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GEOSPATIAL ANALYSIS OF PEDIATRIC TUBERCULOSIS IN BOHOL, PHILIPPINES: DISEASE CLUSTERS AND ACCESS TO CARE

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DEDICATION

To our Bohol research team and the families who participated in this study.

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by

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BACHELOR OF ARTS, St. Edwards University, 2013

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Thank you to my dedicated supervisors, mentor, co-workers, and peers who have supported me through this project.

GEOSPATIAL ANALYSIS OF PEDIATRIC TUBERCULOSIS IN BOHOL, PHILIPPINES: DISEASE CLUSTERS AND ACCESS TO CARE

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Worldwide, children represent approximately 10% of global tuberculosis (TB) cases. We recently reported a high tuberculin skin test (TST)-positive prevalence (355/5,476; weighted prevalence=6.4%) among children (<15 years) throughout the island of Bohol, Philippines, with some geographically isolated communities having prevalence as high as 29%. In this study, we conducted a secondary geospatial and hot-spot analysis of this household-based cluster survey to assess the association between access to care (distance to a health care facility) and TST-positive prevalence. Our analysis indicated that villages with high TST-positive prevalence (≥10%) were significantly further from Provincial Health Office based in the capital city of Tagbilaran in time-distance (p=0.0001, *r*=0.2387) and kilometers (p=0.0011, *r*=0.3170). Similarly, prevalence was positively correlated with distance to the municipal Rural Health Unit (RHU), where most receive their medical care, in time-distance (p=0.0055; *r*=0.0415); however, the association was not significant in kilometers (p=0.3315; *r*=0.0715). Distance to health care facilities could represent an obstacle to access to care, thereby limiting diagnosis and treatment and resulting in increased risk of transmission to others in the community. Health care outreach in geographically isolated areas is critical to treatment and control of efforts for pediatric TB.

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BACKGROUND

Literature Review

Tuberculosis (TB) is an infection caused by the bacteria *Mycobacterium tuberculosis (M. tuberculosis)* (CDC, 2018). This disease is spread through the air when someone infected with *M. tuberculosis* speaks, sneezes, coughs, or sings creating infective aerosol droplets (CDC, 2018; Department of Health, Global Health, USAID, & World Health Organization, 2010). Airborne transmission and low infectious dose of *M. tuberculosis* makes this disease highly communicable and infectious. People with frequent and close proximity for long durations with an infected person, such as family, friends, neighbors, classmates, or coworkers are often the most at risk for acquiring infection (CDC, 2018). *M. tuberculosis* commonly resides in the lungs but can infect other organs of the body such as the brain, spinal cord, and kidneys (CDC, 2018). Symptoms of TB disease include coughing (3 weeks or more), wheezing, shortness of breath, chest pain, hemoptysis, weakness, fatigue, fever, chills, weight loss, or loss of appetite or energy (CDC, 2018).

Diagnosing TB involves a synthesis of several elements: exposure and medical history, clinical examination of symptoms, laboratory tests to detect the presence of *M. tuberculosis*, and radiography. Tuberculosis is classified by exposure, infection, and active disease pathogenesis for clinicians or health-care providers to aide in diagnosis and public health programs (CDC, Ch.4, 2013; Cruz, A.T. and Starke, J.R., 2019; Nachiappan, et al., 2017). These distinctions are important because (1) some individuals are exposed to TB and do not become infected, (2) some are exposed and harbor a latent infection (LTBI) that is subclinical, asymptomatic, and not contagious, (3) some are exposed to TB, harbor LTBI, and it can reactivate later in life and lastly (4), some individuals are exposed and progress to clinically symptomatic active TB disease within one to two years post-exposure (CDC, 2018; Huebner et al., 1993; Nachiappan, et al., 2017).

Microbiological tools can be used to test an individual's immune system for prior exposure to *M. tuberculosis* either by a skin or blood test. The Mantoux Tuberculin Skin Test (TST), the most commonly used tool for the detection of *M. tuberculosis* infection, measures the immune response to injected purified protein derivatives (PPD) of tuberculin and has been a long-standing aid in the diagnosis of TB (Bartalesi, F., et al., 2009; CDC, 2011). The TST is administered by the injection of PPD subcutaneously on an individual's inner forearm to stimulate an immunological response at the intradermal injection site (CDC, 2011). The resultant skin reactions are evaluated, or 'read', 48-72 hours after placement (CDC, 2011). Induration or skin inflammation to the TST is measured in millimeters (mm) and demonstrates an immunologic memory response to the antigens present in PPD. Although an induration of greater than or equal to 15 millimeters is considered to be positive in all individuals, among some populations that are high-risk of TB exposure or high risk of TB disease progression due to immunosuppression a TST induration is considered positive if greater than or equal to 10, and even 5 mm (CDC, 2011).

Concerns regarding limitations of TST sensitivity and specificity, prompted the development of Interferon-Gamma Release Assays (IGRAs), which are in-vitro whole blood tests that measure the amount of interferon gamma (INF-γ) released (the ELISA-based Quantiferon Gold test produced by Qiagen,) or enumerate the number of T cells producing

INF-γ (the ELISPOT-based T.Spot-TB produced by Oxford Immunotec) in response to *M. tuberculosis* specific antigens including ESAT-6, CFP-10 and TB 7.7 (Huebner et al., 1993; Mazurek, et al., 2010). INF-γ is used as a marker of *M. tuberculosis* infection because it is a cytokine responsible for recruiting CD4+ T-lymphocytes upon the detection of antigens and activates the body's immune response to clear the mycobacterium (Bartalesi et al., 2009; CDC, 2011).

Perhaps one of the key advantages of IGRAs compared to the TST is the specificity afforded by utilizing TB specific antigen derived from the region of deletion one which is absent in *Mycobacterium bovis.* Thus, IGRAs do not cross-react with the Bacillus Calmette-Guérin (BCG) vaccine and limit the frequency of false-positive responses in BCG recipients (Pai, et al., 2008). Minimization of false-positive results due to BCG cross-reactivity is especially important in TB high-burden countries which have implemented nationwide mandatory BCG vaccination programs for all children at birth (Zwerling, et al., 2011).

Evidence accumulated over the past decade has demonstrated limitations of both the TST and IGRAs. It is now well recognized that IGRAs, similar to the TST, cannot be used as a stand-alone diagnostic tool but rather are useful as one part of the diagnostic assessment. With neither as a gold standard for diagnosing TB, they are employed based on country resources or clinician preference (Pai, M., et al., 2014). Neither tests can reliably i) distinguish between active TB versus latent infection, ii) determine the stage of infection or reinfection, or iii) predict progression of LTBI to TB disease; further, for all tests, concerns persist regarding reduced sensitivity among the immunocompromised (Pai, M., et al., 2014).

As the TSTs and IGRAs are only adjunctive tests, clinical assessments for TB also rely upon history, physical exam, sputum microbiology tests and radiography to give a more evidence in support of a diagnosis. Whereas, radiography provides a picture of disease history, etiology, and future progression, isolation of sputum in three consecutive tests can differentiate between active and latent infection and determine treatment outcomes (CDC, Ch. 4, 2013). Sputum is collected from an individual presumed to have TB and tested for the presence of *M. tuberculosis*, either by viewing the bacteria under a microscope (smear microscopy), detecting *Mtb* DNA using an automated, cartridge based Nucleic Acid Amplification Test (Gene Xpert), or demonstrating growth in a culture medium (culture); the latter two test can also demonstrate bacterial resistance to anti-TB medications (WHO, TB: key facts, 2018). Radiology exhibits LTBI through the appearance of lymphadenopathy, consolidation, pleural effusion, and miliary nodules or as TB disease when there are consolidations in the apical and upper lung zones, nodules, and cavities infiltrates or lesions (Cruz, A.T. and Starke, J.R., 2019; Nachiappan, et al., 2017).

TSTs and IGRAs are used in screening programs among high risk groups for identification of presumed TB cases but must be incorporated with a complete medical evaluation before determining a more accurate diagnosis (WHO, Screening, 2013). Prompt diagnosis is essential for the treatment, management, and control of TB. Undetected cases and delayed diagnoses can result in longer durations of disease, higher risks of morbidity and mortality, significant financial constraints, and the potential for Multi-drug resistance (MDR-TB) susceptibility (WHO, Screening, 2013). Undetected and untreated LTBI cases can result in a 5-15% disease incidence or recurrence over a lifetime, especially among immunocompromised populations (CDC, 2016; WHO, 2018 Key Facts). Growing evidence suggests TB complicates and advances many widespread diseases such as pneumonia, HIV/AIDS, diabetes, meningitis, malnourishment, and other immunosuppressed conditions ultimately leading to higher mortality rates (CDC, 2016; Huebner at al., 1993; Qu, H-Q., et al, 2012; Mazuerk, et al., 2010; WHO, Screening, 2013; WHO, Global Report, 2018). As a result, the global burden and control of TB is a major focus of many countries, health organizations, and institutions, such as the Centers for Disease Control and Prevention, World Health Organization, and the United Nations.

Public Health Significance

Despite prevention measures and available treatment, TB is one of the top ten causes of mortality worldwide, effecting over one third of the global population (WHO, Global TB Report, 2018). Results of the Global Burden of TB Disease Study found 10.2 million incident cases, 10.1 million prevalent cases, and 1.3 million deaths, and 300,000 TB-HIV deaths in 2015 alone (GBD Tuberculosis Collaborators, 2015; WHO, Global TB Report, 2018). According to the WHO, two thirds of the global TB burden existed in only eight countries: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa (WHO, Global TB Report, 2018).

The Philippines accounts for 6% of all global prevalent TB cases and has the second highest incidence of TB in the world at 554 new cases per 100,000 people (WHO, Global TB Report, 2018). Globally, children (<15 yrs. old) make up an estimated 10% of all TB cases (WHO, Global TB Report, 2018). In the most recent Global TB Report, the WHO estimated that in 2017 1 million children had incident TB, and 253, 000 died as a result of TB disease. Estimated Filipino pediatric incidence was 71 cases per 1,000 people in 2017 (WHO, Global TB Report, 2018). In 2016, the Philippines National Tuberculosis Prevalence Survey bacteriologically confirmed TB among 613 cases per 100,000 (95% CI=403-822) among individuals 15-19 years old. However, data is limited on pediatric TB due to challenges with passive-surveillance, underreporting, the quality microbiology samples for diagnosis, and the etiology of disease in children (CDC, Ch.4, 2013; Cruz, A.T. and Starke, J.R., 2019; Nachiappan, et al., 2017; WHO, Global tuberculosis report, 2018). As a result, children are believed to represent a substantial portion of undetected TB cases (Dodd, et al., 2018; WHO, Screening, 2013). In fact, even in countries with prominent active surveillance systems estimate pediatric TB is underreported by up to 15-20% among children <15 years old (Cruz, A.T. and Starke, J.R., 2019). Research has shown children, especially under the age of 5, are at high risk of TB infection and disease due to their household exposures or close contacts, are vulnerable to many childhood diseases (pneumonia, HIV, malnutrition, etc.), are likely to have long-term sequalae, and develop more severe forms of tuberculosis proving fatal (Dodd, et al., 2018; WHO, Screening, 2013). A mathematical model by Dodd et al. (2018) estimated that up to 159,500 pediatric TB cases and 108,400 deaths among children <15 years could be prevented if all children who were identified during contact tracing investigation were treated as a result of an active TB household exposure. This modeled ideal use of preventive therapy equates to saving 7,305,000 life-years globally.

Due to these uncertainties, Murray et al., with Baylor College of Medicine's National School of Tropical Medicine, and colleagues from the Baylor Global TB Program and the University of the Philippines conducted the first cross-sectional prevalence study on the provincial island of Bohol, Philippines, examining the impact of a 7.2 magnitude earthquake and super typhoon on pediatric TB transmission. TB prevalence was compared in two study arms as a heavily affected (HAAs) or less affected area (LAAs) by the earthquake and aggregated at the municipality (towns) and barangay (villages) level. Barangays are a series villages that make up each municipality boundary, whereas municipalities are seen as cities and towns make up each province. Municipalities indicated by the regions in Figure 1 were enrolled based on their proximity to the epicenter of the earthquake and matched based on population density. Municipalities that were closest to the earthquake epicenter on the west and northwest side of the island and sustained the greatest degree of damage were considered heavily affected areas (HAAs), and the ones on the east and north-east side of the island farthest away from the damage of the earthquake were designated the less affected areas (known as LAAs). HAA municipalities (shown on left) include: Calape, Catigbian, Clarin, Inabanga, Loon, Maribojoc, and Sagbayan. LAA municipalities (right) include: Alicia, Anda, Bien Unido, Candijay, Pres. Carlos P. Garcia, Mabini, and Ubay. In order to test the research hypothesis, the team conducted an island-wide rapid assessment cluster sampling technique based on the WHO's expanded program for immunization (EPI) methods. Children <15 years were expected to have higher prevalence of TB if they lived in an area heavily affected by the earthquake damage, were displaced by the disasters, and subsequently lived in crowded homes or shelters.

Out of the 5,476 (6%) children surveyed, 355 (5%) tested as TST-positive, and 16 (4%) were diagnosed with active TB disease. Of those diagnosed with TB, 3 (19%) were positive by GeneXpert *Mtb*/Rif. Children were more at risk of being TST-positive if they were older (>5 yrs. old, OR=1.6, 95% CI=1.2-2.0), had previously been treated for TB (OR=3.4, 95% CI=1.7-6.7), reported known contact with a TB case (OR=4.9, 95% CI=3.8-6.2), and lived on a remote island barangay (OR=1.5, 95% CI=1.1-2.1). Of note, TST-positive prevalence approached 29% in at least two separate barangays. High prevalence of TST-positives were identified among barangays in the municipalities of Sagbayan, Inabanga, Bien Unido, Pres. Carlos P. Garcia, and Ubay. These findings demonstrate a potential spatial association between the location of TST-positive individuals relative to the health providers in the municipality and the province.

Research Questions & Hypothesis

Municipal rural health units (RHUs) are public clinics regulated by the Bohol Provincial Health Office (PHO) provide clinical care, medical evaluations, Direct Observed Therapy, Short Course (DOTS), and anti-TB medications. RHUs are critical to the identification and management of TB not only through clinical evaluations and DOTS they provide, but by their strategic placement in each municipality. As a result, the vast majority of Boholanos seek out RHUs for convenience of TB diagnosis and treatment. This was shown by the Philippines National Tuberculosis Prevalence Study (NTPS, 2016) who estimated about 76% of all adult TB cases sought treatment at their local health care center or TB DOTS, and 72.3% sourced their medications from these public facilities (Philippines, DOH, 2016). These RHUs rely on the Bohol PHO to provide medical supplies, medications, education, and financial support. The Bohol PHO is located near the Governor's mansion, the city hall, and other government offices in the provincial capital of Tagbilaran City. Closely tied with the governor, the PHO presides over health care centers, RHUs, barangay health stations, hospitals, clinics, and pharmacies in the province, and staffs the TB coordinators of the island. This public reliance on the RHUs, supported by the PHO, prompted us to examine effect of these locations as an indicator of TST-positives aggregated by barangay and municipality. Using TST-positives as a proxy for children presumed to have TB, we hypothesized TST-positive prevalence is higher in barangay and municipalities located the farthest away from their municipal RHU and the PHO. The goal of this thesis proposal is to determine if higher prevalence of pediatric TB is associated with distance from the PHO and the Rural Health Units (RHU) and if so whether children in Bohol, Philippines are at an increased prevalence of TB the farther they live from disease prevention and treatment services.

Specific Aims

1. Determine the spatial relationship between each municipality's aggregated TST-positive prevalence and the geographic distance to the Provincial Health Office (PHO).
2. Determine the spatial relationship between each barangay's aggregated TST-positive prevalence and the geographic distance to the Provincial Health Office (PHO).
3. Determine the spatial relationship between each barangay's aggregated TB prevalence and the geographic distance to their municipality Rural Health Unit (RHU).
4. Investigate the presence of pediatric TB disease clusters in Bohol and their spatial relationship to RHUs.
5. Supplement TST-positive prevalence analysis with municipal and barangay population characteristics related to poverty as potential confounders.

METHODS

Study Design & Study Setting

The proposed project is a secondary analysis of previously collected de-identified cross-sectional pediatric TB prevalence data from a collaborative project between Baylor College of Medicine and the University of the Philippines from 2016-2018. No additional human or animal subjects will be enrolled for the purposes of this study. As a result, there is minimal information to report regarding how subjects are recruited and in what capacity. Instead, geographic coordinates and attribute map layer data will be collected in order to examine TB disease clusters and analyze health care accessibility. This spatial analysis will take place at UTHealth School of Public Health and Baylor College of Medicine in Houston, TX between August 2018 – May 2019.

Sample Size Calculation and Study Power

This geospatial analysis will be based off data collected by Baylor College of Medicine and the University of the Philippines from 2016 to 2018. Municipalities were selected into the study based on their proximity to the earthquake epicenter and resulting devastation and subsequent disruption of health services. Municipalities closest to the epicenter were matched with municipalities less affected by the earthquake and had minimal infrastructure damage. All family households in the Heavily Affected Areas (Calape, Catigbian, Clarin, Inabanga, Loon, Maribojoc, and Sagbayan) and Less Affected Areas (Alicia, Anda, Bien Unido, Candijay, Pres. Carlos P. Garcia, Mabini, and Ubay) were eligible for selection into the study. The research team calculated a sample size of at 5,400 children (2,700 for the HAA and 2,700 for the LAA) to determine a significant difference between their hypothesized post-disaster prevalence of TB infection in children (1%) compared to a reference value of 0.56% prevalence of TB (alpha=0.05, power=80%). On average, 3.8 children were enrolled per household, 7 households per cluster, and 100 clusters per study arm (HAA and LAA). After the enrollment period ended earlier this year 5,442 children were enrolled (2,676 in total for HAAs and 2,766 in total for LAAs).

Study Subjects & Data Collection Procedures

Children under 15 years of age were enrolled by research field nurses for the island-wide rapid assessment cluster sampling using a modified approach based on the WHO's expanded program for immunization methods (EPI) using population proportionate to size (PPS) (Murray et al, 2018). Residence clusters were randomly selected, and the starting house was also selected at random. Parents were approached and were asked if they wanted to participate in the study after determining child eligibility. All children completed TST and answered survey questions regarding earthquake history, TB history, recent TB exposures, and current symptoms as part of the initial screening. Children who tested TST negative and had no compatible TB symptoms or exposures completed their involvement in the study and were compensated for their time. Children who were TST-positive and/or had compatible symptoms for TB and/or exposures were referred for medical examination at their local RHU. Bus passes were given to families for their visits which included a physical exam, laboratory testing through direct sputum smear microscopy (DSSM) ($\geq$ 5 yrs. old), gastric aspirates (<5 yrs. old) through GeneXpert testing, and chest radiographs. Children were considered to be an LTBI case if their TST was read as positive but they did not have TB signs or symptoms. Children were considered an active TB case if they met the three of the following five clinical criteria (1) TST positive (2) exposure to a TB contact (3) evidence of disease in chest radiographs (4) positive sputum or gastric aspirates by smear, Xpert or culture (5) three of the six signs and symptoms compatible with TB disease (cough or wheezing of 2 or more weeks, fever of two or more weeks excluding other relevant etiologies, weight loss or failure to regain weight, failure to respond to at least two weeks of antibiotics, failure to return to baseline health status after 2 or more weeks following infection, and fatigue, lethargy, or reduced playfulness).

The University of the Philippines staff were responsible for the enrollment of study participants and data entry, whereas Baylor staff were responsible for the analysis. All surveys and medical data (i.e. X-rays, TB diagnosis, etc.) was de-identified and shared with Baylor College of Medicine using a secure, password protected network. All data is stored on password protected Baylor College of Medicine server in Houston, TX.

GIS Data Collection Procedures

Census data, poverty rates, health clinics, and other population characteristics will be obtained from Philippines government websites such as Republic of the Philippines Statistics Authority (https://psa.gov.ph) and the Bohol Provincial Planning and Development Office (www.ppdobohol.lgu.ph/). Political boundary maps will be accessed using public data clearinghouses with mega-data of the Philippines such as PhilGIS (Philippine GIS Data Clearinghouse, Ozamiz City, Philippines) and the Philippine Geoportal (NAMRIA, Taguid City, Philippines). Coordinates of the PHO, RHUs, and TST-positive cases will be aggregated to the municipality and barangay-level to protect any personal identifying information, and will be geocoded as latitude and longitude using Google Maps (Google LLC, Mountain View, California). Geocoded data will be combined with Murray et al.'s TST-positive prevalence data and population poverty indicators. Coordinates, prevalence, and characteristics will be documented as worksheets in Microsoft Excel and uploaded into NCSS (NCSS, Inc., Kayesville, Utah) for a linear regression analysis and ArcMap for a geospatial analysis. Minutes and kilometers will be recorded as the minimal values of the route between points. Distance is not calculated as Eucildean, which is a straight-line distance between points, because it doesn't accurately reflect the methods and time of travel by this specific population. Double-entering will ensure quality control of the data. ArcMap's additional spatial analysis tools will be used to produce choropleth maps of TST-positives aggregated to the municipal and barangay level, hot spot maps to determine the presence of statistically significant clusters, and a buffer analysis map to examine the presence of TST-positive clusters and their spatial relationship to the nearest TB facility.

GIS Data Analysis

The regression and the geospatial analysis are used in combination to determine the presence of a statistical relationship between TST-positives and public TB clinics in Bohol. Linear regression of population characteristics with TST-positives will evaluate poverty as a population characteristic as confounders. The ArcGIS maps will show a variety of contextual information regarding the relationship of pediatric TST-positive prevalence in Bohol related to earthquake damage and displacement, population density, and population characteristics. A geospatial analysis will indicate statistically significant TST-positive cluster hot-spots and cool-spots, whereas a floating catchment area map will evaluate the relationship between the frequency of high TST-positive clusters within designated service areas.

Choropleth maps display counts, ratios, or proportions using points and shaded regions to distinguish between disease patterns in an area (ArcGIS, Insights, 2018). A choropleth map of TST-positives will be useful for the comparison of prevalence by municipality and barangay, clarifying areas with a higher burden. A limitation of choropleth maps is they are subjective to bias determined by the selection of categorical outcome display settings. A hot-spot analysis will be used to mitigate choropleth biases but also to identify TST-positive clusters.

Hot-spot analysis uses the Getis-Ord Gi* statistic to calculate statistical significance of TST-positive clusters by assigning a z-score and a p-value to each feature (ArcGIS, Hot-Spot – How Getis-Ord Gi* works 2018). Map features of TST-positives are assigned a weight according to a significance level set by the researcher. Features are determined as statistically significant or not by comparing the neighboring features. In other words, areas with higher TST-prevalence may seem significant, but to be considered a hot-spot, it must be located in an area surrounded by high values (ArcGIS, Hot-Spot – How Getis-Ord Gi* works, 2018). Similarly, cold spots are highlighted in the strength of the cool spots in the surrounding area (ArcGIS, Hot-Spot – How Getis-Ord Gi* works, 2018). The benefit of this analysis is the connection to hypothesis testing which seeks to determine if the observed clustering of high and low values is higher than the expected value of a random distribution (ArcGIS, Hot-Spot –Getis-Ord Gi* Spatial Statistics, 2018). Hot-spot tools are accessed using the ArcToolbox available through the ArcGIS software and can be run through the software.

Analyzing the proximity of statistically significant TST-positive clusters within service areas of RHUs will require a two-step floating catchment area (2SFCA) method in ArcGIS. Developed by Luo and Wang (2003), the 2SFCA measures spatial accessibility of service providers locations to communities or individual points using a supply-demand ratio (Wang, F., 2015). Health care providers are centroids of a service buffer zone usually fixed by distance or time (Wang, F., 2015). These zones are called catchment areas because they capture demand locations with the greatest accessibility (Wang, F., 2015). Point distances in a catchment area are analyzed twice: once by the supply location and once by the demand locations. This accounts for distance decay, which is probability that services will be accessed more frequently by individuals who live closer to a supply area (Luo, W., 2009; Wang, F., 2015).

Ratios of RHUs to statistically significant TST-positives clusters analysis the supply-to-demand in an area to evaluate service accessibility. Service accessibility is classified as potential and revealed access which refers to the presence of supplies versus their utilization (Wang, F., 2015; Wei, L., 2009). In other words, service availability is distinct from the public seeking and taking advantage of the supplies provided. This geospatial analysis must take into account spatial and non-spatial data such as socioeconomic factors that could have significant influence in the population to seek and use health-care resources (Wei, L., 2009).

Discussion

Health-care access, supply chain and anti-TB medication shortages are cause of concern for TB control and treatment in Bohol and the Philippines. Studies have demonstrated high-risk individuals are also those with poor spatial access to TB care (Izumi, et al., 2016). Children, the elderly, previously infected, immuncompromised or immunosusceptible (e.g.. medical conditions such as diabetes, HIV, AIDS, etc.), imprisoned, and the geographically isolated, will have the most difficulty accessing, purchasing, and securing stable and consistent health care, resources, and services (Department of Health, Global Health, USAID, & World Health Organization, 2010). Murray et al. found children who didn't adhere to treatment listed unavailable erratic medicine supplies and distance from the clinic as obstacles to treatment in addition to financial constraints, and side effects, taste, and difficulty with administration of the medicine. The NTPS (2016) had similar findings as costs and distance to health centers contributed to incomplete treatment.

According to the WHO, TB epidemics can be contained if adequate and affordable resources are provided to people with TB. Unfortunately, several challenges still exist. Some barriers to treatment included dosing errors, intensive preparation of medication, provider concern of resistance, and poor adherences to therapy (WHO, 2018, Key Facts). This is problematic because incomplete treatment regimens contribute to the development and spread of multi-drug resistant TB (MDR-TB) and extensively drug resistance TB (XDR-TB) (WHO, 2018, Key Facts; CDC, Tuberculosis, Treatment for TB Disease, 2018).

The purpose of this research is to better understand the underlying pediatric TB prevalence differences and obstacles in accessing TB services in a heavily burdened province within a HBC. The goal of this project is to highlight the persistent geographic barriers that can undermine management and control of TB, with hopes of informing and precipitating effective control strategies, and to advocate for increased case-finding or screening programs among children in the Philippines.

Anticipated Pitfalls and Limitations

Validity and reliability of data sources is an anticipated problem. Coordinate data is accurate but degrees were rounded for simplicity and are subject to variability depending on the location of clinics. RHU locations have been rebuilt and moved as a result of earthquake damage and new clinic funding. Geographic distance over water is subject to inconsistencies, especially with regards to time traveled to remote island communities. Time is dependent on the operators of the boat (commercial vs. private), type of boat used (motor speed), boat crowding and cargo, and weather conditions (monsoon and typhoon season). Travel time to all island communities were based on the most popular routes and the experiences of the nursing team. As a result, these variables could be subject to recall bias.

Limited data resources for Bohol will impede the ability to create specific maps for analysis. Population characteristics gathered by the Philippines could be aggregated at the national level and challenging to find for Bohol barangays. Choropleth maps are subject to biases that can distort the true associations of the data in favor of who is making them. One way to minimize this bias is by relying on ArcTools and a geospatial analysis to display the data in regards to statistical significance.

Survey data may be difficult to compare depending on location, time period, and the groups who conducted the research. Consistent and reliable records is unlikely and most data sets will need to be interpreted with caution. Similarly, limited data on population characteristics at the barangay and municipal level will likely restrict the ability to make strong inferences in the relationship between poverty indicators and TST-prevalence.

Demographic data in this analysis is limited to only poverty indicators as indicated by the Boholano government and does not thoroughly assess all potential confounders of TB (age, sex, exposure, BCG vaccination, parental TB history, parental morbidity and mortality, etc.). Future studies would be useful in addressing this.

Using the TST as an indicator of TB prevalence can be considered a weakness (Al-Kassimi, F., et al., 1991). The TST has wavering sensitivity and specificity depending on the prevalence and burden of TB by geographic region and is subject to increase with age (Al-Kassimi, F. et al., 1993; Huebner et al., 1993). Other reasons for unreliability of the TST include: issues with tuberculin used for testing (contamination, manufacturing, storage, absorption, etc.), immunosuppression of the individual being tested, inconsistencies in administration, inconsistent reading and recording of the test, and cross-reactions to non-tuberculosis *Mycobacterium* antigens, such as in the bacilli Calmette-Guérin (BCG) (Huebner et al., 1993). This vaccine is commonly given in endemic countries, influencing false-positive rates (Al-Kassimi, F. et al., 1991; Heubner et al., 1993). There also appears to be a relationship with immunosuppression reflected in states such as: infections, organ diseases and/or failures, nutritional deprivation, metabolic influences, drug influences, age influences, or stress influences(Huebner et al., 1993). One child in particular in Murray et al, 2018, found a TST negative child who had TB disease, but was immunosuppressed due to malnutrition.

While the TST has limitations, it remains the most commonly used test of infection globally, is a relevant tool as an initial screening test of high risk groups, and should be an accessory to a full medical evaluation for TB disease (WHO, Guidance, 2006; WHO, Screening, 2013; WHO, Global TB Report, 2018; Mazuerk, et al., 2010). The use of the TST has been shown to be particularly valuable for the detection of *M. tuberculosis* infection among children aged ≤5 years of age (Cruz, A.T. and Starke, J.R., 2019; WHO, Guidance, 2006) in whom phlebotomy can pose a challenge for the completion of an IGRA. In our resource constrained study setting, use of the TST had numerous advantages compared to IGRAs including i) acceptance by the local population and health care providers due to the perception of bieng less invasive, ii) cost-effective for a mass screening, iii) required less resources and training of study staff, and iv) was easily stored and transported across great distances due to existing protocols that support its common use. All TSTs were complete with a TB exposure and symptoms survey to support comprehensive evaluation of children with presumed TB. Children with compatible symptoms and/or a positive TST were referred to a clinician for a medical evaluation. TST-positive prevalence was higher among older children and TSTs were negative in over 60 barangays, which could be cause for concern regarding false-negatives. Among 32 participants <1 year of age, 10% (3/32) were TST-positive. As expected, TST-positive prevalence ranged between 4-6% among children 1-7 years of age demonstrating the loss of cross-reactivity to BCG over time. Thereafter, TST-positive prevalence slowly increased to 8-9% among children 8-10 years of ager, and ≥10% among children 11-14 years of age; thus, reflecting the expected increase in TB exposure and *M. tuberculosis* infection expected with increasing age. This combined evidence suggest that TST misclassification due to BCG cross-reactions were minimal in our large data set.

Human Subjects Safety and Ethical Considerations

This research has been approved by the Baylor College of Medicine Institutional Review Board (IRB) and will be reviewed by the University of Texas Health Science Center at Houston School of Public Health IRB Committee for Protection of Human Subjects. Minimal to no risk is involved in this study as a secondary spatial analysis of de-identified data. No human or animal subjects will be enrolled for this retrospective data analysis. Data will be aggregated to the barangay and municipal level, represented by provincial political boundaries. No identifying information will be released.

JOURNAL ARTICLE

Geospatial and hotspot analysis of pediatric tuberculosis in Bohol, Philippines

Epidemiology and Infection

Geospatial and hotspot analysis of pediatric tuberculosis in Bohol, Philippines

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SUMMARY

Worldwide, children represent approximately 10% of global tuberculosis (TB) cases. We recently reported a high tuberculin skin test (TST)-positive prevalence (355/5,476; weighted prevalence=6.4%) among children (<15 years) throughout the island of Bohol, Philippines, with some geographically isolated communities having prevalence as high as 29%. In this study, we conducted a secondary geospatial and hot-spot analysis of this household-based cluster survey to assess the association between access to care (distance to a health care facility) and TST-positive prevalence. Our analysis indicated that villages with high TST-positive prevalence (≥10%) were significantly further from Provincial Health Office based in the capital city of Tagbilaran in time-distance ($p=0.0001$, $r=0.2387$) and kilometers ($p=0.0011$, $r=0.3170$). Similarly, prevalence was positively correlated with distance to the municipal Rural Health Unit (RHU), where most receive their medical care, in time-distance ($p=0.0055$; $r=0.0415$); however, the association was not significant in kilometers ($p=0.3315$; $r=0.0715$). Distance to health care facilities could represent an obstacle to access to care, thereby limiting diagnosis and treatment and resulting in increased risk of transmission to others in the community. Health care outreach in geographically isolated areas is critical to treatment and control of efforts for pediatric TB.

INTRODUCTION

Tuberculosis (TB) is one of the top ten causes of mortality in the world. Globally, children (<15 yrs. old) make up an estimated 10% of all TB cases (WHO, Global TB Report, 2018). In 2017 alone, the WHO estimated 1 million children had incident TB, leading to 253,000 deaths. The Philippines accounts for 6% of all global TB cases and has the second highest incidence of TB in the world (World Health Organization, Global tuberculosis report 2018). In 2016, the Philippines National Tuberculosis Prevalence Survey bacteriologically identified 613 cases of TB per 100,000 (95% CI=403-822) individuals 15-19 years old (National Tuberculosis Prevalence Survey 2016, 2018).

Concern over the burden of TB infection in the pediatric population prompted the first cross-sectional pediatric TB prevalence study on the provincial island of Bohol, Philippines **(manuscript submitted for publication)**. Specifically, this household-based cluster survey screened 5,476 Filipino children for TB and identified a higher than expected prevalence of TST-positivity, with some villages as high as 29%. This initial study identified that the distribution of TB exposure was not uniform across the island, and we began to hypothesize that a spatial relationship between the locations of high prevalence TST-positive villages and distance health facilities could be creating an access to care issue.

The primary health care facilities in the Philippines are Rural Health Units (RHUs), which are community health clinics in the Filipino public health system. They service the general clinical care needs of those living within the municipality, including TB diagnostics and treatment via Direct Observed Therapy, Short Course (DOTS) as both a preventative for those with latent infections and treatment for active disease. The majority of the population relies on the RHUs for clinical care as private health care facilities are uncommon and rarely used in the Philippines (National Tuberculosis Prevalence Survey 2016, 2018). We believe this is an accurate variable for analysis in this study as a recent study in the Philippines found 76% of all adult TB cases sought treatment at their local health care center, and 72.3% sourced their medications from these public facilities (National Tuberculosis Prevalence Survey 2016, 2018). All 47 RHUs throughout the province of Bohol are supported by the Provincial Health Office (PHO) which provides medical supplies (i.e. medications), education, and financial support.

Based on our concern that geographic isolation could be leading to limited access to care, we conducted a study to determine if pediatric TST-positive prevalence at the village level was significantly correlated with distance to their municipal RHU or correlated with the distance from the RHU to the PHO. To achieve this, we analyzed the geospatial relationship between (1) municipality TST-positive prevalence and the time-distance to a healthcare facility (PHO or RHU); and (2) village TST-positive prevalence and the time-distance to a healthcare facility (PHO or RHU).

METHODS

This study was approved by the Institutional Review Boards of the University of the Philippines, Baylor College of Medicine (Protocol Number: H-37167), and the University of Texas Health Science Center (Protocol Number: HSC-SPH-18-0983). Prevalence of children with a positive TST reading was determined as described by Murray et al **(manuscript submitted for publication)**. Census data of populations within municipality and village were obtained from the Republic of the Philippines Statistics Authority and the Bohol PHO. For the purposes of this study, we define an 'island' as being an island belonging to a municipality of mainland Bohol. Islands range in having multiple villages (in municipality Loon) or as little as two (Bilangbilang Dako and Bilangbilgan Diot in municipality Bien Unido) or one village (Gaus in municipality President Carlos P. Garcia) that constitute their boundaries. The pediatric population was randomly selected using the population proportion to size cluster sampling among randomly selected households within randomly selected villages. Children were screened by TST between 2015 to 2018, with positive readings (induration of ≥10mm) indicating TB exposure. Locations of the villages, municipal RHU's, and the PHO included in this study are indicated in **Figure 1**. The prevalence of TST-positive by village is reported in **Supplemental table 1**. Proportions of villages within each participating municipality with a greater ≥10% TST-positive prevalence and overall municipality prevalence was calculated (**Table 1**).

Political boundaries of municipalities and villages were obtained through PhilGIS (Philippine GIS Data Clearinghouse, Ozamiz City, Philippines). Point coordinates were obtained using a handheld Garmin InReach Explorer (Garmin Ltd., Olathe, Kansas, USA) and Google Maps (Google LLC, Mountain View, California, USA). Geospatial analysis was conducted using ArcGIS Desktop 10.6 (ESRI, Redlands, CA). Choropleth maps were developed to visualize TST-positive prevalence of each participating village to identify which communities had the highest burden of disease (**Figure 2**).

Whereas choropleth maps display prevalence data by municipality and village, a hot-spot analysis will compute clusters irrespective of political boundaries. Instead, it analyzes statistically significant clusters in data points by considering their closest neighbor's value variation. The hot-spot analysis uses the Getis-Ord Gi* statistic to calculate each point's z-score, p-value, and confidence interval to determine if clusters are spatial in nature or due to random chance. Z-scores that are unusually low are considered "cold spots", z-scores that are unusually high are considered "hot-spots", and z-scores close to zero are considered "not significant". Confidence intervals are derived from z-scores and are based at 90%, 95%, and 99%. The resulting analysis produces a color map that shaded the geographic areas with their statistically significant z-scores. Z-scores with unusual large negative values are assigned shades of blue for cold spots. Z-scores with unusual large positive values are colored shades of red for hot spots. The darker the color the higher the z-score, and its subsequent statistical significance and given confidence interval. To understand if clustering was occurring irrespective of population density and political boundaries, we conducted a hot spot analysis using the Getis-Ord Gi* statistic using TST-positive prevalence by villages (**Figure 3**) (Esri, 2018).

Next, we conducted linear regression analysis to examine the association between distance to health care facilities and TST-positive prevalence by municipality and village (**Figure 4**). Linear regression analysis was conducted using the NCSS statistical software package (NCSS, Inc., Kayesville, Utah). Distance between village centroids to municipal RHUs, and to PHO was calculated in kilometers (km) and in time-distance (minutes) using Google Maps (Google LLC, Mountain View, California, USA). For island villages of mainland Bohol who were enrolled in the study (16 total), travel data to RHUs and the PHO combined (1) Euclidean (straight-line) distance over bodies of water (from port to port), (2) and time distance from the port to the health care facility on mainland Bohol. All geocoded data including coordinates and distance were double entered to increase internal reliability and quality assurance.

RESULTS

Our previous work indicated an island-wide weighted prevalence of TST-positive screening in the pediatric population of 6.4% [95% CI=6.3-6.5%] (Murray et al., manuscript submitted for publication). To analyze the distribution of the TST-positive burden across Bohol, we calculated the weighted proportion of villages from their municipality with high TST-positive prevalence (≥10%) (**Table 1**). Across all of the participating municipalities, President Carlos P. Garcia (7/10, 70%), Inabanga (12/24, 50%), Maribojoc (4/8, 50%), and Bien Unido (3/6, 50%) had the highest proportion of villages with high TST-prevalence. These municipalities are all coastal, with the exception of Maribojoc, and contain island villages.

Our analysis at the municipality level indicated that variances in disease burden occurred within each municipality, indicating the need to perform analysis at the village level. We created a map displaying TST-prevalence (**Figure 2**) and a list of each village's overall prevalence (**Supplemental Table 1**) indicate varying burden of disease across Bohol. This analysis suggested a pattern that the island villages furthest from health care facilities, had the highest TST-positive prevalence. Island villages of Cauming, Bilangbilangan Diot, and Gaus had the highest TST-positive prevalence at 22%, 22%, and 29%, respectively.

To determine if high TST-positive prevalence was significantly clustered in outlier villages a hot-spot analysis was conducted (**Figure 3**). Cold spots were located only in villages in Calape, Catigbian, Loon, and one in Maribojoc, which are all in closer proximity to the PHO. Cold spots with 99% confidence had a 0% prevalence and were located in Loon. Contrastingly, hot-spots of 90%-95% were predominately in Inabanga, with several in President Carlos P Garcia, Sagbayan, and one in Ubay, and Clarin. Clusters among island villages in President Carlos P. Garcia had statistically significant TST-positive clusters with an assigned 99% confidence interval. This illustrates higher TST-positives were located in municipalities further away from the PHO and the lowest TST-positives nearest the PHO. One of Bien Unido's villages had the highest TST-positive prevalence, but was not considered significant by the hot spot analysis, further illustrating how clusters are not based on prevalence alone and adding value to our geospatial analysis via hot-spot

To determine if variation in TST-prevalence was associated with distance to health care facilities, we conducted univariate linear regression analysis. Regression analysis was run to determine the association between TST-positive prevalence and distance to the PHO, village prevalence and distance to the RHU, village prevalence and distance to the PHO (**Figure 4 A-F**). Analysis (**Figure 4 A-B**) of RHUs to the PHO in kilometers ($p=0.1363$, $r=0.4186$) and time-distance ($p=0.0935$, $r=0.4654$) was not significantly associated with TST-positive prevalence. Village distance to the PHO demonstrated statistical significance in kilometers ($p<0.0011$, $r= 0.2387$), and time-distance ($p<0.0001$, $r=0.3170$) (**Figure 4 C-D**). Village distance to the municipal RHU in kilometers ($p=0.3350$, $r=0.0715$) was not significant; however, there was a significant correlation between prevalence and distance in time ($p=0.0055$, $r=0.2037$). Notably, these findings indicate a discrepancy between distance in kilometers and time-distance. Our analysis demonstrates an association between pediatric TST-positive prevalence and access to care as represented by distance to a health care facility.

DISCUSSION

Access to health care providers plays a critical role in treating and controlling this infection as medication regiments are long and requires frequent medical supervision. We believe the data presented in this study demonstrates that increased time-distance from villages to the PHO and RHUs is a significant barrier to effective TB control. Our analysis highlights this problem is exacerbated among island villages of Bohol, putting them at higher risk for TST-positivity compared to mainland villages. This could be because island communities have more complicated and costly travel routes to mainland clinics, resulting in limited access to care. As a result, the Boholano islands' limited access to mainland Bohol would be further complicated in the event of natural disasters, which will strand them until infrastructure and weather conditions allow for safe travel. This could also demonstrate discrepancies in the distribution of care and health among island villagers compared to mainland villagers. For example, this could represent disparities in (1) BCG vaccine history, (2) health-seeking behavior of adults for TB care and treatment (3) health care outreach to island villages by public health officials and medical staff or (4) availability and distribution of medical supplies.

We believe time-distance served as a better variable for this analysis as it is more representative of the how travel will affect access to care. If driving via car on land, points of interest may not be far in kilometers but can take longer to travel due to road conditions (pedestrians, construction, damaged roads, weather, etc.). Again, if traveling via boat across water, points of interest may not be far away but unforeseen conditions (boat, water, and weather, etc.) can delay the trip. This complicated our measurements of travel.

This study has some noteworthy limitations. Specifically, using Google Maps to calculate time-distance, limited our ability to consider multiple modes of travel to a location (Cromley, E.K. and McLafferty, 2012). Due to the difficulty in analyzing data on multiple modes of land transportation, we standardized all routes to car driving-time. As a result, our variable likely underestimates the amount of time it would take to get to a clinic by motorbike or walking, both common methods of travel in Bohol. Travel from municipalities of mainland Bohol to the island villages and between islands, may be subject to inconsistencies because time traveled by boat was reported by our research nurses and is subject to recall bias. Similarly, Euclidean distance to calculate ocean routes is likely an underestimation.

Another study limitation is our limited data incorporating Bacillus Calmette-Guérin (BCG) vaccination status in this analysis. We did not obtain histories of vaccination status among children enrolled in our parent study, but instead asked if children had been vaccinated within 6 weeks. This data at the village level would have been beneficial for determining if higher TST-positive prevalence could explained by the vaccine. Variations in vaccine status across villages could be analyzed to examine differences in age groups, cold spots and hot spots, and mainland villages against island villages. This could draw a stronger association with villages in the closet proximity to the RHUs or PHO as having better access to care. This study only examines pediatric TST prevalence and did not exam adult TST. Furthermore, this study did not include an analysis on socioeconomic predictors associated with TST-positive prevalence. Lastly, we also recognize univariate analysis is a weak analysis without the consideration of all of these variables.

While our overall finding is high TST-positive prevalence and statistically significant clusters are aggregated among island communities, there are some notable exceptions. The municipality of Loon has an island villages defined as cold spots clusters for TST positive-prevalence with 95% confidence. This presents a unique contrast to the other island villages in Loon, such as Gaus, with a hot spot cluster of 99% confidence. This divergence of Loon having the lowest statistically significant cold spot and President Carlos P. Garcia with having the highest statistically significant hot spot, further reiterates a spatial relationship regarding transmission. While we cannot determine the exact cause of this finding, we believe it is suggestive of the healthcare infrastructure and socioeconomic factors in Bohol. For this analysis, we used RHUs as our clinic care sites.

Pediatric tuberculosis is a disease with a complex epidemiology, access to health facilities is only one factor associated with global burden. Challenges in pediatric diagnosis and treatment are a prominent focus of current public health intervention strategy (Cruz, A.T. and Starke, J.R., 2019). Perhaps it is not all due to health care availability, but also socioeconomic factors associated with isolated communities that is contributing to their disproportionate burden of disease. Populations from isolated communities might may be restricted by money or inability to take leave from work, preventing them from accessing care. More research is needed to elucidate the factors leading to increased disease burden in these communities. Health care outreach is critical in treatment and control of pediatric TB. It is also critical in preventing multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) strains. Access to care, especially in isolated communities, may represent an important public health intervention to reduce the burden on pediatric TB. More research is needed to better understand how other socioeconomic factors influence access to care and subsequently TB transmission. As a result, we are in the process of conducting preliminary analyses examining the effect of distance and poverty indicators on TST-positive prevalence among our pediatric population in Bohol. Additionally, believe limited access to health care facilities and physician shortages are not unique to Bohol or the Philippines. This issue should be explored in other countries with a high burden of pediatric transmission.

In conclusion, this geospatial analysis and regression analysis shows prevalence of TB exposure will increase as distance grows between residences and health clinics (RHU and PHO). A positive correlation was also found of RHU clinics located further from the PHO, which makes us speculate if this is due to possible weaknesses in anti-TB medication supply distribution and could indicate areas for improvement in TB control and prevention strategies. Additionally, this analysis found several municipalities and villages with higher-than-expected TST-positive prevalence. We found prevalence was highest in Inabanga and President Carlos P. Garcia. Actually, these two municipalities were reported by our nurse research staff as being hard to reach, because of terrorism in Inabanga and hard-to-reach villages in President Carlos P. Garcia, indicating issues with safety in traveling and culminating in reduced access to care. Although choropleth maps are helpful, our hot-spot analysis created more granularity in our analysis by helping us identify where high TST-positive clusters were located at the village-level. Our goal was to locate specific communities at risk for high TB transmission and they necessitate an increase in health resources for an immediate public health intervention.

Although many TB control strategies focus on older populations, pediatric infections are indicative of adult transmission patterns, and it is critical to treat all age groups exposed. With that said, we recommend health clinics conduct outreach with these high-risk villages not just for screening and treatment, but to work on identifying and strategizing ways of overcoming barriers to care, especially travel, for individuals requiring DOTS. Finally, more research is needed to understand the distribution of pediatric TB transmission in Bohol, and especially how it relates to socioeconomics, healthcare infrastructure, and access to care. We see the need for more screening programs among the pediatric and adolescent population as an additional strategy for TB control in Bohol by screening and treating all household contacts, regardless of age.

Table 1. Weighted proportion of villages within municipalities with ≥10% TST-positives.

Municipality Name	Villages with TST-positive prevalence ≥10% / total villages enrolled in study from municipality	Percentage
Pres. Carlos P. Garcia	7/10	70.0%
Inabanga	12/24	50.2%
Bien Unido	3/6	50.0%
Maribojoc	4/8	50.0%
Ubay	8/23	34.8%
Sagbayan	2/7	28.6%
Candijay	3/16	18.8%
Clarin	2/11	18.2%
Mabini	2/14	14.3%
Anda	1/10	10.0%
Calape	1/11	9.1%
Catigbian	1/13	7.7%
Loon	1/24	4.2%
Alicia	0/7	0.0%

Figure 1: Map of enrolled villages, rural health units, and the Provincial Health Office.

Map displays the villages (green shaded regions), municipal RHUs (black circle) and the PHO (black star) included for analysis in this study. Time-distance was calculated between barangay centroids to RHUs and PHO, respectively. Time-distance was also calculated between RHUs to the PHO.

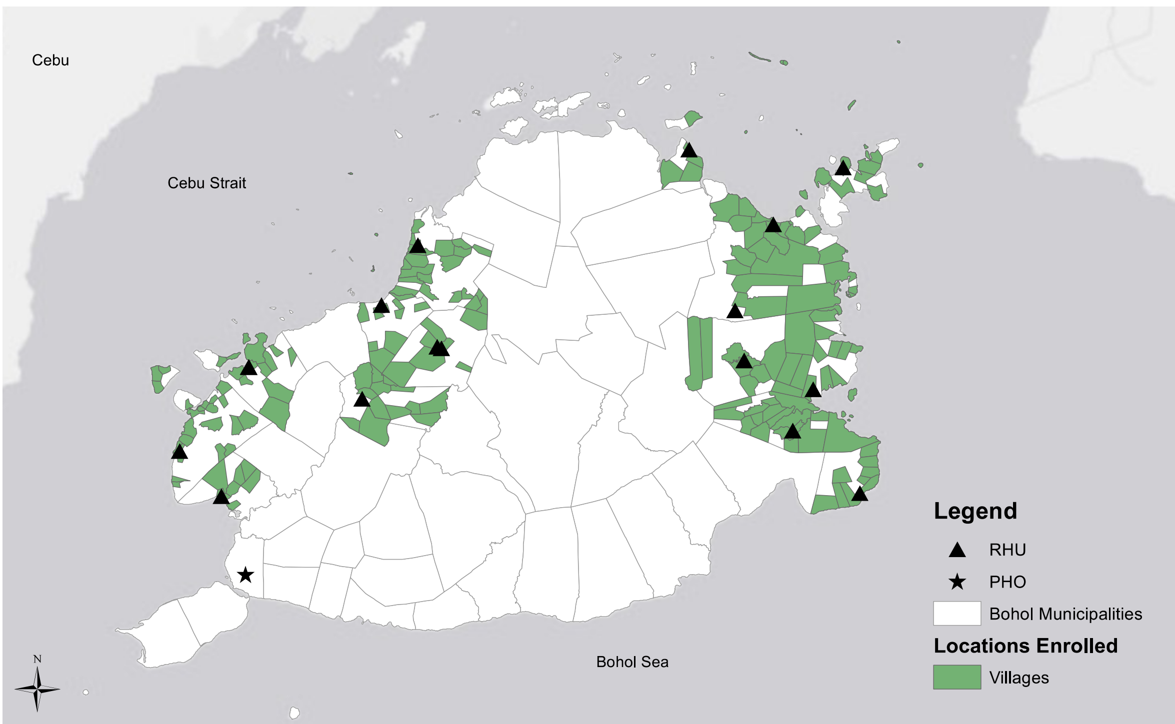


Figure 2. Prevalence of positive TST skin tests aggregated by village.

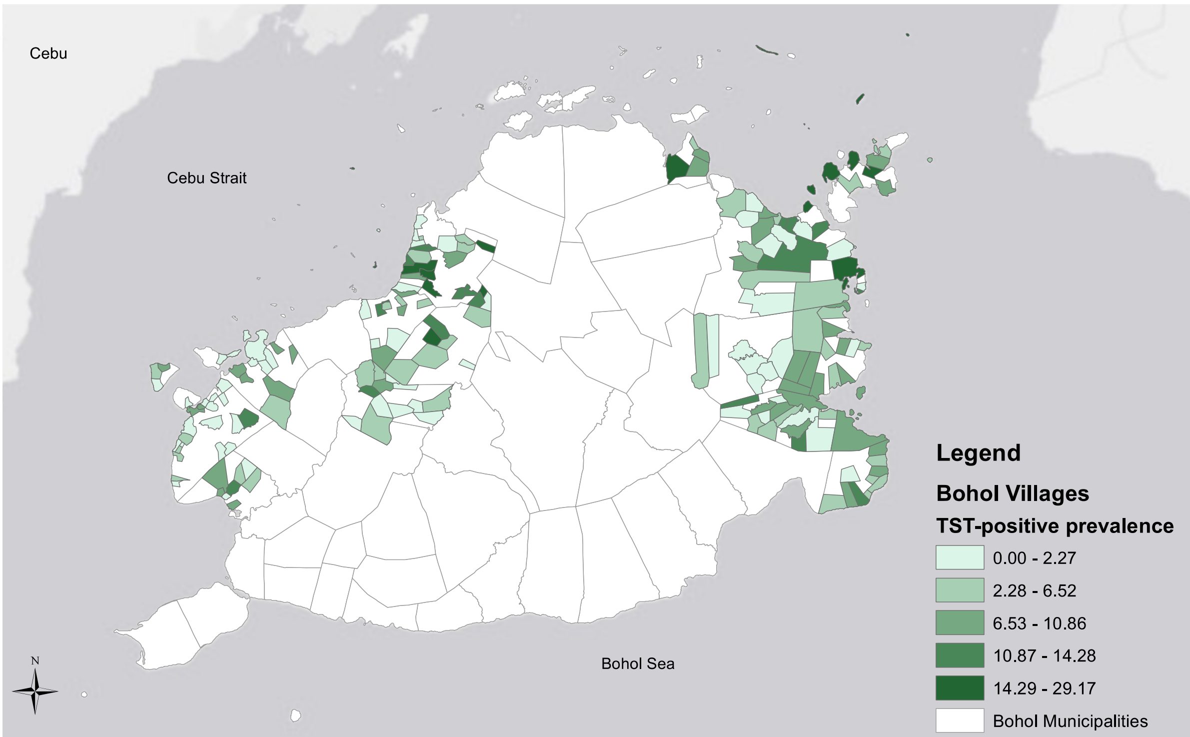


Figure 3. Hot-spot analysis of statistically significant cold and hot spots of TST-positive prevalence aggregated at the village level.

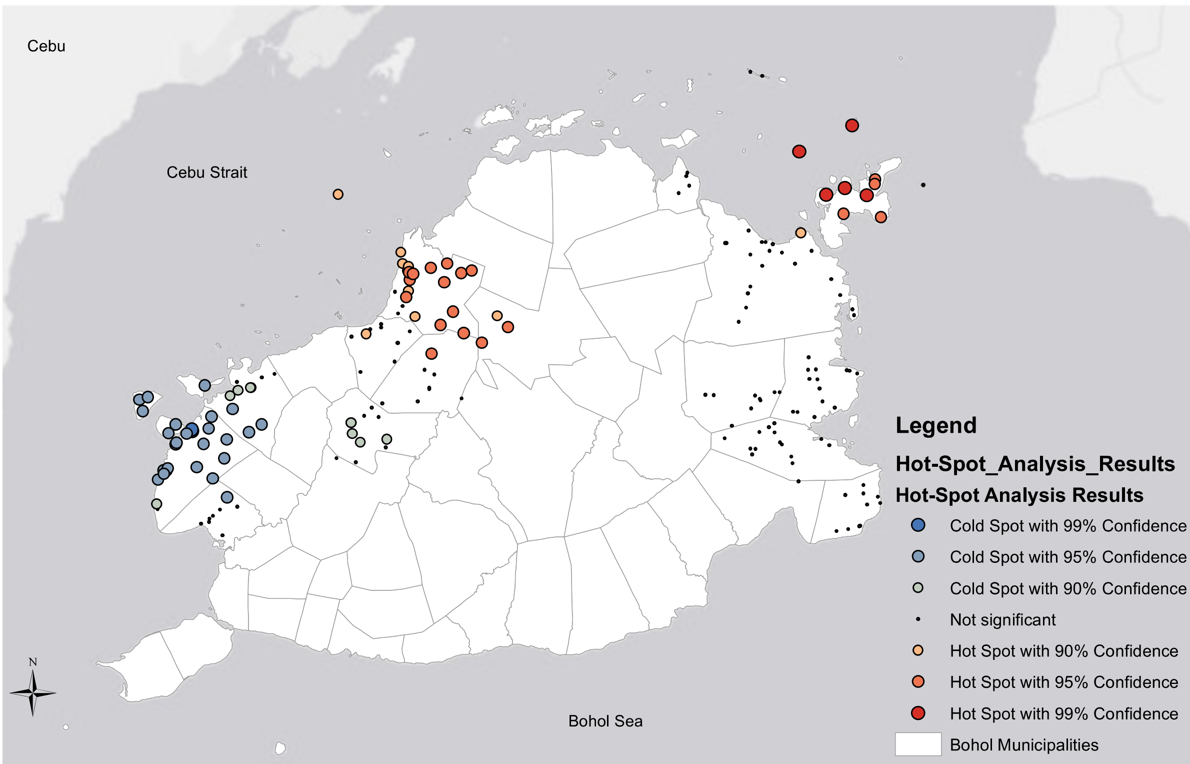
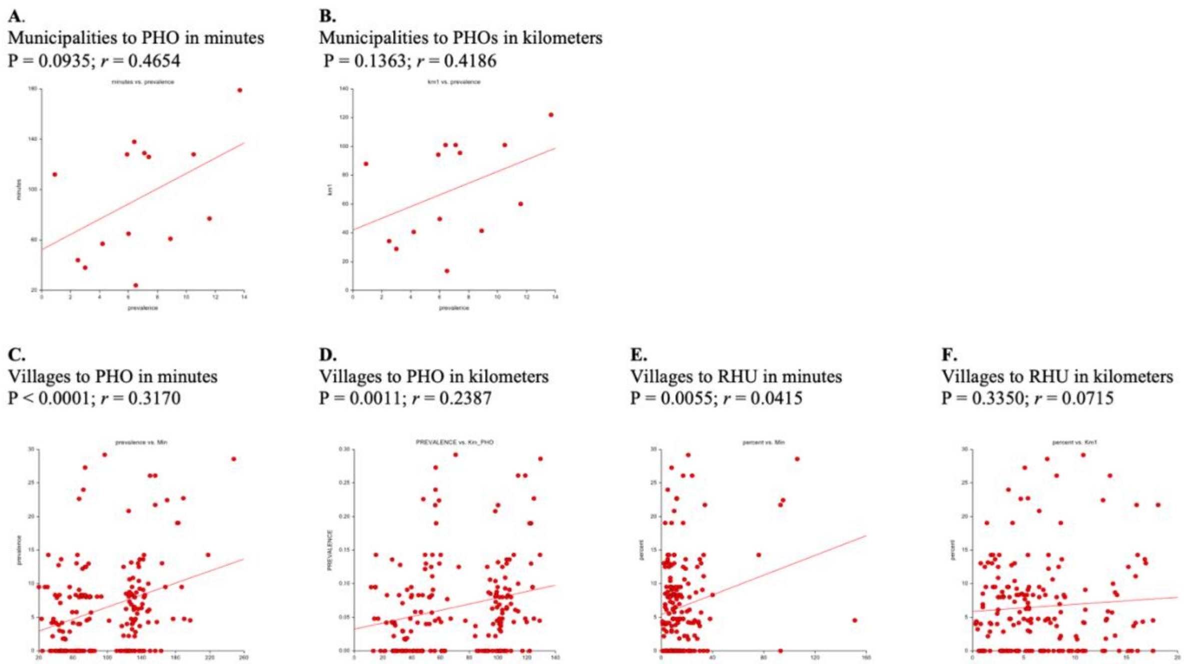


Figure 4. Univariate Regression of TST-positive prevalence and distance.

Analysis of association between TST-positive prevalence at the municipality and village level and distance to the PHO and RHU. Association between TST-positive and time-distance in minutes (A) and kilometers (B) was assessed by linear regression between the municipalities and PHO. Association between TST-positive and time-distance in minutes (C) and kilometers (D) was assessed by linear regression between the villages and PHO. Association between TST-positivity and time-distance in minutes (E) and kilometers (F) was assessed by linear regression between the villages and RHU. P-value and the correlation coefficient for each analysis is listed below the data description.



APPENDICES

Appendix A: Supplemental Table 1.

Boholano village names and their corresponding population, pediatric TST-positive prevalence, hot-spot analysis result, and their accessibility index derived using the Getis-Ord Gi* statistic.

Municipality Name	Village Name	Village Population	TST-positive prevalence	Cold or Hot Spot with CI
Alicia	Cayacay	1713	0.0%	Not Significant
Alicia	Katipunan	2230	3.7%	Not Significant
Alicia	La Hacienda	3710	2.2%	Not Significant
Alicia	Napo	1255	0.0%	Not Significant
Alicia	Poblacion	4064	0.0%	Not Significant
Alicia	Progreso	1019	0.0%	Not Significant
Alicia	Putlongcam	1578	0.0%	Not Significant
Anda	Almaria	392	0.0%	Not Significant
Anda	Bacong	2289	13.2%	Not Significant
Anda	Badiang	1277	9.1%	Not Significant
Anda	Candabong	2297	6.3%	Not Significant
Anda	Linawan	987	6.4%	Not Significant
Anda	Poblacion	1295	3.2%	Not Significant
Anda	Santa Cruz	1123	5.6%	Not Significant
Anda	Suba	1125	2.9%	Not Significant
Anda	Talisay	1048	8.3%	Not Significant
Anda	Virgen	1428	8.1%	Not Significant
Bien Unido	**Bilangbilangan Dako**	**1920**	**0.0%**	**Not Significant**
Bien Unido	**Bilangbilangan Diot**	**845**	**21.7%**	**Not Significant**
Bien Unido	Mandawa	2328	8.5%	Not Significant
Bien Unido	Nueva Esperanza	2205	20.8%	Not Significant
Bien Unido	Poblacion	3082	4.0%	Not Significant
Bien Unido	Tuboran	955	9.5%	Not Significant
Calape	Abucayan Sur	1326	8.3%	Not Significant

Calape	Bentig	1797	0.0%	Cold Spot with 90% Confidence
Calape	Bonbon	1222	0.0%	Cold Spot with 90% Confidence
Calape	Cabayugan	880	4.2%	Cold Spot with 95% Confidence
Calape	Labuon	562	8.0%	Cold Spot with 95% Confidence
Calape	Lawis	617	0.0%	Cold Spot with 95% Confidence
Calape	Liboron	1434	9.5%	Cold Spot with 90% Confidence
Calape	Mandaug	1451	8.3%	Not Significant
Calape	San Isidro	2412	0.0%	Not Significant
Calape	Santa Cruz	2401	0.0%	Cold Spot with 90% Confidence
Calape	Sojoton	664	9.1%	Cold Spot with 95% Confidence
Candijay	Abihilan	1209	0.0%	Not Significant
Candijay	Boyo-An	1612	0.0%	Not Significant
Candijay	Cambane	435	4.5%	Not Significant
Candijay	Can-Olin	2215	0.0%	Not Significant
Candijay	Canawa	1415	0.0%	Not Significant
Candijay	Cogtong	2492	6.5%	Not Significant
Candijay	La Union	1365	0.0%	Not Significant
Candijay	Luan	886	12.5%	Not Significant
Candijay	Lungsoda-An	1461	10.4%	Not Significant
Candijay	Panadtaran	1002	8.3%	Not Significant
Candijay	Panas	1477	8.0%	Not Significant
Candijay	Poblacion	3344	8.5%	Not Significant
Candijay	San Isidro	1042	4.0%	Not Significant
Candijay	Tambongan	1587	3.7%	Not Significant
Candijay	Tubod	928	8.0%	Not Significant
Candijay	Tugas	1640	12.5%	Not Significant
Catigbian	Alegria	1247	7.1%	Not Significant
Catigbian	Ambuan	1197	3.8%	Not Significant
Catigbian	Bagtic	1069	0.0%	Cold Spot with 90% Confidence
Catigbian	Bongbong	579	0.0%	Cold Spot with 90% Confidence
Catigbian	Cambailan	916	1.7%	Not Significant

Catigbian	Candumayao	1545	2.9%	Not Significant
Catigbian	Causwagan Norte	1812	3.0%	Not Significant
Catigbian	Haguilanan	1133	2.2%	Not Significant
Catigbian	Kang-Iras	709	4.2%	Cold Spot with 90% Confidence
Catigbian	Mahayag Norte	577	4.2%	Cold Spot with 90% Confidence
Catigbian	Mantasida	913	0.0%	Not Significant
Catigbian	Poblacion	1810	12.8%	Cold Spot with 90% Confidence
Catigbian	Triple Union	1148	1.9%	Not Significant
Clarin	Bacani	1208	4.0%	Not Significant
Clarin	Bogtongbod	1377	0.0%	Not Significant
Clarin	Buacao	797	0.0%	Not Significant
Clarin	Caboy	571	8.3%	Not Significant
Clarin	Candajec	932	14.3%	Hot Spot with 90% Confidence
Clarin	Danahao	856	0.0%	Not Significant
Clarin	Mataub	700	8.0%	Not Significant
Clarin	Nahawan	2208	8.0%	Not Significant
Clarin	Poblacion Centro	1234	13.0%	Not Significant
Clarin	Poblacion Sur	1159	4.0%	Not Significant
Clarin	Villaflor	345	4.5%	Not Significant
Inabanga	Anonang	721	29.2%	Hot Spot with 95% Confidence
Inabanga	Badiang	1083	24.0%	Hot Spot with 90% Confidence
Inabanga	Baogo	1252	4.5%	Hot Spot with 95% Confidence
Inabanga	Cagawasan	1290	13.0%	Not Significant
Inabanga	Cambitoon	919	12.5%	Hot Spot with 95% Confidence
Inabanga	Cogon	865	22.4%	Hot Spot with 90% Confidence
Inabanga	**Cuaming**	**2826**	**12.5%**	**Hot Spot with 95% Confidence**
Inabanga	Dagohoy	1310	27.3%	Hot Spot with 95% Confidence
Inabanga	Ilaud	954	4.3%	Hot Spot with 90% Confidence

Inabanga	Liloan Norte	1490	4.8%	Hot Spot with 95% Confidence
Inabanga	Liloan Sur	954	7.7%	Hot Spot with 95% Confidence
Inabanga	Lomboy	589	11.1%	Hot Spot with 95% Confidence
Inabanga	Lutao	1173	4.8%	Hot Spot with 95% Confidence
Inabanga	Mabuhay	383	19.0%	Hot Spot with 90% Confidence
Inabanga	Nabuad	1804	0.0%	Hot Spot with 95% Confidence
Inabanga	Ondol	1122	0.0%	Hot Spot with 90% Confidence
Inabanga	Poblacion	930	0.0%	Hot Spot with 95% Confidence
Inabanga	Riverside	260	14.3%	Hot Spot with 95% Confidence
Inabanga	San Jose	1566	0.0%	Hot Spot with 95% Confidence
Inabanga	Santo Rosario	997	9.1%	Not Significant
Inabanga	Sua	554	21.7%	Hot Spot with 90% Confidence
Inabanga	Tambook	490	14.3%	Hot Spot with 95% Confidence
Inabanga	Tungod	1089	0.0%	Hot Spot with 90% Confidence
Inabanga	Ubujan	1064	0.0%	Not Significant
Loon	Bahi	367	0.0%	Cold Spot with 95% Confidence
Loon	Basac	1414	0.0%	Cold Spot with 95% Confidence
Loon	Bugho	285	0.0%	Cold Spot with 95% Confidence
Loon	**Cabacongan**	**1080**	**0.0%**	**Cold Spot with 95% Confidence**
Loon	Calayugan Norte	737	0.0%	Cold Spot with 95% Confidence
Loon	Canhangdon Occidental	848	8.3%	Cold Spot with 95% Confidence
Loon	Canmaag	404	0.0%	Cold Spot with 95% Confidence

Loon	Cansuagwit	291	0.0%	Cold Spot with 99% Confidence
Loon	Cantam-Is Baslay	495	0.0%	Cold Spot with 95% Confidence
Loon	Catagbacan Handig	994	0.0%	Cold Spot with 99% Confidence
Loon	Catagbacan Sur	973	0.0%	Cold Spot with 95% Confidence
Loon	Cogon Norte	1907	4.2%	Cold Spot with 95% Confidence
Loon	Cuasi	1115	0.0%	Not Significant
Loon	Genomoan	362	13.6%	Cold Spot with 95% Confidence
Loon	Lintuan	913	4.2%	Cold Spot with 95% Confidence
Loon	**Looc**	**1070**	**8.3%**	**Cold Spot with 95% Confidence**
Loon	Moto Norte	1369	0.0%	Cold Spot with 95% Confidence
Loon	Moto Sur	1225	4.3%	Cold Spot with 95% Confidence
Loon	Napo	1342	0.0%	Cold Spot with 95% Confidence
Loon	**Pantudlan**	**808**	**4.8%**	**Cold Spot with 95% Confidence**
Loon	Pondol	1476	0.0%	Cold Spot with 95% Confidence
Loon	Tangnan	867	4.2%	Cold Spot with 90% Confidence
Loon	Tubuan	285	0.0%	Cold Spot with 95% Confidence
Loon	Ubojan	486	8.3%	Cold Spot with 95% Confidence
Mabini	Abaca	2349	4.3%	Not Significant
Mabini	Baybayon	1508	6.1%	Not Significant
Mabini	Bulawan	658	7.3%	Not Significant
Mabini	Cabidian	1040	10.6%	Not Significant
Mabini	Cawayanan	1552	6.1%	Not Significant
Mabini	Lungsoda-An	1130	2.2%	Not Significant
Mabini	Minol	1414	9.3%	Not Significant
Mabini	Paraiso	819	10.0%	Not Significant

Mabini	Poblacion II	1697	6.9%	Not Significant
Mabini	San Isidro	1633	7.0%	Not Significant
Mabini	San Jose	1427	5.9%	Not Significant
Mabini	San Roque	2529	6.3%	Not Significant
Mabini	Tangkigan	1438	8.8%	Not Significant
Mabini	Valaga	799	8.0%	Not Significant
Maribojoc	Bayacabac	1601	14.3%	Not Significant
Maribojoc	Dipatlong	1562	9.5%	Not Significant
Maribojoc	Jandig	897	9.5%	Not Significant
Maribojoc	Poblacion	2298	0.0%	Not Significant
Maribojoc	San Isidro	525	4.8%	Not Significant
Maribojoc	San Roque	1177	4.8%	Not Significant
Maribojoc	San Vicente	1115	9.5%	Not Significant
Maribojoc	Tinibgan	614	0.0%	Cold Spot with 95% Confidence
Pres. Carlos P. Garcia	**Aguining**	**2294**	**9.5%**	**Hot Spot with 95% Confidence**
Pres. Carlos P. Garcia	**Bonbonon**	**1286**	**9.5%**	**Hot Spot with 95% Confidence**
Pres. Carlos P. Garcia	**Butan**	**626**	**14.3%**	**Hot Spot with 99% Confidence**
Pres. Carlos P. Garcia	**Campamanog**	**1560**	**22.7%**	**Hot Spot with 99% Confidence**
Pres. Carlos P. Garcia	**Gaus**	**1365**	**28.6%**	**Hot Spot with 99% Confidence**
Pres. Carlos P. Garcia	**Poblacion**	**2700**	**19.0%**	**Hot Spot with 99% Confidence**
Pres. Carlos P. Garcia	**Saguise**	**745**	**4.8%**	**Hot Spot with 95% Confidence**
Pres. Carlos P. Garcia	**Tilmobo**	**197**	**4.5%**	**Not Significant**
Pres. Carlos P. Garcia	**Tugnao**	**1309**	**19.0%**	**Hot Spot with 99% Confidence**
Pres. Carlos P. Garcia	**Villa Milagrosa**	**1273**	**4.8%**	**Hot Spot with 95% Confidence**
Sagbayan	Canmaya Centro	1317	12.2%	Hot Spot with 95% Confidence
Sagbayan	Langtad	570	5.7%	Hot Spot with 95% Confidence
Sagbayan	Libertad Norte	316	0.0%	Not Significant
Sagbayan	Poblacion	3945	5.8%	Not Significant

Sagbayan	Sagbayan Sur	1011	5.8%	Not Significant
Sagbayan	San Antonio	852	2.9%	Not Significant
Sagbayan	Santa Cruz	985	22.6%	Not Significant
Ubay	Achila	1276	0.0%	Not Significant
Ubay	Bay-Ang	1656	4.2%	Not Significant
Ubay	Benliw	2223	0.0%	Not Significant
Ubay	Biabas	2573	4.3%	Not Significant
Ubay	Bood	2717	0.0%	Not Significant
Ubay	Cagting	1597	26.1%	Not Significant
Ubay	Calanggaman	1623	0.0%	Not Significant
Ubay	Camambugan	2251	0.0%	Not Significant
Ubay	Casate	2512	8.0%	Not Significant
Ubay	Cuya	516	13.0%	Not Significant
Ubay	Fatima	3235	13.0%	Not Significant
Ubay	Guintabo-An	686	0.0%	Not Significant
Ubay	Humayhumay	1708	4.8%	Not Significant
Ubay	Imelda	1761	13.6%	Not Significant
Ubay	Katarungan	1524	13.6%	Not Significant
Ubay	Lomangog	2025	4.8%	Not Significant
Ubay	Pag-Asa	1168	8.7%	Not Significant
Ubay	Poblacion	3633	6.5%	Not Significant
Ubay	San Pascual	3127	2.3%	Not Significant
Ubay	Sentinila	969	26.1%	Hot Spot with 90% Confidence
Ubay	Tapon	2481	10.9%	Not Significant
Ubay	Tipolo	2456	0.0%	Not Significant
Ubay	Union	2332	14.3%	Not Significant

*Bolded villages are islands off mainland Bohol

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