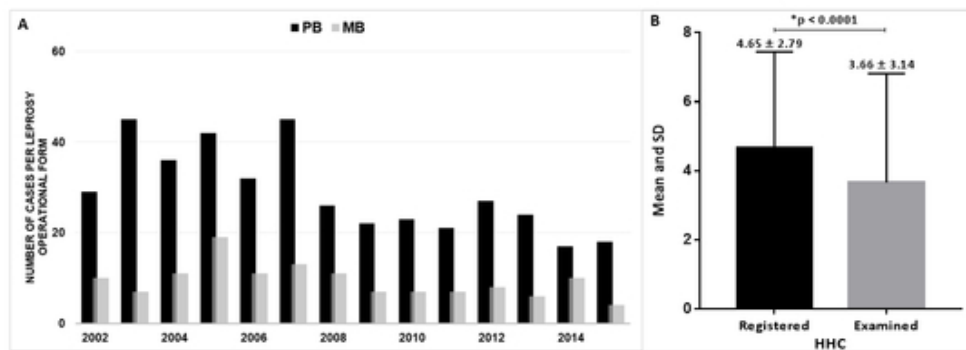


Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Number of leprosy cases according to the clinical operational classification (Paucibacillary - PB (□) and Multibacillary - MB (□) forms). B) Mean and standard deviation (mean ± SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. \* Mann-Whitney test.

46x18mm (300 x 300 DPI)

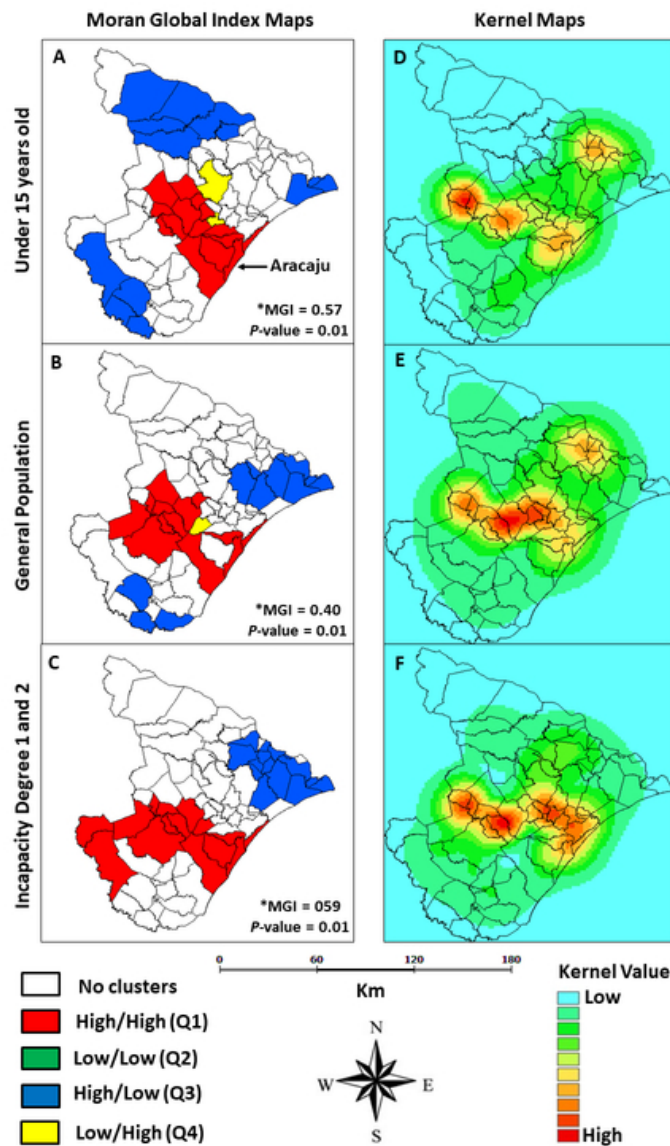


Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were constructed by TerraView Software 4.2.2. The Moran Global Index (\*MGI) was calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy cases in the general population. Moran (E) and Kernel (F) maps of occurrence of incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 - 2015).

48x64mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies***

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	01
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	02
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	04-05
Objectives	3	State specific objectives, including any prespecified hypotheses	05
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	06
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	06
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	06
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	06
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	06-07
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	06
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	06-08
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	08-09
		(b) Describe any methods used to examine subgroups and interactions	08-09
		(c) Explain how missing data were addressed	08-09
		(d) If applicable, describe analytical methods taking account of sampling strategy	08-09
		(e) Describe any sensitivity analyses	08-09
<b>Results</b>			08-09

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	09
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	09-10
		(b) Indicate number of participants with missing data for each variable of interest	--
Outcome data	15*	Report numbers of outcome events or summary measures	09-10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(b) Report category boundaries when continuous variables were categorized	--
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	09-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).