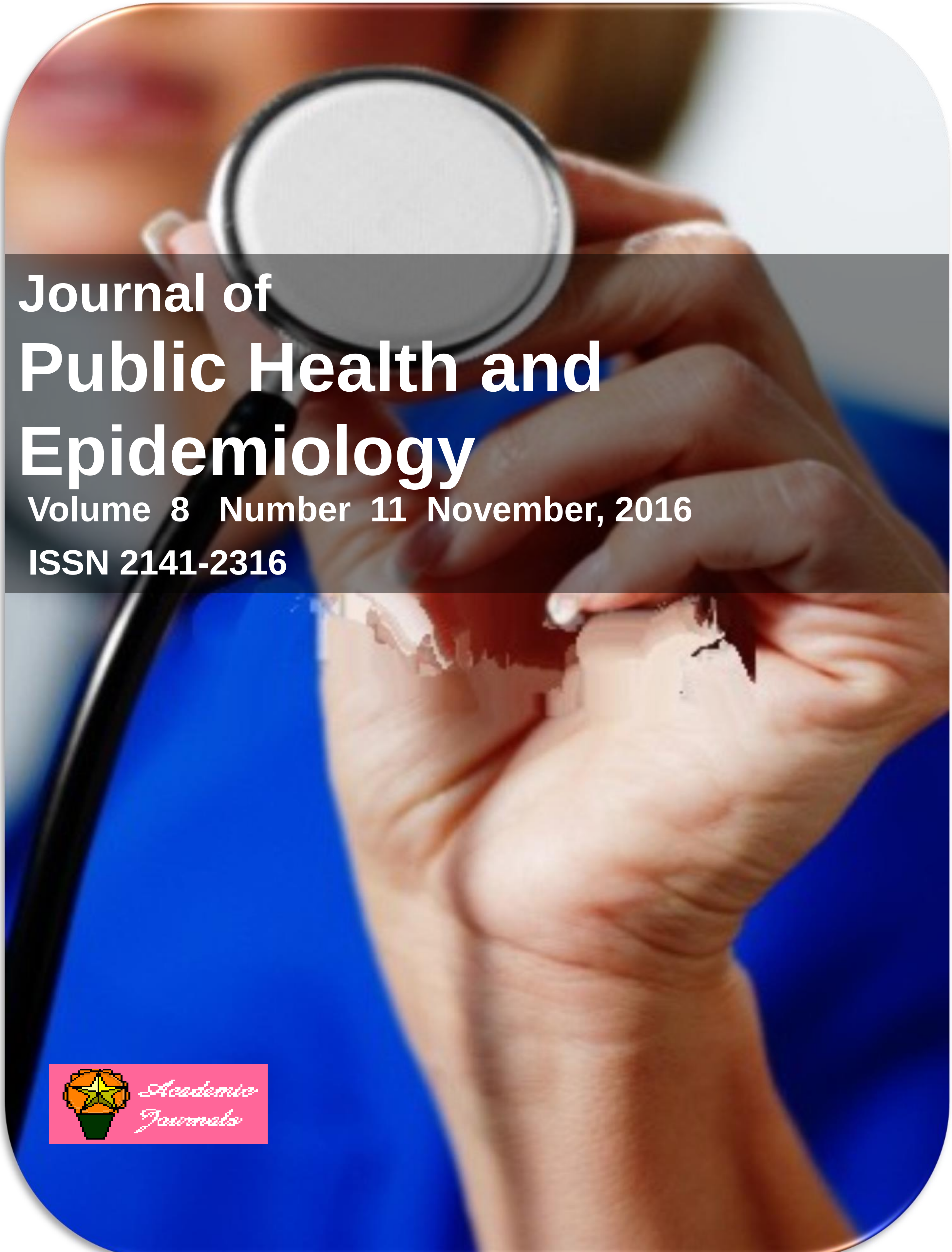

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Full Length Research Paper

The persistence of tuberculosis in the United States: Spatial analysis and predictive modeling in the move toward elimination of tuberculosis (TB)

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Though tuberculosis (TB) prevalence has decreased dramatically in the United States, its continual presence remains a threat to those whose needs are often overlooked. Those already impacted by poverty are the most vulnerable to TB, and stand to bear the worst health impacts, should they contract this disease. Mathematical modeling and spatial analysis have become invaluable tools in TB surveillance monitoring and elimination efforts. In this contribution, we demonstrate the capability of employing a time series, interpolative, vulnerability model to forecasted, state-level TB prevalence in the United States by determining areas influenced by poverty, as well as existing TB data acquired from the Center of Disease Control (CDC). The random effects term in this orthogonal eigenvector spatial filter model was comprised of spatially structured and stochastic effects (that is, spatially unstructured) terms, which were substituted for diagnostic, remote, and clinical covariates in our model. It was assumed that random effects terms in the TB risk model had followed a Gaussian frequency distribution with a mean of zero. The estimate equations were as follows: $\hat{\xi} \sim N(-0.0025,\ 0.6059^2), PS(S-W) = 0.34$ **and** $\hat{p} = \frac{1}{1+e^{10.4180-0.0708T+\hat{\xi}}}$**. The resulting estimated number of cases for a given state and year was** $\hat{n}_{TB} = 0.0885 + 0.9996 \times Population \times \hat{p}$**. The Moran coefficient (MC) was 0.66, and its Geary Ratio (GR) was 0.35. The spatially unstructured random effects terms have only trace levels of spatial autocorrelation, with MC = 0.02, and Gr = 0.89. Thus, the assumption of non-zero spatial autocorrelation was violated. The forecast revealed possible hyperendemic transmission of TB in non-coastal, Northwestern states, as well as in some Northeastern states. As such, more intervention efforts should be directed towards these areas.**

Key words: Tuberculosis (TB), poverty, center of disease control (CDC).

INTRODUCTION

Despite promising headway towards the elimination of tuberculosis in the United States in recent decades, there

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has been recognized a disconcerting stagnation in what had been an encouraging downward trend. The year 2014 marked a record low for new cases of TB in the US Kang et al., 2014). Still, the decline in incidence from 2013 to 2014 represents the least dynamic change in over ten years (Scott et al., 2015). With immigration, both documented and undocumented, as well as forced human displacement are frequently cited explanations for the persistence of US tuberculosis infections, and attention is often directed toward states with higher immigrant populations, particularly when the countries of origin for larger subpopulations are known to be of greater TB endemicity (Greenwood and Warriner, 2011; Ricks et al., 2011; Bennett et al., 2014; Davidow et al., 2015; Stennis et al., 2015). Other discussions include transmission among those experiencing homelessness (CDC, 2012; Feske et al., 2013) and outbreaks among those inhabiting long-term care facilities (Cavanaugh et al., 2012). Appropriate screening, treatment, and other interventional measures are certainly necessary in all subpopulations deemed to be at-risk, but there may yet be pockets within the US population overall which are not being reached. These pockets may include rural areas where, despite a comparatively smaller population size, crowded housing and lack of mobility are still experienced by those living in poverty and extreme poverty. Such living conditions are endured by many American Indian populations inhabiting reservations (Durand, 2015), a subject that often continues to be evaded in public discourse. In addition to those born in the US, more contemporary trends in immigrant dispersion to "new immigrant destination" sites should also be taken into account for TB transmission to be more thoroughly understood and predicted. There may also be yet risk factors that have not been identified which may allow for better prediction of higher TB prevalence. Spatially speaking, if demographic and migration patterns of today are not incorporated into predictive analysis, resources for TB intervention may be allocated around the TB challenges of a different time. Spatial analysis and mathematical modeling of tuberculosis transmission incorporating known risk factors, as well as patterns of movement using bacillus genotyping as an indicator, is already a well-recognized area of study (Ferdinand et al., 2013; France et al., 2015; Said et al., 2016).

As Houben et al. (2014) noted, mathematical modeling of interventional strategies represents a viable alternative to more expensive, time-consuming, and potentially unethical randomized control trials. These studies tend to be conducted in countries where TB is perceived as a greater threat than in the United States, and may prove quite useful in places of higher HIV prevalence, given that TB is one of the most common deadly opportunistic infections in HIV positive individuals (Houben et al., 2014). Other studies concerned themselves with issues specific to the challenges of a particular local area, including Ge et al. (2015) study of the role of regional transportation and high and low elevation in the Shandong Province of China, as well as Munch et al. (2003) investigation of the spatial distribution of TB in Cape Town, South Africa, including cluster analysis of *shebeens* (neighborhood bars), overcrowding, and unemployment (Winston and Navin, 2010). Jacob et al. (2010) and Jacob et al. (2013) investigated multi-drug resistant tuberculosis and its dispersion through the community of San Juan de Lurigancho in Lima, Peru, where prison visitation was proved key to transmission.

To our knowledge, there are no existing empirical models for the United States which geostatistically address country-wide trends. A predictive, empirical approach which encompasses space, as well as time, in prevalence estimations may allow for a more judicious allocation of resources and interventions toward the elimination of tuberculosis in the United States. To date, a promising study by Feske et al. (2011) utilized kernel density maps in ArcGIS to identify statistically significant clusters for TB transmission in Harris State, Texas. We seek to expand upon the merits of this approach in the creation of a TB transmission risk model for the United States. To accomplish this, we shall: 1) produce Poissonian and negative binomial regression models to determine frequentist pseudo R^2 estimates, and 2) construct orthogonal spatial filter eigenvectors using a decompositional algorithm for cartographically displaying predictive abundance values. When creating a risk model for tuberculosis, and other communicable diseases, several measures should be taken to ensure optimal accuracy. For a given form of statistical analysis, certain assumptions are made concerning the distribution used. Any violations of these assumptions may result in misspecifications in the model, the implication being that limited resources may be allocated less efficiently. Spatial analysis represents a special case of predictive model construction which is better able to accommodate both multicollinearity and heteroscedasticity, as well as identify response variables. We further contend that assuming normality is largely impractical for the purposes of spatial epidemiological analysis.

METHODOLOGY

Endemic, TB-related, state-level, parameterizable data including prevalence, race, gender and other socio-demographic data were acquired for each state from 2000 to 2014 from Center for Disease Control (CDC). FLEXIBLE|FLE in SAS 9.2® (Carey, North Carolina) was employed to request the flexible-beta method. The clustering methods in SAS include average linkage, the centroid method, complete linkage, density linkage (including Wong's hybrid and *k*-th nearest-neighbor methods), ML for mixtures of spherical, multivariate, normal distributions with equal variances but possibly unequal mixing proportions, the flexible-beta method, McQuitty's similarity analysis, the median method, single linkage two-stage density linkage, and Ward's minimum-variance method (http://ftp.sas.com). PROC CLUSTER displayed the table of eigenvalues of the covariance matrix for the canonical variables. Generally, in a PROC CLUSTER table output the first two columns list each eigenvalue and the difference between the eigenvalue and its successor, while the last two columns display the individual and

Table 1. Parameterizable clinical, field and remote covariate samples within stratified clusters of TB data in the state study sites as entered in SAS®.

Variable	Description	Units
GCP	Ground control points	Decimal-degrees
EDUC	El	Meters
RCE	Race	Percentage
GEN	Gender	Percentage
AGE	Age	Percentage
PPOS	Previous positive cases	Numeric value
ECON	Income	Percentage

cumulative proportion of variation associated with each eigenvalue (www.sas.com). In the TB distribution model, the squared multiple correlations, pseudo R^2, was the proportion of variance accounted for by the stratified, state-level, geo-referenceable clusters. The approximate expected value of pseudo R^2 was then given in the column labelled "ERSQ". The next three columns displaced the values of the cubic clustering criterion (CCC), pseudo F (PSF), and t2 (PST2) statistics. These statistics were useful in quantitating the number of specified predictive, state-level, parameterizable, intra-cluster, covariate estimators. One method of judging the number of clusters in a dataset in PROC CLUSTER is to examine the pseudo F statistic (PSF) (www.sas.com). The CLUSTER procedure hierarchically clustered the state-level observations using SAS data. The data were then cartographically illustrated by mapping the endemic geocoordinates and squaring Euclidean distance measurements within a flexible-beta method in PROC CLUSTER.

The PROC CLUSTER statement initiated the procedure, which digitally specified a clustering method based on state-level prevalence measures, and then optionally specified each explanatory cluster covariate coefficient. The PROC CLUSTER statement specified a clustering method, and optionally specified details for clustering methods, data processing, and then displayed an output. The model estimated the number of possible transmission centers a person may encounter per state. This was calculated by multiplying the proportional prevalence probability estimates with the proportion of gridded state geolocations stratified by economics and ancestry of origin, and their human population distribution. The agglomerative, hierarchical clustering procedure then utilized geosampled, state-level observations to create geospatial clusters based on asymptotically normalized clinical TB data in a cluster by itself. Clusters were then merged to form a new cluster that replaced the two old clusters, and merging of the two closest clusters was repeated until only one cluster was left.

Beta was set at -100 for epidemiological forecasting cluster-based analyses in SAS PROC CLUSTER. The flexible-beta method began by specifying METHOD=FLEXIBLE. PROC CLUSTER then created an output, interpolative, time series, asymptotically unbiased dataset to reveal a cluster hierarchy of normalized, state-level data feature attributes based on parameterized, covariate coefficient, and estimator values. Since the explanatory estimators were deemed to be equally important, we employed the STD option in PROC CLUSTER to standardize the cluster-based predictor covariate coefficients to mean 0 with standard deviation. Covariates with large variances tended to have a greater effect on the resulting geospatialized TB clusters than variables with small variances. However, if all coefficients are considered equally important in the model, the STD option in PROC CLUSTER standardizes the geo-spatiotemporally geosampled variables.

The STDIZE procedure standardized the covariate estimators in the SAS dataset by subtracting the state-level, stratified, gridded measures, and then dividing them by a scale measure. Finally, a unique identifier was incorporated for each cluster. The PLOTS option in the PROC CLUSTER statement produced plots of the cubic clustering criterion (CCC), the pseudo *F* (PSF) statistic, and the pseudo (PST2) statistic, which were then all plotted against the number of geosampled, state-level TB clusters.

In order to reduce the likelihood of chaining among the TB cluster-based dataset of predictor covariates, a partition that best represented the estimates was identified. This was performed by finding the intersection between a manageable number of state-level, cluster-based, varying and constant, explanatory covariate coefficients and then auto-probabilistically and auto-regressively quantitating them with large jumps in the normalized, Euclidean distance measurements in PROC CLUSTER. The cluster-based, covariate estimators were plotted against ArcGIS-based, Euclidean distance measurements. This revealed a clear flattening of the curve in the digitally overlain data in PROC CLUSTER, indicating that adequate separation of the parameterizable clustering covariate coefficients could not be achieved beyond a specific georeferenced capture point (for example, Veteran Administration Hospital). The number of interpolatable, geosampled TB transmission clusters in the data was also determined by preliminary evaluations with varying numbers of cluster solutions aimed at avoiding trivial error. Evaluation was done by plotting the state-level TB data in discriminant function space in PROC CLUSTER, and seeking adequate separation among group centroids. In order to compute meaningful standardized rates, the individual georeferenced state-level predictors were aggregated geographically into high-low stratified clusters in ArcGIS.

Environmental data analyses

Univariate statistics and regression models were generated by employing the data stored in PROC CLUSTER for regressively summarizing the geospatially clustered covariate coefficients. We generated a misspecification term for constructing an autoregressive, time series model in SAS. Multiple data layers were created using different coded values for the various known data feature attributes. Distance measurements and endemic transmission foci measures were then calculated by using the WV-3 data and the field-sampling information (Table 1).

Regression analyses

The relationship between the state-level, endemic TB data and each individual predictive, geospatially clustering covariate was investigated by single variable regression analysis in PROC NL MIXED. Since prevalence data are binomial fractions, a regression model was employed; as it is a standard practice for vulnerability analysis. Poisson probability regression analyses were employed to infer the relationship between the TB count data variables and the archived empirical, clinical, field and remote-specified state-level characteristics (that is, independent variables) in PROC LOGISTIC.

The regression analyses assumed independent counts (that is, *Ni*) taken at multiple geosampled, state sub-locations $i = 1, 2, \ldots, n$. The geo-spatiotemporal-related state-level counts were then described by a set of variables denoted by matrix $\mathbf{X}_i$, where a $1 \times p$ was a vector of covariate coefficient indicator values for geosampled endemic transmission foci *i*. The expected value of these data was given by $\mu_i(\mathbf{X}_i) = n_i(\mathbf{X}_i)\exp(\mathbf{X}_i\beta)$, where β was the vector of the parameterizable, non-redundant, geosampled covariates in the epidemiological, state-level, risk model, and where the Poisson rates were given by $\lambda_i(\mathbf{X}_i) = \mu_i(\mathbf{X}_i)/n_i(\mathbf{X}_i)$. The rates parameter $\lambda_i(\mathbf{X}_i)$ was both the mean and the variance of the Poisson distribution for each geosampled state location *i*. The dependent variable was state-level prevalence. The Poisson regression model assumed that the predictors were equally dispersed. That implied that the conditional variance equaled the condition mean. Partial correlations were then defined after introducing the concept of conditional distributions. We initially restricted ourselves to only the conditional distributions obtained from the multivariate, normalized distributions. We noted an $n \times 1$ random vector Z, which we partitioned into two random vectors X and Y, where X was an $n_1 \times 1$ vector and Y was an $n_2 \times 1$ vector in the equation $Z = (XY)$. The conditional distribution properties of the regressed, state-level, covariate coefficients were then defined. Thereafter, we partitioned the mean vector and covariance matrix in a corresponding manner: $\mu = (\mu 1\, \mu 2)$ and $\sum = (\sum_{11} \sum_{21} \sum_{12} \sum_{22})$. This way, μ_1 rendered the means for the regressed predictor variables in the set x_1, and $\sum_{11}$ along with the variances and covariances for set x_1. The matrix $\sum_{12}$ thereafter provided the covariances between the predictor variables in set x_1 and set x_2 as did matrix $\sum_{21}$. Any distribution for a subset of variables from multivariate normal, conditional on known values for another subset of variables has a multivariate normal distribution (Griffith, 2003).

It was noted that the conditional distribution of x_1 given the known values for x_2 was multivariate normal with a mean vector covariance $\text{matirx} = \mu 1 + \sum_{12} \sum - 122(x_2 - \mu 2) \sum_{11} - \sum_{12} \sum - 122 \sum_{21}$. The procedure employed ML estimation to find the operationalized, time-series, dependent, regression coefficients. The data were then log-transformed before analysis to normalize the distribution and minimize standard error. There was considerable overdispersion in the regression-based model residual forecasts, so a negative binomial model with a non-homogenous distributed mean was employed to quantitate the covariates associated with the geosampled data. Over-dispersion is often encountered when fitting very simple parametric models, such as those based on the Poisson distribution (Griffith, 2003).

A Poisson mixture model with a negative binomial distribution was employed where the mean of the Poisson distribution was itself a random variable drawn from the gamma distribution. This introduced an additional free parameter in the empirical, state-level, TB distribution model. If over-dispersion is a feature in an asymptotical, predictive risk model, an alternative model with additional free parameters may provide a better fit (Griffith, 2003). Jacob et al. (2013) employed a family of negative binomial distributions for treating over-dispersion in an MDR-TB forecasting, vulnerability model. The Poisson distribution has one free parameter and does not allow for the variance to be adjusted independently of the mean (Griffith, 2003). A parameterization technique was then employed in PROC LOGISTIC such that any two state-level had explanatory regressable variables *p* and *r* with $0 < p < 1$ and $r > 0$. Lack of fit and over-dispersion can be assessed using the Pearson and deviance statistics available in the GENMOD, LOGISTIC, and PROBIT procedures (http://support.sas.com/kb/22/630.html). Under this parameterization, the probability mass function (pmf) of the predictor variables with a NegBin (r, p) distribution took the following form:

For $k = f(k; r, p) = \begin{pmatrix} k + r - 1 \\ k \end{pmatrix} \cdot p^r \cdot (1-p)^k 0, 1, 2,$

Where

$$\begin{pmatrix} k + r - 1 \\ k \end{pmatrix} = \frac{\Gamma(k+r)}{k!\,\Gamma(r)} = (-1)^k - \begin{pmatrix} -r \\ k \end{pmatrix} \text{ and } \Gamma(r) = (r-1)!.$$

Also, an alternative parameterization was employed for quantitating the state-level TB data using the mean $\lambda : \lambda = r \cdot \left(p^{-1} - 1\right) p = \frac{r}{r + \lambda}$. The mass function then became:

$$g(k) = \frac{\lambda^k}{k!} \cdot \frac{\Gamma(r+k)}{\Gamma(r)(r+\lambda)^k} \cdot \frac{1}{\left(1 + \frac{\lambda}{r}\right)^r},$$

where λ and *r* were the parameters. Under this parameterization, $\lim_{r \to \infty} g(k) = \frac{\lambda^k}{k!} \cdot 1 \cdot \frac{1}{\exp(\lambda)}$ was generated, which resembled the mass function of a Poisson-distributed random variable with Poisson rate (i.e., λ.). In other words, the negative binomial distribution generated from the regressed, parameterizable covariates converged to the Poisson distribution, and *r* controlled the deviation from the Poisson. This made the negative binomial habitat model suitable as a robust alternative to the Poisson regression-based framework for risk modeling the interpolatable, time-series, clinical, field and remote-specified predictors.

The negative binomial distribution of the explanatory, state-level, TB covariates arose as a continuous mixture of Poisson distributions where the mixing distribution of the Poisson rate was a gamma distribution. The mass function of the negative binomial distribution of the geosampled transmission predictor variables then was written as:

$$f(k) = \int_0^\infty Poisson(k|\lambda) \cdot Gamma(\lambda | r, (1-p)/p)\, d\lambda$$

$$= \int_0^\infty \frac{\lambda^k}{k!} \exp(-\lambda) \cdot \frac{\lambda^{r-1} \exp(-\lambda p/(1-p))}{\Gamma(r)((1-p)/p)^r}\, d\lambda$$

$$= \frac{1}{k!\,\Gamma(r)} p^r \frac{1}{(1-p)^r} \int_0^\infty \lambda^{(r+k)-1} \exp(-\lambda/(1-p))\, d\lambda$$

$$= \frac{1}{k!\,\Gamma(r)} p^r \frac{1}{(1-p)^r} (1-p)^{r+k} \Gamma(r+k)$$

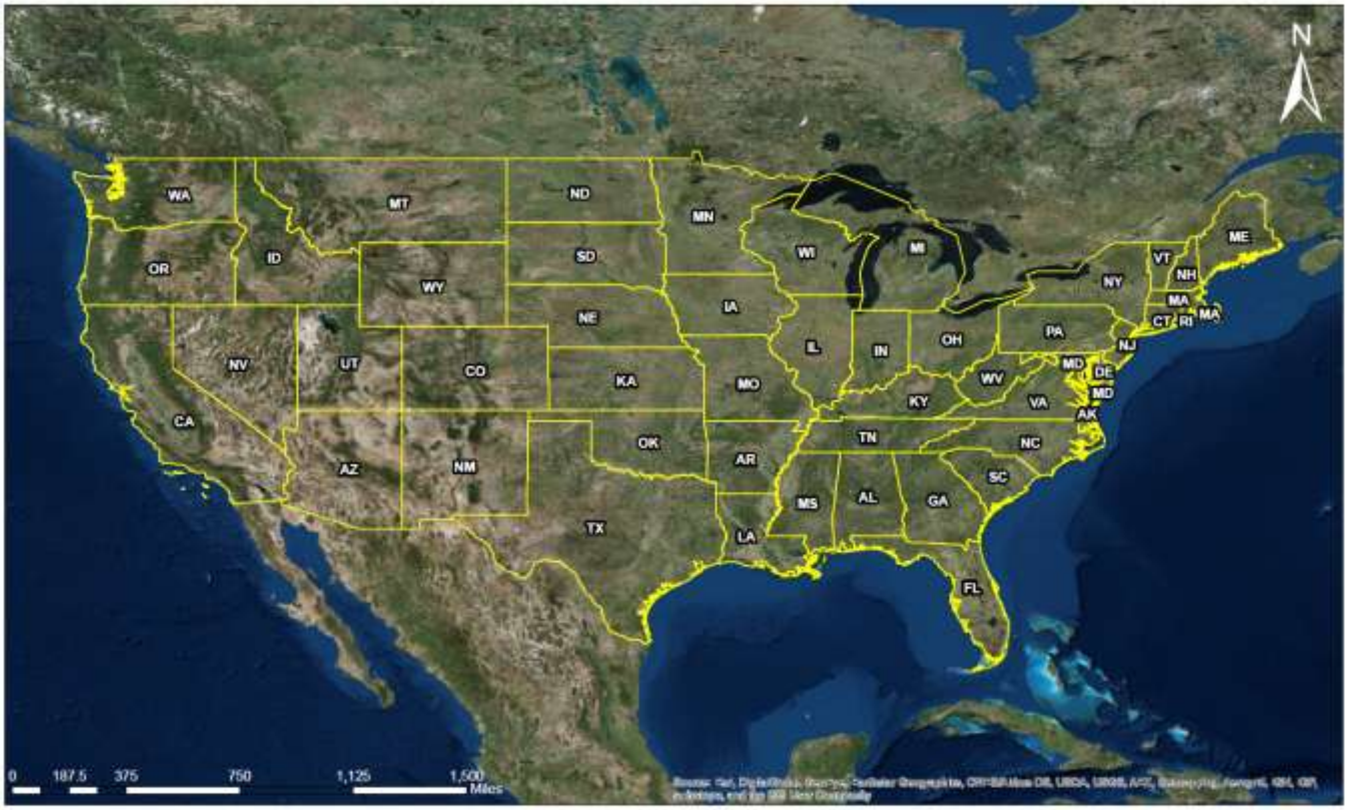

Figure 1. The study site consisted of the contiguous United States.

$$= \frac{\Gamma(r+k)}{k!\,\Gamma(r)}\, p^r (1-p)^k.$$

Spatial analyses

This is represented by Figure 1. Initially, a misspecification perspective for the asymptotically normalized estimation models was generated in SAS/GIS 9.2 assuming that the geo-spatiotemporal, risk model parameter fit was $y = X\beta + \varepsilon^*$ (that is, regression equation). The primary function of the model generation was for quantitating the auto-correlated disturbances ε^* in the residually forecasted, regression-based derivatives. The SAS/Graph mapping functionality allowed us to create choropleth, prism, block, and surface maps. This included the GMAP, GREMOVE, GREDUCE, GPROJECT and MAPIMPORT procedures. Three key techniques were highlighted to deliver SAS/GRAPH auto-regressable, predictive risk maps: Map data, Annotate and the Output Delivery System (ODS). The latent autocorrelation coefficients were decomposed into a white-noise component, ε, and a set of unspecified and/or misspecified model outputs that had the structure $y = XB + \underbrace{E\gamma + \varepsilon}_{=\varepsilon^*}$. White noise is a univariate or multivariate, discrete-time, stochastic process, whose terms are independent and identically distributed (i.i.d.) with a zero mean (Jacob et al., 2013).

The Annotate facility enabled generating a special dataset of graphics commands from which the state-level TB graphic output was created. The annotate output combined with the PROC GMAP output generated multiple customized surface maps. The misspecification term was $S(T) = S(t)\exp$. Quantification of the topographic patterns rendered from the distribution of the regressed, predictive covariates was required to describe independent key dimensions of the underlying spatial processes in the geosampled data for heuristically defining a pattern in the misspecification term. SAS/GIS software provided an efficient interactive tool for organizing and analyzing the state-level TB, clinical, field and remote-sampled data that was referenced spatially.

A geospatialized, time series, autoregressive model was generated employing a predictive, specified variable Y as a function of a nearby geosampled variable Y in the SAS/GIS autoregressive model. A covariate coefficient indicator value *I*, an autoregressive response, and the residual of Y were treated as a function of a nearby geosampled Y residuals, as a spatially autoregressive (SAR) or spatial error specification. For TB transmission risk modeling, the SAR model furnishes an alternative specification that frequently is written in terms of matrix W (Griffith, 2003). As such, the spatial covariance of the geosampled dataset was a function of the matrix $(\mathbf{I}-\rho\mathbf{C}\mathbf{D}^{-1})(\mathbf{I}-\rho\mathbf{D}^{-1}\mathbf{C}) = (\mathbf{I}-\rho\mathbf{W}^T)(\mathbf{I}-\rho\mathbf{W})$, where *T* denoted the matrix transpose. The resulting matrix was symmetric and was considered a second-order specification as it included the product of two spatial structure matrices (i.e., $\mathbf{W}^T\mathbf{W}$). This matrix restricted positive values of the autoregressive parameter to the more intuitively interpretable range of $0 \le \hat{\rho} \le 1$.

Distance between the predictive covariate coefficients was defined in terms of an *n*-by-*n* geographic weights matrix, C, whose

c_{ij} values were 1 if the geosampled locations *i* and *j* were deemed nearby, and 0 otherwise. Adjusting this matrix by dividing each row entry by its row sum then rendered C1, where 1 was an *n*-by-1 vector of ones, and subsequently converted the time series regression-based matrix to matrix W. The resulting SAR model specification with no parameterizable predictor covariates the pure spatial autoregression specification, then took on the form $\mathbf{Y} = \mu(1-\rho)\mathbf{1} + \rho\mathbf{WY} + \varepsilon$, where μ was the scalar conditional mean of Y, and ε was an *n*-by-1 error vector with parameters independently and identically distributed (normally random variates). The spatial covariance matrix for analyzing the state-level covariate coefficients was thereafter expressed employing $E[(\mathbf{Y}-\mu\mathbf{1})'(\mathbf{Y}-\mu\mathbf{1})] = \Sigma = [(\mathbf{I}-\rho\mathbf{W}')(\mathbf{I}-\rho\mathbf{W})]^{-1}\sigma^2$, where $E(\bullet)$ denoted the calculus of expectations, I was the *n*-by-*n* identity matrix denoting the matrix transpose operation and σ^2 was the asymptotical, stochastically/deterministically-related error variance.

The TB predictive model was written as: $X_t = c + \sum_{i=1}^{p} \varphi_i X_{t-i} + \varepsilon_t$, where $\varphi_1, \ldots, \varphi_p$ were the empirical covariate estimators, *c* was a constant and ε_t was the white noise. When coupled with regression and the normal probability model, an autoregressive specification results in a covariation term characterizing spatial autocorrelation by denoting the autoregressive parameter with ρ at a conditional autoregressive covariance specification (Griffith, 2003). This specification involved the matrix $(\mathbf{I}-\rho\mathbf{C})$ where I was an *n*-by-*n* identity matrix. In an autoregressive expression, however, the optimal response variable is on the left-side of the equation, while the spatial lagged version of the variable is on the right side (Griffith, 2003). Therefore, one of the main objectives in this research was to bring the spatially unlagged, TB predictor variable *y* exclusively to the left-hand side of the regression equation in order to decorrelate the normalized state-level TB covariate coefficients. This was accomplished by expanding the weighted regression coefficient matrix term: $(I-\rho V)^{-1} = \sum_{k=0}^{\infty} \rho^k V^k$ as an infinite power series, which was feasible only under the assumption that the underlying spatial process in the normalized, state-level TB datasets was stationary. The autoregressive, interpolatable, forecasting error model was then rewritten as $y - \rho V y = X\beta - \rho V X\beta + \varepsilon$. in AUTOREG. Substituting this transformation rendered:

$$y = (I-\rho V)^{-1}[X\beta - \rho V(X\beta) + \varepsilon],$$

$$y = \sum_{k=0}^{\infty} \rho^k V^k (X\beta - \rho V X\beta + \varepsilon),$$

$$y = \sum_{k=0}^{\infty} \rho^k V^k X\beta - \sum_{k=0}^{\infty} \rho^{k+1} V^{k+1}(X\beta) + \sum_{k=0}^{\infty} \rho^k V^k \varepsilon,$$

$$y = X\beta + \underbrace{\sum_{k=1}^{\infty} \rho^k V^k X\beta - \sum_{k=1}^{\infty} \rho^k V^k (X\beta)}_{=0} + \sum_{k=0}^{\infty} \rho^k V^k \varepsilon,$$

$$y = X\beta + \underbrace{\sum_{k=1}^{\infty} \rho^k V^k \varepsilon}_{misspecification term} + \varepsilon.$$

The misspecification term $\sum \rho^k V^k \varepsilon \; (k = 1, \ldots, \infty)$ remained uncorrelated with the explanatory variable *X*, as the standard OLS assumption of the disturbances ε was uncorrelated with the geosampled residualized variables generated from the parameter estimation process. The spatial lag model was expressed as $(I-\rho V)y = X\beta + \varepsilon$. Substituting the transformation generated:

$$y = \sum_{k=0}^{\infty} \rho^k V^k (X\beta + \varepsilon) \text{ and } y = X\beta + \underbrace{\sum_{k=1}^{\infty} \rho^k V^k (X\beta + \varepsilon)}_{misspecification term} + \varepsilon.$$

The misspecification term $\sum \rho^k V^k (X\beta + \varepsilon)$ $(k = 1, \ldots, \infty)$ then included the exogeneous variables *X*. Consequently, the state-level variables were correlated with the misspecification term. Under this condition, standard OLS results for the basic regression model $y = X\beta + \varepsilon^*$ generated from the regressed covariate coefficients provided biased estimates $\hat{\beta}$ of the underlying regression parameters β.

Eigenvector analyses

The correlation, or lack thereof, between the predictor variables and the misspecification terms in the autoregressive risk model were utilized to design spatial proxy variables so the properties of either model could be satisfied. Unfortunately, misspecification of the main exposure variable, as well as other covariates, is not uncommon in regression models (Jacob et al., 2013).

Functional forms can adversely affect tests of the association between the exposure and response variables (Jacob et al., 2013). In regression analyses, the process of developing a regression model consists of selecting an appropriate functional form for the model and then choosing which variables to be included in the regression procedure (Griffith, 2003). A function shall be defined for our purposes as a set of inputs and a set of permissible outputs with the property that each input is related to exactly one output (Griffith, 2003). An example in transmission risk modeling is the function utilized by Jacob et al. (2014) when constructing the MDR-TB explanatory covariate coefficient *x* to its square x^2. In the model, the output of a function *f* corresponded to an input *x* which then was denoted by *f*(*x*). The input variable(s) are sometimes referred to as the argument(s) of the function (Griffith, 2003). The first step for constructing a robust TB model in a SAS covariance matrix is to specify the model (Jacob et al., 2014). If an estimated covariate coefficient model is misspecified it will be biased and inconsistent (Jacob et al., 2013). In regression-based risk models, the term misspecification covers a broad range of modeling errors including measurement errors and discretizing continuous, normalized explanatory variables (Griffith, 2003).

Two different projection matrices, $M_{(1)} \equiv I - 1\left(1^T 1\right)^{-1} 1^T$ and $M_{(X)} \equiv I - X\left(X^T X\right)^{-1} X^T$. in AUTOREG were considered for autoregressing the state-level TB data. The projection matrix $M_{(1)}$ is a special case of the more general projection matrix $M_{(X)}$ [ww.sas.edu]. The general projection matrix $M_{(X)}$ in the TB model included a constant unity vector 1, as well as additional TB-transmission explanatory variables. A set of eigenvectors $\{e_1, \ldots, e_n\}_{SAR}$ was then extracted from the regressed quadratic form

$$\{e_1, \ldots, e_n\}_{SAR} \equiv evec\left[M_{(X)} \frac{1}{2}\left(V + V^T\right) M_{(X)}\right], \quad (1)$$

which was designed orthogonal to the exogeneous variable *X*. The projection matrix $M_{(X)}$ imposed this constraint. In contrast, the set of operationizable eigenvectors $\{e_1, \ldots, e_n\}_{Lag}$ was extracted from

$$\{e_1, \ldots, e_n\}_{Lag} \equiv evec\left[M_{(1)} \frac{1}{2}\left(V + V^T\right)M_{(1)}\right]. \quad (2)$$

These two different sets of eigenvectors established a basis for constructing a robust, regression-based distribution model, with both expressions solely defined in terms of the regressed exogeneous information. This model feature in AUTOREG enabled us to employ the eigenvector spatial filtering approach for predictions of the regressed, endogeneous variable *y*. The associated sets of eigenvalues $\{\lambda_1, \ldots, \lambda_n\}_{Lag}$ and $\{\lambda_1, \ldots, \lambda_n\}_{SAR}$, with $\lambda_i \geq \lambda_{i+1}$, range were then employed in AUTOREG for properly standardizing adjacent link matrices *V* that related to irregular spatial tessellations generated from the regressed, predictive state-level TB covariate coefficients. The components of each eigenvector, e_i, were then mapped in SAS/GIS onto an underlying spatial tessellation which exhibited a distinctive topographic pattern ranging from positive spatial autocorrelation (PSA), or similar values of log-transformed count data aggregating in space, for $\lambda_i > E(I)$ to negative spatial autocorrelation NSA, which is the aggregation of dissimilar log-values in space for $\lambda_i > E(I)$. Each eigenvector was mapped where $E(I)$ was the expected value of Moran's *I* under the assumption of (a) spatial independences and (b) as outputs from related projection matrices $M_{(1)}$ or $M_{(X)}$, respectively.

It was noted that the associated Moran's *I* autocorrelation coefficient of each eigenvector e_i generated from the risk model was equal to its associated eigenvalue $\lambda_i = \left[e_i^T\left(V + V^T\right)e_i\right] / \left(2e_i^T e_i\right)$, but only if *V* was scaled to satisfy $\left[1^T\left(V + V^T\right)1\right]/2 = n.$. Moran's autocorrelation is often denoted as *I*, which is an extension of Pearson's product moment correlation coefficient, a commonly used measure of the amount of autocorrelation in regressed, empirical, multivariate, estimators (Griffith, 2003). In previous research, Jacob et al. (2014) employed the Pearson's correlation coefficient for spatially summarizing a dataset of autocovariance terms quantitated between multiple empirical, geosampled predictor variables to define the covariance of multivariate parameterized covariates divided by the product of their standard deviations using $\rho_{X,Y} = \frac{\mathrm{cov}(X, Y)}{\sigma_X \sigma_Y} = \frac{E[(X - \mu_X)(Y - \mu_Y)]}{\sigma_X \sigma_Y}$. In this research the formula defined the normalized, state-level population, correlation coefficient. Substituting estimates of the covariances and variances derived from the auto-regressed dataset of covariate coefficients provided the sample correlation coefficient, denoted by:

$$r : r = \frac{\sum_{i=1}^{n}(X_i - \overline{X})(Y_i - \overline{Y})}{\sqrt{\sum_{i=1}^{n}(X_i - \overline{X})^2}\sqrt{\sum_{i=1}^{n}(Y_i - \overline{Y})^2}}.$$

An equivalent expression rendered the correlation coefficient as the mean of the products of the standard scores in AUTOREG. Based on paired normalized, spatial data feature attributes $(\text{i.e.}, X_i, Y_i)$, the sample Pearson correlation coefficient was:

$$r - \frac{1}{n-1}\sum_{i=1}^{n}\left(\frac{X_i - \overline{X}}{s_X}\right)\left(\frac{Y_i - \overline{Y}}{s_X}\right),$$

where $\frac{X_i - \overline{X}}{s_X}$ and $\overline{X}$ were the standard score sample mean and the sample standard deviation, respectively.

The eigenvectors yielded distinct, predictive, geo-spatiotemporal, map pattern descriptions of latent spatial autocorrelation in the empirical, geosampled data. This was interpreted as synthetic map variables that represented specific natures (positive or negative) and degrees (negligible, weak, moderate and strong) of potential spatial autocorrelation.

For the covariates, two counteracting spatial autocorrelation effects were conceptualized (that is, common factors leading to PSA, and competitive factors leading to NSA materializing) at the same time, with a possible net effect being global detection of near-zero spatial autocorrelation. If a parsimonious set of eigenvectors is to be selected for, eigenvectors depicting near-zero spatial autocorrelation should be avoided, as such a set of latent vectors associated with a matrix equation will fail to capture any geographic information (Griffith, 2003).

The eigenvector spatial filtering approach added a minimally sufficient set of eigenvectors as proxy-variables to the set of linear predictors in our predictive model by inducing mutual independence in the covariate estimators. The regression residuals represented geo-spatiotemporally independent, state-level, predictor variable components. The spatial pattern in the eigenvectors was synthetic. In the state level TB model, positive global autocorrelation in the local patterns of the parameters exhibited only positive local autocorrelation and vice versa for negative global autocorrelation. The eigenvectors e_i and e_j within each set of eigenvectors were then mutually orthogonal, as the symmetry transformation $\frac{1}{2}\left(V + V^T\right)$ was a quadratic form as revealed in Equations (2.1) and (2.2).

As mentioned previously, the eigenvectors of specification (2.1) were orthogonal to the time-series, exogeneous, variables *X* of the regression TB forecast model constructed in AUTOREG employing the georeferenced, explanatory covariates. Conversely, the eigenvectors of specification (2.2) were orthogonal only to the constant unity vector 1 in *X*. This quantifiable orthogonality had implications for modeling the geospatialized misspecification terms in the risk model which allowed each collection of eigenvectors to be linked to its specific autoregressive model residual. This was accomplished by letting E_{SAR} be a matrix whose vectors were subsets of $\{e_1, \ldots, e_n\}_{SAR}$. Within-group estimation of higher-order autoregressive panel models were also considered with exogenous regressors and fixed effects, where the lag order was possibly misspecified. Even when disregarding the misspecification bias, the fixed-effect bias formula regressed differently from the correctly specified case, though its asymptotic order remained the same under stationary conditions. A linear combination of this subset was approximated by employing the misspecification term of the autoregressive version of the state-level, TB predictive, risk model which was expressed as

$$(E_{SAR}\gamma \approx \sum_{k=1}^{\infty}\rho^k V^k \varepsilon). \quad (3)$$

The linear combination $E_{SAR}\gamma$ remained orthogonal to exogeneous variables *X*, so the estimated predictor variables $\hat{\beta}$ were unbiased. Also, as a property of the OLS estimator, the estimated term $E_{SAR}\gamma$ was orthogonal to the residuals $\hat{\varepsilon}$. The model $y = X\hat{\beta} + E_{SAR}\hat{\gamma} + \hat{\varepsilon}$ decomposed the endogeneous predictor variable *y* into a systematic trend component, a stochastic signal component and white-noise residuals. The term $E_{SAR}\hat{\gamma}$ removed variance inflation in the mean square error (MSE) term attributable to spatial autocorrelation in dataset of covariate coefficients.

Alternatively, for the spatial lag model (Equation 3), a risk model was constructed employing E_{Lag}, a matrix of those eigenvectors which were a subset of $\{e_1, \ldots, e_n\}_{Lag}$. The approximation of the misspecification term became $E_{Lag}\gamma \approx \sum_{k=0}^{\infty} \rho^k V^k (X\beta + \varepsilon)$. Since $E_{Lag}\gamma$ was correlated with the exogeneous variables *X*, its incorporation into the state-level, TB risk model corrected the bias of estimated plain OLS parameters $\hat{\beta}$ in the analysis of latent spatial lag. The model $y = X\hat{\beta} + E_{Lag}\hat{\gamma} + \hat{\varepsilon}$ was generated from covariates, which were a decomposition of the spatial lag model o, a systematic trend component, a stochastic signal component, and a dataset of white-noise residuals. For the risk model, it was now noted that the trend and the stochastic/deterministic, time-series, signals were no longer uncorrelated and the mean square error (MSE) was deflated.

The set of eigenvectors $\{e_1, \ldots, e_n\}_{Lag}$ of the spatial lag model (Equation 3) was then calculated in AUTOREG independently of the exogeneous, state-level, predictor variables *X*. This calculation was dependent on the underlying spatial link matrix *V*. It was found that this filtering approach was more adaptable to a specification search of the relevant exogeneous variables and spatial predictions with the regressed temporal shifting predictor variable values in our risk model in AUTOREG. In contrast, for the simultaneous autoregressive model (Equation 2), the eigenvectors $\{e_1, \ldots, e_n\}_{SAR}$ depended through the projection of $M_{(X)}$ on the exogenous variables *X*. Thus, any change in the underlying model structure required a recalculation of the eigenvectors to generate more robust tessellations. Thereafter, spatial filtering of either the spatial lag model or the simultaneous autoregressive model with a common factor constraint only required identification of one set of selected eigenvectors, namely E_{SAR} or E_{Lag},. The relevant set of eigenvectors was applied to all the TB predictor covariates in both models. For the generic autoregressive model (Equation 1), however, spatial filtering was applied individually to each covariate coefficient. The generic specification of autoregressive spatial models then associated a specific spatial lag factor with the endogeneous *y* variable and other lag factors for each additional exogeneous variable. The eigenvectors $\{e_1, \ldots, e_n\}_{Lag}$ were employed to filter spatial autocorrelation in the generic, autoregressive vulnerability model employing each geosampled covariate estimator.

The next step was identification of appropriate, parsimonious subsets of eigenvectors E_{SAR} or E_{Lag} from either risk model explanatory specification (Equation 1) or (Equation 2). A particular subset of eigenvectors was deemed suitable if the optimizable residuals $\hat{\varepsilon}$ of the resulting spatially filtered model becomes stochastically independent with respect to the underlying sampled spatial structure *V* (Griffith, 2003). Thereafter, parsimony in model estimation was defined as the smallest possible subset of eigenvectors leading to geospatial independence in the residually forecasted derivatives of the TB model being identified. It was noted that geospatial patterns of different eigenvectors expressed independent and filter autocorrelation of the derivatives of the regression model as formalized by a georeferenced vector. Similar methodology has been employed for extrapolation of predictor covariates associated with hyperendemic transmission foci in other contexts.

RESULTS

Initially, a Poisson regression model was constructed in PROC LOGISTIC using temporospatial TB covariate coefficient measurement values. The Poisson process in our analysis was provided by the limit of a binomial distribution of the sampled state-level explanatory predictor covariate coefficient estimates using:

$$P_p(n \mid N) = \frac{N!}{n!\,(N-n)!}\, p^n (1-p)^{N-n} \qquad (4)$$

The distribution was viewed as a function of the expected number of state-level count variables using the sample size *N* for quantifying the fixed *p* in Equation 1, which was then transformed into the linear equation:

$$P_{\frac{v}{N}}(n|N) = \frac{N!}{n!(N-n)!}\left(\frac{v}{N}\right)^n \left(1-\frac{v}{N}\right)^{N-n}.$$

Based on the sample size *N*, the distribution as it approached $P_v(n)$ was:

$$\lim_{n\to\infty} P_p(n|N) = \lim_{N\to\infty} \frac{N(N-1)\cdots(N-n+1)}{n!}\frac{v^n}{N^n}\left(1-\frac{v}{N}\right)^N \left(1-\frac{v}{N}\right)^{-n} = \lim_{N\to\infty}\frac{N(N-1)\cdots(N-n+1)}{N^n}\frac{v^n}{n!}\left(1-\frac{v}{N}\right)^N\left(1-\frac{v}{N}\right)^{-n} = 1\cdot\frac{v^n}{n!}\cdot e^{-v}\cdot 1 = \frac{v^n e^{-v}}{n!}.$$

The PROC LOGISTIC procedure then fit a generalized linear model to the sampled data by maximum likelihood estimation of the parameter vector β. The PROC LOGISTIC procedure estimated the seasonal-sampled parameters of each state-level TB model numerically through an iterative fitting process. The dispersion parameter was then estimated by the residual deviance and by Pearson's chi-square divided by the degrees of freedom (df). Covariances, standard errors, and *p*-values were computed for the sampled covariate coefficients based on the asymptotic normality derived from the maximum likelihood estimation.

Note that the sample size *N* completely dropped out of the probability function, which had the same functional form for all the sampled state-level parameter estimator indicator values (that is, v). As expected, the Poisson distribution was normalized so that the sum of probabilities equaled 1. The ratio of probabilities was then determined by:

$$\sum_{n=0}^{\infty} P_v(n) = e^{-v}\sum_{n=0}^{\infty}\frac{v^n}{n!} = e^{-v}e^{v} =$$

which was then expressed as

$$\frac{P_v(n=i+1)}{P(n=i)} = \frac{\frac{v^{i+1}e^{-v}}{(i+1)!}}{\frac{e^{-v}v^i}{i!}} = \frac{v}{i+1}.$$

Our model was generalized by introducing an unobserved

heterogeneity term for each sampled state-level observation i. The TB weights were then assumed to differ randomly in a manner that was not fully accounted for by the other covariates. This state-level process was formulated as $E(y_i \mid x_i, \tau_i) = \mu_i \tau_i = e^{x_i'\beta - \varepsilon_i}$, where the unobserved heterogeneity term $\tau_i = e^{\varepsilon_i}$ was independent of the vector of regressors x_i. The distribution of y_i was conditional on x_i and had a Poisson specification with conditional mean and variance $\mu_i \tau_i : f(y_i \mid x_i, \tau_i) = \frac{\exp(-\mu_i \tau_i)(\mu_i \tau_i)^{y_i}}{y_i!}$. We then let $g(\tau_i)$ be the probability density function of τ_i. At this point, the distribution $f(y_i \mid x_i)$ was no longer conditional on τ_i. Instead it was obtained by integrating $f(y_i \mid x_i, \tau_i)$ with respect to $g(\tau_i)$: $f(y_i \mid x_i) = \int_0^\infty f(y_i \mid x_i, \tau_i) g(\tau_i) d\tau_i$.
It was found that an analytical solution to this integral existed in our state-level model when τ_i was assumed to follow a gamma distribution. The model also revealed that y_i was the vector of the sampled predictor covariate coefficients while x_i was independently Poisson-distributed with $P(Y_i = y_i \mid x_i) = \frac{e^{-\mu_i} \mu_i^{y_i}}{y_i!}, y_i = 0, 1, 2 \ldots$, and the mean parameter (that is, the mean number of state-level sampling events per temporospatial period) was given by $\mu_i = \exp(x_i'\beta)$, where β was a $(k+1) \times 1$ parameter vector. The intercept in the model was β_0 and the coefficients for the k regressors were $\beta_1, \ldots, \beta_k$. Taking the exponential of $x_i'\beta$ ensured that the mean parameter μ_i was nonnegative. Thereafter, the conditional mean was provided by $E(y_i \mid x_i) = \mu_i = \exp(x_i'\beta)$. The state-level parameter estimators were then evaluated using $\ln[E(y_i \mid x_i)] = \ln(\mu_i) = x_i'\beta$ in PROC LOGISTIC. Note, that the conditional variance of the count random variable was equal to the conditional mean (i.e., equidispersion) in our model $V(y_i \mid x_i) = E(y_i \mid x_i) = \mu_i$]. In a log-linear model the logarithm of the conditional mean is linear (Haight 1970). The marginal effect of any state-level regressor in the TB model was provided by $\frac{\delta E(y_i \mid x_i)}{\delta x_{ji}} = \exp(x_i'\beta)\beta_j = E(y_i \mid x_i)\beta_j$. Thus, a one-unit change in the jth regressor in the model led to a proportional change in the conditional mean $E(y_i \mid x_i)$ of β_j. The standard estimator for our Poisson model was the maximum likelihood estimator. Since the state-level observations were independent, the log-likelihood function in the model was then:

$$= \sum_{i=1}^{N} (-\mu_i + y_i \ln \mu_i - \ln y_i!) = \sum_{i=1}^{N} (-e^{x_i'\beta} + y_i x_i'\beta - \ln y_i!)$$

Given the sampled dataset of state-level parameter estimators θ and an input vector x, the mean of the predicted Poisson distribution was provided by $E(Y \mid x) = e^{\theta' x}$. This way, the Poisson distribution's probability mass function was then rendered by:

$$p(y \mid x; \theta) = \frac{e^{y(\theta' x)} e^{-e^{\theta' x}}}{y!}.$$

The probability mass function in our targeted TB risk model is the primary means for defining a discrete probability distribution. As such, functions could exist for either scalar or multivariate field-sampled random variables, given that the distribution is discrete (Jacob et al., 2015). Since the geosampled, state-level TB dataset consisted of *m* vectors $x_i i \in \mathbb{R}^{n+1}, i = 1, \ldots, m,$ along with a set of *m* values $y_1, \ldots, y_2 \in \mathbb{R}$, the sampled estimators *θ*, the probability of attaining this particular set of the sampled observations was provided by:

$$p(y_1, \ldots, y_m \mid x_1, \ldots, x_m; \theta) = \prod_{i=1}^{m} \frac{e^{y_i(\theta' x_i)} e^{-e^{\theta' x_i}}}{y_i!}$$

Consequently, the set of *θ* that made this probability as large as possible in the model estimates was obtained. The equation was first rewritten as a likelihood function in PROC LOGISTIC in terms of θ:

$$p(y_1, \ldots, y_m \mid x_1, \ldots, x_m; \theta) = \prod_{i=1}^{m} \frac{e^{y_i(\theta' x_i)} e^{-e^{\theta' x_i}}}{y_i!}$$

Note the expression on the right hand side in our model had not actually changed. Next, we used a log-likelihood $\ell(\theta \mid X, Y) = \log L(\theta \mid X, Y) = \sum_{i=1}^{m} \left(y_i(\theta' x_i) - e^{\theta' x_i} - \log(y_i!) \right)$].

Because the logarithm is a monotonically increasing function, the logarithm of a function achieves its maximum value at the same points as the function itself, and, hence, the log-likelihood can be used in place of the likelihood in maximum likelihood estimation and related techniques (Hosmer and Lemeshew 2011). Finding the maximum of a function often involves taking the derivative of a function and solving for the parameter estimator being maximized; this is often easier when the function being maximized is a log-likelihood rather than the original likelihood function (Jacob et al., 2012). We

Table 2. Summary of backward elimination.

Summary of Backward Elimination							
Step	Variable Removed	Number Vars In	Partial R-Square	Model R-Square	C(p)	F Value	Pr > F
1	Black	21	0	0.5154	21.002	0	0.968
2	Multiple_Races	20	0	0.5154	19.017	0.02	0.902
3	Age_under_5	19	0	0.5153	17.036	0.02	0.889
4	Native_Born	18	0.0025	0.5128	16.239	1.22	0.271
5	Long_Care	17	0.0027	0.5101	15.517	1.29	0.257
6	Age_25_44	16	0.0034	0.5067	15.146	1.65	0.201
7	Age_45_64	15	0.0043	0.5024	15.185	2.06	0.153
8	Age_65_More	14	0.0041	0.4983	15.147	1.97	0.162
9	Age_5_14	13	0.0041	0.4942	15.12	1.97	0.162
10	NonInject_Drug	12	0.0046	0.4896	15.31	2.18	0.141
11	Alcohol	11	0.0049	0.4847	15.648	2.32	0.129
12	Jail	10	0.0049	0.4798	15.992	2.31	0.13

noted the parameters θ only appeared in the first two terms of each term in the summation. Therefore, given that we were only interested in finding the best value for θ in the state-level predictive TB regression model, we dropped the $y_i!$ and simply wrote:

$$\ell(\theta \mid X, Y) = \sum_{i=1}^{m} \left(y_i (\theta' x_i) - e^{\theta' x_i} \right)$$

Thereafter, to find a maximum, we solved an equation $\frac{\partial \ell(\theta \mid X, Y)}{\partial \theta} = 0$ which had no closed-form solution. However, the negative log-likelihood (LL) $-\ell(\theta \mid X, Y)$ was a convex function, and so standard convex optimization was applied to find the optimal value of θ. It was found that, given the Poisson process in our regression model, the limit of a binomial distribution was:

$$p_p(n \mid N) = \frac{N!}{n!(N-n)!} p^n (1-p)^{N-n}.$$

Viewing the distribution as a function of the expected number of successes $\nu \equiv Np$ in the model, rather than the sample size N for fixed P, rendered the equation (2.1), which became:

$$p_{\nu/N}(n \mid N) = \frac{N!}{n!(N-n)!} \left(\frac{\nu}{N} \right)^n \left(1 - \frac{\nu}{N} \right)^{N-n}$$

Our model revealed that as the sample size N became larger, the distribution approached P when the following equations aligned:

$$\lim_{N \to \infty} p_p(n \mid N) \quad \lim_{N \to \infty} \frac{N(N-1)\ldots(N-n+1)}{n!} \frac{\nu^n}{N^n} \left(1 - \frac{\nu}{N}\right)^N \left(1 - \frac{\nu}{N}\right)^{-n} \quad , \quad \lim_{N \to \infty} \frac{N(N-1)\ldots(N-n+1)}{N^n} \frac{\nu^n}{n!} \left(1 - \frac{\nu}{N}\right)^N \left(1 - \frac{\nu}{N}\right)^{-n}$$

$$1 \cdot \frac{\nu^n}{n!} \cdot e^{-\nu} \cdot 1 \text{ and } \frac{\nu^n e^{-\nu}}{n!}.$$

We then considered the Euler product $\zeta(s) = \prod_{k=1}^{\infty} \frac{1}{1 - \frac{1}{p_k^s}}$ where $\zeta(s)$ was the Riemann zeta function and p_k was the k the prime. $\zeta(1) = \infty$. Thereafter, by taking the finite product up to k=n in our TB regression model and pre-multiplying by a factor $1/\ln p_n$, it was then possible to employ $n \to \infty$, which rendered $\lim_{n \to \infty} \frac{1}{\ln p_n} \prod_{k=1}^{n} \frac{1}{1 - \frac{1}{p_k}} = e^{\gamma}$, or 1.431912. To check for non-normalities (for example, heteroskedascity, multicolinearaity) in the regression forecasts a stepwise backward model validating procedure in PROC LOGISTIC was employed (Table 2).

The model for overdispersion was then with a likelihood ratio test. This test quantified the equality of the mean and the variance imposed by the Poisson distribution against the alternative that the variance exceeded the mean. For the negative binomial distribution, the variance= mean + k mean^2 (k≥ 0, the negative binomial distribution reduces to Poisson when k=0) (Jacob et al., 2013). For this study, the null hypothesis was H_0: k=0 and the alternative hypothesis was H_a : k>0. To carry out the test, we used the following steps initially and then ran the model using negative binomial distribution and a record log-likelihood (LL) value. We then recorded LL for the Poissonized TB model. The likelihood ratio (LR) test was employed, and the LR statistic was computed, -2(LL (Poisson) – LL (negative binomial). The asymptotic distribution of the LR statistic had probability mass of one half at zero and one half – chi-square distribution with 1 df. To test the null hypothesis further, the critical value of chi-sq distribution corresponding to significance level 2 was used. That is, H_0 was rejected if LR statistic > 2 $_{(1-2,\ 1\ df)}$.

Next, our predictor covariate coefficient estimates were assumed to be based on the log of the mean, which was a linear function of independent variables, log() = intercept + b1*X1 +b2*X2 + ...+ b3*Xm. This log-transformation implied that the exponential function of independent variables equaled exp(intercept + b1*X1 +b2*X2 + ...+ b3*Xm). Instead of assuming, as we did before, that the distribution of the state-level covariate coefficients Y was Poissonian, a negative binomial distribution was assumed. The implications meant relaxing the generalized linear Poisson regression specification assumption concerning equality of the mean and variance, since it was found in our model that the variance of negative binomial was equal to + k2, where k ≥ 0 was a dispersion parameter. The maximum likelihood method was then used to estimate k as well as the parameter estimators of the model for log(). The SAS syntax for running negative binomial regression is very similar to the syntax for Poisson regression. The only change is the dist option in the MODEL statement is used instead of dist = poisson,dist = nb. The probability mass function of the negative binomial distribution with a gamma distributed mean in the predictive TB model was then expressed using the sampled covariate coefficients estimates as:

$$f(k) \equiv \Pr(X=k) = \binom{k+r-1}{k}(1-p)^r p^k$$

for the variables $k = 0, 1, 2, \ldots$.

In this equation, the quantity in parentheses was the binomial coefficient, and was equal to:

$$\binom{k+r-1}{k} = \frac{(k+r-1)!}{k!\,(r-1)!} = \frac{(k+r-1)(k+r-2)\cdots(r)}{k!}.$$

This quantity was alternatively written as:

$$\frac{(k+r-1)\ldots(r)}{k!} = (-1)^k \frac{(-r)(-r-1)(-r-2)\ldots(-r-k+1)}{k!} = (-1)^k \binom{-r}{k}$$

for explaining the negative binomial qualities in our regression model (Jacob et al., 2013).

Results from both Poissonian and negative binomial model residuals revealed that the covariate coefficient estimates were highly significant, but furnished virtually no predictive power. Inclusion of indicator variables denoting the time sequence and the district location spatial structure were articulated with ArcGIS Thiessen polygons, which also failed to reveal meaningful covariates. Perhaps the presence of noise in the geosampled state –level TB data was attributable for this misspecification. Thus, the state-level TB data were adjusted and quantified for space-time consistency. Next, an Autoregressive Integrated Moving Average (ARIMA) analysis of individual district time-series was conducted in PROC ARIMA. Given our temporospatial data X_t, where t was an integer index and the X_t the values, an ARIMA model was built using:

$$\left(1-\sum_{i=1}^{p}\alpha_i L^i\right) X_t = \left(1+\sum_{i=1}^{q}\theta_i L^i\right)\varepsilon_t$$

where L was the lag operator, α_i were the parameters of the autoregressive portion of the model, θ_i were the parameters of the moving average part, and ε_t were error terms. ARIMA models are, in theory, the most general class of models for forecasting a time series which can be made stationary by transformations such as differencing and logging (Griffith, 2003). The easiest way to think of ARIMA models is as fine-tuned versions of random-walk and random-trend models: the fine-tuning consists of adding lags of the differenced series and/or lags of the forecast errors to the prediction equation, as needed to remove any last traces of autocorrelation from the forecast errors (Griffith 2003). The error terms ε_t were generally assumed to be independently sampled from a normal distribution with zero mean: ε_t~ N(0,σ2), where σ2 was the variance. Thereafter, a random effects term was specified with the time series, state–level data. This random effects specification revealed a non-constant, variable mean across states, which mathematically represented a state–level constant across time. The random effects specification also represented a state-specific intercept term, a random deviation from the overall intercept term, which was based on a draw from a normal frequency distribution. This random intercept represented the combined effect of all explicative state-level predictor covariate coefficients, which caused some states to be prone to greater TB prevalence than others. Inclusion of a random intercept assumed random heterogeneity in the states' propensity or underlying risk of TB prevalence which persisted throughout the entire duration of the time sequence under study. Values were procured for this random effects term, and state-level for prevalence regressed on predicted prevalence rates. The Poisson mean response specification was mu = exp[a + re+ LN(population)], Y ~Poisson(mu).

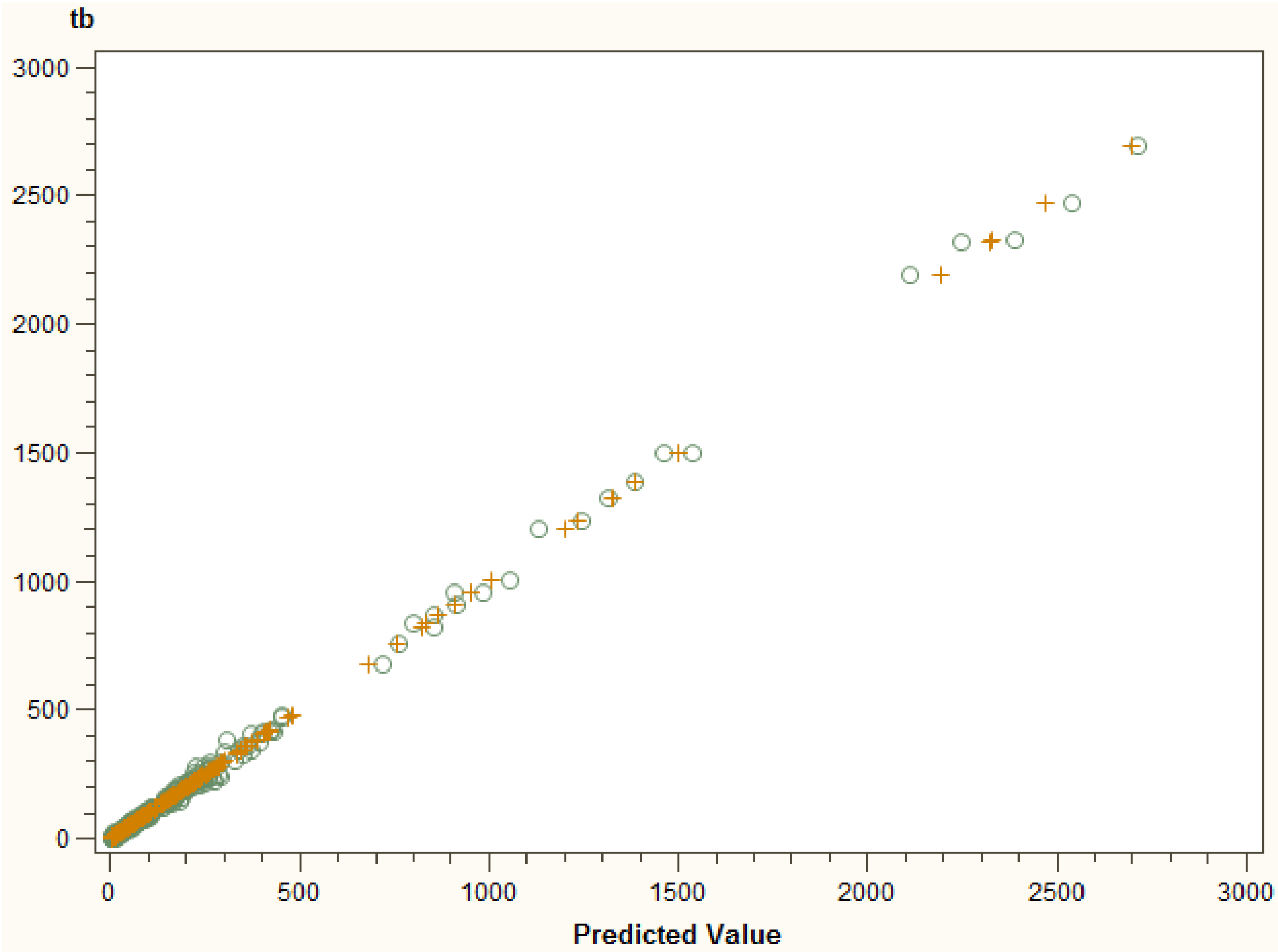

Figure 2. Scatterplot of the predicted and the observed TB rates by state and time period.

A simple space-time binomial mixed model was then estimated, with the random effects term furnishing a common factor through time beyond the simple time sequence fixed component. This random effects term comprised spatially structured and spatially unstructured state-level components. The time sequence covariate alone accounts for roughly 2% of the variation in TB rates across the space-time series. Its combination with the random effects term accounts for roughly 99% of this variation. The deviance statistics for the excess binomial variation is 53.4. Figure 2 portrays the relationship between the predicted and the observed rates. The estimate equations are as follows:

$$\hat{p} = \frac{1}{1 + e^{10.4180 - 0.0708T + \hat{\xi}}}$$

$$\hat{\xi} \sim N(-0.0025,\ 0.6059^2), PS(S-W) = 0.34$$

The resulting estimated number of cases is for a given state for a given year is:

$$\hat{n}_{TB} = 0.0885 + 0.9996 \times \text{Population} \times \hat{p}$$

The random effects term has both a spatially structured and a spatially unstructured component (Figure 3). The spatially structured random effects term contains five eigenvectors representing non-trivial levels of positive spatial autocorrelation, and accounts for roughly 50% of the variation in the random effects term. Its Moran Coefficient (MC) is 0.66, and its Geary Ratio (GR) is 0.35. The spatially unstructured random effects terms has only trace levels of spatial autocorrelation, with MC = 0.02, and Gr = 0.89. All three components closely conform to a bell-shaped curve (Figure 4).

Limitations

As with most predictive analyses, there were limitations in

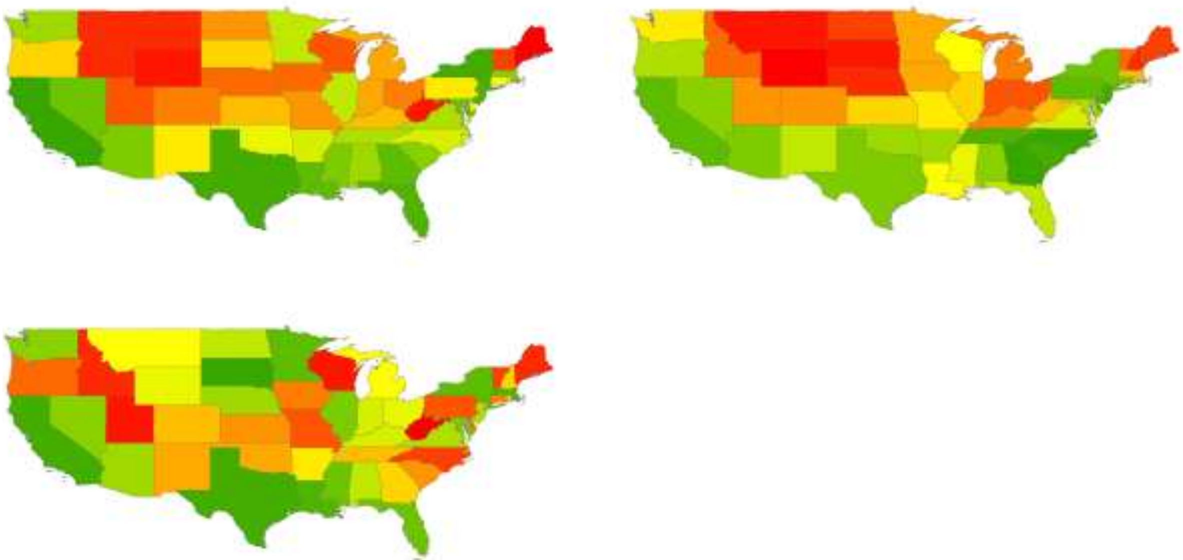

Figure 3. Top left (a): random effects term; MC = 0.33, and GR = 0.55. Top right (b): spatially structure random effects term; MC = 0.66, and GR = 0.35. Bottom left (c): spatially unstructured random effects term; MC = 0.02, and GR = 0.89.

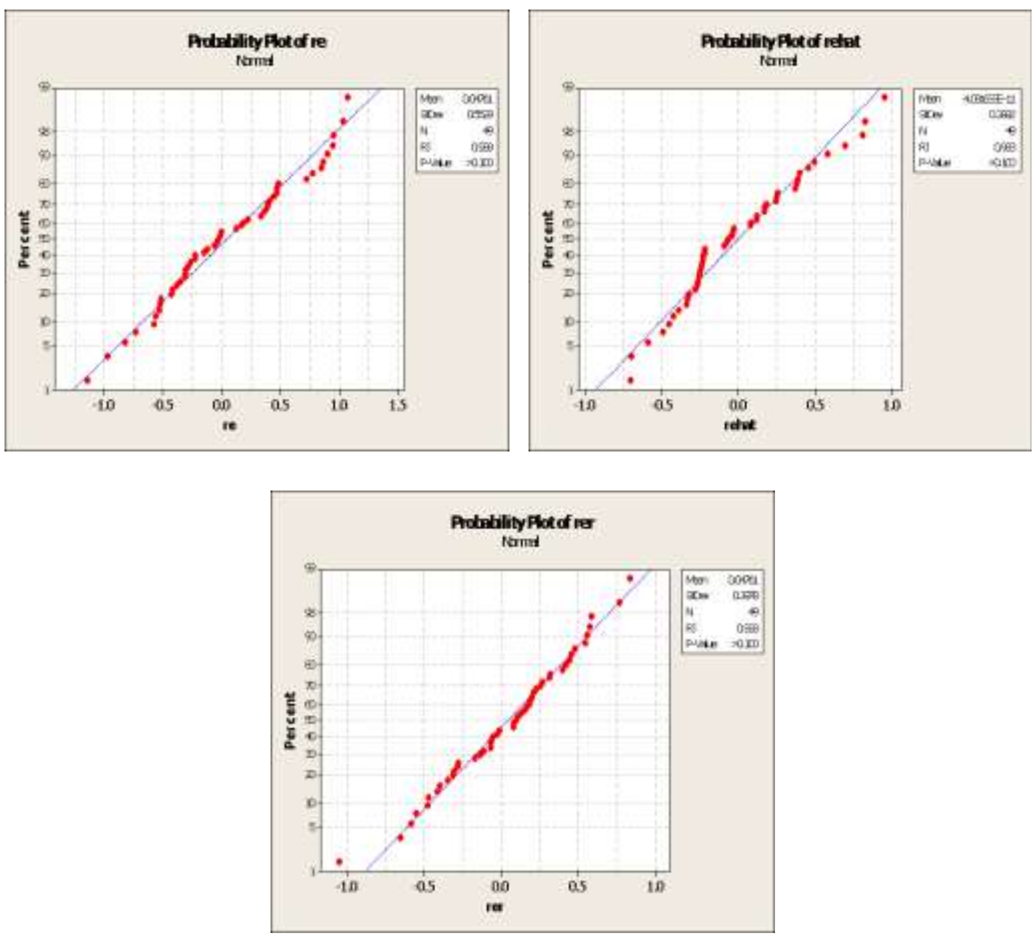

Figure 4. Top left (a): normal quantile plot for the random effects term. Top right (b): normal quantile plot for the spatially structure random effects term. Bottom left (c): normal quantile plot for the spatially unstructured random effects term.

the proposed model which may lead to varying outcomes. The model may have too few variables for the scope of the problem that we are attacking. As stated before, investigation into other potential risk factors, including diabetes is warranted for construction of more robust predictive models. A Bayesian approach may also provide superior methodology for finding local and residual autocorrelation that more traditional frequentist methods may be less sensitive to. An autoregressive integrated moving average (ARIMA) model may also provide output more sensitive to temporality.

DISCUSSION

The clustering of like tendencies, according to this predictive analysis and shown by a Moran's coefficient of 0.66 for our spatially structured random effects model, produced results that, to say the least, would be considered anomalous with conventional wisdom. States that have been historically considered as hubs for immigrant inflow, including California, Texas, Illinois, Florida and New York, do not project higher rates of TB transmission according to our model. In light of these findings, more contemporary patterns of human movement must be considered to fully understand the nature of TB transmission in the United States. Thanks much in part to economic growth in various regions through the 1990s and early 2000s, coupled with hostile policy toward less affluent immigrant populations in states such as California, the modern landscape for immigrant dispersion within the US began to shift dramatically (Ellis et al., 2014). The Migration Policy Institute, citing the Office of Immigration Statistics of the Department of Homeland Security, states that the number of foreign-born individuals grew by roughly 50 percent or more in the states of Alabama, Arkansas, Delaware, Georgia, Idaho, Indiana, Kentucky, Mississippi, Nevada, North Carolina, South Carolina, South Dakota, Tennessee, and Wyoming through the time period of 2000 to 2009 (Terrazas, 2011). These, of course, are not states that were readily equated with heavier inward flow of immigrant populations through much of the last century.

Very recent findings may also indicate an overall decline in tuberculosis in the foreign-born population in the US, some of which can be attributed to demographic changes. In their analysis, Baker et al. (2016) cite three reasons for this shift: 1) changes in the proportion of foreign-born persons through continued movement; 2) changes in the distribution of countries of origin, and 3) actual changes in TB rates for the countries of origin. True decreases in TB case rates in recent immigrants from China, India, and the Philippines were cited for the reason for the decline in these sub-populations, while a decrease in the Mexican sub-population size in the US was cited as the principal reason for the decline in this group. This study is fairly new but nevertheless points to the importance of considering dynamic demographics in the study of TB transmission. Further, as TB is associated with lifestyle, employing an anthropological approach with ethnographic research concerning known risk factors may lend deeper insight into how these variables relate to transmission, as well as allow for existing transmission models to be individually tailored with unique explanatory variables for a given locale. Munch et al. (2003) employed such an anthropological approach in Cape Town, South Africa in an already cited study, as did Ge et al. (2015) with local transportation and population dispersion. Such an approach may not be as useful at the national level, but it may allow for local governments and health departments to better detail individualized intervention and funding needs to their respective states.

Still another set of challenges arises when we consider American Indian peoples, who continue to suffer higher rates of mortality and hospitalization for infectious diseases, including tuberculosis, as compared even with immigrant groups more often implicated in transmission in most research (Bloss et al., 2011; Cheek et al., 2014; Holman et al., 2011; Reilley et al., 2014; Schneider, 2005). Though there is continued decline in rates of tuberculosis among American Indians, as well, they still continue to experience infectious disease transmission disproportionately as compared with other US populations. In South Dakota in 2015, 11 of the 17 reported TB cases (65%) were identified as Native American, with Native Americans maintaining almost consistently higher rates of mortality due to TB (South Dakota Department of Health, 2015). Montana has also continued to see higher rates of TB for American Indian populations over time (Montana Department of Public Health, 2015). It is not uncommon knowledge that many common risk factors for TB, such as poverty, homelessness, and higher levels of alcohol consumption continue to endure in some American Indian communities. These are colonial legacies that have been carried from the fairly recent past of a young nation's history, and may remain as long as apathy remains. It would seem that as much as the general US population seems to diversify and shift, the indigenous people are static by comparison. Further challenges to quantifying the needs for tuberculosis treatment among American Indians lie with lack of coordination of patient records among care providers in several of these communities and use of coding systems that emphasize billing over surveillance (Podewils et al., 2014), as well as lack of adequate funding for the Indian Health Service.

Other factors that must be taken into account are the distributions of other comorbid infections, as well as non-communicable, chronic diseases that have risen alarmingly in the United States. Potential comorbidities with other diseases are often cited as risk factors for TB. These include infectious diseases such as HIV, as well as the more behavioral and psychosocial issues of IV drug use and alcoholism. Coinfection with HIV contributes to higher rates of mortality from tuberculosis, and is already a well-established risk factor for TB, being one of the most common opportunistic infections in those of HIV positive status. Currently, diabetes is being investigated as another potential risk factor for tuberculosis (Demlow et al., 2015; Suwanpimolkul et al., 2014; Gil-Santana et al., 2016). Though more research is necessary, and does not appear at this point in time to affect the transmission of tuberculosis, it does appear to complicate existing cases (Gil-Santana et al., 2016). This may increase overall healthcare costs and personal hardship for those enduring tuberculosis comorbid with diabetes, resulting in greater hardship as well as a greater general burden for healthcare providers. The financial implications alone make diabetes worth investigating as a risk factor. In communities where high rates for diabetes and tuberculosis overlap, more targeted interventions should be considered.

CONCLUSION AND RECOMMENDATIONS

Predictive modeling using GIS, remote sensing and geostatistics, of course, represents only the first step taken. Toward intervention, community-based approaches are already well known and may provide more specialized solutions closer to home for communities more heavily impacted by the persistence of TB. Ecological interventions are best applied when individualized to the needs and wishes of the community in question. Identification of specific target areas within a larger area, potential contact investigations, weak points in community structure, and concerns of individuals specific to a particular locale are more efficient when members of the community are collaborated with by interventionists or researchers. In this vein, the two-phase PRECEDE-PROCEED Model (PPM) may be of use toward TB elimination in and out of the US. The first grand phase encompasses bottom-up assessments of individual behaviors (proximal elements that directly affect an individual), social context and environment (mid-level elements that an individual may), administrative policy (distal elements), as well as potential interplay of these elements (Gielen et al., 2008). The second grand phase is comprised of implementation and evaluation with continuous improvement and modifications as needed (Gielen et al., 2008). For this reason, the PPM need not be applied in a linear manner. General community-based participatory research methods may also show promise in foreign-born populations, who may be prone to reactivation of latent TB. For recent immigrants seeking classes in English as a second language upon arrival to the United States, community centers where these courses are held may be useful spaces for examination of attitudes and knowledge about TB; referrals for screening may also be a possibility (Wieland et al., 2011, 2012, 2013).

Though we have come very far in lowering the prevalence of tuberculosis in the US, further efforts should not fall by the wayside simply because of a leveling-off in decreasing prevalence rates. With more rigorous screening of incoming individuals, including not only immigrants, but any individuals such as students who have spent a significant amount of time in a place of known hyperendemicity) and further research into risk factors that may indicate higher rates of transmission or complication of existing cases of TB, continued decrease in prevalence rates may be possible.

Conflict of Interests

The authors have not declared any conflict of interests.

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Full Length Research Paper

Leukaemia incidence in residents of municipalities in the State of Rio de Janeiro between 2006 and 2014

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This research aims to study incidence of acute leukaemia in adults living under potential environmental exposure to industrial emissions in selected cities in the state of Rio de Janeiro, Brazil. It evaluates the incidence of hospitalizations for leukaemia among residents of 19 metropolitan areas of the State of Rio de Janeiro registered in the Brazilian Health Care System (SUS) between January 2006 and March 2014, according to their residence area. Here, a comparison among the studied cities was performed taking as estimated morbidity indicator the hospitalization rate for leukaemia by residence area. Nineteen of a total of 92 municipalities in the State of Rio de Janeiro were selected for the present study. The adopted selection criteria were distance of each municipality to the City of Rio de Janeiro of less than 180 km, similar health policies, number of public health facilities, urban and rural population distribution and the amount of industries in each municipality. Thus, the selected municipalities were: Belford Roxo, Duque de Caxias, Itaboraí, Itaguaí, Japeri, Macaé, Mage, Marica, Mesquita, Nilopolis, Niterói, Nova Iguaçu, Queimados, Rio Bonito, Rio de Janeiro, São Gonçalo, São João de Meriti, Seropédica and Tanguá. The study thus revealed that among these municipalities, Macaé, Itaboraí, Queimados and Duque de Caxias showed the highest hospitalization rates for leukemia in adults (≥20 years old) for both sexes. Additionally, morbidity was about 6 times higher than the average of the reference municipalities. A common feature of these municipalities is the massive presence of potentially polluting industries, especially oil refining activities. The results presented herein strongly suggest a correlation between environmental pollution by industrial emissions and acute leukaemia in adults. It is important to note that, even in this situation, the causality can only be determined categorically through individual studies.

Key words: Leukemia, environmental contamination, epidemiology, cancer risk.

INTRODUCTION

Industrialization is a process that, over the years, have become a synonym of obtaining power and respect from those who presented technological delay. For many, it is synonym of development, In fact, development is the aim

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of every country, especially economic development, measured through the Gross Domestic Product (GDP) of each country (Maluf, 2000).

Currently, the Southeastern region of Brazil (comprising the States of São Paulo, Rio de Janeiro, Minas Gerais and Espírito Santo) generates 55.4% of the Brazilian GDP, with Rio de Janeiro State contributing with 11.2% of this total, ranked as the second contributor for the Brazilian GDP in 2011 (IBGE, 2011).

This is due to the allocation of several large investments in this area, namely automotive manufacturers in the Médio Paraíba; the Rio Polymers industry, in Duque de Caxias, aiming at the creation of a chemical-gas complex in that area; the reactivation of the naval industry; the enlargement of investments through Petrobrás and oil industries in several municipal districts such as Macaé; the installation of new oil companies in Rio de Janeiro; the creation of an oil and gas complex in Itaboraí (COMPERJ); the installation, of a metallurgical plant in the industrial district of Santa Cruz and, the development of a container port, in Itaguaí, whose project was meant to be the largest port in Latin America (Osorio and Versiani, 2013).

Alongside this exacerbated growth, harmful consequences have been linked to the environment and the human health, due to increased emissions of pollutant gases inherent to these productive processes, the inadequate discard of waste and the lack of public policies that demand manufacturer responsibility for the life cycle of their respective product (Reis et al., 2012). Proof of this environment and health relationship are the countless reports on the increasing incidence of pathologies, such as cancer, in areas of high exposure loading to chemical substances (Snyder, 2014; Koh et al., 2014; Yong et al., 2014; Loeb and Harris, 2008).

One of the most thoroughly studied cancer types in relation to exposure to carcinogenic substances alongside genetic predisposition is leukaemia (Glass et al., 2014; Boothe et al., 2014; Hoeck et al., 2014). Characterized as a clonal proliferation of hematopoietic cells present in the bone marrow, leukaemia can be classified in four subtypes: acute lymphoblastic, acute myeloid, chronic lymphoid and chronic myeloid, with the former occurring more frequently in children, while the other subtypes are more common in adults (Klepin et al., 2014; Couto, 2015).

The relationship between environmental exposure to chemicals and leukaemia has been studied. Steffen et al (2004) reported an association between acute childhood leukaemia and benzene emitting sources, while Raaschou-Nielsen et al (2016) studied the relationship between traffic-related air pollution and the risk of leukaemia in adults and found an association with the acute myeloid type but not for other subtypes. Fillipini et al. (2015) reported an association between risks for leukaemia and environmental exposure to traffic pollution, particularly benzene. Parodi et al. (2015) found a possible aetiological role of air pollution from an industrial area and the risk of leukaemia in adults in Italy. Garcia-Perez et al. (2015) reported similar results for childhood leukaemia and the proximity of industrial and urban sites. Very few scientific works have been published involving Brazilian environmental exposure and none, to the best of our knowledge have focused on exposure to industrial emissions and leukaemia in residents from surrounding regions of industrial areas.

Therefore, the purpose of the present study was to evaluate the situation of hospitalizations due to leukaemia in residents of the metropolitan area of Rio de Janeiro State registered by the Unified Health System, according to residence area from January 2006 to March 2014.

MATERIALS AND METHODS

Study design

This work refers to an epidemiological study with ecological delineation, comprehending the period between January 2006 to March 2014, using secondary data available from the Unified Health System (DATASUS) and of Brazilian Institute of Geography and Statistics (IBGE) electronic websites regarding selected municipalities in the State of Rio de Janeiro. The morbidity indicator selected was the internment rate due to leukaemia. Taking into consideration the residence areas it was possible to compare the situation in each studied district through ratio rates.

Study area

Nineteen of a total of 92 municipalities in the State of Rio de Janeiro were selected for the present study. The adopted selection criteria were distance of each municipality to the City of Rio de Janeiro of less than 180 km; similar health policies; number of public health facilities; urban and rural population distribution and; the amount of industries in each municipality. Therefore, the selected municipalities were: Belford Roxo, Duque de Caxias, Itaboraí, Itaguaí, Japeri, Macaé, Magé, Maricá, Mesquita, Nilópolis, Niterói, Nova Iguaçu, Queimados, Rio Bonito, Rio de Janeiro, São Gonçalo, São João de Meriti, Seropédica and Tanguá. The location of each study area is displayed in Figure 1.

Study groups

The studied cities were classified into two different groups: reference and cases. More than 18% of residents living in rural areas characterized the reference group. In the case group, the number of people involved in industrial activities is larger and they are, consequently, more exposed to chemical substances coming from those sources. Through these criteria, the cities of Rio Bonito and Seropédica comprised the reference group, in accordance to the data displayed in Table 1.

Morbidity indicators

The morbidity indicators were built considering the hospitalization rate due to leukaemia and the average rate of the ones classified as references, allowing for comparisons of the situations present in each evaluated municipality. Therefore, hospitalizations due to

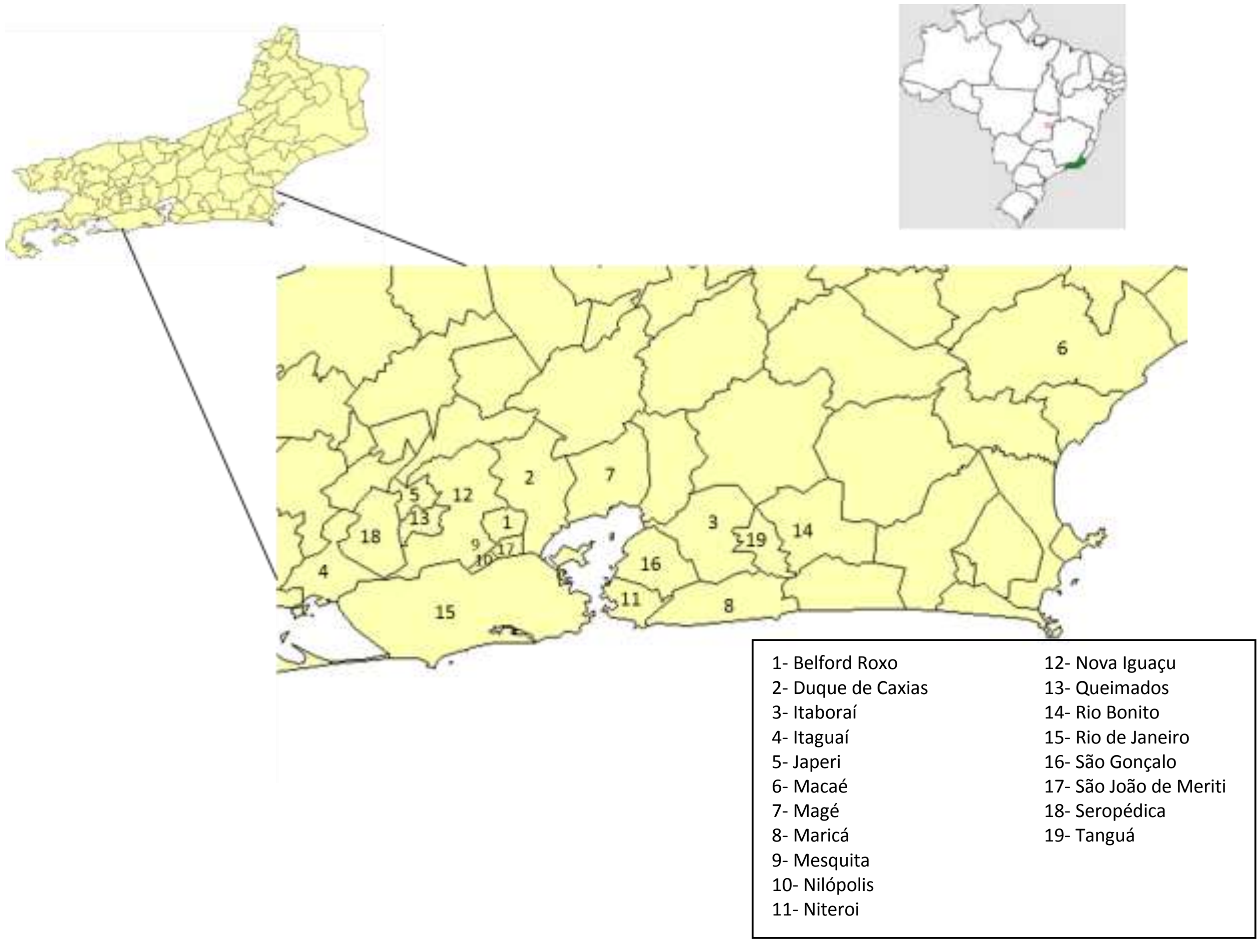

Figure 1. Representative map of Brazil and the State of Rio de Janeiro, highlighting the 19 municipalities selected for this study.

leukaemia selected in Chapter II (Neoplasms (tumours)) and the List of Morbidity (Leukaemia) of the International Classification of Diseases (ICD-10) were included in the numerators. The population at risk was used in the denominators, in other words, the population in which the cases in half of the interval of the studied period arose. Hospitalization data due to leukaemia were obtained from in the Health Information: Epidemiology and Morbidity (TABNET) database found at the electronic portal of the Unified Health System database, DATASUS. The estimates of the resident population in the studied cities were obtained from the Brazilian Institute of Geography and Statistics (IBGE, 2010).

In order to minimize interference promoted by the different age distributions, since the groups were not homogeneous, the standardization of the hospitalization rates due to leukaemia was calculated by the direct method (Pagano and Gauvreau, 2004).

The association of the measures was accomplished through the rate ratio of each municipality, obtained by dividing the rate of each one by the average of the rate of the reference group (Rio Bonito and Seropédica). The rate ratios and 95% Confidence Interval (IC95%) were calculated using the WINPEPI® version 9.3 software package.

Since this study refers to an epidemiological study with ecological delineation, using public population data applied for planning governmental actions without individual identification, there is no need of appreciation by any ethical committee.

RESULTS

The relevant information collected from the different, freely accessible, electronics databases from the selected municipalities in the State of Rio de Janeiro were compiled and are presented in Table 1.

Rio de Janeiro City has the largest population and practically its entirety lives in the urban area, followed by São Gonçalo and Duque de Caxias. Rio Bonito and Seropédica possess about 20% of their total population living in rural areas. Regarding the registration of public health facilities, the municipal districts of Rio de Janeiro and São Gonçalo lead the list, following by the population of each area.

The Human Development Index (HDI), also displayed in Table 1, is an indicator calculated from information obtained on the three basic dimensions of human development (income, education and health) of a certain population and allows for the evaluation of how the public managers of a certain area use financial resources to promote improvements in life quality of its inhabitants.

Table 1. Municipalities selected for herein and relevant information used in this study (IBGE, 2010). HDI - Human Development Index, GDP - Gross Domestic Product.

Municipalities	Total Urban population	Total Rural population	Public Health establishments	HDI	GDP (in thousands – R$)		
					Agricultural	Industrial	Services
Belford Roxo	469261	0	58	0.684	2357	996248	3184746
Duque de Caxias	852131	2915	82	0.711	7923	8403779	14918652
Itaboraí	215503	2587	62	0.693	10718	345855	1672230
Itaguaí	104292	4871	27	0.715	15332	272759	2369806
Japeri	95391	0	15	0.659	2585	86396	769042
Macaé	202873	3875	83	0.764	25649	4297335	5472995
Magé	215941	12209	78	0.709	28087	242540	1677570
Maricá	125532	1987	26	0.765	7614	498272	1073956
Mesquita	168403	0	19	0.737	365	187332	1261123
Nilópolis	157483	0	21	0.753	0	192215	1398300
Niterói	487327	0	87	0.837	15696	1800542	7935680
Nova Iguaçu	786536	8676	104	0.713	8321	1291340	7324182
Queimados	137938	0	15	0.680	2967	466375	1049380
Rio Bonito	41267	14319	35	0.710	6312	126071	654087
Rio de Janeiro	6323037	0	257	0.799	59037	22332352	125151001
São Gonçalo	999161	740	194	0.739	28491	1655305	8200147
São João de Meriti	459356	0	48	0.719	908	477505	4017426
Seropédica	64297	13886	23	0.713	11729	195298	572979
Tanguá	27426	3305	10	0.654	3864	41234	226425

The HDI has the purpose of offering development information under a different perspective from the Gross Domestic Product (GDP) per capita, another routinely applied indicator, which only considers the economical dimension of the municipal district development (PNUD, 2012).

The calculation of the internment rate was made by leukaemia adjusted by age with the data compiled on leukaemia hospitalization according to resident area registered by the Brazilian health care system (SUS) from January 2006 to March 2014 and the census data obtained from the Brazilian Institute of Geography and Statistics (IBGE) for each municipality evaluated in this study, the calculation of the internment rate was performed by leukaemia adjusted by age, as represented in Figure 2. First, the standardization of the rate was accomplished including all of population age groups, categorized only by gender, as displayed in Figure 2(a). Subsequently, only information regarding the adults (≥ 20 years old) were considered, in order to obtain data from the subtypes that occur preferentially in this age group, such as acute myeloid leukaemia, that show positive association with exposure to chemical substances, such as benzene (Keplin et al., 2014; Couto, 2015; Viacava and Bahia, 1999; Barata-Silva et al., 2014; Sahmel et al., 2013). The results obtained for this population stratum are presented in Figure 2(b).

When evaluating the rate ratio of hospitalizations due to leukaemia in adults from each city and the average rate of the reference municipalities (Rio Bonito and Seropédica - Table 2), data demonstrated that, regarding men, Macaé city presents a morbidity force by leukaemia about 6 times higher than the references, followed by Queimados (RR = 5.18; 95% CI: 2.55-10.67) and Itaboraí (RR = 4.50; 95% CI: 2.28-9.19). On the other hand, for women, Queimados presents the highest magnitude, about 7 times higher than the reference average, followed by Itaboraí (RR = 5.53; 95%CI:2.53-12.02) and Duque de Caxias (RR = 5.27; 95% CI: 2.53-11.36). These results are summarised in Figure 3.

DISCUSSION

The classification of the studied municipalities when evaluating the indicators Human Development Index (HDI) and Gross Domestic Product (GDP) per capita lead to different interpretations, indicating disparity between the economic and the human development of each area such as Duque de Caxias, which is classified as the second in the GDP rank and occupies the 12^{th} HDI position among the 19 appraised municipalities, indicating that the revenue generated in this area is not distributed equally nor is invested in the same degree in education and health in this municipality.

An evidence of the welfare rendered by the government on behalf of the population health is the construction of

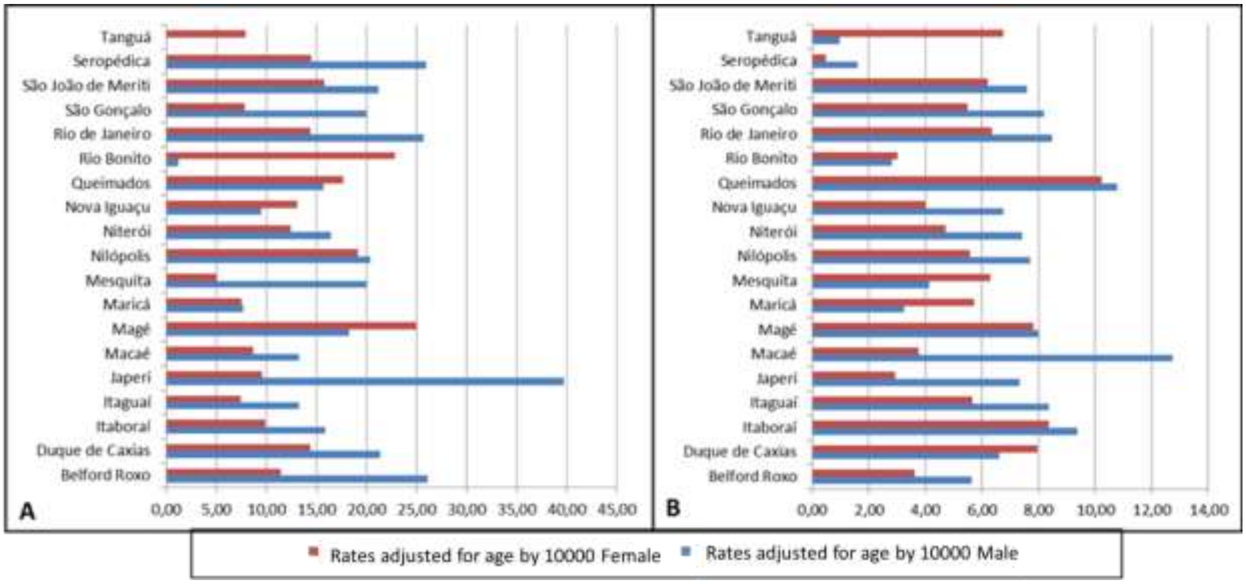

Figure 2. Age-adjusted hospitalization rates for leukaemia observed in 19 municipalities of in the State of Rio de Janeiro. (a) All ages. (b) Adults (≥20 years old).

Table 2. Rate ratio due to leukaemia hospitalization in adults registered in the municipalities of the metropolitan region of the State of Rio de Janeiro.

Municipalities	Rate Ratio (CI: 95%)	
	Male	Female
Belford Roxo	2.70 -1.39-5.50)	2.39 (1.10-5.27)
Duque de Caxias	3.18 (1.64-6.27)	5.27 (2.53-11.36)
Itaboraí	4.50 (2.28-9.19)	5.53 (2.53-12.02)
Itaguaí	4.01 (1.87-8.33)	3.74 (1.58-8.76)
Japeri	3.53 (1.62-7.65)	1.94 (0.72-5.16)
Macaé	6.12 (3.03-11.98)	2.49 (1.12-5.85)
Magé	3.85 (1.90-7.77)	5.16 (2.37-11.30)
Maricá	1.55 (0.67-3.58)	3.77 (1.63-8.60)
Mesquita	1.98 (0.94-4.41)	4.15 (1.92-9.55)
Nilópolis	3.70 (1.87-7.93)	3.69 (1.65-8.38)
Niterói	3.57 (1.78-6.90)	3.12 (1.47-6.82)
Nova Iguaçu	3.25 (1.68-6.43)	2.66 (1.27-5.84)
Queimados	5.18 (2.55-10.67)	6.77 (3.12-15.19)
Rio de Janeiro	4.07 (2.10-7.80)	4.20 (2.04-9.00)
São Gonçalo	3.93 (2.07-7.82)	3.62 (1.72-7.76)
São João de Meriti	3.64 (1.79-6.99)	4,11 (1.95-8.97)
Tanguá	0.47 (0.06-3.77)	4.46 (1.53-12.47)

Public Health Facilities, which should be geographically instituted to include the largest number of inhabitants, in other words, cities with high population density, such as Rio de Janeiro, should have a larger number of these facilities, which was confirmed herein, followed by São Gonçalo and Nova Iguaçu, respectively. However, the existence of public health facilities is not a guarantee of a general preventive and/or health promotion practice, since there is an unequal distribution of the health centres and hospitals with specialized services, privileging the central and the more developed parts of each city when compared to the suburbs, where health care is still very underdeveloped (Viacava and Bahia, 1999).

According to Figure 2a, regarding men, the city of Japeri, considered as a dormitory city, showed the

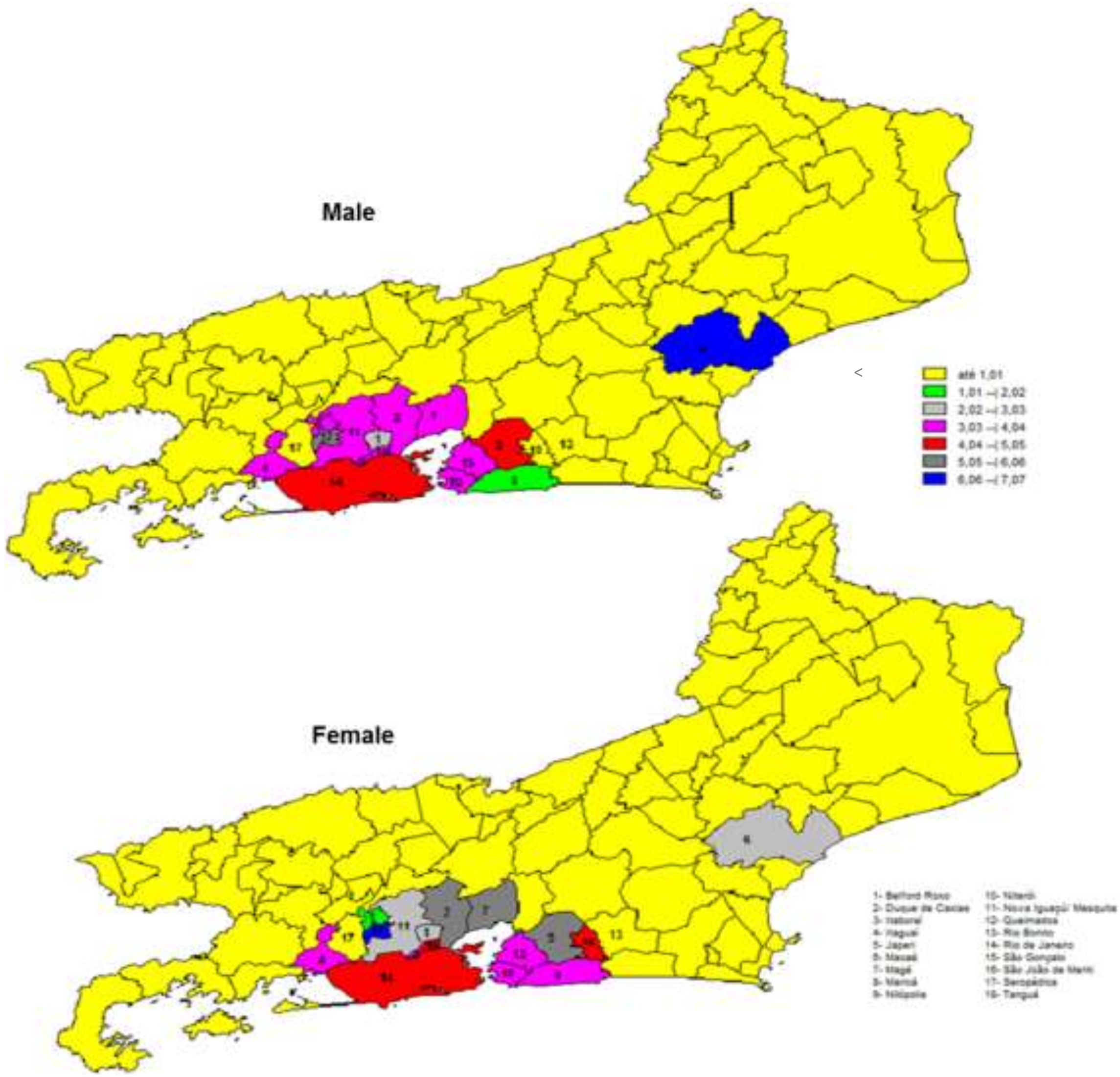

Figure 3. Map representing the leukaemia hospitalization rate ratio adjusted for age in adults of the 19 evaluated cities in the State of Rio de Janeiro, considering the Rio Bonito and Seropédica municipalities as references.

highest hospitalization rate for all types of leukaemia, followed by Rio de Janeiro and Macaé. For women, the city of Magé presented the highest rate, followed by Queimados and Duque de Caxias.

In spite of Japeri and Magé not having any significant industrial complexes, they are registered as comprising extensive agricultural areas, which consequently increases the possibility of population exposure to various pesticides (Araujo-Pinto et al., 2012). The use of pesticides has also been associated to increases in leukemia incidence, mainly Non-Hodgkin's lymphoma and multiple myeloma, in workers exposed during the preparation and application of these substances (Alavanja et al., 2014; Jones et al., 2014). In addition to the workers, their relatives and neighbours are also environmentally exposed to those xenobiotics, whether by dermal or oral or respiratory contamination (Peres et al., 2004).

The standardization of the rates considering only the adult group (≥ 20 years old) revealed a different situation. In this case, the city of Macaé showed the highest hospitalization rate standardized by age, followed by Queimados and Itaboraí, for men, while for women this occurred for the cities of Queimados, followed by Itaboraí and Duque de Caxias.

Macaé city is located in the Northern region of the state of Rio de Janeiro, known as the National Capital of Oil Production, since it holds more than 4 thousand companies linked to oil extraction activities and the production of oil and natural gas in the Campos Basin. Its urban and economic development is linked to the installation and operation of such industries. This city receives royalties linked to oil production, resulting in significant increases in its Gross Domestic Product (GDP) in the last 15 years, leading to the highest GDP among the neighbouring cities (Neto et al., 2007).

This city currently has about 220,000 inhabitants, predominantly adults (≥20 years old), and great part develops occupational activities linked to the oil industry, either direct or indirectly. Intense population migration, responsible for population increases in the order of about 5% a year between 2000 and 2010, as a result of its high GDP, led to fast urban growth without any appropriate urban planning. Consequently, lack of basic sanitation or sewer collection is common. At the same time, increases in the occupational informality inside the productive process was observed, leading to increased occupational health risks due to lack of control of the work conditions that workers in these conditions are submitted to. In general, work opportunities are easier in places with high exposure risks to chemical substances, making the use of protection equipment necessary, which is not the main concern of any informal occupation (Carmo, 2012).

Similarly to Macaé, Duque de Caxias has its main economic activity structured around the oil industry, encompassing a complex of 26 petrochemical, processing and thermo-electrical companies. This is the second largest industrial complex in the state of Rio de Janeiro, with industries such as the Caxias Refinery (REDUC), considered the largest industrial unit of the Rio de Janeiro area, producing fuels, naphtha~~,~~ and LPG (Liquefied Petroleum Gas). A series of chemical industries were built in its vicinity, some of them large-scale industries associated with oil processing, such as PETROFLEX~~,~~ and NITRIFLEX, among others. In addition, a group of small and medium companies that produce resins, paints, candles, paraffin and other chemical products are also located in the area (Irigaray et al., 2013).

Recent increases in other industrial sectors, such as the manufacturing, furniture and food industries are observed in the area, in such a way, except for the REDUC complex, the industrial complex of Duque de Caxias can be considered as formed by several small and medium companies (Irigaray et al., 2013).

Queimados has a 4,000,000 m^2 industrial complex comprising about 40 companies with different activities, ranging from paint factories to recycling industries. This industrial park is located alongside the Camboatá River, which receives great part of the residual residence spilling and industrial waste (Ferreira, 2007). Additionally, environmental impacts are also generated by the Technological Centre of Dangerous Residues (CENTRES), operating since 1988 and responsible for the final destination of the toxic industrial residues of large chemical companies occupying a 70,000 m^2 area. In full operation, about 30,000 m^3 of poisonous residues stored in unidentified iron drums which were buried afterwards were registered. In 1998, the Rio de Janeiro Environment Engineering Foundation (FEEMA) suspended CENTRES activities and determined the removal of all material stocked on that area. However, the environmental liability left at the place could be detected in the soil and in groundwater even 10 years after its closure (Chagas, 2013). The adjacent district, Santo Expedito, with 2 000 inhabitants at that time, registered 21 deaths by cancer up to 2007 (Santos, 2011).

Itaboraí is a 430.374 km^2 municipality located in the metropolitan area of the state of Rio de Janeiro with 225.263 inhabitants. Its main economic activities are agriculture, livestock and mineral extractivism, with the Rio de Janeiro Petrochemical Complex (COMPERJ) currently being built. The construction of complex began in 2008 and foresees the operation of its first refinery in 2016. It is considered the largest Brazilian and international industrial enterprise of the last decades in the petrochemical sector, aiming at refining 165.00 barrels of oil daily (Ferreira et al., 2007).

One of the main observed impacts in this is the intense workforce migration towards participating in the construction of this Complex, occupying areas that were previously used for agricultural activities, such as fruit crops (Sanchez et al., 2009). In addition, other environmental impacts are expected to occur after this Complex begins operations, such as contamination of underground waters and soil, decreases in air quality, physiochemical and biological alterations of the local terrestrial and aquatic webs, significant increases in the population, lack of essential services for the municipal district due to high demands, irregular use and occupation of the soil (“slumization”), real estate speculation and increases in local income values (Pandeff, 2009).

In fact, the municipalities that presented higher hospitalization rates due to leukaemia during the evaluated period share in common the fact of predominantly industrial activities linked to high pollutant loads released into the environment, such as oil activities, processing and recycling of materials, production of paints and plastic and production of several industrial inputs (Koh et al., 2014; Terazaki et al., 2008; Thompson et al., 2009). In addition, a significant increase in records of other activities that use high amounts of chemical substances, such as agriculture, has also been observed (Pignati et al., 2014).

The scientific literature reports several studies that demonstrate a positive association of the xenobiotics originating from these activities with a series of environmental consequences, such as contamination of air, soil and water by volatile organic compounds, such as benzene, as well as human health concerns, like increasing incidence of several pathologies, such as cancer, alterations of abnormal chromosomes that lead to foetus malformations and even male infertility (Koh et al., 2014; Schinatter et al., 2012; Mandani et al., 2013; Xing et al., 2010). However, the inference that environmental exposure is the main driving factor of human diseases is still fragile, since individual susceptibility is considered decisive for these events (Ross and Zhou, 2010; Norppa, 2003; Nebert et al., 2013). Therefore, the evidence should not be discarded, but instead evaluated in parallel to the identification and quantification of the environmental pollutants for a full understanding of this complex cause-effect relationship.

The results obtained herein should be cautiously analysed, since data included in information systems may somehow present typing or data aggregation flaws (inclinations of information). In addition, ecological studies, allow only for the evaluation of data obtained collectively and not from individual reports, which does not allow for the accomplishment of causal inferences.

Therefore, considering only the findings of the present study, the establishment of a cause-effect relationship between exposure to chemical substances and leukaemia occurrence is not possible due to the absence of important information at the individual level, such as exposure load, family health histories, age, previous diseases or conditions and the occupation. However, studies using the ecological methodology are still relevant in generating information on population dynamics, identifying the need for new studies.

Conclusions

The construction of the concept of economic development based on the implementation of industrial technologies that modify the scenario of certain areas may cause serious damage both to the environment and to human beings, due to the unsustainable use of natural resources and high load of contamination, which can become increasingly diversified.

Corroborating this affirmative, the present study verified that cities with higher numbers of potentially pollutant industries in the state of Rio de Janeiro registered the highest hospitalization rates due to leukaemia, for both genders, such as Macaé, Queimados and Itaboraí. However, it is not possible to only attribute exposure to chemical substances as the main factor driving the occurrence of cancer, since this is the result of the sum of several causalities, such as exposure load and genetic susceptibility.

However, the present study indicates that it is possible to presume the occurrence of a significant relationship between the productive processes of the industries located in these cities and hospitalization by leukaemia, although a verified cause-effect relationship cannot be stated with the adopted delineation. Therefore, the obtained results corroborate the need for new studies focusing on the continuous monitoring and quantification of the several variables, especially benzene and other aromatic hydrocarbons that participate in the relationship between chemical exposure and the emergence of leukaemia in adults.

Conflict of Interests

The authors have not declared any conflict of interests.

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Full Length Research Paper

Prevalence of major depressive disorder among Spanish adolescents

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The main objective of this study was to examine the prevalence of major depressive disorder (MDD) among adolescents in a city of 200,000 inhabitants using a psychiatric diagnostic tool. We also looked into how possible internal/external factors may influence prevalence and examined the comorbidity between MDD and other psychiatric disorders. The study population included 1,238 adolescents in their final year of secondary education in Sabadell (Barcelona, Spain). A prospective observational study in two phases: (a) Initial population-based screening using the Beck Depression Inventory (BDI), and (b) Diagnosis using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) with participants who, according to screening, exhibited significant depressive symptoms. The Child Behavior Check-list (CBCL) and the State-Trait Anxiety Inventory for Children (STAIC) were also used in the second phase of the study, which, together with K-SADS, enabled us to examine the comorbidity of MDD with other disorders. According to the initial screening, 7.92% of participants exhibited significant depressive symptoms. The results of the diagnostic interviews showed a prevalence of 1.29% adolescents with MDD. Prevalence was higher in girls (1.92%) than in boys 0.34%) (p=0.002) and at age 16 or over in both genders (p<0.001). 50% of participants with MDD presented comorbidity with other psychiatric pathologies. The low prevalence of MDD observed does not justify generalised screening in adolescents attending school, except in cases of individuals with significant depressive symptoms.

Key words: Depression, major depressive, disorder, adolescence, prevalence, screening, comorbidity.

INTRODUCTION

Major depressive disorder (MDD) is one of the most common (15 to 20%) and debilitating psychiatric disorders observed in primary care settings (Achenbach, 1978; Sanz et al., 2003). In children and adolescents,

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depressive disorders are the second most prevalent diagnosis in Spain, after conduct disorders (Alaéz et al., 2000). Given the high risk of recurrence and chronicity associated with MDD, early diagnosis and intervention is highly recommended to prevent complications (Fergusson and Woodward, 2002; Lewinsohn et al., 1999; Pine et al., 1998). In fact, MDD has been identified as one of the main risk factors for suicide (Ezpeleta et al., 2008). According to the National Institute of Statistics (Instituto Nacional de Estadística, 2008), the total number of suicides in Spain in 2009 was 3,650, almost 5% of whom were adolescents. Consequently, suicide has become the leading external cause of death among adolescents in Spain.

Epidemiological studies in the field of adolescent MDD are usually performed using two distinct methodological approaches: (a) Screening studies, aimed at assessing the degree of depressive symptoms in a specific population or (b) diagnostic tools whose purpose is to estimate the prevalence of MDD using CIE-10 (Organización Mundial de la Salud, 1992) or DSM-IV (American Psychiatric Association, 1994) diagnostic criteria. Although the optimal strategy for assessing the prevalence of MDD would be the use of structured psychiatric diagnostic interviews, current practice favours the implementation of massive screening of specific populations. Such massive screening fails to establish the real prevalence of MDD, and merely offers an estimation of its risk.

Depression screening studies, also referred to as “risk screening”, show highly varied results. This may be attributed to several causes such as: The choice of diagnostic tool, the different diagnostic criteria applied, or individual differences among respondents or the characteristics of the reference population. Investigations carried out on the epidemiology of adolescent depression that used self-report questionnaires yield higher rates. Thus, in a study carried out on a sample of Mexican adolescents who were administered the Beck Depression Inventory (BDI) (Beck et al., 1961), the percentage of participants with significant depressive symptoms was 18.6% (Martínez et al., 2006). Nevertheless, the same questionnaire was administered to Argentinean adolescents, and prevalence reached 25% (Czernik et al., 2006). Similarly high rates have been reported in studies from other countries (De la Peña et al., 1999; Escriba et al., 2005).

In Spain, the results yielded have been inferior to those described in these studies: 10.29% of Spanish adolescents aged 12 to 16 years presented significant depressive symptoms (Escriba et al., 2005). Other authors, such as Canals et al. (1995) also observed that hetero-administered screening tools increase specificity and yield lower percentages. In their study, Canals et al used the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al., 1984) and the results obtained showed that 2.3% of adolescents aged 13 to 14 years and 3.4% of youths aged 17 and 18 years had significant depressive symptoms.

On the other hand, diagnostic studies using psychiatric diagnostic interviews such as the DSM-IV or ICD-10 have estimated the prevalence of MDD among adolescents in Spain to be between 2.8 and 5% (Canals et al., 1997; Ezpeleta et al., 2007). International investigations, such as the extended meta-analysis by Costello et al. (2006), who pooled 26 epidemiological studies of adolescent depression, estimated the prevalence at 5.6%. These figures are closer to the 5.8% observed in a Swedish population study carried out by Olsson and Von Knorring (1999).

Diagnostic tools that examine the entire population of a city are scarce. In Spain, one of the few examples of population research was conducted in a small town near Barcelona, which observed that 5% of 15-year-old adolescents met the criteria for MDD (Ezpeleta et al., 2007). Nevertheless, this study presented one limitation; although it was population-based, the number of participants was reduced (*n*=151).

Diagnostic studies identified differences in prevalence of MDD by sex (Martínez et al., 2006) and age (Modrzejewska and Bomba, 2009). The incidence of this psychiatric disorder, similar in primary school-age boys and girls, tends to increase during adolescence, with a female/male ratio of 2:1, as demonstrated by De la Peña et al. (1999) and Ulloa et al. (2006). Other research indicated that the proportion of MDD in this age group was up to 4 times higher in girls than in boys (Olsson and Von Knorring, 1999). Family history of depression was reported by Klein et al. (2001) and recent published studies show relationship between family history of affective disorders and CBCL to develop psychopathology in high risk adolescents (Simeonova et al. (2015).

Furthermore, depressive disorders are frequently comorbid with other psychiatric conditions. A study in a community sample performed by Essau (2008) detected that 58% of depressed adolescents in a community sample and 63.5% in a clinical sample presented some disorder comorbid with MDD, based on the computer-assisted personal interview (CAPI) (Wing et al., 1990). Greater comorbidity was found between depression and anxiety disorders. The results showed that 72% of the community sample and 62 % of the clinical sample presented comorbid anxiety. Depression was also shown to be often accompanied by Attention Deficit Hyperactivity Disorder (ADHD) (Biederman et al., 1996), and eating disorders which causes high morbidity, disability and a worse long-term prognosis (Blackman et al., 2005).

Given the high prevalence of MDD and associated morbidity, the European Alliance Against Depression (EAAD) was founded in 2004, and now operates in 18 countries. The aim of this programme is to develop multilevel interventions to improve the treatment of

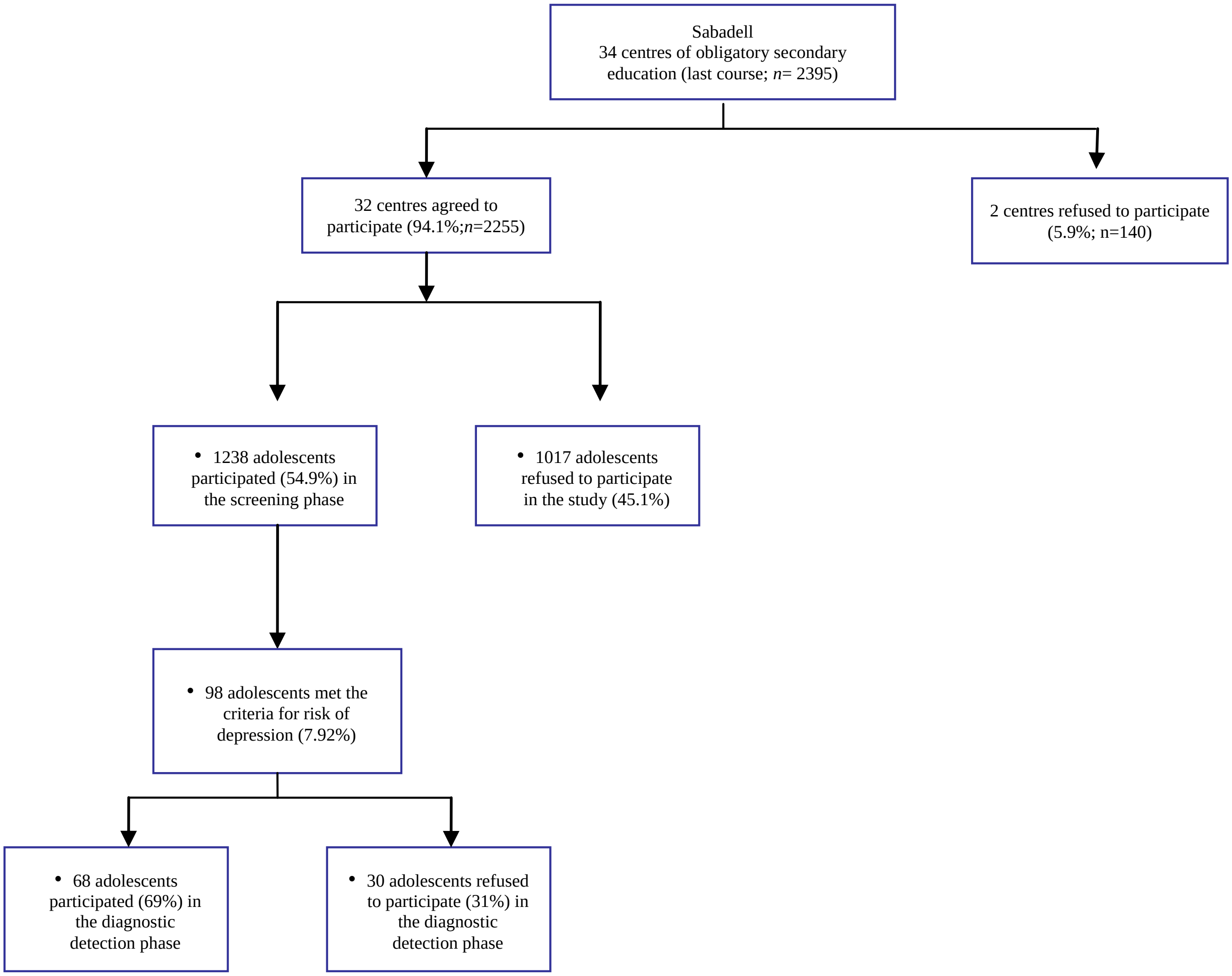

Figure 1. Flowchart of recruitment of participants.

depression and reduce suicidal behaviour (Hegerl et al., 2008). Prevention and depression early detection in adolescents are interventions included in this European program, initiated in Sabadell (Spain) in 2007, with psychoeducational interventions and screening programs in secondary schools. The main objective of our investigation was to examine the prevalence of MDD in the adolescent population of a city of 200,000 inhabitants using a psychiatric diagnostic tool. We also aimed to study the possible differences in prevalence based on internal (sex, age) and external (family history) factors and examine the comorbidity of MDD with other psychiatric disorders.

MATERIALS AND METHODS

Study design and participants

A two-phase prospective observational study: (a) Initial screening phase, to detect adolescents with significant depressive symptoms; (b) Diagnostic phase, to determine whether the adolescents at risk detected in the first phase met the DSM-IV clinical criteria.

The research was carried out in Sabadell, a city of 207,338 inhabitants (Instituto Nacional de estadística, 2010) located in the province of Barcelona (Spain). Sabadell has 34 secondary educational institutions (63.7% of which are state schools and the rest private with public financial support). Thirty-two (94.1%) of these schools agreed to take part in our study. A total of 1,238 adolescents in their final year of compulsory secondary education (15 to 16 years old) in Sabadell (*n* = 2,395) agreed to participate (54.9% of adolescents enrolled). The flow chart of participants included in the study is shown in Figure 1.

Instruments

Depressive symptomatology

The Beck Depression Inventory (BDI): BDI is a 21-item self-administered screening questionnaire that includes the main symptoms of depression used as diagnostic criteria in the DSM-IV (Beck et al., 1961). It is applicable to adolescents from 13 years of age and allows reliable identification of adolescents who may suffer from depression. Sanz et al. (2003) validated this tool in a Spanish population; using 17 points as a cut-off.

Diagnosis of depression and psychiatric comorbidity

Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS): *Full interview* of K-SADS) is given in previous study (Kaufman et al., 1997). K-SADS is a semi-structured interview for children and adolescents aged 6 to 18 years, based on DSM-IV diagnostic criteria (these criteria were not modified in DSM V). It has been shown to be a valid and reliable instrument for the cross-sectional and longitudinal evaluation of psychopathology in children and adolescents, and one of the most widely used in children and youth research. The Spanish version was adapted and validated by Ulloa et al. (2006).

Complementary scales

The parents' version of the *Child Behavior Check-list* (CBCL): CBCL is a self-report instrument designed to assess adaptative behaviours and problem behaviour in children aged 4 to 18 years (Achenbach, 1978; Achenbach and Edelbrock, 1985**)**. CBCL is composed of 113 items classified into two main categories: Internalising problems (such as anxiety, depression, somatic complaints and inhibited behaviour) and externalising problems (such as aggression and dissocial behaviour). It also addresses social, thought and attention problems. This instrument was validated by Ezpeleta et al. in a Spanish population (Ezpeleta et al., 2008).

***State-Trait Anxiety Inventory for Children* (STAIC) (Spielberger et al., 1973; Spielberger et al., 1982):** STAIC is a self-report instrument for measuring anxiety in children and adolescents. This questionnaire was validated for the Spanish population by Seisdedos (1990). It consists of two 20-item separate scales that measure State Anxiety (S/A) and Trait Anxiety (T/A).

Procedure

The study was approved by the Clinical Research Ethics Committee (CEIC) at the Corporació Sanitària i Universitària, Parc Taulí de Sabadell (CSUPT) and the local Department of Education. A letter providing information about the study was sent to the Board of Directors at the 34 secondary education centres in Sabadell. It included detailed information about the research and the main objectives of our study and all pupils in their final year of secondary school were invited to participate in the study. Thirty-two (94.1%) of these centres agreed to collaborate in the study. Written informed consent from parents and the explicit assent of adolescents were required to participate in the study. The youths had the option of refusing to participate and 54.9% agreed to take part.

The two phases of the study were implemented as scheduled. The first phase consisted of initial *screening* to identify adolescents with significant depressive symptoms, likely to be at risk of MDD. Between December, 2007 and March, 2008, various (check) CSUPT investigators visited the collaborating schools to administer the BDI screening questionnaire. The criterion used to establish whether a participant was at risk for this pathology was a score equal or superior to 17 on this instrument. A lower cut off point than that reported in other studies (cut off 21) was established in order to increase sensitivity.

Subsequently, participants identified as being at risk were contacted by telephone to visit the Child and Adolescent Mental Health Centre in Sabadell (CSMIJ) and participate in the second phase of the study: diagnostic detection. Between April and June, 2008, a specially trained clinical psychologist administered the K-SADS clinical interview to adolescents and their parents in order to determine whether these adolescents suffered from MDD. A blind external reviewer assessed the patients to guarantee inter-observer reliability. Clinical exploration was completed with the administration of the STAIC to the youths and CBCL to their parents. Patient's parents were asked about family story of depression, too. The information collected from these questionnaires and from K-SADS allowed us to assess the comorbidity of MDD with other psychiatric disorders.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 17 was used for statistical analysis. A frequency analysis was performed to study the percentage of risk and prevalence of MDD, in total and according to certain sociodemographic characteristics (e.g. sex and age), and determine the rate of comorbid psychiatric disorders associated with MDD. The chi-square test or Fisher exact test as appropriate was used to compare proportions in categorical variables (sex, age groups, family history, comorbid psychiatric disorders, etc.) and continuous variables were analysed with Pearson's bivariate correlation. For all statistical analysis performed, a level of $p < 0.05$ was considered statistically significant.

RESULTS

Study population

Of the 1,238 adolescents who took part in the study, 509 were male (41.11%) and 729 female (58.93%). The vast majority [*n*=1137 (91.85%)] were 15- or 16-year-olds (mean age=16.06, SD=0.630). The percentage of immigrants was 10.8% (*n*=134) and grade repeaters in any academic course accounted for 19.46% (*n*=236). Further details are shown in Table 1.

Prevalence of major depressive disorder in adolescents

The initial screening showed that 7.92% of the participants (95% Confidence Interval=6.54 to 9.56%, *n*= 98) were at risk for depression (BDI ≥ 17). The percentage of risk was higher in girls (10.28%) than in boys (3.54%) (χ^2=19.59, *p*=0.001, *OR*=3.12, 95% *CI*=1.8419 to 5.29) without differences by age (χ^2=0.03, *p*=0.874). Of these 98 adolescents, 68 attended the interview in the second phase of the study.

After completion of both phases of the study, prevalence of MDD in the adolescent population of Sabadell was estimated at 1.29% [95% *CI*= 0.80% to 2.09% (n=16)] (Table 2).

The statistical data shown in Table 2 indicate there was a significant difference in the prevalence of MDD by sex and age, but not according to family history of depression. Thus, the prevalence of MDD was almost 5 times higher in girls (1.92%) than in boys (0.39%)

Table 1. Sociodemographic characteristics of study population

Sociodemographic characteristics	Study population (n=1238)	
	Count	Percentage
Sex		
Men	509	41.11
Women	729	58.89
Birth place		
Catalonia	1104	89.17
Others Spanish communities	26	2.1
Abroad	108	8.7
School type		
State	735	59.36
State subsidised	503	40.63
Age (years)		
15	690	55.74
16 or above	527	44.26
Repeater		
Non repeater	977	80.54
Repeater	236	19.46

Table 2. Risk of depression and MDD among Spanish adolescents.

Phase	n	Tools	Risk of depression	MDD	Anxiety	CBCL
1st phase: screening	1238	BDI	7.92%			
2nd phase: diagnosis	98	K-SADS STAIC/S STAIC/T CBCL		1.29%	41.94 (m) 45.69 (m)	Associated scale II (somatic complaints)

(O*R*=0.202; 95% CI= 0.046 to 0.892) and in adolescents aged 16 and older (2.74%) than in 15-year olds (0.14%) (O*R*=0.050 to 95%; CI=0.07 to 0.376).

Comorbidity with other psychopathological disorders

The K-SADS diagnostic interview showed that 50% of individuals diagnosed with MDD had other comorbid psychiatric disorders (Table 3). Significant differences were found between adolescents with MDD and those without. Adolescents with MDD presented comorbidity mainly with eating disorders, followed by anxiety disorders, ADHD and tic disorder.

Regarding the linear association between the variables measured in the questionnaires, BDI scores for depressive symptoms were positively associated with scales of trait anxiety (STAIC T/A; r=0.319*, p=0.039) and state anxiety (STAIC S/A; r=0.326, p=0.034). Thus, adolescents with high scores in depressive symptomatology presented high levels of trait and state anxiety. Depressive symptoms evaluated with the BDI positively associated with scale 2 of the CBCL (somatic complaints) (r=0.262, p =0.047) but no linear association was found between the other subscales of this instrument (Table 4).

DISCUSSION

A total of 1.29% (95% *CI*=0.80% to 2.09%) of the adolescent in our sample *presented MDD*. This prevalence is slightly lower than that observed in previous Spanish studies, such as that performed by Canals et al. (1997) who estimated the prevalence of adolescent depression at 2.4%, according to *Schedules for Clinical Assessment in Neuropsychiatry (SCAN)* (Wing et al., 1990). These discrepancies may be explained by the fact that their study was conducted on a random sample of subjects aged 17 to 18 years, whereas the students recruited for our study were younger (15 to 16 years), as well as the use of a different diagnostic

Table 3. Prevalence of major depressive disorder by sex, age and family history.

Sociodemographic characteristics of interest	Study population (*n*=1238)		Participants with major depressive disorder (*n*=16)				
	Count	Percentage	Frequency (*f*)	Percentage	Pearson's Chi-square (χ²) / Fisher Test	*p*	*OR* (*CI 95% for OR*)
Sex							
Men	509	41.11	2	0.39	5.466	0.019	0.202(0.046 to 0.892)
Women	729	58.89	14	1.92			
Age							
15	690	55.74	1	0.14	-	0.000	0.050 (0.007 to 0.376)
≥16 years	527	44.26	15	2.74			

Table 4. Psychiatric comorbidity of major depressive disorder in adolescents interviewed.

Psychiatric disorder	Participants with MDD (n=16)		Participants without MDD (n=52)		Pearson's Chi square *(χ²)*	df	*p*
	Frequency (*f*)	Percentage	Frequency (*f*)	Percentage			
Any psychiatric disorder	8	50.00	13	25.00	5.448	1	0.020

MDD: Major depressive disorder.

instrument. Despite these differences, both studies seem to indicate that the prevalence observed in Spain is far from the estimated 5.6% of young 13- to 18-year-old Americans, according to an exhaustive meta-analysis by Costello et al (2006), and the 5.8% obtained in Sweden (Olsson and Von Knorring, 1999).

Although the prevalence of depression in Spain has been found to be lower than in other countries, it should not be overlooked that 7.92% (95% IC=6.54% to 9.56%) of participants presented important depressive symptoms, though only a minority met the diagnostic criteria for MDD. These values are intermediate between the 3.4% observed by Canals et al. (1995) according to CDRS-R scores (Poznanski et al., 1984) and the 10% estimated by other studies performed in Spain (Escriba et al., 2005) and the USA (Bazargan-Hejazi et al., 2010). Factors like family structures in our country and primary care training in mental health could differences.

Detecting depression in children is a difficult task as, unlike externalising disorders, depressive symptoms are often unrecognised by others and rarely the main reason for seeking help. Nevertheless, early identification of these adolescents is fundamental as it allows early intervention and, consequently, a reduction in the chronicity of the pathology and effective prevention of suicidal behaviours. We should bear in mind that depression is the second most common risk factor for suicide in adolescents (the first is a previous suicide attempt) , and that depressed adolescents are more likely to attempt suicide than non-depressed subjects (Simeonova et al., 2015).

Having established the prevalence of MDD in our study population, we sought to determine whether this prevalence was different according to certain internal (sex and age) and external (family history of depression) variables. With regard to differences by sex, we found 1.92% of girls and 0.34% of boys were diagnosed with MDD. These results coincide with most epidemiological studies published that observed a higher prevalence of depression in female subjects (Canals et al., 1997; Martínez et al., 2006; Poznanski et al., 1984). Indeed, certain pubertal factors (such as increases in sex steroid hormones) have been associated with the increase of depression rates among girls (Costello et al., 2006). The prevalence of MDD increases dramatically from the age of 16 years. This may be explained by the fact that adolescents gradually undergo a process of complex physical, psychological, cognitive and sociocultural changes. Adolescents are thus forced to develop strategies to cope with such important challenges and allow them to build a sense of identity, autonomy and achieve personal and social success. Failure to meet these needs may lead to various psychiatric problems (Blum, 2000). In Spain, 16 years old is the start of the working age and it could be another factor to explain this ratio. Finally, unlike the findings of Klein et al. (2001), the adolescents with MDD assessed in our study did not have a family history of depression.

The high comorbidity of MDD (50%) in our study is similar to that obtained in an English study in which 58% of depressed adolescents included in a community sample presented other psychiatric disorders (Essau, 2008). Other studies Biederman et al., 1995; Biederman et al., 1996; Czernik et al., 2006; De la Peña et al., 1999;

Essau, 2008 have also shown that adolescents with MDD presented a higher percentage of psychiatric disorders than non-depressive adolescents. Eating and anxiety disorders were the two most frequently associated disorders, in agreement with the study by Czernik et al. (2006)

To the best of our knowledge, this is one of the first epidemiological studies on depression performed in Spanish adolescents. The results obtained have allowed us to determine the prevalence and degree of depression in 15 to 16 year olds, which is slight lower than in previous studies.

In conclusion, our study found that although a high percentage of adolescents were at risk of developing depression (7.92%; 95% CI=6.54 to 9.56%), only 1.29% (95% CI=0.80 to 2.09%) of the study population met the diagnostic criteria for MDD. This disorder was more frequent in girls and in youths over 16 years of age and presented high comorbidity with other psychiatric disorders. Specific screening is recommended for students with depressive symptoms in the school environment. Thus, the training of health and education professionals is vital to improve the identification of signs and symptoms of depression in adolescents. Using screening questionnaires like the BDI can facilitate early detection of MDD in youth and allow initiation of treatment in the early stages of the disorder to reduce the recurrence, chronicity and morbidity associated with depression in adolescents, especially suicide behaviours prevention.

Limitations

Despite the strengths of our study, especially with respect to specific data on 15/16-year-olds, there are some limitations which should be outlined. The refusal rates in the screening period (45%) and in the second phase (33%) are higher than expected and the prevalence of depression may have been partially underestimated. Furthermore, we are the sole psychiatry department in our health area, so if patients with depressive symptoms are missed in this period, they would be detected by primary care or school nurses and referred to our department for treatment.

Another limitation of our study is that we did not use structured tools to identify participants' family history, which may explain why we were not able to replicate the association found in the literature. While the use of these tools is desirable and recommended for future studies, it was reluctantly decided that due to the size of the population of our catchment area and the limited psychiatric services available, administration of these instruments would not have been practical within the study time frame.

Further studies are required to corroborate these results and determine with greater accuracy where resources can best be employed to improve the effectiveness and focus of interventions designed for adolescents at risk of MDD.

Conflicts of Interests

The authors declared no conflict of interest related to this.

Abbreviations: MDD, Major depressive disorder; **K-SADS,** Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children; **BDI,** Beck Depression Inventory; **EAAD,** European Alliance Against Depression; **SPSS,** Statistical Package for the Social Sciences; **CBCL,** Child Behavior Check-list; **STAIC,** State-Trait Anxiety Inventory for Children; **CEIC,** Comité Ético de Investigación Clínica; **CSUPT,** Corporació Sanitaria i Universitària del Parc Taulí.

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Risk factors associated with cholera outbreak in Bauchi and Gombe States in North East Nigeria

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This study investigated the risk factors associated with cholera epidemic during the 2010 cholera outbreak in some States in Nigeria. Semi-structured questionnaires were administered to consented patients and/or their parents/guardians in Bauchi and Gombe States in North East Nigeria. Few (33.7%) respondents had access to safe and clean drinking water through the pipe-borne system compared to well (47.8%) and river (19.6%). Respondents' means of sewage disposal were: pit/latrine (77.2%); bush (15.2%); and water closet (4.3%). Only 34.8% knew water, food and poor sanitation as transmission routes for cholera. There was a significant gender difference in knowledge of lack of safe and clean drinking water and poor sanitation as contributing factors to cholera infection (p<0.05). Observation showed poor sanitation and food hygiene practices in the communities visited.The results provided insights for planning educational programmes through information, education and communication/behavioral change communication efforts to boost knowledge on cholera in the communities.

Key words: Knowledge, perception, environmental sanitation, health behavior, cholera outbreak, Nigeria.

INTRODUCTION

Cholera remains a global threat to public health and a key indicator of lack of social development (Talavera and Perez, 2009; World Health Organization, 2010). It is an acute enteric infection caused by the ingestion of bacterium *Vibrio cholerae* present in faecally contaminated water or food. It has been classified as re-emerging global threat. The disease is primarily linked to insufficient access to safe, clean water supplies, crowded living conditions and poor hygiene and sanitation(Kindhauser, 2003; Zuckerman et al., 2007; Sasaki et al.., 2008; Penrose et al.., 2010; World Health Organisation/UNICEF, 2010). It has a more severe impact in areas where basic environmental infrastructures are disrupted or have been destroyed (World Health Organisation, 2004; 2010).

Having categorized cholera as a water- and food-borne disease transmitted majorly through faecal-oral route, contaminated water is more common as the usual

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transmission route in developing countries such as Nigeria (Sack et al.., 2004). The lack of infrastructure to provide amenities such as clean and safe water in many sub-Saharan countries make the population susceptible to cholera (Griffith et al.., 2006). The poor practice of excreta disposal and drainage are risk factors of transmission of *Vibrio cholera* through the deification of infected persons around the home environment that increase its spread through rain water floods that cause contamination of water sources that include shallow wells, rivers and streams (Sasaki et al.., 2008).

Every year, mostly African and Asian countries record 3-5 million cholera cases and 100,000-130,000 deaths due to the disease (IRIN Global, 2011). In 2009, a total of 217,333 cases with a case fatality rate (CFR) of 2.25% (4,883 deaths) were reported in 30 African countries alone. Of these, eight countries, including Nigeria accounted for 191,537 cases with a CFR of 2.26% representing 88% of reported cases and deaths from the continent with the CFR in many of these countries higher than the accepted 1% threshold (World Health Organisation, 2010).

In Nigeria, series of outbreaks of cholera have been reported over the decades (Lawoyin et al., 1999; Utsalo et al., 1999; Hutin et al., 2003; Usman et al., 2005; Oguntoke et al., 2009). Outbreaks of the disease have been reported in the country with increasing frequency since the first outbreak in 1970 (Lawoyin et al.., 1999).

Behaviors related to personal hygiene and food preparation contribute significantly to the occurrence and severity of outbreaks (Kindhauser, 2003). Health education aimed at behavioral change combined with good surveillance and preparedness, frank reporting and transparent information policy are important in the effective cholera prevention and control (Kindhauser, 2003). It is in the realization of this that it became imperative to investigate the knowledge, perception, health behavior and sewage and waste disposal practices among patients with acute watery diarrhoea as risk factors associated with cholera epidemic. Consequently, during the 2010 cholera outbreak in some States in Nigeria, the Emergency Preparedness Response Research Group of the Nigerian Institute of Medical Research was deployed to the affected States to provide cholera research intervention and humanitarian services with the supply of relief materials. The research component of the intervention entailed both laboratory and social epidemiological studies of the epidemic. This paper is based on social epidemiological data generated from two of the States (Bauchi and Gombe) visited in North East Nigeria.

METHODS

Study design and setting

This study was a cross-sectional description of the knowledge, perception, health behavior and sewage and waste disposal practices among carers of all patients hospitalised for treatment of acute watery diarrhoea at the Treatment Centre, Abubakar Tafawa Beluwa Teaching Hospital in Bauchi State and at the Mother and Child Care Centre, London Mai Dorowa, Shamaki Ward, Gombe LGA, Gombe State, North East Nigeria sequel to an epidemic outbreak between May and September 2010.

Bauchi and Gombe are adjoining States in North East Nigeria with coordinates of 10°30′N 10°00′E and 10°15′N 11°10′E and projected population of 5.2 million and 2.7 million people respectively based on the 2006 National Population Census (National Bureau of Statistics, 2009; National Population Commission [Nigeria] and MEASURE DHS ICF Macro, 2009). Bauchi and Gombe States are divided into 20 and 11 local government areas (LGAs) and occupy a total land area of 49,119 km^2 and 18,768 km^2 respectively (Figure 1). The two States span two distinctive vegetation zones, namely, the Sudan savannah and the Sahel savannah. The two States comprise of many tribal groups who are mainly Hausa, Fulani, Tangali, Tera, Bolewa, and Kanuri with Hausa being the common language. The people of both States are mainly farmers producing both food and cash crops. There are Tertiary, Secondary and Primary health facilities located across the LGAs of each State.

Data collection and analysis procedures

Approval for the work was obtained from the Nigerian Institute of Medical Research Institutional Review Board with the reference number IRB/10/104.

Semi-structured questionnaires were administered to parents/guardians of all the patients receiving treatment at the treatment camps visited following their informed consent. The questionnaires were used to elicit information relating to socio-demographic characteristics, frequency of stooling and vomiting, perceived cause of the disease, sources of drinking water, method of sewage disposal, hand washing practices and extent of community awareness and health education. In addition, in-depth interview was conducted with the Head of the Gombe State Epidemiology Unit. The observation method of data collection was also used and some secondary data in the form of records of reported cases of the disease and deaths from the eleven LGAs of the State were obtained from the Epidemiology Unit of the State Ministry of Health. The investigators who are mainly public health professionals observed the environment of some communities visited in the two States taking into cognizance personal, household and environmental hygiene practices, food hygiene and safety practices and waste (domestic and sewage) disposal practices.

Following the data collection, the questionnaires were screened, edited for clarity, completeness and uniformity of the responses, and then coded. The coded data were entered into the computer using Statistical Package for Social Sciences (SPSS) package version 15. Statistical analyses of the data set included univariate analysis to show the relative frequency distribution of each variable on the questionnaire, and bivariate analyses at a 95% level of significance to examine associations between selected independent and dependent variables relative to the objectives of the study.

RESULTS

Socio-demographic characteristics of respondents

The socio-demographic characteristics of the respondents are presented in Table 1. Of the 92 respondents interviewed, 73 (79.3%) were from Bauchi State while 19 (20.7%) were from Gombe State. Most

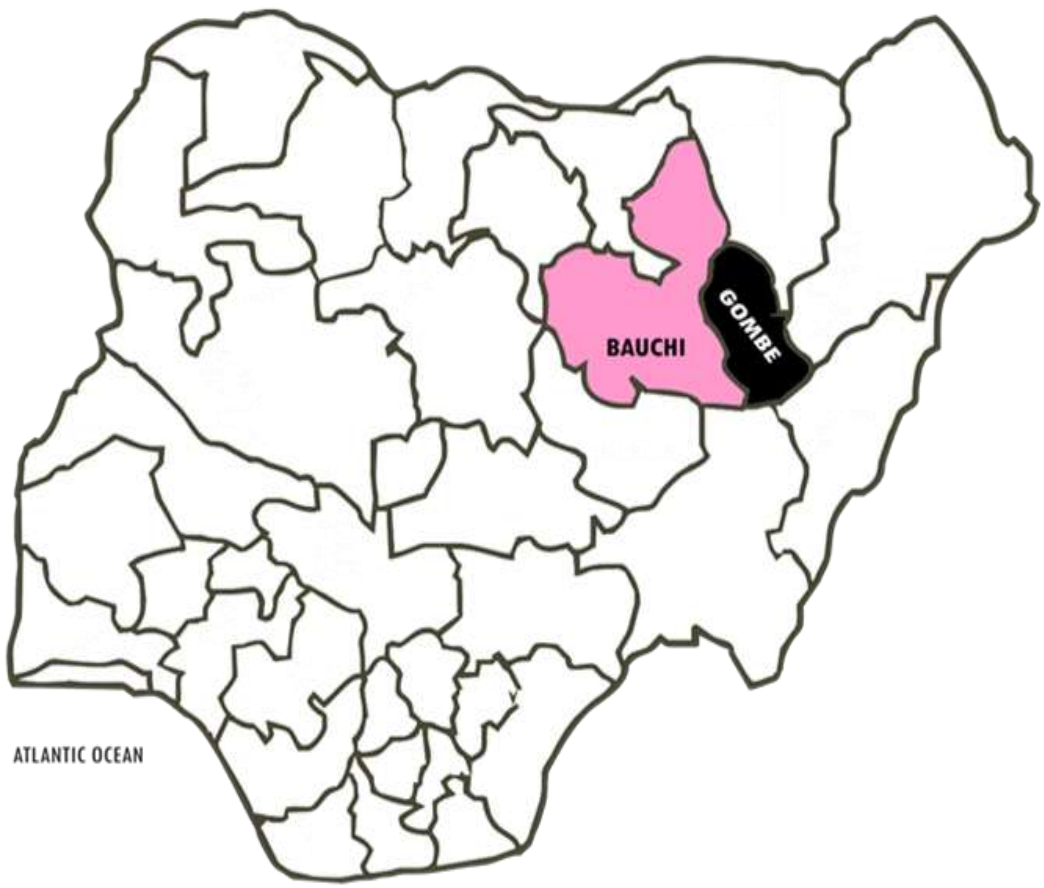

Figure 1. Map of Nigeria showing the location of Bauchi and Gombe States.

(16.3%) of the respondents were traders [11.0% Bauchi vs. 36.8% Gombe] and students [13.7% Bauchi vs. 26.3% Gombe] respectively. Similarly, Table 1 shows that a larger proportion of the interviewed respondents affected by the cholera outbreak were females, never married, and had little or no formal education. Their ages ranged from 16 years to 57 years with an average age of 32 years [31 years Bauchi vs. 29 years Gombe] and a median age of 35 years [35 years Bauchi vs. 36 years Gombe].

The ages of the patients ranged from 1 year to 60 years with an average age of 17.7 years [17.4 years Bauchi vs. 20.6 years Gombe] and a median age of 15.0 years [17 years Bauchi vs. 15.0 years Gombe]. Their age distribution is: children under five years (23.9%); adolescents aged 13 to 24 years (23.9%); and adults aged 25 years and above (34.8%).

The condition ofliving of the patients as described by the respondents showed that they live with a range of 1 to 7 persons in a household. Those from Gombe State were found to live with an average of 5 persons and a median of 6 persons in a household compared to an average and median of 4 persons respectively among those from Bauchi State.

Respondents' perceived onset of infection among patients

When the respondents were asked about the food or drink taken by the patients twenty-four hours before the onset of diarrhoea, most (41.2%) did not know what was eaten while 27.2% mentioned *Tuwo* (corn meal) as displayed in Table 2.

Overall, the date of onset of diarrhoea in virtually all the patients, according to the respondents ranged from 1 to 2 days prior to the interview date. The reported frequency of stooling ranged from 1 to 27 times in the last twenty-four hours preceding the interview with an average of 8 times and a median of 7 times. The frequency of vomiting of the patients ranged from 0 to 20 times in the last twenty-four hours preceding the interview with an average of 4 times and a median of 3 times.

Knowledge of and perceived causes of cholera among respondents

The results of the survey showed that a small proportion (44.6%) of those interviewed correctly mentioned lack of

Table 1. Socio-demographic characteristics of respondents.

Socio-demographic characteristics	Bauchi number (%)	Gombe number (%)	Total number (%)
Age (in years)			
15-24	7 (9.6)	3 (15.8)	10 (10.9)
25-34	11 (15.1)	5 (26.3)	16 (17.4)
35-44	28 (38.3)	7 (36.8)	35 (38.0)
45-54	19 (26.0)	3 (15.8)	22 (23.9)
55+	81 (1.0)	1 (5.3)	9 (9.8)
Total	73 (79.3)	19 (20.7)	92 (100.0)
Sex			
Male	31 (42.5)	8 (42.1)	39 (42.4)
Female	42 (57.5)	11 (57.9)	53 (57.6)
Total	73 (79.3)	19 (20.7)	92 (100.0)
Marital status			
Never married	36 (49.3)	8 (42.1)	44 (47.8)
Married	36 (49.3)	9 (47.4)	45 (48.9)
Widowed	1 (1.4)	2 (10.5)	3 (3.2)
Total	73 (79.3)	19 (20.7)	92 (100.0)
Religion			
Christianity	2 (2.7)	1 (5.3)	3 (3.2)
Islam	71 (97.3)	18 (94.7)	89 (96.7)
Total	73 (79.3)	19 (20.7)	92 (100.0)
Education			
No formal	20 (27.4)	5 (26.3)	25 (27.2)
Quoranic	12 (16.4)	3 (15.8)	15 (16.3)
Primary	12 (16.4)	5 (26.3)	17 (18.5)
Secondary	7 (9.6)	4 (21.1)	11 (12.0)
Tertiary	1 (1.4)	1 (5.3)	2 (2.1)
No response	21 (28.8)	1 (5.3)	22 (23.9)
Total	73 (79.3)	19 (20.7)	92 (100.0)
Occupation			
Farming	5 (6.8)	1 (5.3)	6 (6.5)
Trading	81 (1.0)	7 (36.8)	15 (16.3)
Civil servant	-	2 (10.5)	2 (2.2)
Student	10 (13.7)	5 (26.3)	15 (16.3)
Unemployed	10 (13.7)	1 (5.3)	11 (12.0)
Housewife	81 (1.0)	1 (5.3)	9 (9.8)
No response	32 (43.8)	2 (10.5)	34 (37.0)
Total	73 (79.3)	19 (20.7)	92 (100.0)

safe and clean water for drinking, poor sanitation and food contamination as the routes through which cholera infection could be transmitted. On the contrary, a large proportion (50.0%) either did not know or had misconceptions such as overcrowding, fever, hot weather and fate of God (Allah) as the causes of the disease. The distribution of the respondents' perceived causes of cholera infection, according to State is displayed in Figure 2.

Statistical test using Chi square showed gender difference in knowledge of lack of safe and clean water for drinking [25.0% males vs. 5.4% females] ($p<0.05$) and

Table 2. Food eaten by patients 24 h before the onset of diarrhoea according to respondents.

Food eaten by patients before onset of diarrhoea	Number (%)
Tuwo (corn meal)	25 (27.2)
Kunu (Guinea corn beverage)	8 (8.7)
Fruits	1 (1.1)
Breastmilk and water	1 (1.1)
Pap (porridge)	5 (5.4)
Rice and stew	9 (9.8)
Roasted corn	1 (1.1)
Fura (street-vended home-made cow milk)	2 (2.2)
Egg	1 (1.1)
Talia	1 (1.1)
Don't know	38 (41.2)
Total	92 (100.0)

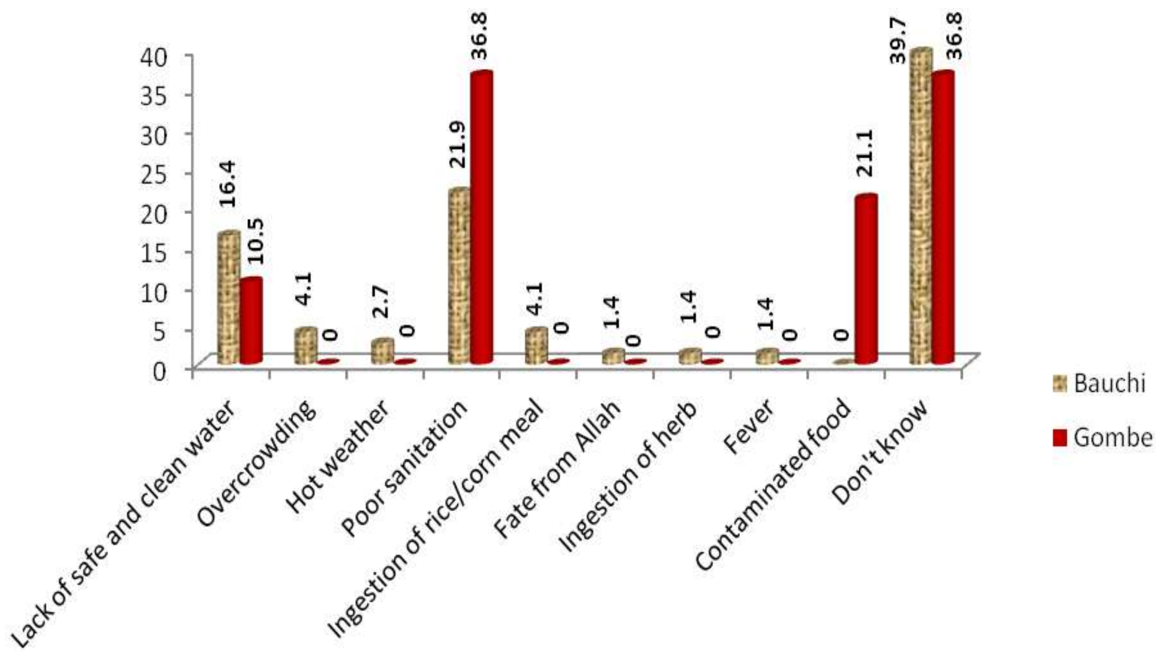

Figure 2. Perceived causes of cholera infection among respondents according to State.

poor sanitation [27.8% males vs. 19.6% females] ($p < 0.05$) as possible causes of cholera infection.

Sources of drinking water

On the sources of drinking water, the majority of the respondents had access to well (47.8%), river (19.6), rain water (4.3%) and pond (2.2%) as their main sources of water for drinking and other domestic use. On the contrary, only 33.7% had access to safe and clean drinking water through a pipe-borne system and borehole. This is unlike 22.2% who access their drinking water from the well and water-vending trucks. Figure 3 illustrates the distribution of the sources of drinking water mentioned by the respondents according to their State.

Preventive measures taken against cholera infection among respondents

When asked if any preventive action is taken against cholera infection during the outbreak, a very few (18.5%) of the respondents [64.7% Bauchi vs. 35.3% Gombe]

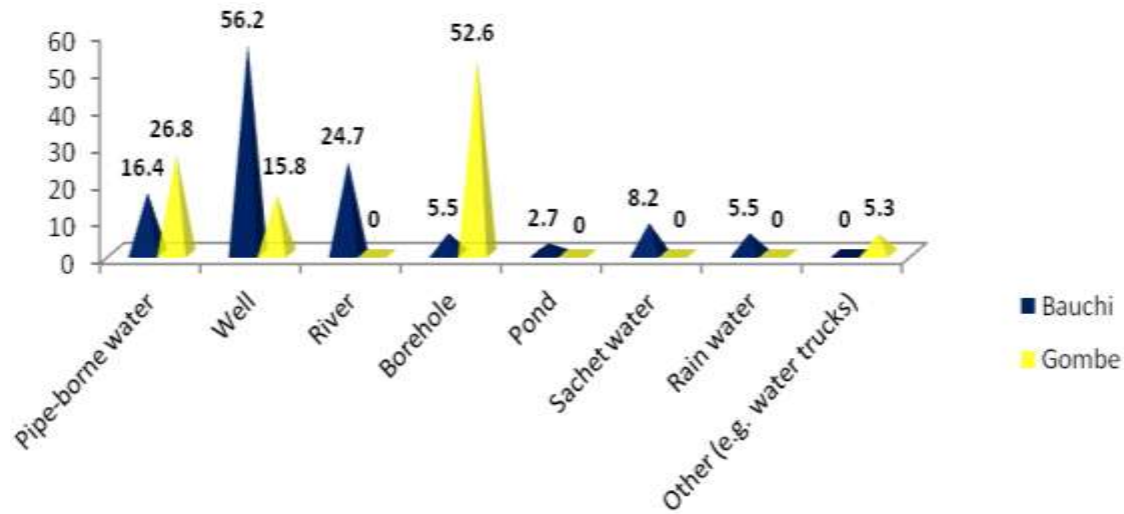

Figure 3. Sources of drinking water in respondents' communities.

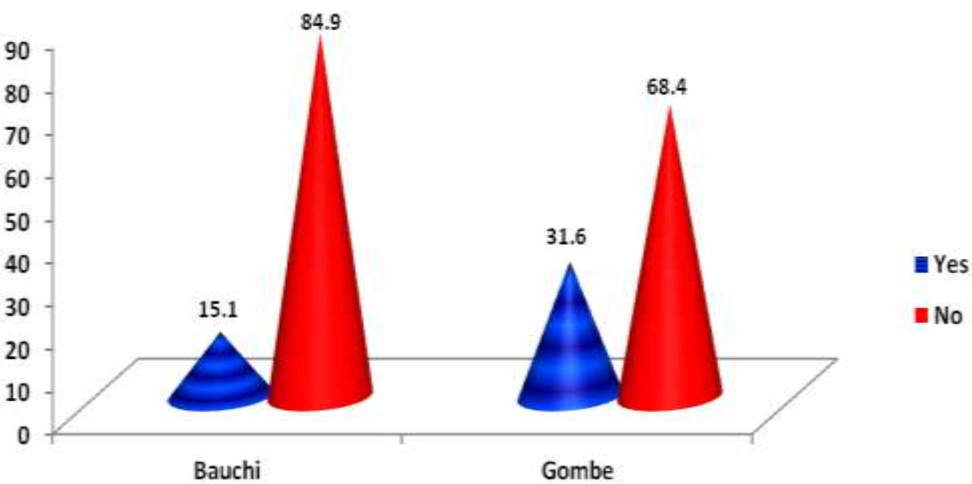

Figure 4. Responses on whether any preventive measure is taken against cholera infection or not.

were affirmative in their response. More respondents in Gombe State reported taking preventive action than those from Bauchi State as illustrated in Figure 4. The different preventive measures mentioned included taking antibiotics (17.6%), regular sanitation and good hygiene (17.6%), regular hand washing with soap (5.9%), boiling of water (5.9%). Statistical test using Chi square suggests that gender maynot be a major determinant of health seeking behavior of taking preventive action against cholera infection among the two groups ($p > 0.05$).

Environmental sanitation, sewage and waste disposal practices

Observation of the environments of some communities visited in the two States showed poor hygiene, sanitation and food hygiene and safety practices.

The poor sewage disposal practices were demonstrated by the respondents interviewed in the States visited as most of them reported using the pit/latrine (77.2%), open field (bush) (15.2%) and bucket (3.3%) to dispose their faeces. Only a very few (4.3%) use water closet.

Similarly, poor disposal of domestic wastes was exhibited by most respondents interviewed. Half (50.0%) of the respondents pointed out that they dispose their domestic wastes directly into the bush while, 34.8% dispose theirs into pits dug around their homes. Other methods of waste disposal mentioned included: public waste disposal bins (6.5%); burning (2.2%); dump into the river (2.2%); and others (1.1%). Three (3.2%) of the respondents were undecided in their response as

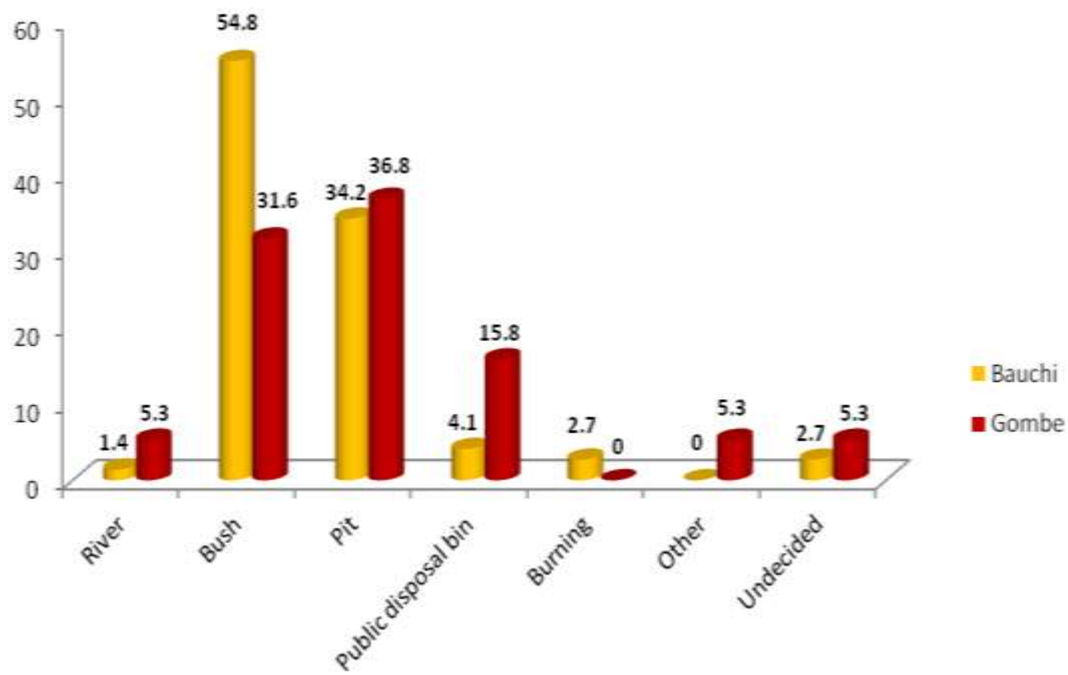

Figure 5. Methods of waste disposal mentioned by respondents according to State.

illustrated in Figure 5.

Respondents' hand washing practices

It is encouraging that more (52; 56.5%) of those interviewed in the States [57.5% Bauchi vs. 52.6% Gombe] adopted good hand washing practice of washing their hands with water and soap after using the toilet. On the contrary, 40 (43.5%) reported washing their hands with only water after toilet use.

Ways through which cholera infection is perceived to spread

The respondents had poor knowledge of cholera can spread in the community. Overall, only a few (34.8%) correctly mentioned water, food and poor sanitation as the transmission routes through which cholera spreads in vulnerable communities. More than half of the respondents (52.2%) did not know how cholera spreads in the community while some had misconceptions such as perceived act of divination (7.6%), hot weather (2.2%), fever (2.2%) and proximity of hospital to home (1.1%).

Awareness of any public health education on how to prevent cholera among respondents

About 52.0% of the respondents [56.2% Bauchi vs. 36.8% Gombe] had not heard or seen any public health education programme on the cause, mode of transmission and preventive measures against cholera in their communities by the health authorities while about 48.0% had a contrary view as presented.

There was a gender difference between the respondents on the awareness of any community or public health education efforts on the cause, mode of transmission and how to prevent cholera by the health authorities as statistical test using Chi square showed that more males (63.9%) were more likely to be aware than the females (35.7%) ($p < 0.05$).

The opinions of respondents on how to curb future outbreak of cholera are presented in Table 3. The opinion of most respondents in Bauchi State is regular vaccination of people against cholera in vulnerable communities. On the other hand, most of those in Gombe State opined that adequate provision of safe and clean water for drinking and other domestic use is the perceived effective way of curbing the outbreak of cholera in their communities.

Epidemiological mapping of cholera outbreak in Gombe State

With no secondary data obtainable in Bauchi State, secondary data obtained from the Epidemiology Unit of Gombe State as presented in Table 4 showed that only two of the eleven local government areas (LGAs) had no cases of the disease while the remaining nine LGAs had reported cases and deaths from the disease.

In-depth interview with the Head of the Gombe State

Table 3. Respondents' opinion on how to curb the outbreak of cholera according to State.

Respondents' opinion on how to curb the outbreak of cholera	Bauchi (n=73) Number (%)	Gombe (n=19) Number (%)
Provision of safe and clean water	46 (21.9)	8 (42.1)
Good housing facilities	20 (27.4)	4 (21.1)
Women empowerment	14 (19.2)	2 (10.5)
Regular vaccination	21 (28.8)	1 (5.3)
Adequate toilet facilities	3 (4.1)	--
Good personal and food hygiene	2 (2.7)	1 (5.3)
Better drainage system	1 (1.4)	- -
Divine intervention	2 (2.7)	2 (10.5)
Good environmental hygiene	5 (6.8)	5 (26.3)

Table 4. Reported cases of cholera in Gombe State for weeks 17-35 2010 (May-September 2010).

LGA	Population	Cases	Deaths	Attack rate/100,000	Case fatality rate (CFR)
Akko	383,219	266	14	69.4	5.3
Balanga	241,089	608	23	252.2	3.8
Billiri	229,287	11	2	4.8	18.2
Dukku	235,011	0	0	0.0	0.0
Funakaye	267,788	0	0	0.0	0.0
Gombe	303,986	752	44	247.4	5.9
Kaltungo	169,920	84	7	49.4	8.3
Kwami	221,522	5	1	2.3	20.0
Nafada	156,740	8	1	5.1	12.5
Shongom	171,866	10	2	5.8	20.0
Yamaltu/Deba	289,522	254	19	87.7	7.5
Total	2,669,949	1,998	113	74.8	5.7

Source: Epidemiological Unit, Gombe State Ministry of Health, September 2010.

Epidemiology Unit showed that the first case of the outbreak was reported in Bambam Ward, Balanga LGA of the State in week 17. Coincidentally, the first series of rainfall started in the same week 17 of the year 2010 across the State. It was in week 18 that reports of cases were received from other three LGAs namely: Akko, Gombe and Kaltungo. The Head of the Gombe State Epidemiology Unit pointed out that, '*Human and water samples collected from Bambam Ward of Balanga LGA and tested at the State Specialist Hospital tested positive for Vibrio cholerae isolates*.'

As at Week 35 (5^{th} September 2010), nine of the eleven LGAs of Gombe State had reported Cholera outbreaks. The LGAs most affected included: Gombe (752 cases), Akko (266 cases), Yamaltu/Deba (254 cases), and Balanga (608 cases). With all State health workers on strike, surveillance activities were shut down after Week 35, with no reporting of cases.

DISCUSSION

Taking responses of the respondents on theages of their hospitalised relations/wards with acute watery diarrhoea at the treatment centres into cognizance, children aged 1-5 years were found most affected alongside adolescents aged 13-24 years by the epidemic. This finding of more cases of infection among children under five years is similar to that of a previous study in which it was attributed to interfamilial spread through family contacts under similar unhygienic circumstances that characterized the study areas (Sasaki et al., 2008). This finding perhaps simply affirms the results of the 2008 and 2013 National Demographic and Health Surveys in the country which showed that children of this age group are more prone to diarrhoeal diseases and that children of this age group in the North East zone of the country are more susceptible to episodes of diarrhoeal diseases than children of same age in other zones of the country (National Population Commission and MEASURE DHS ICF Macro, 2009; National Population Commission (NPC) [Nigeria] and ICF International, 2014). The finding that no child under one year was seen to be affected among those surveyed is similar to the finding of an earlier study on cholera outbreak in Ibadan, South-West Nigeria (Lawoyin et al., 1999).

The high case fatality rates (CFRs) reported in many of the LGAs of Gombe State as shown in the secondary data from the Epidemiological Unit of the Gombe State Ministry of Health in Table 4 is of serious concern as the CFRs for each of the affected LGAs and the State as a whole are higher than the WHO accepted 1% threshold (World Health Organisation, 2010). This perhaps cannot be unconnected to the limited access to proper health care for the most vulnerable people, limited capacity of the surveillance system to trigger a timely response to the epidemic outbreak and insufficiencies in a State's health care system which contributed to the agitation that culminated into the prolonged strike action by the State health workers at the time of the epidemic.

The first case of the outbreak reported in Gombe State following the onset of the first series of rainfall in week 17 of 2010 validates the notion that rainfall is often one of the precursors to cholera outbreaks in vulnerable areas (Sasaki et al., 2008; IRIN Global Health, 2011; IRIN Plus News, 2009). It is suggested that a reliable forecasting system that would monitor rainfall patterns needs to be developed to trigger pre-emptive measures such as the mobilization of public health teams or emergency vaccination efforts to prepare for any outbreak in vulnerable areas such as the communities studied in Bauchi and Gombe States. It therefore becomes imperative to establish an early warning surveillance system, including mechanisms for the rapid investigation of rumors and suspected outbreaks, and organized workshops for capacity building in case management and epidemic preparedness as successfully implemented in Somalia with assistance from WHO and some non-governmental organizations following the 1995-2000 seasonal outbreaks and in Perufollowing 1991outbreak (Kindhauser, 2003). The multi-sectoral Epidemic Preparedness and Response (EPR) approach that has contributed to the reduction in case fatality rates over the years need be strengthened and sustained as emphasized by the finding of a study that examined the factors associated with recurrent cholera epidemics and the management of the epidemics and health outcomes in Kano State of Northern Nigeria (Usman et al., 2005). The EPR will be facilitated with sufficient pre-positioned, medical supplies such as rapid diagnostic test kits for diarrhoeal disease, ringers lactate, antibiotics, oral rehydration salt (ORS) packets, water testing kits and aquatabs for water treatment for better case management by the States.

The State health workers' strike action at the time of the survey, which depleted the capacity to give meaningful treatment to patients as only volunteer corps mainly constituted by students from the State School of Health Technology and some members of any religious organization calls for concern about the quality of care provided to affected patients at the treatment camps. Since the capacity of the volunteer corps is inadequate, government should provide documented guidance at the treatment camp sites for the volunteer corps to improve patient management/treatment. In the future, efforts need be made by the non-striking senior Medical Consultants in the State Ministry of Health provide some medical supervision at the treatment camp sites under such similar circumstance.

There is a need to emphasize that the observed gap in the surveillance system as it relates to the cholera outbreak in Gombe State for about two weeks preceding the survey period compromised the disease notification and reporting system and would have resulted in inaccurate and incomplete surveillance data in the State due to under-reporting of new cases which has remained a problem as emphasized by WHO (World Health Organisation, 2010). Effective public health interventions such as adequate case management, improved environmental management, and adequate use of oral cholera vaccines all depend on an accurate surveillance data that would inform policy and programmes.

The findings of the present study, suggested that a high proportion of the respondents demonstrated poor hand washing habits by washing their hands with only water after toilet use was very high predisposing factor in transmission of diarrhoea-causing agents including cholera infection through the faecal-oral route.

The outbreak of the disease in the States could be attributed to transmission through faecally contaminated water following the onset of rainfall in week 17 when the first case of the disease was reported. The complicity of the situation is explained where the people practice poor method of sewage disposal as many those interviewed used the bush for open defecation and pit system, indulged in poor hand washing practice after toilet use and many drinks unsafe water from the wells and rivers. This is possible considering the fact that the incubation period of the infection is very short (Kindhauser, 2003). This is because new outbreaks can occur sporadically anywhere that water supply; sanitation, food safety, and hygiene are inadequate as observed in many of the places visited. The greatest risk occurs in over-populated communities and settings characterized by poor sanitation, unsafe drinking-water, and increased person-to-person transmission. This perhaps explains the high proportion of children affected among those surveyed having possibly been exposed to the diarrhoea-causing agents through the use of contaminated water combined with unhygienic practices in food preparation and the disposal of excreta and domestic wastes (Sasaki et al., 2008; National Population Commission and MEASURE DHS ICF Macro, 2009). Therefore the need for coordinated stakeholders' activities to improve the physical and environmental health conditions of the people such as the construction of deep well facilities. This can be achieved through collaboration between the Ministry of Health, Ministry of Environment, Ministry of Works, Ministry of Finance and the local government authorities.

The finding that the majority of the respondents depend on wells as their major source of domestic water corroborates the finding of a study of association of waterborne disease morbidity pattern and water quality in parts of Ibadan, Nigeria reported by Oguntoke et al., (2009).

The poor community awareness and health education on the cause of the disease, how it spreads and how to prevent its transmission as demonstrated by a large number of the patients and parents/guardians interviewed should be a cause for concern. This could perhaps be responsible for the high incidence of the disease.

Therefore a need to complement epidemic preparedness and response with prevention in order to avert outbreaks by expanding access to improved sources of drinking-water and sanitation. This can be achieved through advocacy and embracing simple and inexpensive methods of domestic water disinfection and storage and by working with communities to encourage behavioral change to diminish the risks of infection as recommended by earlier studies and advocated by WHO (World Health Organisation, 2010; Sasaki et al., 2008; Shultz et al., 2009).

Improvements in water supply and storage, sanitation, hygiene and food safety practices, proper waste management and community awareness through improved communication and public information to dispel the misconceptions about the cause of cholera infection, how it spreads and how to prevent infection by the Ministry of Health will go a long way in contributing to curbing outbreak of cholera.

Measures for the prevention of cholera should consist of the provision of clean water and maintenance of environmental sanitation and personal hygiene by populations who do not yet have access to basic services. Health education and good food hygiene are equally important. At the community level, people need to be educated and reminded of basic hygienic behaviors, including the necessity of systematic regular hand-washing with soap after defecation and before handling food or eating as pointed out by earlier studies (Curtis and Cairncross, 2003; Dubois et al., 2006) as well as safe preparation and conservation of food. Through public health education and hygiene promotion, communities can be encouraged to take action to protect themselves from outbreaks of cholera. Appropriate media such as radio, television and or posters should be involved and used in disseminating health education messages. Community and religious leaders considering the power they wield and their charismatic influence in their domains should also be associated with social mobilization campaigns. This can be achieved with the collaboration between the Ministry of Health and the Ministries of Information and Education.

It needs be emphasized that people in the communities, particularly those in Bauchi State who take antibiotics as chemo-prophylaxis to prevent cholera infection as shown in Table 4 should be educated that this practice has no effect on the prevention and spread of cholera, rather it is inimical to the bacterial culture and could have adverse effects by increasing the antimicrobial resistance.

The need and regular use of oral cholera vaccines as suggested by some of the respondents as one of the strategies of preventing future recurrence of cholera outbreaks in Table 3 cannot be over emphasized as an additional public health tool to improve cholera control activities in high-risk areas such as Bauchi and Gombe States. The importance of careful planning and preparation for mass delivery of oral cholera vaccines to vulnerable populations during outbreaks cannot be over emphasized.

Conclusions

The findings of the study showed poor sanitation and food hygiene practices in communities of the States visited. These factors could possibly be attributed to the outbreak of cholera in the States. The results provide insights for planning educational programmes and show that information, education and communication/behavioral change communication (IEC/BCC) programmes are needed to boost knowledge about cholera in the communities across the studied States. The implications of the key findings of the study on possible causes of outbreaks of cholera in the States suggest the need to advocate and embrace simple and inexpensive methods of domestic water disinfection and storage for use, intensify public health education discouraging open defecation by emphasising its dangers and encourage improved sanitation and regular hand washing particularly after using the toilet in the communities emphasising the benefits. People need to take the potentially encouraging step of taking preventive measures against the disease at the individual, household and community levels which would eventually transcend the whole States.

Conflict of Interests

The authors have not declared any conflict of interests.

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Full Length Research Paper

Nutritional status and associated factors among primary school adolescents of pastoral and agro-pastoral communities, Mieso Woreda, Somali Region, Ethiopia: A comparative cross-sectional study

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Globally, malnutrition among adolescents is a major public health concern. Despite the emergence of a number of advancements in areas of health and nutrition services in developing countries including Ethiopia, nutritional status of adolescents is not yet commonly included in health and nutrition surveys and an up-to-date overview of their nutritional status across the world is not available. Even the existing studies conducted on nutritional status of adolescents in Ethiopia and other parts of the world overlooked the pastoral and agro-pastoral area contexts. Thus, the objective of this study was to assess nutritional status and associated factors among adolescents of pastoral and agro-pastoral communities. Comparative cross-sectional study was conducted at Mieso Woreda on 655 primary school adolescents selected by multistage random sampling. Data were collected by face-to-face interview using pre-tested structured questionnaire and anthropometric measurements. Bivariate and multivariate binary logistic regressions were conducted to identify independent predictors of stunting and thinness (wasting). The overall magnitude of stunting and thinness were 11.5 and 22.9%. The magnitude of stunting was higher in agro-pastoral (14.5%; 95%CI: 10.7-18.3%) than pastoral (8.3%; 95%CI: 5.3-11.3%) communities. Meanwhile the magnitude of thinness was higher in pastoral (26.2%; 95%CI: 21.4-31.0%) than agro-pastoral (19.6%; 95%CI: 15.3-23.9%) community. Stunting was significantly associated with place of residence, sex, age, family size, source of drinking water, wealth tertiles and child food insecurity. Meanwhile thinness was significantly associated with family size, the source of drinking water, availability of latrine, household wealth tertiles, washing hands with soap after toilet, diarrheal illness and child food insecurity. The study revealed significantly higher magnitude of stunting in agro-pastoral communities and higher magnitude of thinness in pastoral communities though not significant. Interventions should focus on factors identified in this study to reduce magnitude of malnutrition among adolescents.

Key words: Stunting, wasting, school adolescents, pastoralist, agro-pastoralist, Somali.

INTRODUCTION

As defined by WHO, adolescents are individuals between the ages of 10 and 19 years, which make up approximately 20% of the world's population. Adolescence is a time of intense growth, second only to infancy (Cordeiro et al., 2005; WHO, 2006). During adolescence, individuals can gain 15% of their ultimate adult height and 50% of their adult weight. This rapid growth is accompanied by an increase in nutrient demand (Cordeiro et al., 2005).

Nutrition is a basic human need that remains unmet for vast numbers of adolescents, who are thus unable to achieve their full genetic developmental potential (Cordeiro et al., 2005). Adolescents are the future generation of any country and their nutritional needs are critical for the wellbeing of society. Good nutrition during adolescence is critical to cover the deficits suffered during childhood. If adolescents are well nourished, they can make optimal use of their skills, talents and energies today, as well as be healthy and responsible citizens and parents of healthy babies tomorrow (WHO, 2006).

Adolescents are vulnerable groups for malnutrition and its consequences, because it is the dynamic period of physical growth and mental development. Globally, malnutrition among school age adolescents is a major public health concern. Nutritional status has powerful influence on an adolescent's learning and how well the adolescent performs in school. Literatures show that there is strong link between nutrition and academic performance of adolescents. Both acute and chronic malnutrition (under nutrition) impairs children's ability to perform effectively at school (The Partnership for Child Development, 1997). According to many researchers, poor nutritional status in primary school-age adolescents is among the most common causes of low school enrollment, high absenteeism, early dropout and unsatisfactory classroom performance (Andrews, 2013; The Partnership for Child Development, 1999; Walker et al., 2007). In Ethiopian context, focusing on school age adolescents is particularly pertinent as this age group represent more than 30% of the total population (Demographics of Ethiopia, 2014).

Although adolescence is a time of enormous physiological, cognitive, and psychosocial change, they remain "a neglected, difficult-to-measure and hard-to-reach population". Most studies of malnutrition in developing countries have concentrated on young children or on the pregnancy period, thus neglecting adolescents (Cordeiro et al., 2005).

The concept of nutrition and its manifestation as malnutrition, involves complex processes at multiple levels, from the individual to the household, community, national and international levels. Besides poverty, there are other factors that directly or indirectly affect the nutritional status of adolescents (Cordeiro et al., 2005). Conditions such as food security, clean water, safe sanitation facilities, hygiene practices, maternal care practices and access to health services can have impact on overall nutrition status of adolescents (Benson, 2005). However, the relative importance of these factors may vary from area to area. In Ethiopia, these may include cultural and environmental factors as the country has a habits and practices are highly diversified (Abera, 2016). The livelihood of societies is also another factor that affects nutritional status of their members. There is severe poverty level in pastoralist than agro-pastoral societies (Adugna and Sileshi, 2013) because pastoralists are dependent only on herding and agro-pastoralists practice both herding and land cultivation. Thus, we hypothesized that there may be a difference in nutritional status of school adolescents between pastoral and agro-pastoral communities.

Despite the emergence of a number of advancements in areas of health and nutrition services in developing countries including Ethiopia, nutritional status of adolescents is not yet commonly included in health and nutrition surveys and an up-to-date overview of their nutritional status across the world is not available (Uauy et al., 2008; Walker et al., 2007). They were not included in Ethiopian Demographic and Health Surveys (EDHS) which provide nutritional status data of children under five-years-old at national and regional levels (Black et al., 2008). The existing studies conducted on nutritional status of adolescents in Ethiopia and other parts of the world also overlooked the pastoral and agro-pastoral area contexts (Assefa et al., 2013; Cordeiro et al., 2005; Dambhare et al., 2010; Gebreyohannes et al., 2014; Mulugeta et al., 2009; WHO, 2006; Wolde et al., 2014). Therefore, taking this into account, the aim of the present study was to assess nutritional status and identify associated factors among primary school adolescents of pastoral and agro-pastoral communities of Mieso Woreda, Somali Region, Ethiopia, to focus the attention of policy makers towards this group.

MATERIALS AND METHODS

Study design, area and period

Comparative cross-sectional study was conducted from March 10 to April 11, 2014 at Mieso Woreda, Shinele Zone, Somali Region. The woreda (administrative district) is located at a distance of 327 and 312 km from the capital of the region, Jigjiga town, and the capital of the country, Addis Ababa city (Figure 1). The woreda is typically rural and organized into 10 administrative kebeles. It is characterized by pastoral and agro-pastoral livelihood of the society. Ecologically agricultural, the Mieso Woreda is divided in to dry mid-highland, semi-arid and arid zones. Information is not available on the land area and rainfall of Mieso Woreda. The woreda had an estimated total population of 85,570 (47,589 males and 37,981 females) in 2013 which was projected from 2007 population census. The woreda had a total of 11 primary schools (6

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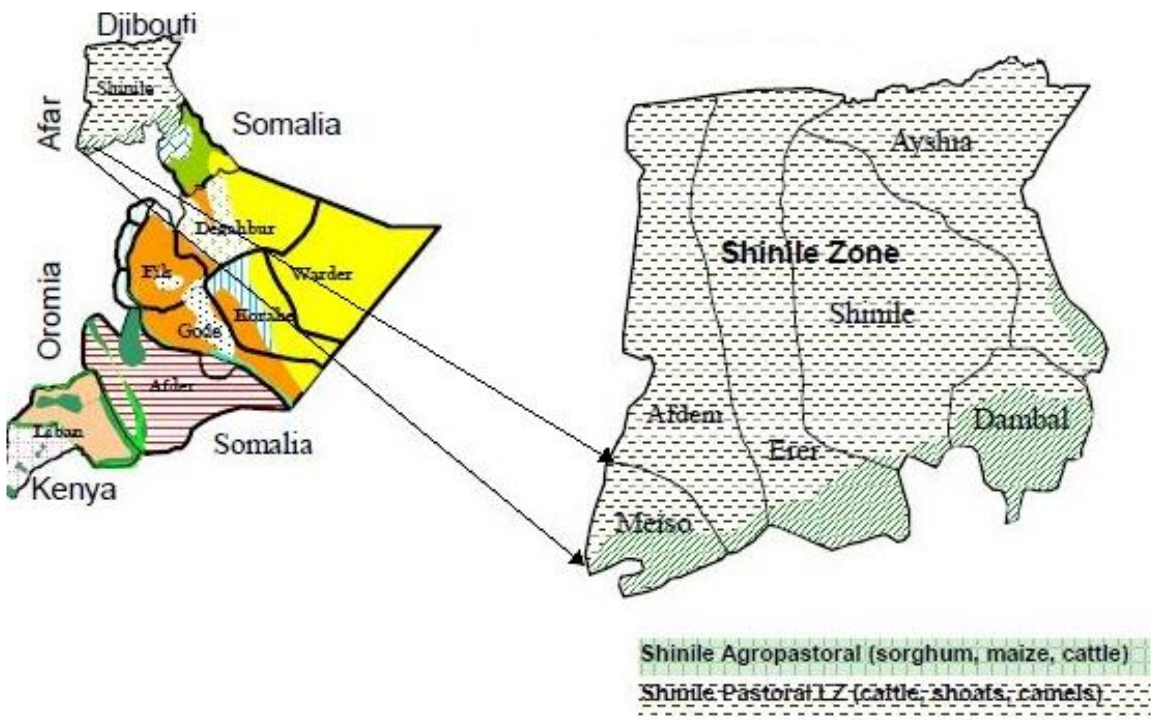

Figure 1. Map of the study area (source: Save the Children, 2001).

serving grades 1-6 and 5 full cycle primary schools; that is, grades 1-8) and 1 general and upper secondary school (grade 9-12) in 2013 to serve an estimated 20,218 (11,243 males and 8,974 females) school age children. There were 3 health centers and 10 health posts in the woreda though the facilities were not equipped with necessary medical supplies, equipments, pharmaceuticals and even some were nonfunctional. The woreda had seasonal roads because of its topographical features.

Participants and sampling procedures

Study participants were sampled 10-19 years old students attending grades 4 to 8 at full cycle primary schools mentioned previously and who had no physical deformity or chronic illness. Sample size was determined by double population proportion formula using EpiInfo Software. 23.1% prevalence of wasting were assumed (Hall et al., 2008) among school children of agro-pastoral community, 10% difference in prevalence of wasting between the two communities which gave 33.1% prevalence of wasting among school children of pastoral community, 5% type I error (a), 80% power, 10% non-response rate and equal sample size as the two communities had nearly equal size of school children population. Thus, the final sample size was 348 for each community.

Participants were selected by multistage random sampling from each community. First, two schools were randomly selected from each community. Then, study participants were randomly selected, proportional to the size of each grade level (Figure 2). Selected participants were classified as pastoral or agro-pastoral within same school by asking them the livelihood of their family.

Variables, data collection procedure and measurement

Outcome variable was malnutrition (Stunting assessed by Height-For-Age and Wasting/Thinness assessed by BMI-For-Age) whereas independent variables included socio demographic/economic characteristics (age and sex of the child, parents' educational level and occupation, head of the household, family size, type of family, number of siblings, religion, ethnicity, wealth and place of residence), health status (sickness in the last 2 weeks and type of illness (diarrhea, fever, cough and others)), feeding practice (breakfast intake, meal frequency per day, adolescent food insecurity), environmental factors (source of drinking water, availability of latrine at home, hand washing practice at critical times).

Data were collected by face-to-face interview using a structured questionnaire which was developed after reviewing different literatures of similar studies. The questionnaire was prepared in English, translated to Somali language and back translated to English to check consistency. Questionnaire was pre-tested on 5% of the sample in both communities and necessary corrections were made accordingly. Eight BSc Nurses who speak Somali were data collectors and there were also two BSc Health Officers supervising the data collection. Two days training was given for the data collectors and supervisors. Overall process of data collection was supervised by principal investigator.

Data were collected from adolescent students. To reduce the possible recall bias on age of the school adolescents, school age records were used and cross-checked with parents' response. Weight was measured using a well calibrated Seca digital scale to the nearest 0.1 kg and height was measured using measuring board with a moveable headboard to the nearest 0.1 cm. Height measurement was taken while the participant was barefoot.

Adolescent's food insecurity was measured using a four item index adopted from household food security questionnaires used in developing countries (Frongillo and Nanama, 2006). Adolescents were asked four food security questions. These were whether in the last three months adolescent (1) had ever worried about having enough food, (2) had to reduce food intake because of shortages of food or money to buy food, (3) had to go without having eaten because of shortage of food or money to buy food and (4) had to

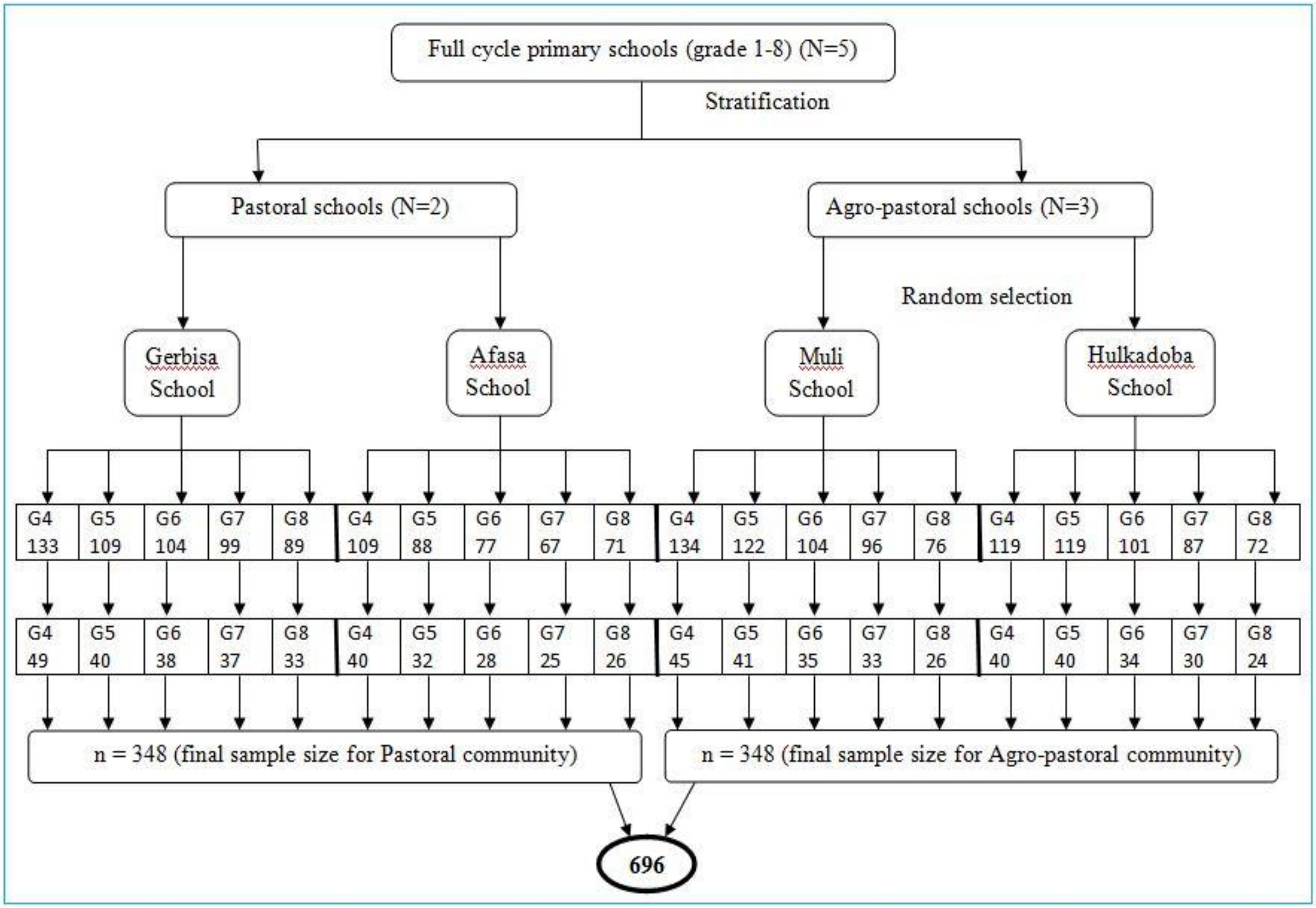

Figure 2. Schematic diagram of sampling procedure (N is number of schools, G represents grade level and numbers included in each box beneath grade level are size of each grade level).

ask outside the home for food because of shortage of food or money to buy food. A “Yes” response to food security question was labeled to have score of “1” and “No” was labeled to have score of “0”.

The values were summed to produce a food insecurity index. The index of food insecurity is defined as the number of items with a positive answer. The index was dichotomized as “food insecure” for adolescents having a value of 1 and above and “food secure” for those who had a value of 0. The index has high internal consistency (Cronbach’s Alpha=0.82) which is above the cut off point for reliability (Nunnally, 1978).

Household wealth was assessed by the adolescent’s reporting of ownership of asset items consisting of animal assets (Goat, Cattle, Camel, Donkey, Ox), ownership of house, and ownership of farming land; all commonly used as an indication of wealth status in the study area.

Data processing and analysis

Data were entered into EpiData 3.4, exported to SPSS 20, cleaned, explored and recoded before analysis. BMI was calculated by dividing weight in kilogram by square of height in meters. Anthropometric indices (Height-For-Age and BMI-For-Age) were calculated by WHO AnthroPlus software 1.0.4 using WHO child growth references.

Principal component analysis was done and the results were converted into tertiles and categorized into “higher”, “medium” and “lower” tertiles within each community. Chi-square test was conducted to check adequacy of cells. Bivariate binary logistic regression was done for variables that fulfill chi-square test criteria to examine their association with the outcome variables. After checking multicollinearity among predictor variables in linear regression, variables with p-value less than 0.05 in bivariate analysis were entered into multivariable binary logistic regression using backward stepwise method.

Finally, variables with p-value less than 0.05 in multivariable analyses were considered as having statistically significant association with outcome variables. Adjusted odds ratio (AOR) with 95% CI was used to show the strength of association.

Ethical consideration

Ethical clearance was obtained from the Institutional Review Board (IRB) of College of Health Sciences, Jimma University. IRB has specifically approved this study and provided a letter of confirmation. Support letter was obtained from the department of Epidemiology and submitted to Somali Regional Health Bureau and Mieso Woreda administrative body, woreda health office, education office and respective schools. Written informed consent and verbal informed assent were obtained from parents/guardians and children respectively. Privacy of student was kept during anthropometric measurements. Confidentiality of collected information was also ensured.

Operational definitions

Community: A region, within which most people tend to follow the same patterns.
Pastoralist community: Community that practices herding as primary source of their family income.
Agro-pastoralist community: Community that practices both crops production and herding as primary source of their family income.
Woreda: It is the third level administrative district next to region/state and zone in Ethiopia.
Body Mass Index (BMI): It is weight in kilograms divided by the square of height in meters
Nutritional status: In this study, this term refers to either under nutrition (stunting or wasting/thinness) or not under nutrition.
Chronic malnutrition (stunting): It refers to height-for-age (HAZ) < -2 SD of median value of the NCHS/WHO international growth reference (WHO, 2009).
Acute malnutrition (wasting/thinness): It refers to BMI-for-age (BAZ) < -2 SD of the median value of the NCHS/WHO international growth reference (WHO, 2009).
Past episode of diarrhea: It refers to having three or more loose stools in 24 h in the past two weeks from the date of survey.
Food insecurity: It refers to having food insecurity index (produced from four food security questions) of 1 and above.

RESULTS

Socio-demographic and economic characteristics

A total of 655 (324 from pastoral and 331 from agro-pastoral community) school adolescents were included in the study making response rate of 94.1% (93.1 and 95.1% respectively). Thirty three adolescents were absent during data collection time and eight were excluded from analysis for incompleteness and inconsistency of the information.

"The majority of participants were male, both from the pastoral (54.0%) and the agro-pastoral (52.0%) communities. The mean age was similar in both groups, 12.9 (SD = 1.9) and 12.7 (SD = 2.0) for participants of pastoral and agro-pastoral community respectively. The majority of participants were Somali (97.5% pastoral, 97.3% agro-pastoral) and Muslim (99.1% pastoral, 99.4% agro-pastoral). Almost half (49.4%) of pastoral and majority (55.0%) of agro-pastoral participants live within a family size of greater than five. The majority of households were male headed (98.1% pastoral, 95.8% agro-pastoral) and monogamous (86.4% pastoral, 92.1% agro-pastoral). The majority of both mothers (97.5% pastoral, 95.8% agro-pastoral) and fathers (88.0% pastoral, 81.3% agro-pastoral) were unable to read and write. Majorities (93.2% pastoral, 88.8% agro-pastoral) of the mothers were housewives and majorities (79.9% pastoral, 74.0% agro-pastoral) of the fathers were farmers. Sorghum is the main staple food (38.0% pastoral 44.7% agro-pastoral) for both communities (Table 1).

Magnitude of malnutrition and associated factors

Magnitude of malnutrition

Overall magnitude of stunting was 11.5% (95% CI: 9.1-13.9), with a lower magnitude in the pastoral community [8.3% (95% CI: 5.3-11.3)] than in the agro-pastoral community [14.5% (95% CI: 10.7-18.3)]. This difference was statistically significant. Overall magnitude of wasting/thinness was 22.9% (95% CI: 19.7-26.1), with higher magnitude in the pastoral community [26.2% (95% CI: 21.4-31.0), than in agro-pastoral community [19.6% (95% CI: 15.3-23.9)] though it was not statistically significant.

Factors associated with stunting

Stunting was significantly associated ($p < 0.05$) with type of community, sex of the adolescent, age of the adolescent, grade level, number of siblings, family size, source of drinking water, household wealth (tertiles), daily meal frequency, cough illness, and adolescent's food security at bivariate level (Table 2).

The multivariable analysis was performed for variables showed statistically significant association with stunting at bivariate level. Type of community, sex of adolescent, age, family size, source of drinking water, household wealth (tertiles) and adolescent food insecurity were found independently associated with stunting (Table 3). From the table, adolescents of agro-pastoral community were 2.5 times more likely to be stunted than that of pastoral community [AOR: 2.52, 95%CI: (1.36,4.67)]. Female adolescents were 2.4 times more likely to be stunted than males [AOR: 2.36, 95%CI: (1.29,4.33)]. Adolescents in the age range of 15-18 were nearly 11 times more likely to be stunted than those of ages 10 to 14 [AOR: 10.85, 95%CI: (4.82, 24.41)]. Adolescents whose family's size was greater than 5 were 2 times more likely to be stunted than adolescents whose family's size was 5 or less [AOR: 1.92, 95%CI: (1.03, 3.57)]. Adolescents whose family's source of drinking water was unprotected were 3.6 times more likely to be stunted than their counterpart [AOR: 3.59, 95%CI: (1.79, 7.20)]. Adolescents whose household wealth (tertile) was lower were 3.2 times more likely to be stunted than adolescents whose household wealth (tertile) was higher [AOR: 3.19, 95%CI: (1.47-6.94)]. Food insecured adolescents were 2.6 times more likely to be stunted than food secured adolescents [AOR: 2.57, 95%CI: (1.35, 4.88)].

Table 1. Socio-demographic/economic characteristics of the study participants and their family, Mieso Woreda, Shinile Zone, Somali Region, March to April 2014.

Socio-demographic/economic characteristics		Pastoral No. (%)	Agro-pastoral No. (%)	Total No. (%)
Sex of adolescent	Male	175 (54.0)	172 (52.0)	347 (53.0)
	Female	149 (46.0)	159 (48.0)	308 (47.0)
Age	10-14	246 (75.9)	258 (77.9)	504 (76.9)
	15-18	78 (24.1)	73 (22.1)	151 (23.1)
Grade level	4th	88 (27.2)	79 (23.9)	164 (25.0)
	5th	69 (21.3)	82 (24.8)	151 (23.0)
	6th	61 (18.8)	65 (19.6)	126 (19.2)
	7th	53 (16.4)	58 (17.5)	111 (16.9)
	8th	53 (16.4)	47 (14.2)	100 (15.3)
Religion	Muslim	321 (99.1)	329 (99.4)	650 (99.2)
	Orthodox	3 (0.9)	2 (0.6)	5 (0.8)
Ethnicity	Somali	316 (97.5)	322 (97.3)	638 (97.4)
	Others	8 (2.5)	9 (2.7)	17 (2.6)
Number of sibling	≤3	179 (55.2)	157 (47.4)	336 (51.3)
	>3	145 (44.8)	174 (52.6)	319 (48.7)
Family size	≤5	164 (50.6)	149 (45.0)	313 (47.8)
	>5	160 (49.4)	182 (55.0)	342 (52.2)
Sex of head of the household	Male	318 (98.1)	317 (95.8)	635 (96.9)
	Female	6 (1.9)	14 (4.2)	20 (3.1)
Type of family	Monogamy	280 (86.4)	305 (92.1)	585 (89.3)
	Polygamy	44 (13.6)	26 (7.9)	70 (10.7)
Mother's educational status	Can't read and write	316 (97.5)	317 (95.8)	633 (96.6)
	Can read and write	8 (2.5)	14 (4.2)	22 (3.4)
Father's educational status	Can't read and write	285 (88.0)	269 (81.3)	554 (84.6)
	Can read and write	39 (12.0)	62 (18.7)	101 (15.4)
Mother's main occupation	House wife	302 (93.2)	294 (88.8)	596 (91.0)
	Others	22 (6.8)	37 (11.2)	59 (9.0)
Father's main occupation	Farmer	259 (79.9)	245 (74.0)	504 (76.9)
	Merchant/trade	48 (14.8)	50 (15.1)	98 (15.0)
	Others	17 (5.2)	36 (10.9)	53 (8.1)
Main staple food	Sorghum	123 (38.0)	148 (44.7)	271 (41.4)
	Wheat	62 (19.1)	79 (23.9)	141 (21.5)
	Maize	42 (13.0)	73 (22.0)	115 (17.6)
	Rice	81 (25.0)	14 (4.2)	95 (14.5)
	Others	16 (4.9)	17 (5.1)	33 (5.0)

Table 1. Contd.

Household ownership of assets	Goat	249 (76.9)	129 (39.0)	378 (57.7)
	Cattle	90 (27.8)	116 (35.0)	206 (31.5)
	Camel	168 (51.9)	96 (29.0)	264 (40.3)
	Donkey	103 (31.8)	41 (12.4)	144 (22)
	Ox	7 (2.2)	33 (10.0)	40 (6.1)
	House	322 (99.4)	326 (98.5)	648 (98.9)
	Land	31 (9.6)	225 (68.0)	256 (39.1)
Household wealth (tertiles)	Higher	108 (33.3)	110 (33.2)	218 (33.3)
	Middle	109 (33.6)	111 (33.5)	220 (33.6)
	Lower	107 (33.0)	110 (33.2)	217 (33.1)

Table 2. Binary logistic regression of factors associated with stunting among school adolescents, Mieso Woreda, Shinile Zone, Somali Region, March to April 2014.

Factors		Nutritional status		COR (95%CI)	p-value
		Stunted	Not stunted		
Socio-demographic/economic characteristics					
Type of community	Pastoral	27	297	1	0.01*
	Agro-pastoral	48	283	1.87 (1.13,3.07)	
Sex of adolescent	Male	29	318	1	0.01*
	Female	46	262	1.93 (1.18,3.15)	
Age (years)	10-14	30	474	1	< 0.001*
	15-18	45	106	6.71 (4.04,11.14)	
Grade level	4th	12	152	1	
	5th	15	136	1.40 (0.63,3.09)	0.41
	6th	16	110	1.84 (0.84,4.05)	0.13
	7th	18	96	2.38 (1.10,5.15)	0.03*
	8th	14	86	2.06 (0.91,4.66)	0.08
Number of sibling	≤3	30	306	1	0.04*
	>3	45	274	1.68 (1.03,2.73)	
Family size	≤5	25	288	1	0.01*
	>5	50	292	1.97 (1.19,3.28)	
Sex of head of the household	Male	71	564	1	0.23
	Female	4	16	1.99 (0.65,6.11)	
Type of family	Monogamy	69	516	1.43 (0.60,3.42)	0.43
	Polygamy	6	64	1	
Mother's education	Can't read and write	73	560	1.30 (0.30, 5.69)	0.72
	Can read and write	2	20	1	
Father's education	Can't read and write	64	490	1.07 (0.54,2.11)	0.85
	Can read and write	11	90	1	

Table 2. Contd.

Mother's main occupation	House wife	70	526	1.44 (0.56,3.72)	0.45
	Others	5	54	1	
Father's main occupation	Merchant	9	89	1	
	Farmer	59	445	1.31 (0.63,2.74)	0.47
	Others	7	46	1.51 (0.53,4.30)	0.45
Household wealth (tertiles)	Higher	14	204	1	
	Middle	25	195	1.87 (0.94,3.70)	0.07
	Lower	36	181	2.90 (1.52,5.55)	< 0.001*
Adolescent's food security	Food secure	12	171	1	0.02*
	Food insecure	63	409	2.20 (1.15, 4.17)	
Water, sanitation and hygiene factors					
Source of drinking water	Protected	50	511	1	< 0.001*
	Unprotected	25	69	3.70 (2.15,6.37)	
Availability of latrine in the compound	Yes	34	304	1	0.25
	No	41	276	1.33 (0.82,2.15)	
Adolescent's hand washing practice with soap after toilet	Yes	7	63	1	
	No	68	517	1.18 (0.52,2.69)	0.69
Adolescent's hand washing practice with soap before meal	Yes	11	97	1	0.65
	No	64	483	1.17 (0.59,2.30)	
Adolescent care, feeding and illness					
Breakfast before coming to school	Yes	53	439	1	
	No	22	141	1.29 (0.76,2.20)	0.35
Daily meal frequency	≥3 times	45	456	1	< 0.001*
	2 times	30	124	2.45 (1.48,4.05)	
Any illness in the last two weeks	Yes	28	156	1.62 (0.98,2.68)	0.06
	No	47	424	1	
Diarrhea illness in the last two weeks	Yes	12	62	1.59 (0.81,3.11)	0.18
	No	63	518	1	
Fever illness	Yes	9	48	1.51 (0.71,3.22)	0.29
	No	66	532	1	
Cough illness	Yes	18	64	2.55 (1.41,4.59)	< 0.001*
	No	57	516	1	

COR = Crude odds ratio; CI = confidence interval; * Statistically significant at p-value cut off point 0.05.

Factors associated with wasting/thinness

Wasting/thinness was significantly associated ($p < 0.05$) with type of community, number of siblings, family size, father's main occupation, source of drinking water, availability of latrine in the compound, household wealth

Table 3. Multivariable logistic regression of factors independently associated with stunting among school adolescents, Mieso Woreda, Shinile Zone , Somali Region, March to April 2014.

Factors		Nutritional status		COR	AOR (95%CI)
		Stunted	Not stunted		
Type of community	Pastoral	27	297	1	1
	Agro-pastoral	48	283	1.87	2.52 (1.36, 4.67)
Sex of adolescent	Male	29	318	1	1
	Female	46	262	1.93	2.36 (1.29, 4.33)
Age (years)	10-14	30	474	1	1
	15-18	45	106	6.71	10.85 (4.82, 24.41)
Family size	≤5	25	288	1	1
	>5	50	292	1.97	1.92 (1.03, 3.57)
Household wealth (tertiles)	Higher	14	204	1	1
	Middle	25	195	1.87	1.67 (0.99, 2.81)[†]
	Lower	36	181	2.90	3.19 (1.47, 6.94)
Adolescent's food security	Food secure	12	171	1	1
	Food insecure	63	409	2.20	2.57 (1.35, 4.88)
Source of drinking water	Protected	50	511	1	1
	Unprotected	25	69	3.70	3.59 (1.79, 7.20)

COR = Crude odds ratio, AOR = Adjusted odds ratio, CI = confidence interval; [†]Not statistically significant at p-value cut off point 0.05.

(tertiles), daily meal frequency, adolescent's hand washing practice with soap after toilet, any illness in the last two weeks, diarrhea illness and adolescent's food security (Table 4).

The multivariable analysis was performed for variables showed statistically significant association with wasting at bivariate level. Family size, the source of drinking water, availability of latrine in the compound, household wealth (tertiles), adolescent's hand washing with soap after toilet, diarrhea illness in the last two weeks and adolescent food security were significantly associated with wasting (Table 5). From the table, children whose household family size was greater than 5 were 1.7 times more likely to be wasted than children whose household family size was 5 or less [(AOR: 1.71, 95%CI: (1.13, 2.58)]. Children whose family's source of drinking water was unprotected were 3.6 times more likely to be wasted than their counterpart [AOR: 3.64, 95%CI: (2.14, 6.18)]. Adolescents whose family did not have latrine at home were 1.6 times higher at risk of being wasted than their counterparts [AOR: 1.59, 95%CI: (1.02, 2.44)]. Adolescents who did not have hand washing practice after toilet were 5.6 times more likely to be wasted than their counterparts [AOR: 5.56, 95%CI: (1.16,11.50)]. Adolescents who had diarrhea illness in the last two weeks were 3 times higher at risk of being wasted than who did not [AOR: 3.05, 95%CI: (1.37, 6.79)]. Adolescents whose household wealth (tertile) was lower and middle were 1.9 and 1.7 times more likely to be wasted respectively than adolescents whose household wealth (tertile) was higher [AOR: 1.88, 95%CI: (1.10, 3.22) and AOR: 1.70, 95%CI: (1.01, 2.86) respectively]. Food insecured adolescents were 2 times more likely to be wasted than food secured ones [AOR: 2.04, 95%CI: (1.24, 3.34)].

DISCUSSION

Comparative cross-sectional study was conducted from March 10 to April 11, 2014 at Mieso Woreda, Somali Region, to assess nutritional status of school adolescents and identify associated factors. The overall prevalence of stunting and wasting were 11.5 and 22.9%. The overall prevalence of stunting was lower than findings from different studies conducted in Northwest Ethiopia where stunting reports range from 15 to 30.7% (Amare et al., 2013, 2012; Mekonnen, 2013) and another study conducted in Ashanti region of Ghana which was 56.7% (Danquah et al., 2013). These differences could be due to the differences in their animal product consumption and food culture.

Table 4. Binary logistic regression of factors associated with wasting/thinness among school adolescents, Mieso Woreda, Shinile Zone, Somali Region, March to April 2014.

Factors (variables)		Nutritional status		COR (95%CI)	p-value
		Wasted	Not wasted		
Socio-demographic/economic characteristics					
Type of community	Pastoral	85	239	1.46 **(**1.01,2.10)	0.045*
	Agro-pastoral	65	266	1	
Sex of the adolescent	Male	72	275	1	0.16
	Female	78	230	1.30 (0.90,1.87)	
Age (years)	10-14	115	389	1	0.93
	15-18	35	116	1.02 (0.66,1.57)	
Grade level	4th	43	121	1.42 (0.78,2.59)	0.25
	5th	39	112	1.39 (0.76,2.57)	0.29
	6th	28	98	1.14 (0.60,2.18)	0.69
	7th	20	94	.85 (0.43,1.69)	0.65
	8th	20	80	1	
Number of sibling	≤3	61	275	1	< 0.001*
	>3	89	230	1.74 (1.21,2.53)	
Family size	≤5	53	260	1	< 0.001*
	>5	97	245	1.94 (1.33,2.83)	
Sex of head of the household	Male	142	493	1	0.07
	Female	8	12	2.32 (0.93,5.77)	
Type of family	Monogamy	133	452	1.08 (0.59,1.97)	0.81
	Polygamy	15	55	1	
Mother's education	Can't read and write	142	491	1	0.13
	Can read and write	8	14	1.97 (0.81,4.80)	
Father's education	Can't read and write	129	425	1.16 (0.69,1.94)	0.58
	Can read and write	21	80	1	
Mother's main occupation	House wife	138	458	1.18 (0.61,2.29)	0.62
	Others	12	47	1	
Father's main occupation	Merchant	12	86	1	
	Farmer	115	389	2.12 (1.12,4.01)	0.02*
	Others	22	31	5.09 (2.25,11.48)	< 0.001*
Household wealth (tertiles)	Higher	34	184	1	
	Middle	56	164	1.85 (1.15,2.97)	0.01*
	Lower	60	157	2.07 (1.29,3.31)	< 0.001*
Adolescent's food security	Food secure	27	156	1	
	Food insecure	123	349	2.04 (1.29,3.22)	< 0.001*

Table 4. Contd.

Water, sanitation and hygiene factors					
Source of drinking water	Protected	99	462	1	< 0.001*
	Unprotected	51	43	5.54 (3.49,8.77)	
Availability of latrine in the compound	Yes	57	281	1	< 0.001*
	No	93	224	2.05 (1.41,2.97)	
Adolescent's hand washing practice with soap after toilet	Yes	7	63	1	0.01*
	No	143	442	2.91 (1.30,6.50)	
Adolescent's hand washing practice with soap before meal	Yes	19	89	1	0.15
	No	131	416	1.48 (0.87,2.51)	
Adolescent care, feeding and illness factors					
Breakfast before coming to school	Yes	104	388	1	
	No	46	117	1.47 (0.98,2.20)	0.06
Daily meal frequency	≥3 times	100	401	1	
	2 times	50	104	1.93 (1.29,2.88)	< 0.001*
Any illness in the last two weeks	Yes	53	131	1.56 (1.06,2.30)	0.03*
	No	97	374	1	
Diarrhea illness in the last two weeks	Yes	33	41	3.19 (1.93,5.27)	< 0.001*
	No	117	464	1	
Fever illness	Yes	15	42	1.23 (0.66,2.28)	0.52
	No	135	463	1	
Cough illness	Yes	24	58	1.47 (0.88,2.46)	
	No	126	447	1	0.14

COR = Crude odds ratio, CI = confidence interval;* Statistically significant at p-value cut off point 0.05.

Prevalence of stunting was found to be higher (14.5%) in agro-pastoral than pastoral (8.3%) community while prevalence of thinness (wasting) was higher (26.2%) in pastoral than agro-pastoral (19.6%) community. These differences in nutritional status among pastoral and agro-pastoral communities were statistically significant and stunting remained significant even after adjusting to other factors. The likelihood of being stunted was 2.5 times more in agro-pastoral than pastoral community. There was scarcity of previous research conducted on children of similar age groups and communities to compare with present findings. However, this finding was in agreement with a study conducted on 6 to 36 months old children in Shinile zone of Somali region, Ethiopia (Save the Children, 2001; 2007). This could be due to the differences in main staple foods in the two communities. It could also be because of historical difference in stunting, that is, in the years past when these adolescents would have been affected, pastoral communities might have been wealthier than the agro-pastoral ones.

The overall prevalence of thinness (22.6%) was much higher than the reports of studies conducted in Adama town, Ethiopia (1.4%) (Belay et al., 2011), Gondar, Ethiopia (8.9%) (Amare et al., 2013), Kenya (4.5%) (Chesire et al., 2009) and Eastern Uganda (10.1%) (Acham et al., 2012). Since wasting reflects acute nutritional deficiency caused by inadequate food intake and/or infections (de Onis et al., 2007), this higher prevalence could be attributed to dry season (March to April) when pasture and water could be a problem and might have led to food shortage and infection during survey period.

Gender differential in the studies of nutritional status of children in less developed countries has frequently reported that boys were favored in that they were breast-fed longer, received better quality diet, child care time, health treatment and had better nutritional status (Shariff et al., 2000). In Ethiopia, in contrast to boys, girls often face a reduction in freedom and opportunities during puberty. These restrictions are frequently increased in

Table 5. Multivariable logistic regression of factors independently associated with wasting/ thinness among school adolescents, Mieso Woreda, Shinile Zone, Somali Region, March to April 2014.

Factors		Nutritional status		COR	AOR (95%CI)
		Wasted	Not wasted		
Type of community	Pastoral	85	239	1.46	1.21 (0.78,1.85)
	Agro-pastoral	65	266	1	1
Sex of adolescent	≤ 3	61	275	1.74	1.11 (0.42,2.92)
	> 3	89	230	1	1
Father's main occupation	Merchant	14	84	1	1
	Farmer	115	389	1.77	1.75 (0.88,3.45)
	Others	22	33	3.64	2.28 (1.01,5.03)*
Family size	≤5	53	260	1	1
	>5	97	245	1.94	1.71 (1.13,2.58)*
Household wealth (tertiles)	Higher	34	184	1	1
	Middle	56	164	1.85	1.70 (1.01,2.86)*
	Lower	60	157	2.07	1.88 (1.10,3.22)*
Adolescent's food security	Food secure	27	156	1	1
	Food insecure	123	349	2.04	2.04 (1.24,3.34)*
Source of drinking water	Protected	99	462	1	1
	Unprotected	51	43	5.54	3.64 (2.14,6.18)*
Availability of latrine in the compound	Yes	57	281	1	1
	No	93	224	2.05	1.59 (1.02,2.44)*
Adolescent's hand washing practice with soap after toilet	Yes	7	63	1	1
	No	143	442	2.91	5.56 (1.16,11.50)*
Daily meal frequency	≥3 times	100	401	1	1
	2 times	50	104	1.93	1.56 (0.99,2.47)
Any illness in the last two weeks	Yes	53	131	1.56	1
	No	97	374	1	1.22 (0.66,2.22)
Diarrhea illness in the last two weeks	Yes	33	41	3.19	3.05 (1.37,6.79)*
	No	117	464	1	1

COR = Crude odds ratio, AOR = Adjusted odds ratio, CI = confidence interval; *Statistically significant at p-value cut off point 0.05.

rural parts of Ethiopia, where more than 85% of the girls live and where work burdens for adolescent girls are especially heavy. Puberty is also a time when girls' bodies prepare for the nutritional demands of pregnancy and lactation required in later life (Berheto et al., 2015). The findings of this study showed significant difference of stunting between sex groups. Females adolescents were 2.4 times more likely to be stunted than males. However, this was not in agreement with reports of studies conducted in Morocco (Hioui et al., 2011) where females were less likely to be stunted than males (AOR: 0.41, CI: 0.94-0.03) and Uganda (Acham et al., 2012) which showed that girls were less vulnerable to malnutrition compared to boys (AOR: 0.96, CI: 0.56-1.66).

This study showed that stunting was significantly associated with age; 15 to 18 years old adolescents had higher odds to be stunted compared with 10 to 14 age groups. This was congruent to the reports of many studies which showed prevalence and severity of stunting has been found to increase with age, with older children diverging further from the reference medians for height until puberty (Acham et al., 2012; Al-Saffa, 2009; 2013; Awoyemi et al., 2012). This might be due to inadequate nutrient intake besides increased requirement during adolescents' faster growth period or it could be that conditions are improving over time and that those older adolescents were more severely affected by malnutrition as preschoolers than the younger adolescents.

While it was expected that parental occupation appears to be one of the household factors that can influence the nutritional status of children, in this study, however, both parents' occupational status did not show significant difference on their children's nutritional status. This may be due to the fact that almost all mothers were housewives and majority of fathers were farmers.

Both stunting and wasting were more likely among larger families and this was in line with finding of studies done in Pakistan (Mian et al., 2002) and Jimma, Ethiopia (Assefa et al., 2013). Adolescents whose household's wealth tertile were lower were 3.19 times more likely to be stunted than adolescents whose household's wealth tertile was higher. This is in agreement with a study done in Jimma, Ethiopia (Assefa et al., 2013) where household income was positively associated with Height for Age z-score. Wasting was also more likely among adolescents of households with middle and lower wealth tertile than higher ones. This was in agreement with a study done in Jimma, Ethiopia (Assefa et al., 2013) where household income showed a positive association with BMI for Age z-score though not statistically significant.

This study revealed that food insecured adolescents were nearly 3 times more likely to be stunted than food secured adolescents. This may indicate the presence of chronic adolescent food insecurity in the study area since stunting shows chronic malnutrition. The finding was in line with study done in Jimma, Ethiopia (Central Statistical Agency [Ethiopia], 2014) where food insecurity is negatively associated with the linear growth of adolescents. Wasting is an indicator of acute malnutrition and it is usually the result of acute or short-term insufficient food intake often combined with frequent illness (de Onis et al., 2007). The result of this study supported the above idea as food insecured adolescents were 2 times more likely to be wasted than food secured adolescents.

The findings of this study support the fact that unfavorable environmental and personal conditions such as inadequate and unsafe water, poor sanitation, and poor personal hygiene can increase the probability of infectious diseases and, in turn, cause or aggravate malnutrition. In this study, stunting and wasting were significantly associated with the use of unprotected water source for drinking. Adolescents whose household did not have latrine at home were more likely to be wasted than their counter part. This was in consistent with the study done in Tigray, Northern Ethiopia (Mulugeta et al., 2009). Hand washing with soap after use of toilet also showed a significant association with wasting where adolescents who did not practice hand washing with soap after toilet were more likely to be wasted than those who did.

It is known that infection and under-nutrition are interrelated. The finding of this study showed that the likelihood of being wasted was 3 times higher among individuals who experienced diarrhea in the last two weeks than those who did not.

In general, since the findings of this study might have been affected by method of our data collection where household level information was obtained from adolescents, it should be used with caution.

Conclusion

This study revealed that the prevalence of stunting was significantly higher among adolescents of agro-pastoral community while the prevalence of wasting was higher among adolescents of pastoral community. Factors significantly association with stunting were type of community, sex of adolescent, age, family size, source of drinking water, household wealth tertile and adolescent food insecurity. Factors significantly association with wasting were family size, source of drinking water, latrine availability, after toilet hand washing practice, diarrhea illness in the last 2 weeks, household wealth tertile and adolescent food insecurity.

Recommendation

Based on our findings, scientific literature and current practice of the National Nutrition Program (NNP), the following nutrition specific and nutrition sensitive interventions are suggested for the NNP and other stakeholders to improve the nutrition condition of school children in the study area:

1. The Somali Regional State Health Bureau and Mieso Woreda Health Office should design interventions which targets adolescents' malnutrition specific to pastoralist and agro-pastoral livelihood systems.
2. Mieso Woreda Education Office and Health Office should provide health education on personal hygiene integrating with regular educational activities in the school.
3. The Woreda Health Office should strengthen community education on family planning and environmental sanitation through health extension workers (HEWs).
4. The Woreda Water Service Office should strongly work to improve sources of drinking water.
5. Mieso Woreda Agriculture Office should strongly work and co-operate with other sectors and NGO's to improve household economy and ensure adolescents' food security through broadened microfinance institutions or other development and income generating activities.
6. Finally, other community based studies with different and stronger study designs, and improved source of information (e.g. parents) are encouraged to better understand adolescent malnutrition.

Conflicts of Interests

The authors have not declared any conflict of interests.

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Full Length Research Paper

Internal medicine resident knowledge and perceptions regarding electronic cigarettes

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Electronic cigarettes are an important public health concern. Smoking remains the leading cause of preventable death and morbidity worldwide and is a risk factor for six of the eight leading global causes of death. E-cigarettes have been proposed as an enticing prospect to reduce the harms of conventional tobacco use. However, they are increasingly used by middle-school and high-school students and threaten important barriers that have slowly protected the public against tobacco products including renormalization, price barriers, limitations on advertising and access, and bans on flavoring. Physicians have poor knowledge about the potential harms of e-cigarettes and limited data exists regarding potential long-term outcomes. We explored resident physician beliefs and practices regarding e-cigarettes. Several themes were identified: (1) Conversations regarding e-cigarettes are becoming more frequent in physician offices; (2) A lack of knowledge regarding potential harms and benefits of e-cigarettes exists among resident physicians; (3) Physicians falsely believe that e-cigarettes are safer alternatives to conventional smoking products; (4) More education is needed regarding evidence based smoking cessation techniques.

Key words: Electronic cigarettes, public health, nicotine, smoking.

INTRODUCTION

Electronic cigarettes are an important public health concern. Although tobacco use has decreased by more than half since 1965, it remains the leading cause of preventable death and morbidity worldwide. Smoking is a risk factor for six of the eight leading global causes of death including heart disease, cerebrovascular disease, lower respiratory infections, tuberculosis, chronic obstructive lung disease, and lung cancer (Crowley, 2015). E-cigarettes have been proposed as an enticing prospect to reduce the harms of conventional tobacco use. They are also increasingly used by middle-school and high-school students.

Electronic cigarettes have only been available within the past fifteen years. They were originally marketed without evaluation of safety or health impact. Only recently has there been a societal interest in investigating related health outcomes and regulating safety measures. Electronic cigarettes do not contain tobacco. They are

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Table 1. Survey questions regarding electronic cigarettes.

1. Do you typically ask patients about their tobacco use?
2. Do you counsel patients to quit?
3. Have you ever asked patients about their e-cigarette use?
4. Have any of your patients ever asked you about e-cigarettes?
5. Do you recommend e-cigarettes to patients?
6. Do you believe e-cigarettes are less harmful to patients than conventional cigarettes?
7. Do e-cigarettes have a role in harm reduction?
8. Are e-cigarettes FDA approved for smoking cessation?
9. Do e-cigarettes have any significantly documented adverse effects?
10. Has e-cigarette use exceeded that of nicotine replacement therapy?

devices that produce an aerosol by heating a liquid that contains a solvent, one or more flavorings, and/or nicotine (Noel et al., 2011). The evaporation of the liquid at the heating element is followed by rapid cooling to form an aerosol. The user directly inhales it though a mouthpiece. There is no smoke, no carbon monoxide, and no odor. Only the e-cigarette user inhales the vapor. This mechanism is what has made e-cigarettes to be considered safe by many individuals and has contributed to the rapid acceptance and use by the public.

Though advances have been made in the fight against conventional cigarettes, the principal route of tobacco-related disease, e-cigarettes threaten important barriers that have slowly protected the public against tobacco products. Recent studies have shown that experimentation, use, and promotion of e-cigarettes via conventional as well as online marketing have grown exponentially (Noel et al. 2011). Though most users have used tobacco at some time, a third of current e-cigarette users have never smoked tobacco or were former tobacco users. Of particular concern regarding public health is the increased experimentation with and use of e-cigarettes among persons younger than 18 years of age. Other ties worrisome to public health include renormalization, price barriers, limitations on advertising and access, and bans on flavoring (Crowley, 2015). Of utmost concern is the risk that e-cigarette use will romanticize smoking, rescinding decades of efforts by public health and medical communities.

Despite growing e-cigarette use, how physicians perceive them is not fully understood (Brandon, 2015). Since current tobacco use counseling guidelines taught in medical school do not address e-cigarettes, understanding what guides physicians' practice when asked about e-cigarette is important. The manner in which resident physicians approach e-cigarette discussions, and the factors, which contribute, to their beliefs, perceptions, and decisions to recommend e-cigarettes are largely unknown. The purpose of this study was to explore resident beliefs and practices regarding e-cigarette use.

MATERIALS AND METHODS

Study participants

Participants were internal medicine residents at a university training program in New Brunswick, NJ. Residents represented individuals from heterogeneous training medical schools, geographic backgrounds, and levels of training. In December 2015, we emailed all residents within our institution (n=69) to participate in the study. To be eligible for participation, residents had to be categorical residents who participated in a continuity outpatient clinic and discussed tobacco use with at least one patient. Participants did not receive compensation for participation. All subjects gave informed consent for voluntary participation. The study was approved and exempt from IRB as the use of survey procedures was performed only to observe resident beliefs and behaviors. There was no abstraction of patient specific material or chart abstraction.

Data collection

A descriptive pilot study utilized survey instruments to measure e-cigarette knowledge, perceptions and awareness among internal medicine residents. The authors developed the survey. The survey collected demographic (age, gender, race, future career interests, year of training) from each participant. Prior training in smoking cessation, whether patients had asked about e-cigarettes, whether the physician recommended e-cigarettes, and attitudes toward harm reduction were also assessed. For analysis, data was focused on responses to questions in Table 1. Data were analyzed using descriptive analysis using SPSS 21.0 software was used.

RESULTS

57 residents participated in the study Table 2. The mean age was 27 (range 25 to 37). Residents were distributed across varied levels of training (21 pgy-1, 18 pgy-2 and 18 pgy-3). Respondents were evenly distributed by gender (that is, 51% male and 49% female). Nearly 46 of 57 (80%) of resident physicians reported being asked about e-cigarettes by their patients. When probed as to whether those conversations resulted in any specific recommendations, 49% reported they have recommended e-cigarette use to at least one of their patients (Table 3).

In addition, more than two thirds believed in a harm-

Table 2. Demographics of surveyed residents (n=57).

Median age (range)	27 (24 - 37)
Level of training	
Pgy-1	21
Pgy-2	18
Pgy-3	18
Male gender	29 of 57
Personal smoking history	3 of 57
Parental smoking history	18 of 57
Prior smoking cessation training	26 of 57
Prior education on E-cigarettes	3 of 57

Table 3. Resident survey responses (n=57).

Responses	Yes	Percentage
1. Do you typically ask patients about their tobacco use?	56	98
2. Do you counsel patients to quit?	54	95
3. Have you ever asked patients about their e-cigarette use?	15	26
4. Have any of your patients ever asked you about e-cigarettes?	46	80
5. Do you recommend e-cigarettes to patients?	28	49
6. Do you believe e-cigarettes are less harmful to patients than conventional cigarettes?	40	70
7. Do e-cigarettes have a role in harm reduction?	38	66
8. Are e-cigarettes FDA approved for smoking cessation?	40	70
9. Do e-cigarettes have any significantly documented adverse effects?	29	51
10. Has e-cigarette use exceeded that of nicotine replacement therapy?	0	0

reduction approach and nearly half believed that there were no documented adverse side effects. Most (75%) believed that the FDA approved its use for smoking cessation. No resident identified e-cigarette use as exceeding that of nicotine replacement therapy. Male and female physicians were just as likely to recommend e-cigarettes and endorse a harm reduction approach. Responses were not significantly different based on age, gender, level of training, personal smoking history, if their parents were smokers, or prior experience to smoking cessation counseling.

DISCUSSION

To date, no study has investigated resident physician perspectives on e-cigarette use. Our data suggests that young physicians lack professional education of e-cigarettes. Societally, interest in e-cigarettes appears high, despite the absence of evidence regarding its long-term health impact. E-cigarettes continue to be one of the most polarizing products to ever reach the market and raise many public health concerns for which there are few answers.

Short and long term health impact

Increasing evidence is being gathered concerning the short-term side effects of e-cigarettes. Depending upon concentration, liquid nicotine is known to be toxic and can cause harm when inhaled and ingested. In higher levels, a tablespoon can kill an adult and a teaspoon can kill a child. There is no regulation of the amount of liquid nicotine in e-cigarettes and studies have shown a wide variance in nicotine levels that often exceed that of tobacco cigarettes (Kim and Baum, 2015). In the US, telephone calls to the CDC poison control line, regarding e-cigarettes, have increased from one/month in 2010 to 125/month in 2014. In all poison control emergency calls, 51% of calls involved poisoning of children aged 5 and under (Center for Disease Control, 2015).

If e-cigarettes carry any lifelong harm, the dangers will stem from the poor knowledge base of our physicians who are at the forefront of tackling nicotine addiction. Nicotine is not the primary cause of cigarette-related morbidity but is the addictive agent (Yamin, 2010). Youths are particularly marketed and advertising has been effective. A large majority of adolescents today are aware of e-cigarettes (Crowley, 2015) and surveys of e-cigarette users have found that they perceive them as a less harmful, less addictive, and healthier alternative to conventional cigarettes (Pearson et al., 2012). In many ways, e-cigarettes represent the new gateway to cigarettes (Duke et al., 2014). As our survey study indicates, resident physicians too perceive e-cigarettes to be less harmful and a healthier alternative, though this belief is not supported by evidence.

Unethical and false marketing

Several societies have recommended that e-cigarettes be regulated and treated like cigarettes. The recent FDA regulation to restrict the marketing of these nicotine delivery devices seems appropriate given the lack of evidence regarding safety and potential harm. The absence of warnings can be seen as an endorsement of their safety. There have been limited consumer protection requirements or product quality standards.

To date, no study has demonstrated superiority of E-cigarettes over smoking cessation pharmacotherapy approved by the U.S. Food and Drug Administration for combustible cigarette cessation. In fact, a meta-analysis of 20 studies that included control groups showed that e-cigarettes were associated with significantly lower odds of quitting cigarettes than either nicotine-replacement therapy or no cessation aid (odds ratio, 0.72, 95% confidence interval [CI], 0.57 to 0.91) (Kalkhoran and Glantz, 2016).

Areas of further study

Although the health risks of e-cigarettes are still being elucidated, early findings suggest that nicotine addiction is a concern. In addition, e-cigarette nicotine solutions, carrier agents and flavoring, generate known toxins and carcinogens when vaporized, although in lower concentrates compared to cigarettes (Hecht et al., 2015). E-cigarette use has also been associated with respiratory symptoms in young adults whose airways were naïve and not yet irritated by cigarette smoke (Wang et al., 2016). Secondary and tertiary exposure risks of e-cigarettes are under study. Despite their reduced risk promise, many questions remain regarding efficacy for smoking cessation, the potential increased uptake by nontobacco users, discouragement of cessation promoted by dual use, or encouraged relapse to cigarette use among former smokers. It is unknown whether e-cigarettes have a role in risk modification.

Current shortcomings

As our study highlights, it is imperative that physicians stay current with evidence-based research on e-cigarettes and that medical education follows the growing literature on electronic cigarettes. Without dissemination of clear, evidence-based research on e-cigarettes, it is likely these discrepancies will continue and patients could be given inaccurate information.

Many questions remain unanswered. Aside from addiction, are there other risks incurred from inhaling nicotine vapor? Are other harmful substances present? Can "second-hand vapor" cause harm? Until further studies are conclusive, physicians are left to weigh uncertainties with available data. Regulation by the Food and Drug Administration is a good first step to regulate marketing, youth access, and quality control. During the upcoming years and decades, more studies will demonstrate long-term safety or harm. Though a tremendous amount of ambiguity surrounds e-cigarettes, we must educate our young (and seasoned) physicians regarding the data behind electronic cigarettes in order to best counsel our patients.

Limitations

The results described should be interpreted in the context of several limitations. First, the study is collected relatively early in a rapidly evolving e-cigarette market. The applicability of the findings thus should be interpreted with caution as future trainees may be more exposed to the growing controversy. Second, residents interviewed were limited to one training institution in the northeast and thus, may not be generalizable. Third, there may be important themes and both physician and patient factors not identified by the survey questions that have not been validated. Nevertheless, the study offers important insight into resident beliefs and practices regarding e-cigarettes.

Conclusions

In conclusion, resident physicians lack knowledge about e-cigarette safety and efficacy in general and in smoking cessation in particular. When patients initiate discussions with physicians, some physicians recommend e-cigarettes to patients who smoke, both for smoking cessation and a harm reduction strategy. Such findings renew the importance of generating and rapidly disseminating evidence based guidelines regarding e-cigarette safety and efficacy for smoking cessation. Without continued efforts, physicians will continue to recommend their own beliefs that in the long run, will be difficult to change once established.

Conflicts of Interests

The authors have not declared any conflict of interests.

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Full Length Research Paper

Patient knowledge and behavioral factors leading to non-adherence to tuberculosis treatment in Khartoum State, Sudan

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Although tuberculosis is a curable and preventable disease, defaulting from treatment can prolong infectiousness leading to increased transmission, an increased risk of drug resistance, relapse and death. Our objective was to identify patient related determinants (including knowledge and awareness, opinion about TB services and behavioral factors) of treatment defaulting among TB patients in Khartoum State, Sudan. Between May 2010 to May 2011., we conducted a case control study where the patients defaulting from treatment were considered as 'cases' and those completing treatment as 'controls'. There were 2727 TB patients who attended TB treatment clinics during study period. Out of these 2399 patients (86%) had continued their treatment while 328 patients (14%) had interrupted it. 105 cases were traced and interviewed. In addition 210 patients who had continued their treatment were included as controls. In the multivariate analysis the variables that remained in the model were: rural residence (OR= 2.16; 95% CI= 1.19-3.90), "had never heard about TB before had it (OR= 1.81; 95%CI=1.02-3.20), lack of knowledge on when to stop TB medication (OR= 2.00; 95% CI= 1.10 -3.64), less support by families, friends and colleagues (OR= 3.23; 95% CI= 1.62- 6-46), too many patients when visiting the TB center (OR= 2.24; 95% CI =1.29 - 3.88), and lack of counseling about TB and its treatment (OR= 4.79; 95% CI= 2.57 -8.95). The results of this study show that patient's knowledge about TB, its treatment and the experienced professional and peer support are associated with TB treatment continuation. Hence, adequate counseling of patients, including counseling of their peers for social support, and adequate training of the health care providers who have enough time to attend to their patient's need are potential measures to reduce TB treatment default.

Key words: Tuberculosis, non-adherence, adherence, defaulter.

INTRODUCTION

Tuberculosis (TB), is a global health concern for both developing and developed countries (Nezenega et al., 2013). It has reached epidemic proportions in many developing countries, with a third of world population

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being infected with Mycobacterium tuberculosis (Khan et al., 2006). Although it is a curable and preventable disease, Worldwide TB is the second most common cause of death in adults attributable to a single infectious agent (World Health Organization, 2015). In 2010, it was estimated that in Sudan there were 209 cases of active TB per 100.000 of the population with an annual incidence of new cases of 119/100.000, resulting in approximately 37.000 new cases each year. Hence, Sudan shoulders about 15% of TB burden in the Eastern Mediterranean Region and has the second highest active TB prevalence of the countries in this region. In addition, the estimated death rate related to TB, including HIV infected TB patients, was 24/100.000 per year (Federal Ministry of Health, Sudan, 2011).

The health authority of Sudan subscribes to the strategies for TB prevention and treatment recommended by the WHO including the therapeutic regimens given under direct observation short course therapy (DOTS) programme. Despite the efforts that had been undertaken by health authorities still some patients fail to adhere to TB treatment and eventually default before completing the treatment. As defined by the WHO, patients who fail to collect their TB treatment for 2 consecutive months are reported as defaulters (World Health Organization, 2002). The role of human behavior in health and illness has been increasingly recognized (Suleiman et al., 2014).

In any cultural context, a precondition of health-seeking behavior is the recognition and interpretation of symptoms by individuals affected by a disease and by those around them (Ayisi et al., 2011).

In the case of TB, personal experiences, perceived etiology of the disease, associated beliefs and attitudes could be important for appropriate health- seeking behavior, i.e. completing treatment. Hence, health education and counselling to TB patients may increase successful treatment completion (Ayisi et al., 2011; Rubel and Garo, 1992).

Many studies have addressed behavioral, biological, socio-demographic factors, and patient knowledge factors that were associated with TB treatment default or leading to delays in seeking TB treatment (Carolyn et al., 2009). Thus, understanding of patient knowledge, opinion, cultural believes and behavioral patterns, in addition to knowledge of health staff and their practice and their association with defaulters from TB treatment is crucial.

The present study was conducted to identify patient related determinants (including knowledge and awareness, opinion about TB services and behavioral factors) of treatment defaulting among TB patients.

MATERIALS AND METHODS

This was an observational case control study where the patients defaulting from treatment were considered as 'cases' and those completing treatment as 'controls'.

Setting

This study was conducted in KhartoumState. In 1993, the Ministry of Health in Khartoum State established a tuberculosis control program. The decentralized healthcare system in Khartoum is divided into seven districts and 19 health areas. Its health facilities include 43 hospitals, 147 health centers, 185 NGOs centers, 235 dispensaries and 365 primary health care units. TB services are delivered in primary health care along with all other routine health services. A registered nurse is designated responsible for treatment and follow up for continuation of treatment in the primary health care unit. This primary health care unit is the basic unit of management of the program and also the unit of reporting. Personnel at the primary health care unit responsible for tuberculosis services include a medical assistant, a laboratory technician and a clerk. The program provides care through the DOTS strategy (Directly Observed Treatment with Short course chemotherapy) as recommended by WHO. TB patients receive their treatment through 53 TB treatment units distributed all over the State (Suleiman and Sodemann, 2009).

Population

The interview process was done in the period from 1th of May 2011 to 15th of July 2011, but in order to reach the target defaulted group for the interviews we used the clinics records for the patients registered in the period from May 2010 to 2011. The inclusion criteria for both cases and controls were; patients age more than 15 years and clinically and laboratory diagnosed as tuberculosis, registered at the treatment units in Khartoum States. Cases were those patients identified as TB treatment defaulting during the data collection period. Following identification of each case (defaulter) without exclusion criteria, the next 2 subsequent patients without exclusion criteria, who had completed their treatment without defaulting, and requested to come for follow up, either to do the final sputum smear or to collect the smear results, in the same TB treatment unit or the near one in the same area, were taken as control into the study. The patients were excluded from the study if they were: too ill for interview, had a psychiatric illness, or gave incorrect address and could not be traced.

Definition of variables

The following definitions were applied according to the World Health Organization (WHO, 2002). Pulmonary TB: a patient with tuberculosis disease involving the lung parenchyma. Extra-pulmonary TB: a patient with tuberculosis of organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges). A patient in whom both pulmonary and extra-pulmonary TB has been diagnosed was classified as pulmonary TB (World Health Organization, 2002).

Categories of treatment outcomes'

Treatment default**:** is defined as an interruption of TB treatment for two or more consecutive months during the intended treatment period (World Health Organization, 2002). Adherence to TB treatment may be defined as the extent to which the patient's history of therapeutic drug-taking coincides with the prescribed treatment (Urquhart, 1996). Complementary and alternative medicine (CAM): is a medical intervention which is not taught widely at medical schools or is not generally available in hospitals, seek folk remedies treatment: are those patients who seek alternative treatment other than TB recommended therapeutic chemotherapy (herbal, traditional and spiritual treatment) (Hirofumi et al., 2006).

Data collection

Information on demographic factors, disease related factors and treatment related factors were retrieved from patients' medical records. In addition, a face to face interview was held, using a standardized questionnaire by trained interviewers to elicited information on the various factors possibly associated with treatment defaulting. All TB patients who had defaulted prior to data collection period were identified and their address had been retrieved from patient records. Then, the interviewers used the following sequence of contact attempts: calls – first to the patient and thereafter to known family members or friends - home visits - first to patient and thereafter to known family members or friends. Before the start of data collection the interviewers had been trained on how to interview the respondents, and had been given instructions on how to fill the questionnaire. After that, pretesting was conducted by interviewing few patients. Based on the pretesting results the questionnaire was used without any major changes. The data collected included demographic and clinical variables (age, gender, site of TB infection, co-infection with HIV), patient's knowledge of TB and its treatment, the patient's rating of the TB treatment services provided and behavioral factors (Rubel and Garo, 1992; Finlay et al., 2012; Chuah, 1991; Marlucia et al., 2012; Comolet et al., 1998; Jaggarajamma et al., 2007; Nyi et al., 2001; Pardeshi, 2010; Muture et al., 2011). The abbreviated list of questions asked is detailed in Tables 1 and 2.

Statistics

The sample size was calculated according to Fleiss (1981) using a two sided type one error of 0.05 and a power of 80% and the ability to detect an odds ratio of 2.0 with a exposure frequency of 30% in the control group and a ratio of cases to controls of 1:2. This yielded a sample size of 105cases and 210 controls. Data were reviewed for consistency and completeness. Data analysis was performed in Statistical package of Social Sciences (SPSS) version 16. The demographic characteristics of cases and controls were compared using χ^2 test for qualitative variables and student's t tests for continuous variables. Univariate and multivariate analysis were conducted. Descriptive statistics were calculated for all dependent variables. Logistic regression was used to calculate the odds ratio and its 95% confidence interval. Variables that were related to treatment default with a p-value less than 0.20 were entered in a multivariate model, using a backward approach (Fleiss, 1981).

Ethical considerations

Ethical approval was obtained from the Ministry of Health Khartoum State' ethical Committee. Permission was granted by public committee leaders in the localities through official letters. Informed verbal consent was secured from every eligible patient included in this study before the interview. Privacy and confidentially was maintained. Prior to the arrival of the data collection team the respondents had been informed regarding all relevant aspects of the study, including the purpose of the study, interview process and potential benefits. The interviewers introduced themselves to respondents and outlined the scope of interview and its approximate length to the potential respondents at the beginning of each interview.

The respondents had been informed that the participation was entirely voluntary, and that privacy and confidentially will be maintained during data processing and reporting. Potential respondents also were informed that they had the right to refuse to participate, or to end the interview at any time.

RESULTS

Patients

There were 2727 TB patients who attended TB treatment clinics during study period. Out of these, 2399 patients (86%) had completed their treatment while 328 patients (14%) had interrupted it. Out of these, 185 patients had defaulted prior to the data collection period. Hence, 143 patients were potentially eligible as cases. Of these, 15 had given a wrong address and 12 had moved out of Khartoum State and could not be interviewed. A further 11patients refused the interview. Hence, 105 cases were traced and interviewed. In addition 210 patients who had completed their treatment were included (controls).

Among cases, 70.5% were males and 29.5% were females compared to 60.9% of males and 39.1% of females among the controls. The mean ages were respectively 32.8 years and 34.6 years for cases and controls. 53.3% of the study cases were aged 15 to 30 years and 46.7% were more than 30 years old compared to respectively 47.6% and 52.4% for controls. Among cases, 61% were living in urban area and 39% in rural area compared to respectively 80.5% and 19.5% for controls. Also about 61% of cases were ready to stop taking treatment according to the health care workers advice and 39% can stop taking treatment due to other factors such as feeling better compared to respectively 81.4 and 18.6% for controls. However, 29.5% of these cases were treated differently by their families, friends and colleagues of having TB compared to controls (11.0%). Hence, cases felt that the medical center in which they were treated had more attendants than controls (59 vs 42.9%). Compared to controls, cases were less often received less health education (41.9 vs 11.9%) while more of them did not hear about TB disease before they had it (44.9 vs 27.1%. The demographic and TB characteristics are given in Tables 1 and 2.

Patient's knowledge and opinion

The distribution of factors related to knowledge of TB and its treatment as well as the opinion and attitudes of cases and controls is given in Table 1 and 2. Univariate odds ratios and their 95% confidence intervals are given in Table 3 and 4. In general, cases were more likely to lack adequate knowledge of TB such as; had never heard about TB before had it (OR: 1.93, 95% CI: 1.18-3.17), when to stop TB medication (OR: 2.81, 95% CI: 1.66-4.74), treatment duration (OR: 2.96, 95%CI: 1.62-5.41) and can TB be cured (OR: 2.54, 95%CI: 1.13-5.71). Hence, cases were more living in the rural areas (OR:2.64 and 95%CI: 1.57- 4.44) and having more social problems because they had TB. Especially, cases reported feeling more ashamed (OR:1.88,95%CI:1.04-3.39) and embarrassment because of having TB(OR:2.17,95% CI:1.16-4.07), and were less likely to

Table 1. Patients knowledge and awareness factors affecting non adherence to TB treatment.

Patients knowledge and awareness factors:	**Cases (105)**	**Control (210)**	**P-value**
Age – mean (SD)	32.8 (14.4)	34.6 (14.9)	
15 - 30 years	56 (53.3%)	100 (47.6%)	0.339
Over 30 years	49 (46.7%)	110 (52.4)	
Sex			
Male	74 (70.5%)	128 (60.9%)	0.98
Female	31 (29.5%)	82 (39.1%)	
Site of tuberculosis			
Pulmonary TB	92 (87.6%)	180 (85.7%)	0.39
Extra-pulmonary TB	13 (12.4%)	30 (14.3%)	
Residential locality			
City	64(61%)	169(80.5%)	0.000
Village	41(39%)	41(19.5%)	
Did you hear about TB before you had it?			
Yes	61(58.1%)	153(72.9%)	0.006
No	44(41.9%)	57(27.1%)	
What do you expect if you stop TB treatment?			
Know the consequences	95(90.5%)	183(87.1%)	0.251
Don' know the consequences	10(9.5%)	27(12.9%)	
Know the consequence if stop TB treatment			
Not cured	16(16.8%)	48(26.3%)	
Relapse	42(44.2%)	80(43.7%)	0.215
Start treatment again	12(12.7%)	22(12.0%)	
Died	25(26.3%)	33(18.0%)	
Treatment duration			
Known	76(72.4%)	186(88.6%)	0.000
Not known	29(27.6%)	24(11.4%)	
Mentioned the treatment duration			
6 months duration	39 (51.3%)	131(70.3%)	0.065
8 month duration	37(48.7%)	55(29.7%)	
Can TB be cured?			
Yes	91(86.7%)	198(94.3%)	0.020
No	14(13.3%)	12(5.7%)	
When should you stop taking treatment?			
When a health worker tells me	64(61%)	171(81.4%)	0.000
Others	41(39%)	39(18.6%)	
Are you ashamed to have TB?			
Yes	25(23.8%)	30(14.3%)	0.038
No	80(76.2%)	180(85.7%)	
Do you try to hide that you have TB?			0.560

Table 1. Contd.

Yes	24(22.3%)	42(20.0%)	
No	81(77.7%)	168(80.0%)	
Do your family, friends and colleagues treat you different because of TB?			0.000
Yes	31(29.5%)	23(11.0%)	
No	74(70.5%)	187(89.0%)	
How do you feel about being observed taking treatment?			
Embarrassed	23(21.9%)	24(11.4%)	0.012
Not embarrassed	82(78.1%)	186(88.6%)	

Table 2. Patients opinion about TB services and behavior factors affecting non adherence to TB treatment.

Patient behavior and opinion about TB services	Cases (Non-adherence) 105 (33.3%)	Control (adherence) 210 (66.7%)	P-value
Do you smoke?			
Yes	15(14.3%)	44(21%)	0.099
No	90(85.7)	166(79%)	
Do you use alcohol?			
Yes	7(6.7%)	18(8.6%)	0.364
No	98(93.3)	192(91.4%)	
Do you have AIDS?			
Yes	2(1.9%)	4(1.9%)	1.000
No	103(98.1%)	206(98.1%)	
Do you use intravenous drugs?			
Yes	1(1.0%)	2(1.0%)	1.000
No	104(99.0%)	208(99.0%)	
Do use other drugs?			
Yes	4(3.8%)	3(1.4%)	0.194
No	101(96.2%)	207(98.6%)	
What is your opinion on TB services?			
Good	99(95%)	205(97.6%)	0.118
Not good	6(5%)	5(2.4%)	
How do you rate the health workers attitude?			
Receptive	101(96.2%)	206(98.1%)	0.256
Unreceptive	4(3.8%)	4(1.9%)	
How do you rate the health center appearance?			0.21
Suitable	91(86.7%)	173(82.4%)	
Not suitable	14(13.3%)	37(17.6%)	
How do rate the number of patients at the TB center?			0.005
Suitable	43(41%)	120(57.1%)	
Not suitable	62 (59%)	90(42.9%)	
What was your average waiting time at the TB center?			0.211
<60 min	94(89.5%)	195(92.9%)	
>60 min	11(10.5%)	15(7.1%)	

Table 2. Contd.

Are you satisfied with the given TB treatment?			
Yes	97(92.4%)	198(94.3%)	0.515
Not	8(7.6%)	12(5.7%)	
Did you receive health education about the disease TB and its treatment?			
Yes	61(58.1%)	185(88.1%)	0.000
No	44(41.9%)	25(11.9%)	

Table 3. Distribution of Patients knowledge and awareness factors.

Patient knowledge and awareness factors:	OR	95% CI
Age group		
15 - 30 years vs. Over 30 years	0.80	0.50 -1.27
Sex		
Male vs.Female	1.53	0.93-2.53
Site of tuberculosis		
Pulmonary vs. Extra-pulmonary	1.18	0.60-2.37
Residential locality		
City vs Village	2.64	1.57- 4.44
Did you hear about TB before you had it?		
Yes vs No	1.93	1.18-3.17
What do you expect if you stop TB treatment		
Know the consequences vs Don' know the consequences	1.40	0.65-3.02
Treatment duration		
Known vs Not known	2.96	1.62 -5.41
Can TB be cured?		
Yes vs No	2.54	1.13-5.71
When should you stop taking treatment?		
When a health worker tells me vs Others	2.81	1.66-4.74
Are you ashamed to have TB?		
Yes vs No	1.88	1.04-3.39
Do you try to hide that you have TB?		
Yes vs No	1.19	0.67-0.21
Do your family, friends and colleagues treat you different because of TB?		
Yes vs No	3.41	1.86-6.22
How do you feel about being observed taking treatment?		
Embarrassed vs Not embarrassed	2.17	1.16-4.07

Table 4. Distribution of Patients opinion about TB services and behavior factors.

Patient opinion about TB services and beahviour factors	OR	95 %CI
Do you smoke?		
Yes vs No	1.59	0.84-3.02
Do you use alcohol?		
Yes vs No	0.76	0.31-1.89
Do you have AIDS?		
Yes vs No	1.00	0.18-5.55
Do you use intravenous drugs?		
Yes vs No	1.00	0.09-11.16
Do use other drugs?		
Yes vs No	2.73	0.60-12.44
What is your opinion on TB services?		
Good vs Not good	2.49	0.74-8.34
How do you rate the health workers attitude?		
Receptive vs Unreceptive	0.49	0.12-2.00
How do you rate the health center appearance?		
Suitable vs Not suitable	0.72	0.37-1.40
How do rate the number of patients at the TB center?		
Suitable vs Not suitable	1.92	1.20-3.09
What was your average waiting time at the TB center?		
<60 min vs >60 min	1.52	0.67-3.44
Are you satisfied with the given TB treatment?		
Satisfied vs Unsatisfied	1.36	0.54-3.44
Did you receive health education about the disease TB and its treatment?		
Received health education vs Not educated	5.34	3.02-9.44

have support of their families, friends and colleagues (OR:3.41, 95%CI: 1.86-6.22). The perception of health services was similar. However, cases had often received less counselling on TB and its treatment (OR: 5.34, 95% CI:3.02-9.44) and felt there were too many patients when visiting the TB center (OR:1.92,95%CI:1.20-3.09) (Tables 3 and 4).

Risk factors for defaulting

In the multivariate analysis the variables that remained in the model were residential locality (P value: 011, OR:2.16; 95% CI: 1.19-3.90), 'lack of knowledge on when to stop TB medication'(P value: 0.023, OR: 2.00; 95%CI:1.10-3.64), "had never heard about TB before had it (P value:0.041, OR: 1.81; 95%CI:1.02-3.20), 'less support by families, friends and colleagues'(P value: 0.001; OR: 3.23; 95%CI: 1.62-6.46), 'too many patients when visiting the TB center'(P value: 0.004; OR: 2.24; 95%CI: 1.29 -3.88), and 'lack of counseling about TB and its treatment' (P value: 0.000; OR: 4.79; 95%CI: 2.57 - 8.95), (Table 5).

DISCUSSION

The present study showed that patients with less opportunity to receive health education and counseling about TB and its treatment and those living in the rural areas are at higher risk of defaulting TB treatment. Other potentially modifiable factors associated with TB treatment default identified in this study were lack of support by families, friends and colleagues, and

Table 5. Multivariate results: Patients knowledge and awareness, opinion about TB services and behavior factors leading to TB default.

Factor	P value	Odds Ratio (OR)	95% CI
Living in rural areas	0.011	2.16	1.19-3.90
When should you stop taking treatment?	0.023	2.00	1.10-3.64
Did you hear about TB before you had it?	0.041	1.81	1.02-3.20
Do your family, friends and colleagues treat you different because of TB?	0.001	3.23	1.62-6.46
How do rate the number of patients at the TB center?	0.004	2.24	1.29-3.88
Did you receive health education about the disease TB and its treatment?	0.000	4.79	2.57- 8.95

overcrowding of the TB centers and its associated issues of long waiting times. Our study observed a default rate of 14% among TB treatment patients in Khartoum State. This high default rate was similar to rates reported in previous studies conducted in Khartoum State [(Federal Ministry of Health, Sudan, 2011, Suleiman and Sodemann, 2009). This observed rate is much higher than the World Health Organization's recommended target rate of 3% (World Health Organization, 1994). Similar high default rates were reported in other developing countries e.g. in Ethiopia and India with default rates of 23 and 10%, respectively (Damte et al., 2013; Pradesh, 2010). Such high default rates has a negative impact on the treatment outcome and may lead to spread of disease, treatment failure, drug resistance and death (Muture et al., 2011). In the present study a substantial proportion of cases 44(42%), and controls (12%), did not receive health education and counseling when diagnosed with TB. While the intention of the TB-control program in Khartoum State is to provide adequate health education and counseling to patients diagnosed with TB, the fact that this did not happen in a substantial proportion of patients may be explained by shortage of health education personnel, increased health care burden, lack of training and supervision of health staff by the TB coordinators. This may indicate that the program and its allocated resources deserve a re-assessment.

Our observation that patients with less opportunity to receive health education and counseling about TB and its treatment increase the default rate confirms the results of previous studies conducted in both developed and developing countries (World Health Organization (WHO), 2002, Muture et al., 2011; Marlucia et al., 2012). However, Nyi from Malaysia did not find an association between health education and counseling and TB treatment default (Nyi et al., 2001). In general, a large proportion of participants in this study had low knowledge about TB, duration of treatment, and whether TB is curable or not. The knowledge and behavioral factors contributing to TB default may vary in different communities and populations. Part of this can be attributed to patients' traditions and believes. In addition, health services, health staff receptiveness and patients' opinions towards those services are also contributing factors. Moreover, TB is a disease largely present in settings of the poor with limited resources. The association of TB treatment default with lack of family, friends and colleague support, rural residence and overcrowding of the TB centers has been recognized before as it was in this study (World Health Organization (WHO), 2002; Rubel and Garo, 1992; Marlucia et al., 2012; Ifebunandu et al., 2013). However, our findings were in contrast to those reported by Chuah (1991) and Nyi et al. (2001) from Malaysia.

In our study population, HIV infection and intravenous drug users (IVDU) were rare, as might be expected among the population of Krartoum state (unpublished data). With regard to HIV infection status, it was interesting to note that about 15% of TB patients were not screened, while the intention of the TB control program is to perform the HIV testing in all TB patients. This is another indication for the need of reassessment of the TB control program in Khartoum state. Surprisingly, behavioral factors including cigarette smoking, alcohol abuse, feeling ashamed and other stigmatizing factors were not associated with TB default in this study, in contrast to some earlier studies (Muture et al., 2011; Caylà et al., 2009). The findings of this study might help health providers and policy makers in Sudan and other developing countries in planning and developing health policies to strengthen TB control programs in general. Of special importance seems that there is insufficient staff dedicated to counseling and education of the patients as well as their social support networks. Also more efforts should be taken to enhance the community participation and upgrading of the health personnel's communication and counseling skills.

Some methodological aspects of this study need attention: Firstly, this study was conducted in Khartoum State, capital of Sudan which is the most populated state in Sudan. The population in this state could be safely stated to represent the whole country as most of the inhabitants come from various parts of Sudan. In addition, the TB patients included in this study were selected from all tuberculosis treatment units (health centers and hospitals) in the state. Thus, the generalization of the study findings to the total tuberculosis population in the state and Sudan could be done and seems logical as well as in the communities with similar settings. Secondly, recall bias was minimized by reviewing the patient medical records and cross checking for each study variable and using a standardized questionnaire during the interview. Thirdly, the reliability of information gathered from each subject could not be counterchecked but questions about sensitive issues were carefully dealt with to maximize the reliability of the responses obtained. Fourthly, possible confounders were taken into consideration in the design (by restricting the diagnosis criteria) and by using logistic regression. Lastly, the major problem we faced during this study was how to reach the defaulting patients (cases) for this study. This problem was tackled stepwise. First, their medical records were traced and identified and all contact information was reviewed. Then, study personnel used the following sequence of contact attempts: calls – first to the patient and thereafter to known family members or friends - home visits - first to patient and thereafter to known family members or friends. Interestingly, it appeared during the study that many of the defaulting patients did not have access to mobile telephones, a risk factor not previously described nor evaluated in this study. The interviewers made an average of three attempts to contact each defaulter before deciding that a defaulter was a non-respondent.

Conclusions

This study confirms that health education and counseling to patients and their families on TB disease and it's treatment are of paramount importance and are strongly associated with treatment default, which is related to treatment failure and microbial resistance to antibiotics. Hence adequate counseling is highly recommended. In addition, fostering social support (family and community) and adequate training of the health care providers to adopt a warm and respectful approach towards patients and their families are also important. Also, reducing the number of patients attending health units e.g by increasing number of treatment centers may help reduce TB treatment default.

Conflict of Interests

The authors have not declared any conflict of interests.

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