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Exploring spatial variation in BCG vaccination among children 0–35 months in Ethiopia: spatial analysis of Ethiopian Demographic and Health Survey 2016

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ABSTRACT

Objective Tuberculosis is a major public health problem and is the second leading cause of death worldwide. BCG vaccination is a life-saving and important part of standard tuberculosis control measures, particularly in Ethiopia where tuberculosis is endemic. The End Tuberculosis Strategy targets of 2020 have not been achieved. Exploring spatial variations in BCG vaccination among children is vital to designing and monitoring effective intervention programmes. Therefore, this study aimed to explore the spatial variation in BCG vaccination among children in Ethiopia.

Design Cross-sectional study design.

Setting Ethiopia.

Participants Children aged 0–35 months.

Primary outcome BCG vaccination coverage.

Methods Data from the 2016 Ethiopian Demographic and Health Survey were used and a total of 4453 children aged 0–35 months were included. Spatial autocorrelation analysis, cluster and outlier analysis, hotspot analysis, spatial interpolation, and spatial scan statistics were carried out to identify geographical risk areas for BCG vaccine utilisation. ArcGIS V.10.6 and SaTScan V.9.6 statistical software were employed to explore spatial pattern and significant hotspot areas for BCG vaccination among children.

Results BCG vaccination was spatially clustered in Ethiopia at the regional level (Global Moran's I=0.516, p<0.001). A total of 51 most likely clusters of low BCG vaccination were identified in the Somali and Afar regions (log-likelihood ratio=136.58, p<0.001). Significant secondary clusters were also identified in North West Gambela, South Amhara, South West Addis Ababa, North East Southern Nations, Nationalities, and People's Region, and South West Oromia.

Conclusion A low probability of receiving BCG vaccination was found among children in the Somali and Afar regions. Therefore, these areas should be given attention when designing effective immunisation strategies to improve BCG vaccination among children in order to reduce the burden of tuberculosis in Ethiopia.

Strengths and limitations of this study

- A strength of this study is that it was based on nationally representative weighted data and can be generalised at the national level.
- A limitation of this study is that data were collected at a point in time, and these data are survey data with different limitations, for example, missing data on BCG vaccination status.
- Other limitations include missing data on global positioning system coordinates, inaccuracies in vaccine cards and/or parental recall, and displacement of data for privacy reasons.
- The SaTScan analysis detects only circular clusters, and irregularly shaped clusters were not detected.

BACKGROUND

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* and is a major public health problem accounting for high morbidity and mortality. TB usually affects the lungs (pulmonary TB), but can also affect other sites (extrapulmonary TB).[1]

Globally, according to the WHO, there were an estimated 10 million TB incident cases in 2017, and among these children accounted for 1 million cases.[2] A high number of TB-related deaths were also recorded, which was around 1.6 million. TB is the second leading cause of mortality worldwide,[2] and BCG is the only accessible vaccine to fight TB and is the most universally used vaccine in the world.[3 4] Even though the BCG vaccine was introduced in Ethiopia 10 years ago, TB is at the top 9 of the high-burden cases in the country.[5] The efficacy of BCG against pulmonary TB has been determined, and BCG vaccination is a life-saving and important part of standard TB control measures, particularly in low-income countries where TB is endemic.[6 7] A systematic review and meta-analysis showed that BCG vaccine prevents disseminated childhood TB and protects against *M. tuberculosis* infection, and among infected children BCG reduces disease progression by 58%.[8] Evidence also indicated that BCG provides some protection against leprosy[9] and malaria among under-5

children.[10] Even though children were a vulnerable group for TB, childhood vaccination in Ethiopia is low and varies from setting to setting. TB also remains a highly infectious disease and accounts for a high mortality rate.[11] The End Tuberculosis Strategy determined the targets for 2020: 35% reduction in TB deaths and 90% reduction in TB incidence worldwide. Even though the annual rate is declining, the target still has not been achieved. The annual incidence of TB is 192 per 100 000 population and the annual death due to TB is 26 per 100 000 in 2015 in Ethiopia.[12] Furthermore, the burden of TB in Ethiopia varies across different geographical locations,[13 14] which might be due to regional variations with regard to immunisation coverage during infancy. Full immunisation coverage can be affected by the mother's education, place of delivery and access to information from the media.[15] Industrialised geographical regions, family characteristics and healthcare organisations can also affect BCG vaccination coverage.[16] Therefore, to decrease the incidence of TB in different settings, policies and programmes for TB control should account for the spatial heterogeneity in BCG vaccination.

In different sub-Saharan African countries including Ethiopia, there is variation with regard to vaccination coverage. This leads to weakened herd immunity and unequal disease risk.[17] The rate of incomplete immunisation is also high in different regions of Ethiopia and there are different hotspot areas with incomplete immunisation.[18]

To our knowledge, the risk (hotspot) areas for BCG vaccination coverage among children aged 0–35 months have not been identified in Ethiopia. Identifying geographical variations in BCG vaccination is very important to prioritise and design targeted prevention and intervention programmes to improve BCG vaccination coverage at the national level.

METHODS

Study design, setting and period

The Ethiopian Demographic and Health Survey (EDHS) is a community-based cross-sectional study conducted from 18 January to 27 June 2016. The study is conducted in Ethiopia, which has two administrative cities (Addis Ababa and Dire Dawa) and nine regional states (Tigray, Amhara, Afar, Oromia, Benishangul-Gumuz, Gambela, Harari, Somali, and Southern Nations, Nationalities, and People's Region (SNNPR)). Ethiopia is an agricultural country, which accounts for 43% of the gross domestic product. More than 80% of the country's total population live in the regional states of Amhara, Oromia and SNNPR.[19]

Ethiopia is the 13th in the world and 2nd in Africa as the most populous country. Currently, Ethiopia follows three tiers of health systems: primary healthcare (primary hospital, health centre, health post, primary clinic and medium clinic), secondary healthcare (general hospital, specialty clinic and specialty centre) and tertiary healthcare (specialised hospital). The number of hospitals varies from region to region in response, partly, to differences in population size. The most populous region, Oromia, has 30 hospitals. The other two predominant regions, Amhara and SNNPR, have 19 and 20 hospitals, respectively, while Tigray, the fourth most populous region, has 16 hospitals. Gambela has only one hospital and Benishangul-Gumuz has two hospitals.[20]

Sample population and variable measurement

The EDHS used a stratified two-stage cluster sampling technique selected in two stages using the 2007 Population and Housing Census (PHC) as the sampling frame. Stratification was achieved by separating each region into urban and rural areas. In total, 21 sampling strata were created, since the Addis Ababa region is entirely urban. In the first stage, 645 survey clusters (202 in the urban area) were selected with probability proportional to the survey cluster size and with independent selection in each sampling stratum. In the second stage, because time has passed since the PHC, a complete household listing operation was carried out in all selected survey clusters before the start of field work, and on average 28 households were systematically selected. Finally, 18 008 households and 4453 children were included in the analysis. The detailed sampling procedure is presented in the full EDHS 2016 report.[19] Children's vaccination status was categorised into vaccinated or not vaccinated. Vaccinated children are children who had evidence of BCG vaccination on their card, whereas unvaccinated children are children with no evidence of vaccination. The proportion of unvaccinated children was used for further spatial analysis.

The geographical coordinates XY data (latitude and longitude coordinates) were also taken from selected enumeration areas in each survey. The survey data sets and location data were accessed through the international Demographic and Health Survey Program website after justifying the purpose of data access and after being deemed an authorised user.

Spatial data analysis

Data on coordinates and weighted frequency of outcome variable with cluster numbers were extracted and merged in STATA V.14 and exported to Excel. Survey clusters with missing longitude and latitude data were dropped. ArcGIS V.10.6 was used for analysis. Among the 645 survey clusters, 2 were not included initially from the Demographic and Health Survey coordinates file. Of the 643 survey clusters, 622 were included in our analysis; the remaining 21 survey clusters were excluded due to missing global positioning system (GPS) cells. The spatial autocorrelation indicated that the pattern of BCG vaccination in this study area was dispersed, clustered or randomly distributed. The Global Moran's I spatial statistics were used to measure spatial autocorrelation by taking the entire data set and producing a single output value that ranges from −1 to +1. Global Moran's I values close to −1 indicate dispersed BCG vaccination coverage,

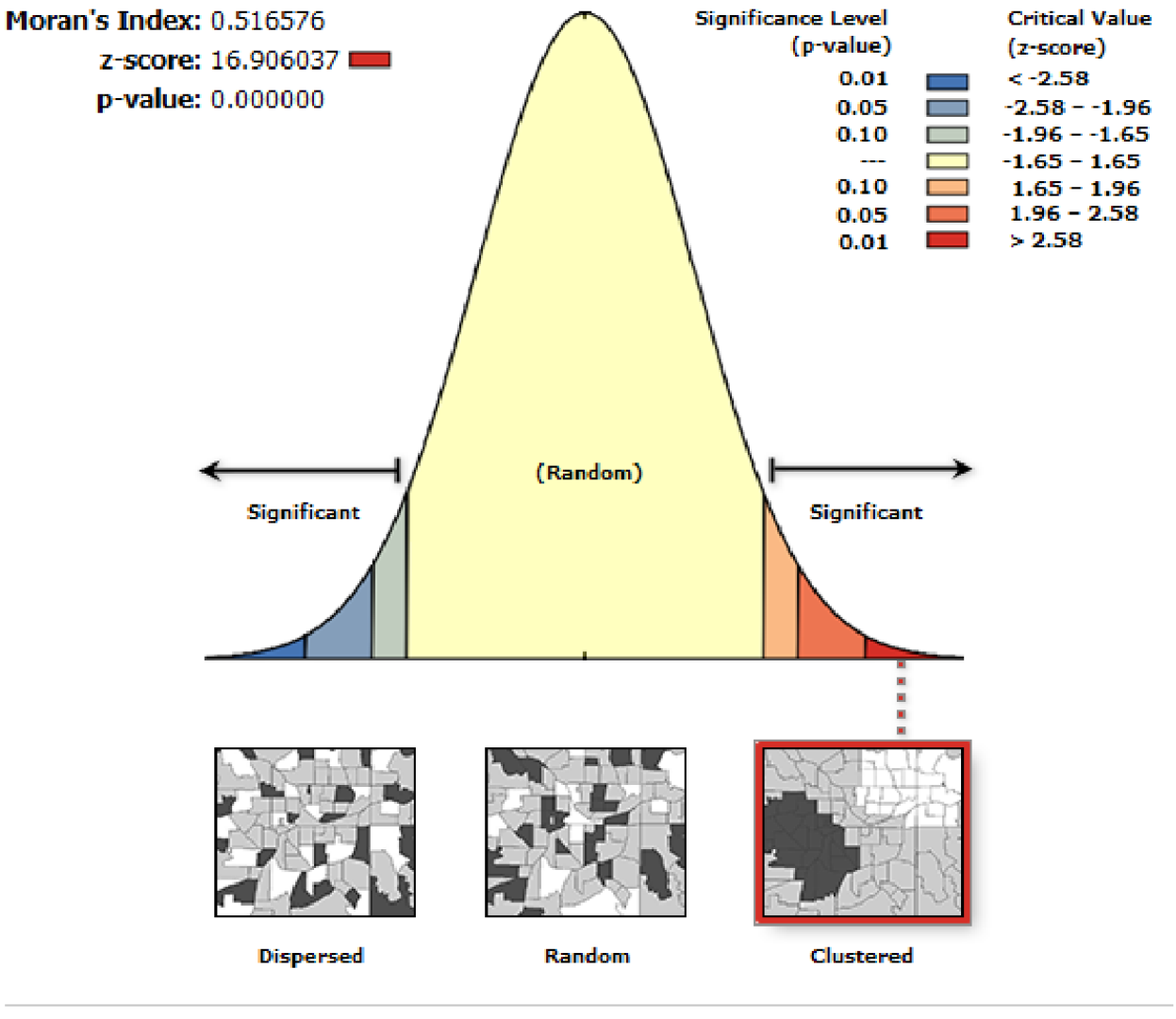

Figure 1 Spatial autocorrelation analysis of BCG vaccination among children aged 0–35 months.

whereas Moran's I values close to +1 indicate clustered BCG vaccination coverage, and an I value of 0 indicates randomly distributed BCG vaccination coverage. A statistically significant Global Moran's I ($p<0.05$) leads to rejection of the null hypothesis (BCG vaccination coverage is randomly distributed) and indicates the presence of spatial autocorrelation.

Cluster and outlier analysis

Local Moran's I measures whether there were correlated (low coverage BCG vaccination–low coverage BCG vaccination) and low–low (high coverage BCG vaccination–high coverage BCG vaccination) clusters, or negatively correlated (low coverage BCG vaccination–high coverage BCG vaccination) and high coverage (BCG vaccination–low coverage BCG vaccination) clusters of high values (low coverage BCG vaccination–low coverage BCG vaccination) and clusters of low values (high coverage BCG vaccination–high coverage BCG vaccination). It also measures an outlier where a low coverage BCG vaccination is surrounded primarily by high coverage BCG vaccination, and an outlier where a high coverage BCG vaccination is surrounded primarily by low coverage BCG vaccination. A cluster is a case with a positive Moran's I and bounded by neighbouring cases with similar values, whereas an outlier is a case with a negative Moran's I but surrounded by cases with dissimilar values.[21 22]

Hotspot analysis (Getis-Ord Gi* statistics)

Spatial autocorrelation varies across the study setting. This variation was computed Getis-Ord Gi* statistics by calculating by the GiBin statistic for each area. In addition the z-score (CI) and the p value were computed to identify the statistical significance of clustering.[23] Statistical output with high GiBin* indicates 'hotspot', which means different geographical areas with low BCG vaccination coverage, whereas low Gi* indicates 'cold spot',

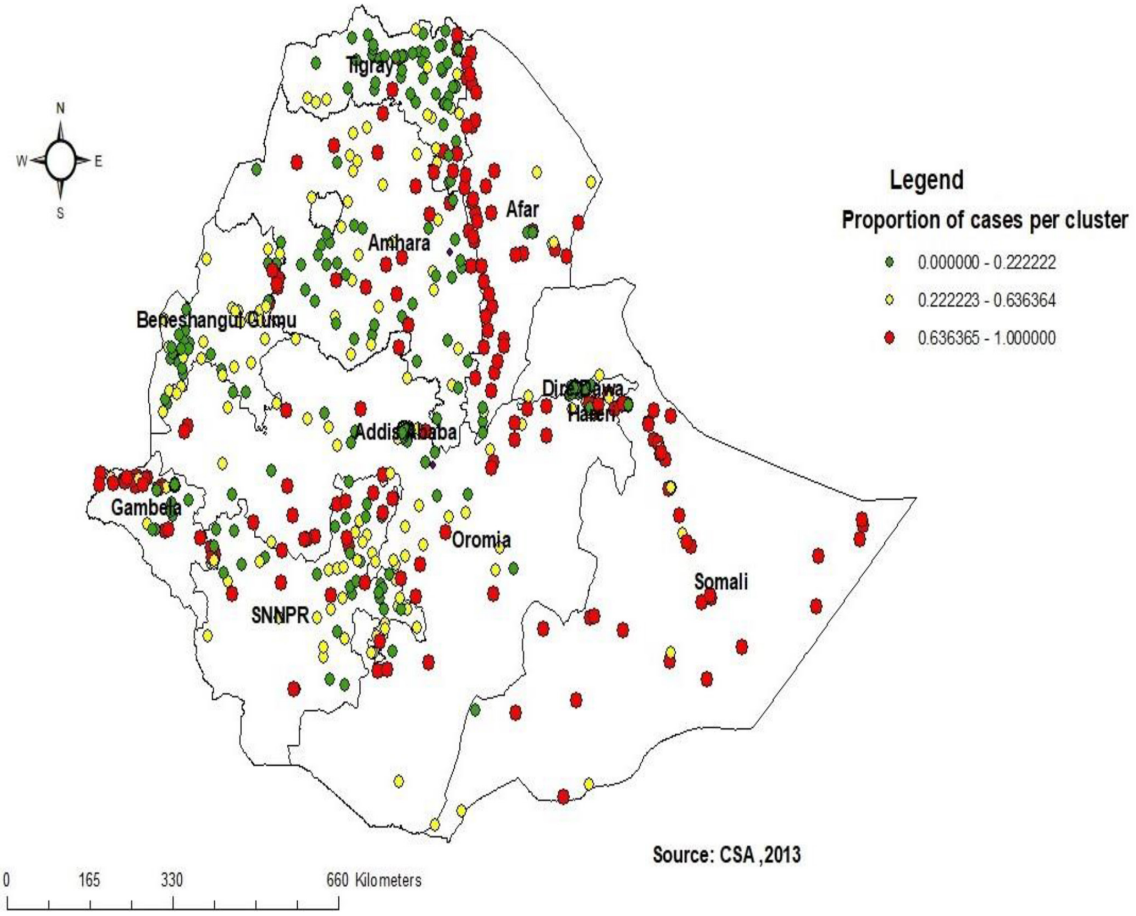

Figure 2 Spatial distribution of BCG coverage among children aged 0–35 months, 2016 Ethiopian Demographic and Health Survey. CSA, Central Statistics Agency; SNNPR, Southern Nations, Nationalities, and People's Region.

which means areas with high BCG vaccination coverage, among children aged 0–35 months in Ethiopia.[21 22 24]

Spatial interpolation

There are deterministic and probabilistic types of interpolation methods that predict vaccination coverage in unobserved areas based on observed data. Commonly the probabilistic type of interpolation methods, that is, ordinary kriging, universal kriging and empirical Bayesian kriging, is the most appropriate method for prediction. Using this evidence we ran and compared the three techniques using residuals and root mean square error. Based on the parameters, ordinary kriging has the lowest residuals and root mean square error value, and we chose this interpolation technique for this study. Kriging spatial interpolation is a technique used to predict the percentage of BCG vaccine coverage among children 0–35 months in unsampled areas in the country based on observed measurements.[25] Finally, ordinary kriging spatial interpolation method was used to predict BCG vaccination coverage among children 0–35 months in unobserved areas of Ethiopia since it includes spatial autocorrelation and statistically optimises the weight.[26]

Spatial scan statistical analysis

The spatial scan statistical method is widely suggested and performs very well in identifying local clusters and has higher power than other available spatial statistical methods.[27] Spatial scan statistical analysis was employed to test for the presence of statistically significant spatial hotspots (clusters of low BCG vaccination coverage) using Kulldorff's SaTScan V.9.4 software.[28] Children not taking BCG vaccination were cases, whereas those taking BCG vaccination were considered as controls and fitted in the Bernoulli model. The number of cases in each location showed a Bernoulli distribution and the model required data on cases, controls and geographical coordinates. The default maximum spatial cluster size of <50% of the population was used as an upper limit, which allowed both small and large clusters to be identified and ignored clusters that contained more than the maximum limit. The null hypothesis was that there is no risk difference within and outside the scanning window. Areas with high log-likelihood ratio (LLR) and $p<0.05$ were considered at high risk as compared with areas outside the window. Finally significant and most likely clusters with LLR, relative risk and p value were reported. ArcGIS V.10.6 was used to identify the location where the most likely clusters can be found. The primary and secondary clusters

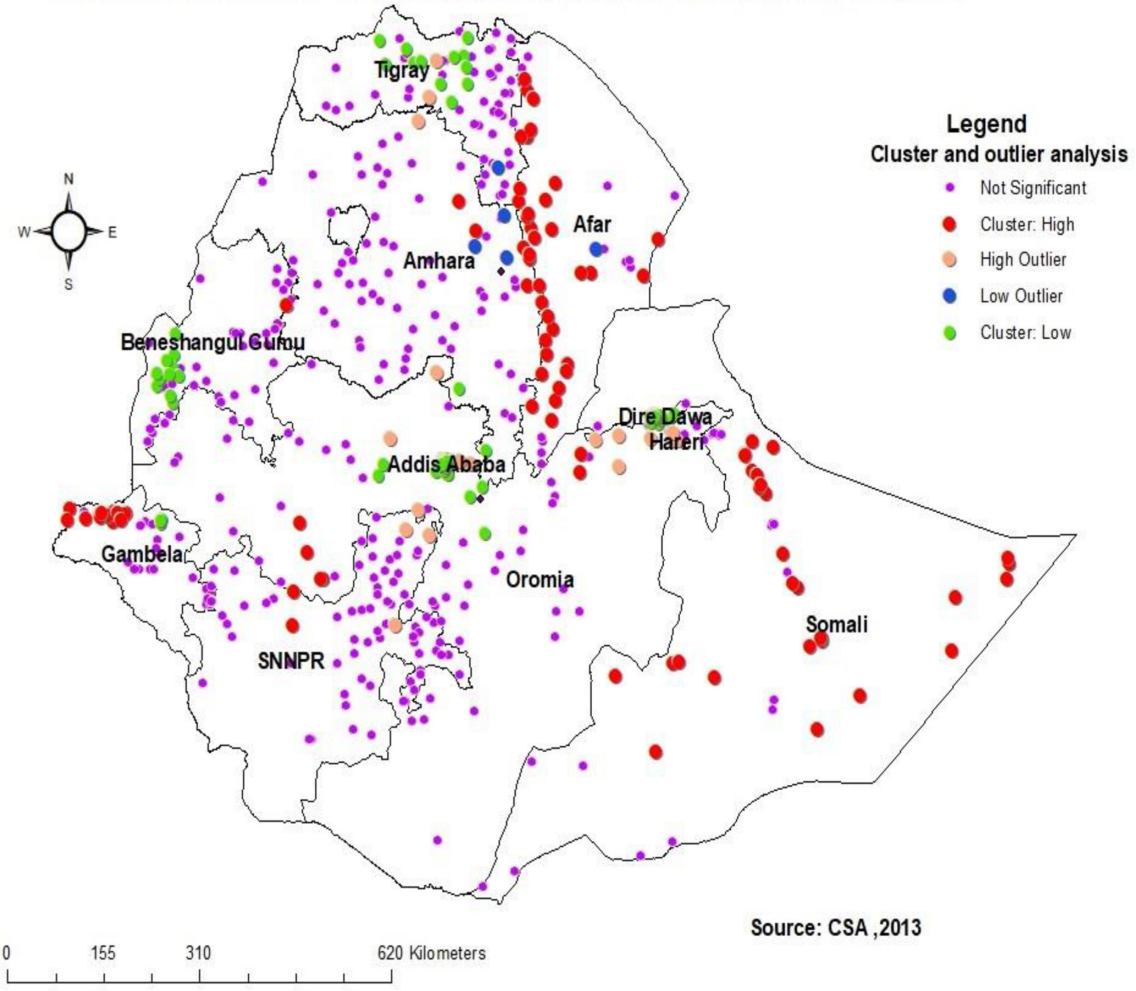

Figure 3 Cluster and outlier analysis of BCG coverage among children aged 0–35 months, 2016 Ethiopian Demographic and Health Survey. CSA, Central Statistics Agency; SNNPR, Southern Nations, Nationalities, and People's Region.

are identified and assigned p values and ranked based on their likelihood ratio test, based on 999 Monte Carlo replications.

Ethical consideration

Permission letter for data access was obtained from the main Demographic and Health Survey through an online request at http://www.dhsprogram.com. The institutional review board-approved procedures for Demographic and Health Survey public-use data sets do not in any way allow respondents, households or sample communities to be identified. There are no names of individuals or household addresses in the data files. The geographical identifiers only go down to the regional level (where regions are typically very large geographical areas encompassing several states/provinces). Each enumeration area (primary sampling unit, PSU) has a PSU number in the data file, but the PSU numbers do not have any labels that indicate names or locations. In surveys that collect GIS coordinates in the field, the coordinates are only for the enumeration area as a whole and not for individual households, and the measured coordinates are randomly displaced within a large geographical area so that specific enumeration areas cannot be identified.

Patient and public involvement

Patients and the public were not involved in the design and data analysis in this secondary study, but were very important during the initial data collection process.

RESULTS

Spatial autocorrelation

The spatial distribution of BCG vaccination coverage among children aged 0–35 months was found to be clustered (non-random) in Ethiopia, with Moran's index of 0.516 ($p<0.001$) (figure 1).

Spatial distribution of low BCG coverage among children aged 0–35 months

A total of 622 clusters were included in the spatial analysis of BCG vaccination among children. Low BCG vaccination coverage (red colour) was aggregated in Somali, North and South West Afar, North West Gambela, North East SNNPR and the entire Amhara

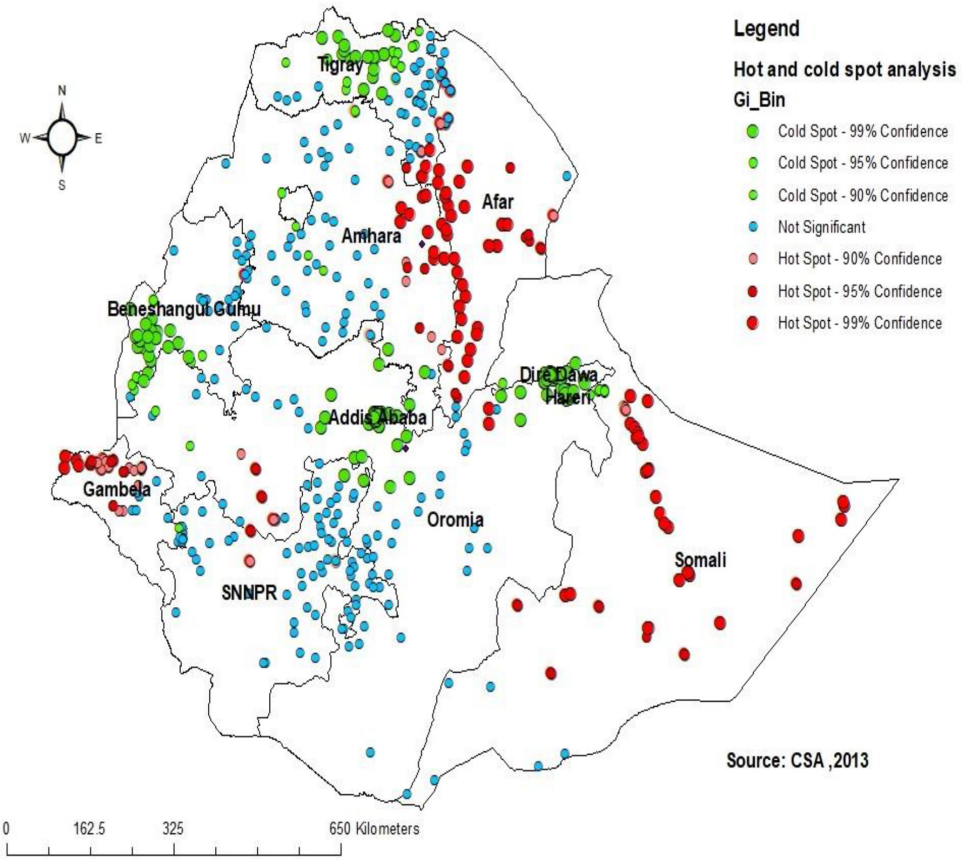

Figure 4 Hotspot analysis of BCG coverage among children aged 0–35 months, 2016 Ethiopian Demographic and Health Survey. CSA, Central Statistics Agency; SNNPR, Southern Nations, Nationalities, and People's Region.

region. High BCG vaccination coverage was identified in Tigray, North West Amhara and North West Benishangul-Gumuz (figure 2).

Cluster and outlier analysis of low BCG vaccination among children aged 0–35 months

Cluster and outlier analysis was conducted using Anselin Local Moran's I to identify the nature of clustering. The red colour indicates high–high cluster areas of low BCG vaccination coverage, whereas the green colour indicates low–low cluster areas of BCG vaccination. Somali, Afar, Gambela, South West Addis Ababa and North East Oromia were significant clusters with low BCG vaccination coverage among children aged 0–35 months (figure 3).

Hotspot identification of low BCG vaccination among children aged 0–35 months

The dark red colour indicates significant ($p<0.001$) clusters of low BCG vaccination (risk areas), whereas the green colour indicates significant ($p<0.001$) clusters of high BCG vaccination (non-risky areas). Hence, Afar, Somali and North West Gambela were identified to have low BCG vaccination (hotspot areas) in the past 5 years. Tigray, Harari, South West Benishangul-Gumuz and North East Addis Ababa were identified as cold spot areas for BCG vaccination (non-risky areas) (figure 4).

Interpolation of BCG vaccination coverage among children aged 0–35 months

Afar, Somali and North West Gambela were identified as the more risky areas for BCG vaccination coverage or with low BCG coverage. However, Tigray, Benishangul-Gumuz, Dire Dawa, Central Addis Ababa and North West Amhara were found to be low-risk areas for BCG vaccination coverage (figure 5).

Spatial SaTScan analysis of BCG vaccination coverage (Bernoulli-based model)

Spatial scan statistics were done using SaTScan V.9.6 to identify the most likely clusters, and a total of 13 significant clusters with 212 enumeration areas were identified. From the identified clusters, 2 were a primary (most likely) cluster and 11 were secondary clusters. The primary cluster's spatial window red colour was located in Afar, North West and East Somali and was centred at 6.023458 N, 44.807507 E in geographical location, with 463.24 km radius, with an LLR of 136.58 at $p<0.001$, and was identified as the most likely cluster with maximum LLR. It showed that children within the spatial window had 1.97 times higher risk of low BCG vaccination than

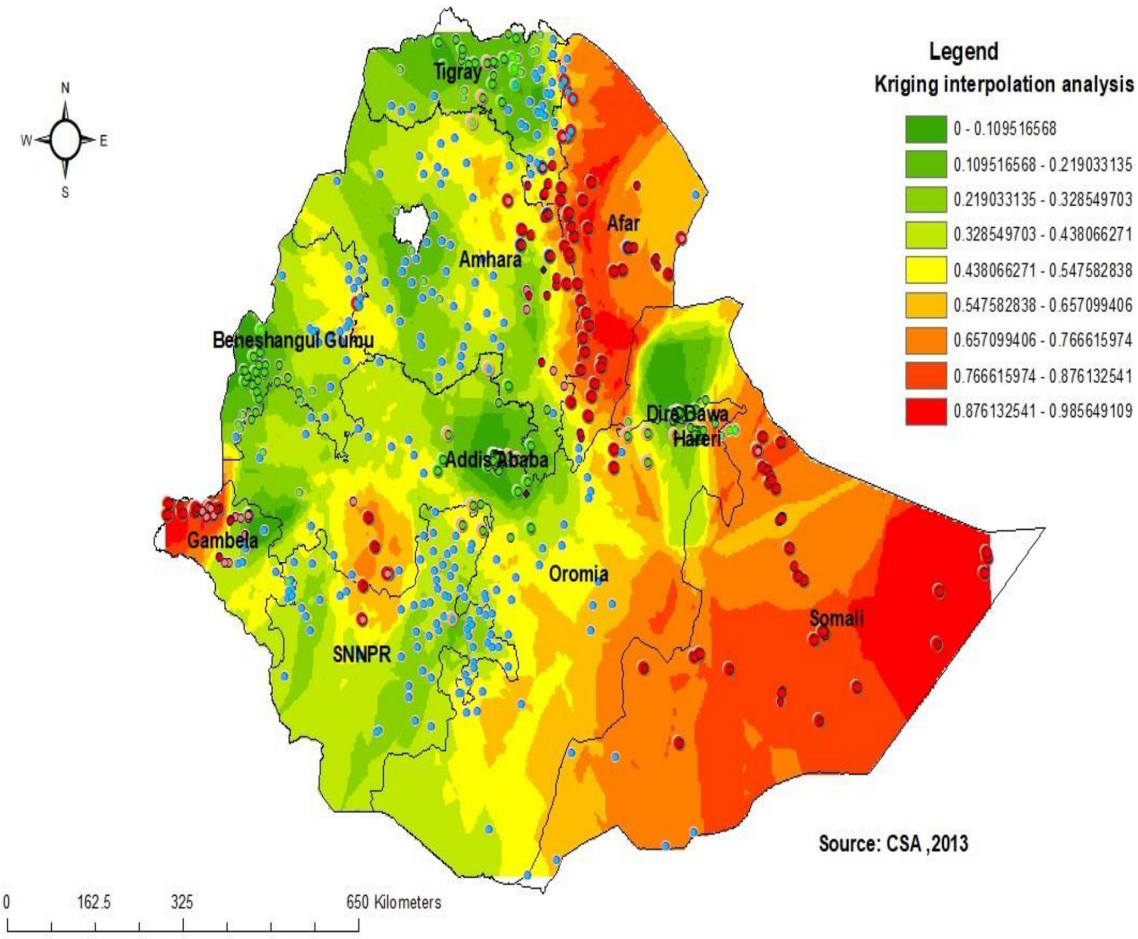

Figure 5 Spatial interpolation of BCG coverage among children aged 0–35 months, 2016 Ethiopian Demographic and Health Survey. CSA, Central Statistics Agency; SNNPR, Southern Nations, Nationalities, and People's Region.

children outside the window. The other secondary clusters are described in detail in table 1 and figure 6.

DISCUSSION

The findings of this study showed that BCG vaccination coverage among children aged 0–35 months was non-random (clustered) in the country. In the global autocorrelation analysis, a clustering pattern in BCG vaccination coverage across the country was observed (Global Moran's I=0.516, p<0.001). This indicates that nearly the same coverage of BCG vaccination was aggregated in specific areas. The hotspot cluster of low BCG vaccination coverage was identified in Afar, Somali and North West Gambela (p<0.01). Despite outreach plans and supplementary vaccination schedules, there is low vaccination coverage in these regions. The possible reasons could be that mothers who lived in the above-mentioned regions have poor knowledge about the importance of vaccination as compared with other regions,[29] and that they are nomads and do not undergo antenatal care follow-up. This leads to most children not getting BCG vaccination.

The BCG vaccination coverage map prediction identifies and estimates that South West Afar, East Somali and North West Somali are at risk of low BCG vaccination coverage. The possible explanation could be because these regions are border areas and hence could not access and use healthcare services. Also, people who live in these regions may have lower educational status and may live far from healthcare institutions.[30] Women's rural residency could be another factor that contributes to low BCG vaccination coverage.[31] Most of these regions are entirely rural, which may be why BCG vaccination coverage was low.

The purely SaTScan spatial analysis identified 13 statistically significant most likely SaTScan clusters of areas with low BCG vaccination coverage. The most likely primary SaTScan cluster of low BCG vaccination coverage was identified in Afar and in North West and East Somali (LLR=136, p<0.01). The entire Somali region was identified as the most likely secondary SaTScan cluster (LLR=131, p<0.01). Other most likely SaTScan clusters of low BCG vaccination coverage were identified in North West Gambela, East Addis Ababa, South West Addis Ababa, North West Amhara, North West Oromia, North East SNNPR and South Amhara. This local clustering of low BCG vaccination coverage indicates that children who lived in the above-mentioned geographical locations had a low probability of receiving BCG vaccination compared

Table 1 SaTScan analysis of BCG vaccination among children aged 0–35 months in Ethiopia, 2016

Cluster	Enumeration area (cluster) identified	Coordinate/radius	Population	Case	RR	LLR	P value
1 (51)	146, 138, 92, 490, 543, 492, 85, 358, 164, 77, 171, 198, 629, 95, 497, 278, 521, 588, 458, 553, 269, 318, 378, 187, 630, 214, 251, 573, 556, 239, 116, 22, 520, 33, 568, 277, 480, 527, 208, 64, 439, 57, 8, 210, 186, 394, 454, 436, 566, 212, 501	(6.023458 N, 44.807507 E)/463.24 km	476	377	1.97	136.58	<0.001
2 (35)	366, 4, 427, 632, 440, 75, 596, 178, 499, 205, 334, 570, 599, 348, 544, 389, 241, 344, 332, 172, 571, 488, 191, 130, 249, 368, 189, 511, 55, 585, 547, 128, 254, 276, 442	(12.401068 N, 42.163134 E)/274.51 km	316	273	2.11	131.29	<0.001
3 (41)	138, 164, 85, 358, 146, 492, 92, 490, 543, 278, 171, 198, 95, 318, 77, 187, 497, 556, 520, 629, 521, 588, 553, 458, 480, 208, 214, 251, 573, 239, 269, 116, 22, 394, 378, 630, 568, 33, 277, 286, 527	(5.589269 N, 44.175032 E)/420.35 km	363	294	1.98	112.88	<0.001
4 (15)	266, 618, 309, 435, 370, 507, 592, 104, 260, 233, 69, 426, 603, 346, 315	(8.389747 N, 33.258557 E)/91.71 km	125	112	2.09	59.03	<0.001
5 (4)	362, 127, 235, 263	(13.889667 N, 39.944065 E)/16.79 km	54	54	2.3	44.64	<0.001
6 (12)	566, 1, 186, 622, 8, 436, 210, 212, 419, 357, 288, 501	(9.455401 N, 42.455144 E)/34.72 km	108	90	1.93	36.33	<0.001
7 (33)	230, 51, 49, 564, 71, 484, 624, 39, 122, 506, 201, 295, 336, 476, 412, 245, 333, 102, 121, 491, 529, 637, 135, 37, 283, 125, 40, 310,93, 372, 303, 319, 620	(9.336076 N, 40.167711 E)/137.00 km	266	182	1.61	33.96	<0.001
8 (8)	432, 486, 62, 447, 227, 76, 489, 586	(7.858150 N, 36.733552 E)/78.67 km	91	72	1.82	23.85	<0.001
9 (4)	515, 615, 498, 548	(11.074357 N, 36.455218 E)/18.98 km	25	24	2.19	16.11	<0.001
10 (2)	21, 398	(5.725346 N, 38.264768 E)/19.88 km	27	25	2.11	14.58	<0.001
11 (1)	610	(9.370004 N, 42.102751 E)/0 km	14	14	2.28	11.49	0.0079
12 (5)	204, 359, 139, 633, 54	(8.159210 N, 38.189388 E)/38.09 km	31	26	1.91	10.57	0.019
13 (1)	232	(6.125907 N, 38.306106 E)/0 km	12	12	2.28	9.85	0.033

LLR, log-likelihood ratio; RR, relative risk.

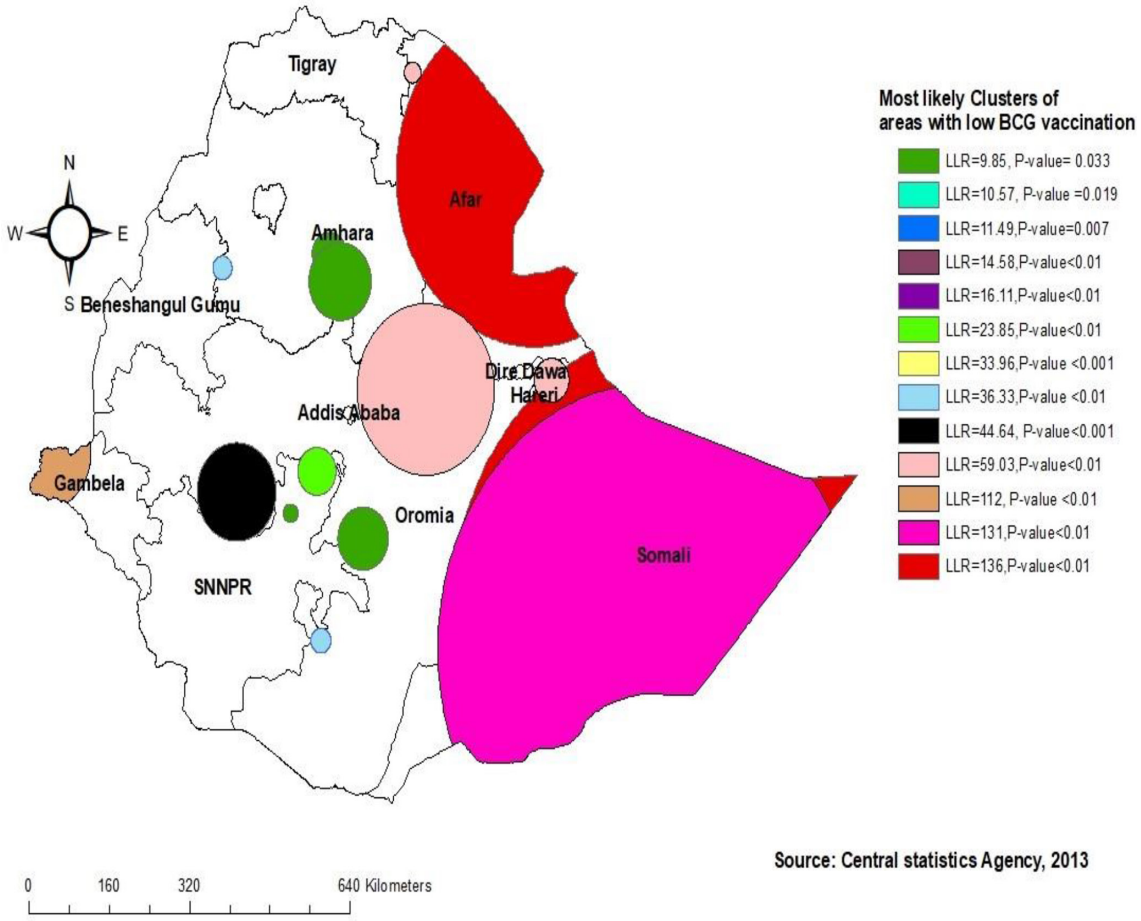

Figure 6 Spatial SaTScan analysis BCG coverage among children aged 0–35 months, 2016 Ethiopian Demographic and Health Survey. CSA, Central Statistics Agency; LLR, log-likelihood ratio; SNNPR, Southern Nations, Nationalities, and People's Region.

with children who lived outside the SaTScan clusters. This may be due to differences in health service accessibility and utilisation, aside from sociocultural differences in the community. Studies showed that women who live in Afar and in other remote areas delivered at home due to lack of confidence among their health providers.[32] Also, women of the pastoralist community predominantly live in the Afar and Somali regions and therefore their children do not have the opportunity to receive birth dose of vaccinations such as BCG.

Limitations of this study include the data being collected at a point in time and the study's retrospective nature. These result in further limitations such as missing data on BCG vaccination status and GPS coordinates, inaccuracies in vaccine cards and/or parental recall, and displacement of data for privacy reasons. Finally the SaTScan analysis detects only circular clusters, and irregularly shaped clusters were not detected.

Based on the findings of this study, policy makers or programmers should provide better interventions to hotspot areas (low BCG vaccination coverage) and design different strategies to improve BCG vaccination among children 0–35 months in Ethiopia.

CONCLUSION

The spatial variation in BCG vaccination coverage among children in Ethiopia was non-random (clustered). High-risk areas for low BCG coverage were found in the far North West and East Somali regions. TB is a high-burden disease in developing countries especially in Ethiopia, and to reduce this highly infectious disease BCG vaccination is a very important tool. High-risk areas for low BCG vaccination are prone to TB and should be given priority and be targeted for interventions to reduce the burden of TB in Ethiopia.

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Contributors CDA and AZA were involved in the design and conception of the study and in the analysis and interpretation of the findings. Both authors read and approved the manuscript, starting from the first step up to publication.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Permission for data access was obtained from a major Demographic and Health Survey through an online request at http://www.dhsprogram.com. The data used for this study were publicly available with no personal identifier. Our study was based on secondary data from Ethiopian Demographic and Health Survey and we have secured the permission letter from the main Demographic Health and Survey.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as supplementary information. All relevant data are available and can be uploaded when requested.

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