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# Characterization of tuberculosis (TB) in Lebanon: epidemiology and risk factors for extrapulmonary TB

By

Lana O'Son, MD
Master of Public Health

Hubert Department of Global Health

____________________________________________

Kenneth G. Castro, MD, FIDSA
Committee Chair

____________________________________________

Susan T. Cookson, MD, MPH
Committee Member

____________________________________________

Erin N. Hulland, MPH
Committee Member

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By: Lana O'Son

M.D., Lebanese American University School of Medicine, 2013

B.S. University of California, Irvine, 2008


Thesis Committee Chair: Kenneth G. Castro, MD, FIDSA

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
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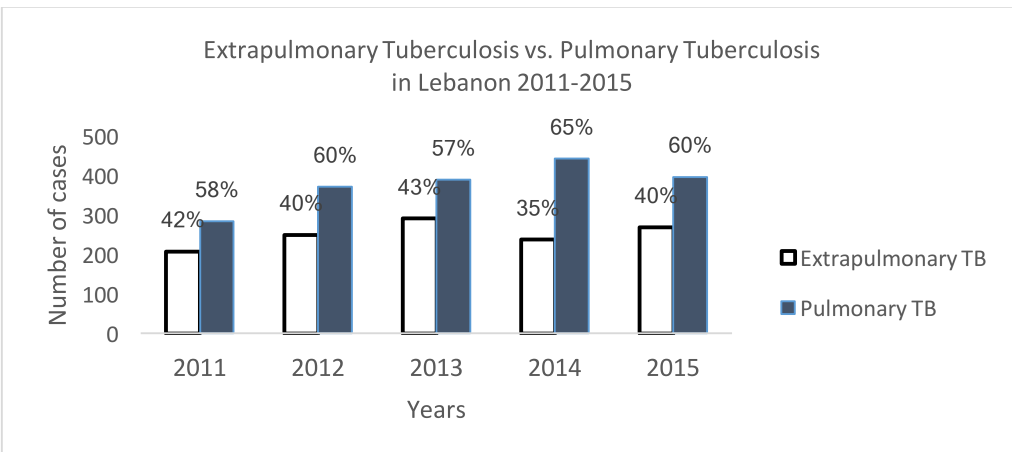
# Abstract

Introduction: Lebanon is working to strengthen their National Tuberculosis Programme (NTP), and in 2014 began collecting more detailed data on their cases. We analyzed the data to identify risk factors for developing extrapulmonary tuberculosis (EPTB) and to assess the impact of Syrian refugees on rates of TB in Lebanon.

Methods: Line list data of all cases reported to the Lebanese NTP between 2014-2015 were extracted. To test for differences between pulmonary (PTB) and EPTB, Chi-square tests and Student's T-tests were performed. Factors significantly associated with EPTB were assessed using stepwise multivariable logistic regression models comparing EPTB cases with PTB cases. To evaluate trends, aggregate TB data from 2011-2013 were assessed in conjunction with the 2014 and 2015 line listed data.

Results: For 2014-2015, 1347 cases were reported; of those, 507 (37%) were EPTB cases. Combined with the aggregate data, the overall TB and EPTB numbers stabilized.




The proportion of all TB cases among Syrians increased from 3% in 2011 to 29% in 2015 (overall median=15%) of cases; however, the proportion of EPTB cases among Syrians decreased relative to Lebanese in these same years (2011: 33%, 2015: 24%, overall median=30%). Given the limited number of complete variables (i.e., gender, age, nationality), all were put into a multivariable logistic regression model and were found to be independent risk factors for having EPTB: female (OR: 1.79, 95% CI: 1.34-2.67), Lebanese (OR: 2.43, 95% CI: 1.85-3.18), and ages 5-15 years old (OR: 3.05, 95% CI: 1.33-6.98) ( >15 years old [OR: 2.43, 95% CI: 1.85-3.18]).

Conclusions: Syrians had an increasing contribution to overall TB rates in Lebanon; however, their proportional contribution to EPTB decreased. Given the high rates of EPTB among Lebanese, additional reasons, such as prevalence of chronic diseases and immunosuppression, and etiology, such as contribution of *Mycobacterium bovis* and BCG need exploring.

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# Literature Review of Extrapulmonary Tuberculosis

## INTRODUCTION

Although tuberculosis (TB) is one of the oldest human diseases, it was not declared a public health emergency by the World Health Organization (WHO) until 1993 (WHO, 1994). This declaration allowed the WHO to make controlling TB a top priority. As a consequence of this prioritization accompanied by concerted efforts, the average rate of TB incidence declined from 2000-2015 by 1.4% annually. Although it is difficult to accurately determine the mortality rate from TB, the number of TB related deaths have been steadily decreasing in HIV negative people (WHO, 2016). Despite these favorable trends, tuberculosis remains a major health problem in many middle and low-income countries.

Tuberculosis is a disease most often caused by the bacterium *Mycobacterium tuberculosis* complex. M. tuberculosis complex representative species include the following: tuberculosis, bovis, africanum, and microti ((Frothingham, Hills, & Wilson, 1994); other less common species of this include canetti, caprae, pinnipedi, suricattae, and mungi (Fitzgerald, Sterling, & Haas, 2015). *Mycobacterium bovis* is part of this complex, and a less frequent cause of human TB disease. Humans are the main reservoirs of *M. tuberculosis* complex, but animals can be infected as well (Fitzgerald et al., 2015). There are two major classifications of TB disease: pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB). WHO defines PTB as TB that affects the lungs and EPTB as "any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs" (WHO, 2016). PTB is more commonly seen than EPTB; of the 6.1million notified incident cases of TB in 2015, EPTB accounted for only 15% (WHO, 2016).

In the early stages of pulmonary tuberculosis, symptoms may be non-specific and include the following: anorexia, fatigue, weight loss, fever, chills, and night sweats (Fitzgerald et al., 2015). EPTB is often more difficult to diagnose than PTB due to heterogeneous manifestations and difficulty of obtaining specimens (Houston & Macallan, 2014). Often these patients are being seen by physicians who do not have much experience with non-pulmonary symptoms of TB, thus delaying diagnosis of TB.

**LEBANON**

Lebanon in a small country on the Mediterranean sea, which is bordered by Syria to the East and North and Israel to the South. The current population is estimated to be 6,237,738 (CIA Factbook, 2016). Since the end of its 15-year civil war in 1990, Lebanon has been politically unstable. In 2011, the civil war in Syria started. There was a major influx of Syrian refugees especially in 2013, during which time over 1 million refugees entered the country (UNHCR, 2017). Lebanon does not allow refugee camps to be established; therefore, Syrian refugees that cannot afford to live in housing live in informal tented settlements across the country. The Lebanese National Tuberculosis Programme worried that the large number of refugees would cause an increase in the number of TB cases in Lebanon, similar to what has been found in other refugee contexts (Kimbrough, Saliba, Dahab, Haskew, & Checchi, 2012).

**EPIDEMIOLOGY**

Tuberculosis was the fifth leading cause of mortality in the world in 2015 (WHO, 2016). It is estimated that in 2015, there were about 10.4 million incident cases of tuberculosis, of which 6.1 million were reported to the WHO (WHO, 2016). About 15% of the reported cases worldwide were classified as extrapulmonary; the Eastern Mediterranean Region had the highest global percentage of EPTB at 23% of reported incident cases (WHO, 2016). According to the WHO's Global Tuberculosis Report in 2015, Lebanon reported 673 new or relapsing TB cases, with 238 of those classified as EPTB (WHO, 2016). Magee, et al. estimated that the percentage of EPTB in Lebanon in 2015 was 37% which is more than double the estimated global estimate of EPTB cases of 15% (Magee, Foote, Ray, Gandhi, & Kempker, 2016).

In past years, TB control efforts promulgated by WHO focused on the detection of acid fast bacilli (AFB) in microscopic examination of persons seeking care for signs and symptoms of PTB (Obermeyer, Abbott-Klafter, & Murray, 2008). In this context, EPTB was not considered contagious and did not receive the same amount of attention as PTB. However, many countries have noted that EPTB is a significant public health problem (Al-Hajoj et al., 2015; Kruijshaar & Abubakar, 2009; Prakasha, Suresh, Shetty, D′sa, & Kumar, 2013) A study of reported cases of tuberculosis conducted in the European Union between 2001 and 2011, found that although the number of reported cases of EPTB was stable, the absolute number of PTB cases reported decreased. Therefore, the proportion of EPTB cases increased among all TB cases reported (Sandgren, Hollo, & van der Werf, 2013). A similar trend of increasing proportion of EPTB in relation to all TB cases was also reported in Turkey between 2005 and 2009 (Sevgi et al., 2013).

**RISK FACTORS**

Worldwide, the most common risk factors for developing EPTB are either a concomitant diagnosis of HIV or young age. Other risk factors include but are not limited to: being female, having diabetes, other types of immunosuppression, and chronic renal failure (Lee, 2015; Magee et al., 2016; Yang et al., 2004). Rates of HIV are low in Lebanon; however, diabetes rates are relatively high, with 12.9% of the population diagnosed with diabetes, making it a more critical risk factor than HIV (Deek et al., 2015).

**CLINICAL MANIFESTATIONS**

EPTB can affect almost any organ in the body. The most common sites of disease are the following: lymph nodes, pleura, central nervous system, skeletal system and gastrointestinal organs (Houston & Macallan, 2014; Norbis et al., 2014). Because any organ can be affected, the clinical manifestations of tuberculosis vary widely. Some clinical manifestations will be described below.

By far, the most common presentation of EPTB is TB lymphadenitis. Patients usually present with a single unilateral or multiple painless masses that develop over time (Norbis et al., 2014). Depending on which lymph nodes are affected, the symptoms are different. For example, mediastinal TB lymphadenitis may present with dysphagia and abdominal lymphadenitis may present with non-specific abdominal pain (Houston & Macallan, 2014). Pleural TB often presents as an acute febrile illness associated with cough, pleural chest pain, and dyspnea. Although TB meningitis is not common, it is the most dangerous form of EPTB and is considered an emergency. Clinical findings of TB meningitis patients may include the following: focal neurological deficits, seizures, and loss of consciousness (Fitzgerald et al., 2015). Spinal TB, also known as Pott's disease, can present with non-specific back pain, but untreated may lead to vertebral fractures and potential spinal cord compression (Norbis et al., 2014). Another common form of EPTB is genitourinary TB which includes renal, ureteric, and genital disease. As with other forms of EPTB, patients are either asymptomatic or the symptoms are not very specific and can resemble other more common genitourinary infections (Houston & Macallan, 2014). Long-term consequences for genitourinary TB include renal insufficiency and infertility (Fitzgerald et al., 2015). The most common site of gastrointestinal TB is the ileocecal area of the intestines; although, it can affect any part of the gastrointestinal system from the esophagus to the rectum. The clinical manifestation of ileocecal TB can resemble Crohn's disease; thus, it is difficult to distinguish the two without biopsies. Symptoms of gastrointestinal TB include but are not limited to: abdominal pain, nausea, vomiting, and constitutional symptoms. Untreated disease can lead to ascites, intestinal obstruction, and malabsorption among other conditions (Norbis et al., 2014). Although EPTB is not considered to contribute significantly to the transmission of TB, it carries high levels of morbidity and may lead to long-term sequelae and lifelong disabilities (Sandgren et al., 2013).

**DIAGNOSIS**

EPTB is often more difficult to diagnose due to heterogeneous manifestations and difficulty of obtaining specimens (Norbis et al., 2014). Furthermore, even if a specimen is obtained, EPTB is often paucibacillary, which decreases the sensitivity of diagnostic tests (Lee, 2015). There is not a single reliable highly specific test for EPTB; therefore, a diagnosis of EPTB usually relies on several factors, such as microbiology, clinical findings, other test results, and follow-up treatment evaluations (Norbis et al., 2014). The selection of diagnostic procedure for EPTB depends on the suspected organ of involvement. For example, fine needle aspiration may be used for TB lymphadenitis, while an open biopsy would likely be used for skeletal TB (Lee, 2015; Norbis et al., 2014). Characteristic histology of tuberculosis disease includes presence of granulomas and caseation (Fitzgerald et al., 2015; Houston & Macallan, 2014; Lee, 2015). The newest test – Cepheid's GeneXpert MTB/RIF® (Xpert MTB/RIF) assay, an automated cartridge-based nucleic acid amplification test - holds more promise of rapid diagnosis. Based on a 2014 meta-analysis conducted by Denkinger et. al., which demonstrated overall sensitivity of the Xpert MDR/RIF assay of 83.1% and an overall specificity of 98.7%, the WHO now recommends use of this test for rapid diagnosis of EPTB (Denkinger et al., 2014). All suspected cases of

EPTB should be assessed for concomitant PTB, as it is estimated that 10-50% of EPTB patients have pulmonary involvement (Lee, 2015).

## ***MYCOBACTERIUM BOVIS* and TRANSMISSION**

*Mycobacterium bovis* is a slow growing acid fast bacillus (Thoen, Steele, & Gilsdorf, 2008) and part of the *Mycobacterium tuberculosis* complex. *M. bovis* has a wide range of hosts, with the most common being cattle. One of the most common ways humans are infected is through consumption of unpasteurized milk or cheese from infected cows (CDC, 2005). Another less common method of *M. bovis* transmission is through inhalation of infective airborne droplets (Guerrero et al., 1997; Walker, Crook, Peto, & Conlon, 2016). Because *M. bovis* is naturally resistant to the first line antibiotic, pyrazinamide, this can be used as a screening test (Jong et al., 2005). The only way to identify the causative agent of TB is through advanced laboratory testing to differentiate the species of *M. tuberculosis* complex, because TB caused by *M. bovis* and *M. tuberculosis* cannot be differentiated clinically, radiologically, or through pathology (Grange, 2001).

## **TREATMENT**

The CDC and WHO have similar treatment guidelines for extrapulmonary TB (Nahid et al., 2016; WHO, 2010). Both pulmonary and extrapulmonary TB, except TB meningitis and skeletal TB, are given the same treatment duration. There are two phases, the initial two-month intense phase followed by a four-month continuation phase for pan-sensitive organisms. The following four antibiotics are given daily for the first two months: isoniazid, rifampicin, pyrazinamide, and ethambutol. After two months, only isoniazid and rifampicin are given daily for four months. In cases of TB meningitis or skeletal TB, the continuation phase is extended for a total of 9-12 months of treatment.

# Methods

In 2014, the Lebanese National Tuberculosis Programme (NTP) began collecting more detailed information of all reported tuberculosis (TB) cases, including both EPTB cases, defined as TB of any area except when present in the lungs, and PTB cases, defined as TB of the lung parenchyma, regardless of whether extra-pulmonary sites existed as well. For this study, de-identified line-listed data from 2014 and 2015 were acquired from the NTP to be analyzed. The NTP also shared aggregate EPTB and PTB data from 2011-2013, with counts broken down by age, gender, and nationality.

The data were cleaned to remove duplicates, ensure that all variables were spelled correctly and consistently, and values that were blank or recorded as unknown were considered missing. For the available clinical and outcome data, due to low counts, those that died were combined with those that failed treatment, and those that were not evaluated were combined with lost to follow up. Those that were considered not cured included the following categories: died, lost to follow-up, still under treatment, not evaluated, and treatment failed. An assumption was made that those who completed treatment were completed/cured; thus, those categories were combined. In the end, outcome of treatment variables were re-categorized into two groups: completed/cured and not cured. To assess exposure to unpasteurized dairy reported home district in Lebanon was re-categorized into urban and rural to act as a proxy for exposure, with the four largest districts in Lebanon – Beirut, Saida, Tripoli, and Zahle – considered urban while all other districts in Lebanon were considered rural; this was only done for Lebanese nationals, as home district was not reported for other nationalities. Nationalities were grouped into four categories: Lebanese, Syrian, Ethiopian, and all others. All other nationalities were combined because it was a relatively small group of individuals.

Descriptive analyses of EPTB and PTB cases were carried out and frequencies and percentages were calculated. The data were analyzed using SAS 9.4 (Cary, NC). Chi-Square tests were done to compare categorical characteristics of the study population. For variables in which there were low expected cell counts (n<5), Fisher's Exact test was used to test for significance. Student's t-tests were done to compare continuous variables. Variables were considered significant if p-value was <0.05. Factors associated with EPTB were assessed using multivariable logistic regression models comparing EPTB cases with PTB cases. The following variables were included in the model as potential explanatory factors of EPTB infection: age category, gender, and nationality category. Location of home district (i.e., urban versus rural) was only evaluated for Lebanese cases, because the home location of non-Lebanese was unknown. Another model was run looking at treatment outcome (i.e., completed/cured versus not cured) as the outcome and included the following variables: gender, nationality category, age category, and TB classification. The multivariable models were built using stepwise approach. To evaluate trends, aggregate TB data from 2011-2013 were assessed in conjunction with the 2014 and 2015 line listed data.

This project constituted an evaluation of routine public health activities conducted by the Lebanese NTP and relied on an analysis of a de-identified database in a way that safeguarded personal health information collected by Lebanon's NTP. As such, this assessment was deemed to qualify as "nonresearch" and exempted from IRB review based on specific requirements stipulated under USC 45 CFR 46.101(b)(4).

## Results

Between 2014 and 2015, a total of 1347 cases of tuberculosis were reported to the National Tuberculosis Programme in Lebanon. Of those, 507 (37%) cases had EPTB. The median age of all TB cases was 30 years (IQR=23-43 years), while that of EPTB cases was 29 years (IQR=21-45 years) and PTB cases was 30 years (IQR=24-42 years). Among the 507 EPTB patients, 63% (n=318) were female, 37% (n=189) were male. In contrast, PTB cases were more commonly male (54%, n=547) than female (46%, n=383) ($p=0.003$) (Table 1). The greatest number of EPTB and PTB cases were reported among Lebanese, 301 (59%) and 347 (41%), respectively ($p<0.001$). The other three nationalities had a similar lower number and proportion of reported EPTB cases: 67 (13%) cases among Syrians, 68 (13%) cases among Ethiopians, and 71 (14%) cases reported among all other nationalities combined (Table 1). Among Lebanese, there were more cases of both EPTB and PTB reported from rural cities than from urban cities of Lebanon; however, this finding was not statistically significant ($p=0.9048$) (Table 2).

Aggregate data from 2011-2015 showed that the proportion of all TB cases increased among Syrians compared with Lebanese (Figure 1). However, the proportion of cases of EPTB cases among Syrians decreased when compared with EPTB cases among Lebanese (Figure 2). These data also showed that the proportion of EPTB cases remained relatively stable (2011: 33%, 2015: 30%, median 32%) (Figure 3).

Four significant risk factors for extrapulmonary tuberculosis were identified through multivariable logistic regression model: being female, being Lebanese, being between 5 and 15 years, and being completed/cured following treatment for tuberculosis (Table 4). The odds of having EPTB were significantly lower for males versus females (OR: 0.56, 95% CI: 0.43-0.72). The odds of having EPTB among Syrians and Ethiopians were both 0.44 times lower than among

Lebanese ( 95% CI: 0.31-0.61 and 95% CI: 0.30-0.63, respectively). The odds of having EPTB for all other nationalities were significantly lower than for Lebanese (OR: 0.59, 95% CI: 0.42-0.83).

Multivariable logistic regression model for factors associated with an outcome of treatment completion/cure identified being from Ethiopia (OR: 3.40 95% CI: 2.45-4.73), being of any other non-Lebanese nationality (OR: 3.00 95% CI: 2.14-4.21), or having PTB (OR: 1.58 95% CI: 1.20-2.06) (Table 5). All other nationalities had their highest proportion of TB cases in 2011 and 2015 with 37% of EPTB cases (median=32%) ; in 2014, the proportion dropped to its lowest at 28% (Figure 3).

Table 1. Characteristics of tuberculosis patients in Lebanon in 2014-2015 (N=1,347).

| | Extrapulmonary (N=507) n (%) | Pulmonary (N=840) n (%) | Chi-square* Value (p-value) |
|---|---|---|---|
| Gender | | | |
| Male | 189 (37.28) | 383 (45.60) | 8.95 (0.003) |
| Female | 318 (62.72) | 457 (54.40) | |
| Nationality Category | | | |
| Lebanese | 301 (59.37) | 347 (41.31) | 42.93 (<0.001) |
| Syrian | 67 (13.21) | 181 (21.55) | |
| Ethiopian | 68 (13.41) | 166 (19.76) | |
| All Others | 71 (14.00) | 146 (17.38) | |
| Age Category (years) | | | |
| <5 | 20 (3.94) | 25 (2.98) | 51.43 (<0.001) |
| 5-15 | 57 (11.24) | 18 (2.14) | |
| >15 | 430 (84.81) | 797 (94.88) | |

*p-value <0.05 considered significant

Table 2. Characteristics of TB among Lebanese based on home district location (N=621)†

| TB Classification | Rural | Urban | Chi-square* Value (p-value) |
|---|---|---|---|
| Extrapulmonary | 224 (36.07) | 66 (10.63) | 0.01 (0.905) |
| Pulmonary | 257 (41.38) | 74 (11.92) | |

†Note: 27 casess had missing home district so they were not add included
*p-value <0.05 considered significant

Table 3. Characteristics of EPTB vs PTB from 2011-2015 in Lebanon.

| | EPTB | | | | |
|---|---|---|---|---|---|
| | 2011 (N=208) n (%) | 2012 (N=250) n (%) | 2013 (N=291) n (%) | 2014 (N=238) n (%) | 2015 (N=269) n (%) |
| Gender | | | | | |
| Male | 64 (30.8) | 79 (31.6) | 109 (37.5) | 83 (34.9) | 106 (39.4) |
| Female | 144 (69.2) | 171 (68.4) | 182 (62.5) | 155 (65.1) | 163 (60.6) |
| Age Category (years) | | | | | |
| 0-4 | 10 (4.8) | 10 (4.0) | 16 (5.5) | 11 (4.6) | 9 (3.3) |
| 5-14 | 9 (4.3) | 17 (6.8) | 27 (9.3) | 25 (10.5) | 24 (8.9) |
| 15-24 | 55 (26.4) | 57 (22.8) | 60 (20.7) | 47 (19.8) | 56 (20.8) |
| 25-34 | 65 (31.3) | 82 (32.8) | 88 (30.2) | 63 (26.5) | 76 (28.3) |
| 35-44 | 22 (10.6) | 25 (10.0) | 37 (12.7) | 36 (15.1) | 29 (10.8) |
| 45-54 | 21 (10.1) | 30 (12.0) | 27 (9.3) | 16 (6.7) | 31 (11.5) |
| 55-64 | 15 (7.2) | 14 (5.6) | 15 (5.2) | 22 (9.2) | 23 (8.6) |
| ≥65 | 11 (5.3) | 15 (6.0) | 21 (7.2) | 18 (7.6) | 21 (7.8) |
| Nationality Category | | | | | |
| Lebanese | 136 (65.4) | 162 (64.8) | 173 (59.5) | 138 (58.0) | 163 (60.6) |
| Syrian | 5 (2.4) | 9 (3.6) | 37 (12.7) | 33 (13.9) | 34 (12.6) |
| Ethiopian | 18 (8.6) | 51 (20.4) | 44 (15.1) | 37 (15.5) | 31 (11.5) |
| All Others | 49 (23.6) | 28 (11.2) | 37 (12.7) | 30 (12.6) | 41 (15.2) |

| | PTB | | | | |
|---|---|---|---|---|---|
| | 2011 (N=285) n (%) | 2012 (N=372) n (%) | 2013 (N=390) n (%) | 2014 (N=443) n (%) | 2015 (N=397) n (%) |
| Gender | | | | | |
| Male | 116 (40.7) | 132(35.5) | 173 (44.4) | 194 (43.8) | 189 (47.6) |
| Female | 169 (59.3) | 240 (64.5) | 217 (55.6) | 249 (56.2) | 208 (52.4) |
| Age Category (years) | | | | | |
| 0-4 | 5 (1.8) | 8 (2.2) | 5 (1.3) | 14 (3.2) | 11 (2.8) |
| 5-14 | 4 (1.4) | 10 (2.7) | 4 (1.0) | 6 (1.4) | 8 (2.0) |
| 15-24 | 71 (24.9) | 95 (25.5) | 94 (24.1) | 111 (25.1) | 78 (19.6) |
| 25-34 | 107 (37.5) | 135 (36.3) | 141 (36.2) | 149 (33.6) | 149 (37.5) |
| 35-44 | 39 (13.7) | 45 (12.1) | 57 (14.6) | 69 (15.6) | 58 (14.6) |
| 45-54 | 39 (13.7) | 37 (9.9) | 44 (11.3) | 36 (8.1) | 42 (10.6) |
| 55-64 | 12 (4.2) | 23 (6.2) | 25 (6.4) | 28 (6.3) | 27 (6.8) |
| ≥65 | 8 (2.8) | 19 (5.1) | 20 (5.1) | 30 (6.8) | 24 (6.0) |
| Nationality Category | | | | | |
| Lebanese | 154 (54.0) | 164 (44.1) | 163 (41.8) | 198 (44.7) | 149 (37.5) |
| Syrian | 10 (3.5) | 28 (7.5) | 67 (17.2) | 76 (17.2) | 105 (26.4) |
| Ethiopian | 37 (13.0) | 110 (29.6) | 83 (21.3) | 92 (20.8) | 74 (18.6) |
| All Others | 84 (29.5) | 70 (18.8) | 77 (19.7) | 77 (17.4) | 69 (17.4) |

Table 4. Logistic regression model determining risk factors for having EPTB (N=1347)

| | Odds Ratio | 95% CI | p-Value* |
|---|---|---|---|
| Gender | | | |
| Male | **0.56** | **0.43- 0.72** | <0.0001 |
| Female | 1.00 | Referent | |
| Nationality Category | | | |
| Lebanese | 1.00 | Referent | |
| Syrian | **0.44** | **0.31-0.61** | <0.0001 |
| Ethiopian | **0.44** | **0.30-0.63** | |
| All Others | **0.59** | **0.42-0.83** | |
| Age Category (years) | | | |
| <5 | 1.00 | Referent | |
| 5-15 | **3.31** | **1.47-7.45** | <0.0001 |
| >15 | 0.70 | 0.38-1.31 | |

*p-value <0.05 considered significant
Note: values in **bold** are statistically significant at the 0.05 level

Table 5. Logistic regression model determining factors for being completed/cured (N=1347)

| | Odds Ratio | 95% CI | p-Value* |
|---|---|---|---|
| Nationality Category | | | |
| Lebanese | 1.0 | Referent | |
| Syrian | 1.33 | 0.93-0.1.91 | <0.0001 |
| Ethiopian | **3.40** | **2.45-4.73** | |
| All Others | **3.00** | **2.14-4.21** | |
| TB Classification | | | |
| Extrapulmonary | 1.0 | Referent | 0.0009 |
| Pulmonary | **1.58** | **1.20-2.06** | |

*p-value <0.05 considered significant
Note: values in **bold** are statistically significant at the 0.05 level

Figure 1. Proportion of all TB cases among Syrians vs Lebanese from 2011-2015

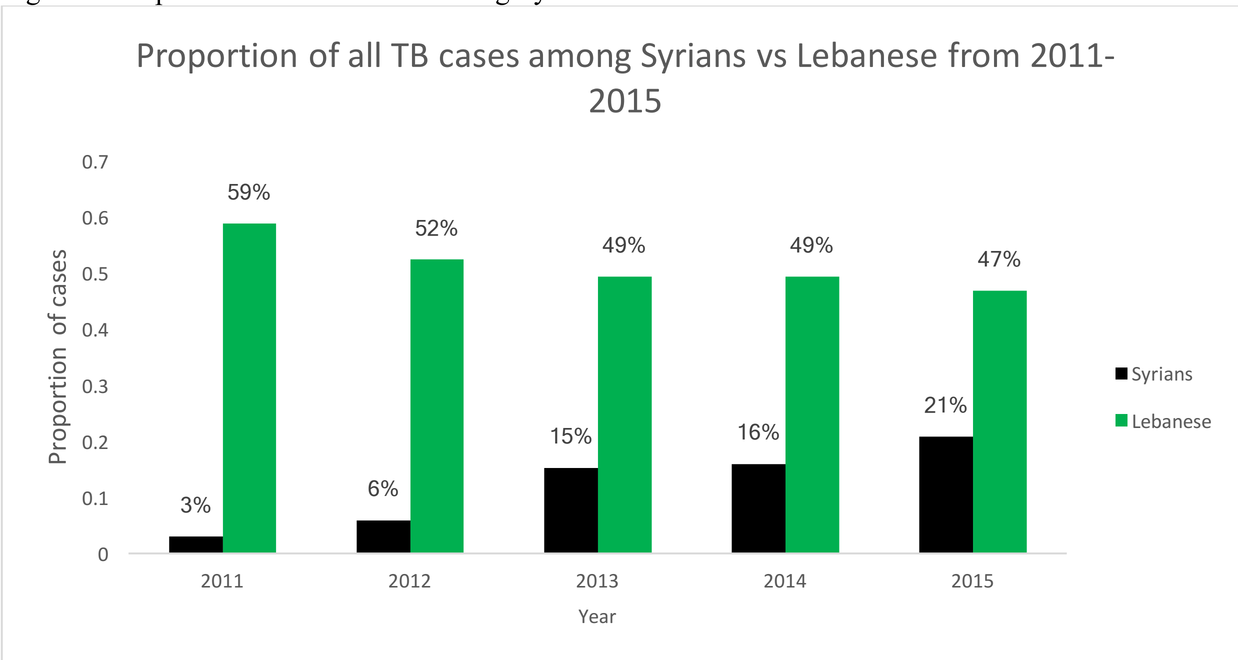



Figure 2. Proportion of all EPTB cases among Syrians vs Lebanese from 2011-2015

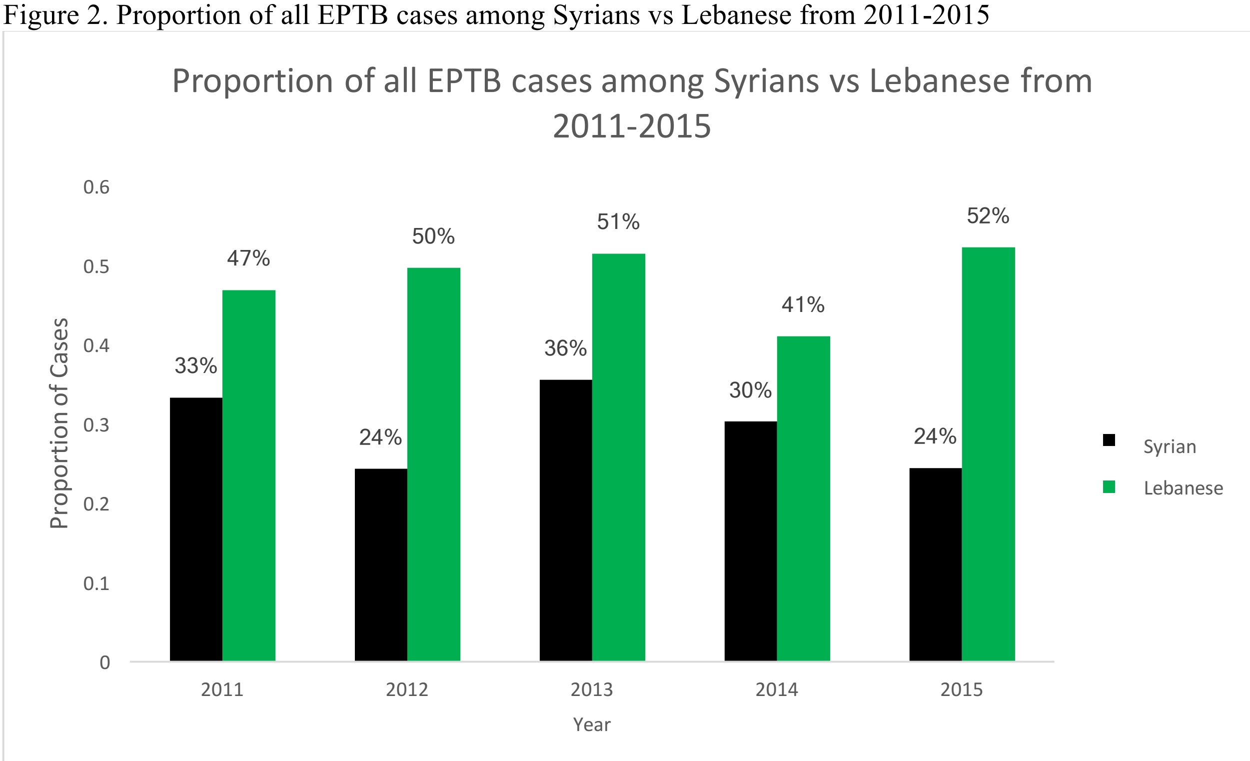
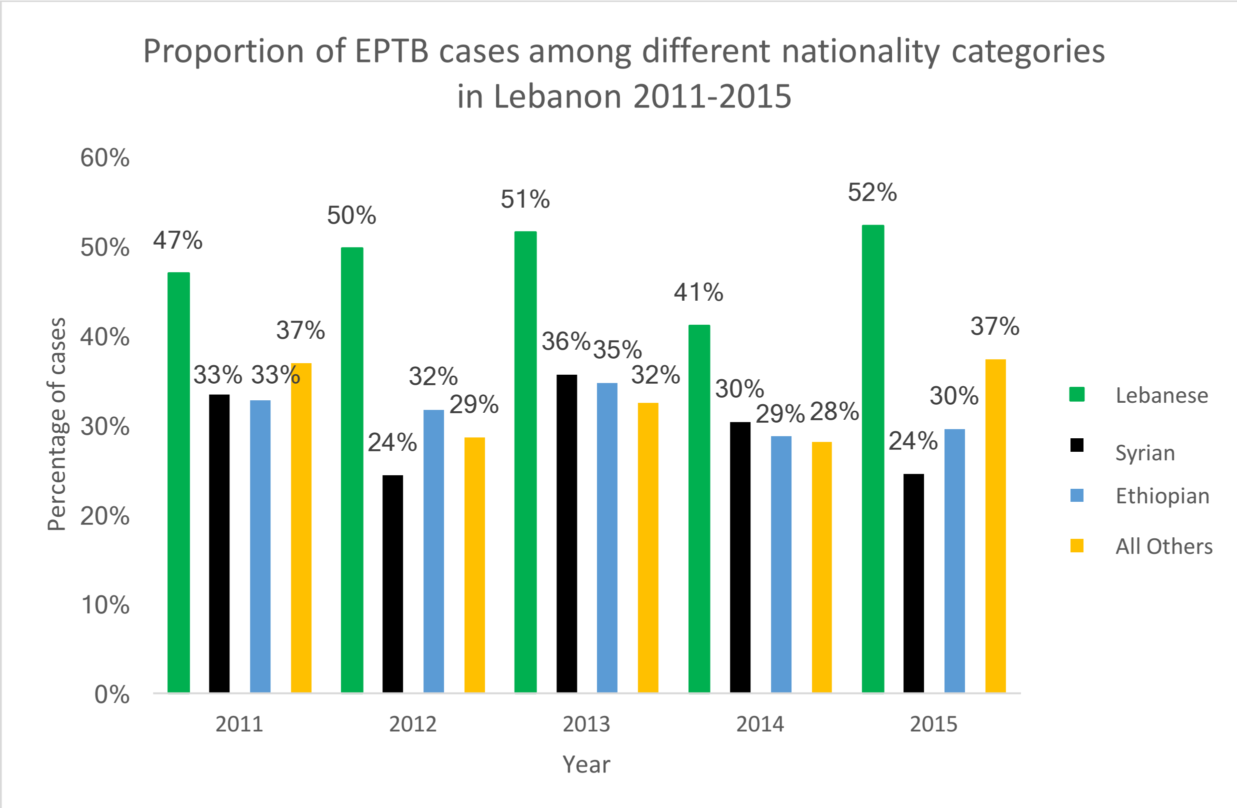


Figure 3. Proportion of EPTB cases among different nationality categories in Lebanon 2011-2015




## DISCUSSION

Public health officials in Lebanon are worried that the arrival of 2 million Syrian refugees into Lebanon will dramatically increase the number of EPTB cases in Lebanon. Analysis of TB cases in Lebanon from 2011-2015 found that Syrians were contributing to the overall number of TB cases, but the proportion of EPTB cases among Syrians decreased compared to the number of EPTB among Lebanese, indicating that Syrians are more likely to contributing to the PTB incidence in Lebanon.

The proportion of EPTB cases among all TB cases reported by Lebanon to the WHO has been consistently higher than the worldwide average (WHO, 2016). This analysis validated those reports finding an incidence of 35% in 2014 and 40% in 2015. Unlike what has been observed in other countries in which the proportion of EPTB has been increasing due to decreased reporting of PTB cases, the proportion of EPTB has remained relatively stable from 2011-2015. We speculate that one potential reason for the high proportion of EPTB in Lebanon may be due to the high rates of diabetes in Lebanon (Deek et al., 2015) which has been shown to be associated with EPTB (Magee et al., 2016). Lebanon was also found to have the highest incidence rate of cancer in the Eastern Mediterranean Region, with women having a higher incidence rate than men (Kulhánová et al., 2017). A combination of being female and having an immunosuppressive condition, both of which are risk factors for developing EPTB (Lin et al., 2009; Yang et al., 2004), may also explain the relatively high rates of EPTB.

The multivariable logistic regression model found that being between 5-15 years old had the greatest odds of developing EPTB. This model also showed that Lebanese had greater odds of having EPTB than the other nationality categories. In contrast, previous studies show that children less than 5 years of age and adults older than 65 years are at higher risk of developing EPTB (Lin et al., 2009; Yang et al., 2004). Like many other studies (Lee, 2015; Lin et al., 2009; Yang et al., 2004), this study found that being female was an independent risk factor for having EPTB. The reason for why women are more likely to have EPTB remains unexplained.

A , multivariate logistic regression model to assess treatment outcomes found that, compared with Lebanses-born TB cases, being from Ethiopia or a nationality other than Syrian or Lebanese had greater odds of being cured/ or completing successful treatment. Having PTB was also found to be associated with greater odds being cured/or completing successful therapy, which is very desirable with respect to public health programs, as PTB is considered a source of contagion in the community. One plausible reason for PTB having better odds of being cured/completing therapy than EPTB could be related to Lebanese NTP practice of using directly observed therapy for PTB cases to ensure adherence with treatment.

EPTB has been shown to be associated with infection by *M. bovis,* which is most often contracted by consuming unpasteurized dairy products (Grange, 2001). Because there was no information on previous consumption of unpasteurized dairy, this study used location of home district (urban versus rural) of EPTB cases among Lebanese as a proxy for exposure to unpasteurized products. This study did not find a significant difference in home district among Lebanese; however, because the variable analyzed was only a proxy, it cannot be conclusively said that there is no association between consumption of unpasteurized dairy and development of EPTB. Those living in rural districts do not necessarily consume unpasteurized dairy, and conversely, urban dwellers may have consumed unpasteurized dairy. Home district was not analyzed for other nationalities, because there was no information regarding the location of their homes in their respective home countries.

Diagnosis of EPTB is difficult and often requires expensive invasive procedures. Lebanon does not currently have the capability to run Xpert MTB/RIF tests which is the current WHO recommended test for rapid diagnosis. The mode of diagnosis was unknown for most of the reported cases in Lebanon; therefore, it is difficult to verify with accuracy the diagnosis and characterization of EPTB cases.

**LIMITATIONS**

A major limitation of this study is that population data are highly politicized and an official census has not been conducted in Lebanon since 1932; therefore, it is very difficult to get accurate population numbers to estimated age-, sex-, and nationality-specific population-based TB incidence rates over time. Another important limitation of this analysis is the absence of information regarding potentially relevant co-morbid conditions, such as HIV status and diabetes, both of which are known risk factors for EPTB. Furthermore, there is no information regarding history of consumption of unpasteurized dairy products, occupation, education level, and socioeconomic status, all of which may play a role in the risk factors associated with the development of EPTB. This analysis is also limited by the need to group together many nationalities into one category of “other” and collapsing different treatment outcomes into two broad categories of “cured/completed” and “not cured.” Although this was done due to small sample sizes, it risks masking potentially important variability that was not accounted for.

## CONCLUSION

The Lebanese National Tuberculosis Programme has taken many strides in strengthening their TB program. Syrians in Lebanon have an increasing proportion of overall TB cases compared to Lebanese, but the proportion of EPTB cases among Syrians is decreasing. Therefore, one recommendation for the Lebanese NTP is to focus its efforts regarding Syrian refugees on PTB and less on EPTB. Lebanese had the greatest odds of developing EPTB compared to the other nationality categories, but the odds of cure/treatment completion was significantly lower for Lebanese TB cases, when compared to Ethiopians and all other nationalities. To better understand and target interventions for persons with EPTB, the Lebanese NTP should strive to collect more detailed information on the known risk factors of EPTB such as chronic diseases, HIV status, underlying immunosuppression, and behavioral factors, such as comsumption of unpasteurized dairy products. It is also important to improve diagnostic capacity, as recommended by WHO, to accurately identify the causative agent (i.e., *M. tuberculosis* versus *M. bovis*) of EPTB in these cases to know where to focus future TB control programs. This study is the first step in characterizing the sociodemographic profile and risk factors associated with the occurrence of EPTB in Lebanon, which will hopefully help inform future efforts aimed at the eventual elimination of TB, consistent with the 2015 United Nations' Sustainable Development Goals (Nino, 2015).

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