ABSTRACT • Background: In the absence of surveillance data and consolidated information about tuberculosis (TB) and its drug resistance burden in Lebanon, this retrospective study was conducted to shed light on TB and its other relevant aspects over the last 15 years in this country.

Methods: To generate the TB data for this retrospective study, two main sources were used: 1) the records of patients in the National Tuberculosis Program (NTP); 2) the results of the Clinical Microbiology Laboratory (CML) at the American University of Beirut Medical Center (AUBMC). The TB data review pertained to its epidemiological aspect, implementation of the directly observed therapy strategy (DOTS) all over, the gender distribution, the impact of high risk groups (non-national population, Syrian refugees, patients with multi-drug resistance-TB [MDR-TB] and the inmate population) on the trend of TB in Lebanon between 1999 and 2013. Reviewed also are TB in children, extrapulmonary tuberculosis and the mycobacterium other than tuberculosis (MOTT).

Results: During the last 15 years, 7548 TB cases were diagnosed and evaluated at the NTP; After the decreasing of TB incidence from 13/100 000 population in 2001 to 9/100 000 in 2006, the incidence started to increase in 2007, reaching 20/100 000 in 2013, mostly due to increased cases among non-national population. Fluctuations in TB rates over the years were seen among children, inmates, MDR-TB, and HIV patients. MOTT isolates recoveries also fluctuated during the study period, M. simiae being the most common.

Conclusion: After the decreasing trends of TB incidence between 1999 and 2006, Lebanon has been experiencing an increasing incidence in tuberculosis population since 2007. This is mainly attributed to the dramatic increase of TB patients among nonnationals and the influx of Syrian refugees. The ongoing collaboration between the public and private sectors, improvements of the surveillance system and TB control are important factors for successful elimination of TB in this country.

Keywords: TB burden in Lebanon, epidemiological aspect, high risk groups, MDR-TB, MOTT.
a death toll of 940,000 to 1.3 million out of 8.6 million TB cases with 320,000 deaths out of 1.1 million HIV-associated TB cases. The emergence of multi-drug resistant TB (MDR-TB) continues to pose an extra challenge with an estimated 170,000 deaths from a total of 450,000 cases [1]. The majority of TB cases occur in Asia (58%) and Africa (27%); mostly in India, China, former Soviet republics, South Africa and Bangladesh [1,2].

In the Eastern Mediterranean region (EMR), TB and MDR-TB cases have been on the rise with 292,512 TB reported cases in 2005 and 430,789 TB cases in 2012. There were 350 MDR-TB cases reported in 2005 and 2249 MDR-TB cases in 2012 [1].

In Lebanon, there is a lack of published studies on the TB epidemiology and its burden. Thus, this study is warranted to address those needs and also to shed light on the historical aspects, TB in Lebanon, the activities of the National TB Program (NTP), the current status of MTB prevalence and drug resistance, and other relevant aspects in this country. Data presented in this study, primarily pertains to the joint activity of the NTP and its designated National Reference Clinical Microbiology Laboratory (CML) at the American University of Beirut Medical Center (AUBMC).

**METHODS**

**Patients and data**

The data presented is generated from investigating patients suspected with active pulmonary tuberculosis and evaluated by the NTP. These patients were diagnosed in the private sector (85% of all TB cases) and referred to the NTP for treatment, while 15% of total TB patients were diagnosed and treated in the public sector at the central and/or peripheral centers of the TB program. Moreover, data is generated from reports of patients’ specimens, submitted from local laboratories for further mycobacterial investigation to the Clinical Microbiology Laboratory (CML) of the Department of Pathology and Laboratory Medicine (PLM) at AUBMC. This CML has been designated by the Ministry of Public Health (MOPH) as the National Central Mycobacteriology Laboratory for the NTP since 2002.

**Culture and identification of mycobacterial isolates**

Processing of sputum and other clinical specimens as well as identification of isolates as MTB complex or mycobacteria other than tuberculosis (MOTT), were done according to standard procedures, using Middlebrook 7H12 broth medium (BACTEC 12B/ MGIT medium), and Lowenstein-Jensen solid medium (Becton Dickinson Microbiology Systems, Cockeysville, MD, USA) [3-6].

**Susceptibility testing to anti-TB drugs**

In vitro susceptibility testing of MTB isolates against the four primary anti-TB drugs: isoniazid (INH), rifampin (RIF), streptomycin (STM), and ethambutol (ETH) was done using the MGIT automated system according to the manufacturer’s instruction (BD).

**Quality control**

A control strain of *M. tuberculosis* (H37Rv, ATCC 27294), susceptible to all standard anti-TB drugs, was included in each run.

**RESULTS**

**TB cases-Overall numbers**

The annual number of TB cases in Lebanon, since the introduction of directly observed therapy strategy (DOTS) in 1999 to 2013, is outlined in Figure 1. A marked decrease of reported cases from 663 in 1999 to 375 cases in 2006 was observed. This decrease was followed by a gradual rise reaching 689 TB cases in 2013.

The WHO report on the epidemiology of TB in Lebanon during the year 2013 indicated a prevalence of 19 per 100,000 population with an overall TB related mortality of 72 cases (1.5/100,000 population), a detection rate of 77% and a cure rate of 80% [1]. This relative low cure rate is due to the high number of non-national

![Figure 1. Lebanon: Evolution of Tuberculosis cases vs Years (1999-2013)](image-url)
TB patients and the return of most of them to their own countries during the first month of treatment.

**Different aspects of TB cases**

The gender distribution among TB cases in 1999, showed 373 males and 290 females (ratio of 1.29 M/F). In 2006, there were 193 males and 182 females (M/F ratio = 1.06). Subsequently, this trend reversed and in 2011 there were 313 TB cases in females and 186 in males (M/F ratio = 0.60). The latter ratio is particularly due to the increasing number of TB in females among non-national population and especially in the Ethiopian community.

The annual TB cases among nationals (Lebanese) and non-nationals (NN) reported between 2003 and 2006 have been stable: 311 to 331 cases among the Lebanese non-nationals (NN) reported between 2003 and 2006 population and especially in the Armenian community.

The annual TB cases among nationals (Lebanese) and non-nationals (NN) reported between 2003 and 2006 have been stable: 311 to 331 cases among the Lebanese non-nationals (NN) reported between 2003 and 2006. However, since 2007, the number of TB cases among the NN has been gradually increasing, reaching 200, 300 and 348 in 2011, 2012 and 2013, respectively, thus leading to the increasing incidence of TB in Lebanon.

Concerning children, the percentage of reported cases of children with TB over the years (1999-2011), ranged between 10.8% and 5.2% of all TB cases. This decrease in percentage reflects the performance of the NTP in minimizing the smear positive cases among Lebanese patients, and consequently decreasing the number of TB in children.

Concerning inmates, it is estimated that there are 5000 inmates in Lebanese prisons per year, though the exact number is not known due to rapid turnover and transfer. According to the NTP registry, the annual number of inmates with TB was 70, 4, 15 and 19 cases in 1996, 2006, 2009 and 2010, respectively. Noteworthy, the first MDR- TB case among prisoners was detected in 2010. The high number of TB detected cases in 1996 was the result of the first TB screening in prison conducted by the NTP during this year. After this date, a regular screening for TB in prisons was repeated by NTP every 2 to 3 years, in order to detect TB cases without significant diagnosis delay.

The number of cases with TB/HIV co-infection in the NTP registry ranged between 3 and 10 cases per year from 2006 to 2011 with a cumulative number of 39 cases during this period.

The extrapulmonary tuberculosis (EPTB) in Lebanon does not cease to increase, as noted by the NTP. In the NTP review of 5078 TB cases over a decade (2000 to 2010), 2108 (41.5%) cases were found to be EPTB. The localization site of involvement revealed: 42% lymph nodes, 30% pleural effusion, 10% abdominal, 6% osteo-articular, 6% urogenital, 2% meningitis, 1% miliary and 3% for other sites.

The percentages of MOTT isolates recovered among all cultured specimens ranged between 30% and 44%, *M. simiae* being the most common (CML-AUBMC statistics 2009 to 2013). However, the MOTT recovery from a study on cultures of AFB smear-positive specimens was 8%.

**Drug resistance among MTB isolates**

An increasing trend in drug resistance was observed for each of the primary tested anti-TB drugs over the years, as shown from published studies and CML data of AUBMC (Table I).

The overall MDR-TB prevalence was variable but indicated increasing trends: 11% in 1995, 15% in 1998, 5.3% in 2004, 9% in 2006-7, and 25% in 2012-13. These rates were higher among re-treated cases (67%) than among newly diagnosed cases (1.1%) as was reported by the NTP to WHO in 2012 [1].

**DISCUSSION**

Tuberculosis cases in Lebanon were historically controlled in dedicated health facilities, especially sanatoriums. The concept of establishing a sanatorium was undertaken by devoted individuals and nongovernmental organizations (NGO). In March of 1900, a group of Lebanese physicians and dignitaries founded a preparatory committee tasked with the control of TB. This was followed by the establishment of “The Healthy TB Society Shelter” in the spring of 1906. In 1908, the first sanatorium was built in Maameltein (north of Beirut) and was later transferred to Hemline near Hammana-Mount Lebanon. Between February 1909 and early 1914, the construction of Daher Elbachek sanatorium was completed. During the same period, a third sanatorium was built, Bannes Sanatorium.

During World War I, all Lebanese sanatoriums were closed. By the end of the war, one last sanatorium was added: the Armenian Sanatorium which was built by the Armenian community at Maameltein in 1923 and transferred to Azounieh in 1937. To date, the latter is the only functional sanatorium.

**Historical aspect of TB control in Lebanon**

- During the first period, at the beginning of the twentieth century, TB treatment regimen in Lebanon remained similar to the Avicenna regimen of the tenth century emphasizing the use of calcium, iron and antipyretics. In the 1920s, treatment emphasized rest, fresh air and adequate food. The cure rate with this regimen was reported at 25%.

- The second period: In the late 1930s, a novel method of treatment known as pneumothorax was introduced by Dr. Nekho, which raised the cure rate to 50%. In the 1940s, other surgical treatments enhanced the cure rate.

- During the third period, by the end of World War II, the availability of new anti-TB drugs improved the cure rate. These drugs included: para-amino-salicylic acid in 1943, streptomycin in 1947, isoniazid and pyrazinamide in 1952, ethambutol in 1961, and rifampicin in 1965. Control of TB patients at the time was performed in private clinics, public centers (Karantina TB center, first public anti-TB center was established in 1950), and sanatoriums.
The fourth period: the collapse of most public services due to the civil war (1976-1990). It witnessed the important role of the private sector in diagnosing and treating patients with TB, and the emergence of TB drug resistance.

The fifth period started with the launching of the National TB Program in 1992 by the MOPH. Its mandate was to strengthen and standardize the diagnosis, treatment, and control of TB in the country. Initiating collaboration with the CML at AUBMC secured reliable access to a state-of-the-art microbiology laboratory. In addition, during this period, DOTS all over became a real fact by 2000, covering several activities including: fully adopting smear microscopy to diagnose and follow up pulmonary TB, organizing systemic monitoring and supervision at the national, provincial and peripheral levels, and evaluating outcome of smear positive patients quarterly. Moreover, notification of cases from the six provincial levels to the central level provided the NTP a clear idea about the TB situation in Lebanon; its geographical distribution, categories, distribution by gender and age group, resistance (MDR), and TB/HIV co-infection.

Number of cases
The increasing number of TB cases since 2007 has been mostly attributed to the increase in non-national TB persons. Simultaneously, the average age of TB patients was increasing, reflecting an active TB endemic situation.

The influx of Syrian refugees plays a major role in this problem. Furthermore, the Ethiopian population poses additional difficulties for effective TB control in Lebanon. During 2013, there were 127 TB patients among the estimated 50,000 Ethiopians living in Lebanon, compared to 108 TB patients among the 1,000,000 Syrian refugees in 2012 as per NTP annual reports. Such a situation entails extra burden on the NTP to face the problem of the non-national and the refugee population.

Comparing the incidence of TB cases (per 100,000 population) among some Arab and other countries in our region for the year 2012, Lebanon’s reported incidence of 17 is almost similar to Bahrain (16.9), higher than Iran (15), Saudi Arabia (13.3), Egypt (10.7), Oman (10.4), Israel (6.4), Jordan (5.4), but lower than Morocco (89.1), Algeria (56.3), Sudan (52.2), Yemen (40.8), Tunisia (29.9), Iraq (27.2), Libya (24.9), and Turkey (19.6) [1]. It is worth noting that political upheaval and popular uprising in many of the above mentioned countries lead to the interruption of public health services and inaccuracies in reporting incidence data [1].

TB/HIV co-infection
Globally, it is estimated that the number of TB/HIV cases and the number of deaths among them in 2012 were 1.1 million and 320,000, respectively [1,2].

In Lebanon, the AIDS program reported a total of 1455 HIV cases from 1984 to Nov 2011. This was lower than the UNAIDS estimates of 4000 HIV cases in this country (NTP Annual Reports [1]). In addition, the NTP indicated that the number of TB/HIV co-infection cases for the last 6 years was 39 cases. Generally, though the current impact of HIV on TB burden in Lebanon appears to be negligible (0.2/1000 population) [1], it is advisable to regularly conduct TB screening for HIV patients in this country.

Extrapulmonary TB (EPTB)
The EPTB in Lebanon does not cease to increase, as noted by the NTP. The lymph nodes and pleural site being the most commonly involved, as noted under results. The demographic aspects of patients with EPTB showed a 0.68 male/female sex ratio, and a peak in age between 15 and 35 years (50% of EPTB) with predominance (60%) of females. Among the 39 cases with TB/HIV co-infection, 28 (71.8%) had EPTB, but this did not have repercussion on the overall EPTB data.

Though 31% of all TB cases in the non-national population had EPTB, the high EPTB prevalence in Lebanon is not related to HIV status or to non-national TB patients. It is predominant in the female group and the young age group.

Due to the different sites of involvement, mycobacterial infection should always be considered in the differential diagnosis when assessing individuals presenting with symptoms from such sites.

Drug-resistance
MTB resistance to mycobacterial agents may develop as a result of inappropriate management or the lack of compliance. MDR-TB is defined as resistance to at least INH and RIF [1]. Moreover, it was reported that molecular screening for 6 codons (rpoB 531 & rpoB 526 for RIF, katG 315 for INH, rrs513 & rpsL 43 for STM, and embB 306 for EMB) can predict 90% of the resistance for the primary anti-TB drugs [7]. In Lebanon, the prevalence of mutations for RIF, INH & EMB among MTB isolates revealed RIF rpoB 531 mutation (61%), INH Kat gene S315 → S315T mutation (35%), and EMB embB mutation (71%) [8-12].

Lebanon reported increasing rates of single and MDR among M. tuberculosis isolates over the years (Table I). For individual drug, resistance against INH remains the highest followed by RIF, STM and EMB. This data is comparable to those generated from the NTP and CML-AUBMC previously published studies [4-6].

The exact extent of the MDR-TB burden in Lebanon remains to be determined in a nationwide prospective study. Although the data presented in this study provides relevant information, it remains non comprehensive since it was generated based on requests by primary providers or the NTP director (not routinely done on all recovered MTB isolates) (Table I). The exception, however, was for the study conducted on isolates between 2002 and 2004, as this was part of a WHO sponsored initiative [6].
The overall rates of MDR-TB from the first study (1994-1995) conducted after the end of civil war was 11% (7% among new vs 33% among retreated cases) [4], in the second study was 15% [5], and in the WHO sponsored study (2002-2004), on smear-positive TB cases, was 7% (0.5% among new cases and 62% among old/retreated cases) [6]. Comparing data between years 2006-7 and 2012-13, reveals a remarkable increase (9% vs 25%) in MDR-TB cases (not differentiating new from old or re-treatment cases). Table I.

Regionally, in 2012, WHO estimated that the rate of MDR-TB among newly diagnosed cases to be 3.4% in Lebanon, being higher than those estimated for Algeria (0.7%), Oman (0.8), Morocco (2.2%), Jordan (2.8%), Saudi Arabia (3.0%), Kuwait (3.3%) and lower than rates reported for Egypt (5.6%), Syria (6.7%), Sudan (10.1%) and Yemen (12%) [1].

A recent article reviewing a decade of TB drug-resistance among the Gulf Cooperation Council (GCC) countries revealed that the overall MDR-TB prevalence rate as 4%, being highest in UAE (9%), Kuwait (5.9%) and KSA (4.3%) [13].

Interestingly, discrepancies have been shown between local reports and WHO estimates. For example in 2012, EMRO countries reported a total of 2,236 MDR-TB cases, while the WHO estimate reported 18,000 such cases. It is well recognized that for each reported case, 20 are not reported [1].

Unfortunately, it is becoming noticeable that MDR-TB is replacing drug susceptible TB strain in many areas of the world, probably due to treatment mismanagement [14].

**XDR-TB & TDR-TB**

In addition to the toll of MDR-TB, the world is facing more serious problems related to the emergence of extensively drug-resistant tuberculosis (XDR-TB), defined as MDR isolates plus resistance to fluoroquinolone and at least 1 out of 3 injectable 2nd-line drugs (i.e. amikacin, kanamycin, or capreomycin [15]. In 2012, the global incidence of XDR-TB was 50,000 (3.6% of all TB cases) [1].

Testing for such resistance requires highly specialized TB laboratories only available in selected countries. In Lebanon, the incidence of XDR-TB remains undetermined with only one case reported. The NTP sends isolates to TB reference laboratories in Latvia or Egypt for second-line drugs susceptibility testing when such isolates are suspected.

Most critically ominous are the emerging reports of patients with total drug-resistant TB (TDR-TB), reported from: Italy [16], Iran [17], South Africa [18] and India [19].

New drugs available on the market such as delamanid and bedaquiline are hoped to be effective against XDR and TDR strains. However, such patients had poor outcome even with long-term treatment using multidrug capreomycin-based regimen [20]. In addition, the cost of treatment per patient with MDR-TB or XDR-TB is extremely high in low income countries, as well as in the USA [21,22].

| TABLE I | PATTERNS OF DRUG RESISTANCE AMONG M. tuberculosis ISOLATES vs YEARS |
|-----------------|--------------------------|--------------------------|--------------------------|--------------------------|
| n = 96 | n = 74 | n = 206 | n = 44 | n = 61 |
|Susceptible to all drugs | 71 (74) | 56 (76) | 156 (76) | 34 (77) | 32 (52) |
|Resistant to one drug only | 11 (12) | 5 (7) | 21 (10) | 3 (7) | 10 (16) |
|Isoniazid (INH) | 10 (10) | 2 (3) | 8 (4) | 1 (2) | 3 (5) |
|Rifampin (RIF) | 0 | 1 (1) | 3 (1) | 2 (4) | 3 (5) |
|Streptomycin (STM) | 1 (1) | 2 (3) | 7 (3) | 0 | 3 (5) |
|Ethambutol (EMB) | 0 | 0 | 4 (2) | 0 | 1 (2) |
|Resistant to two drugs only | 10 (10) | 4 (5) | 19 (9) | 3 (7) | 6 (10) |
|INH + RIF | 7 (7) | 2 (3) | 3 (1) | 2 (4) | 3 (5) |
|INH + STM | 2 (2) | 2 (3) | 14 (7) | 1 (2) | 3 (5) |
|STM + RIF | 1 (1) | 0 | 0 | | |
|Resistant to three drugs only | 2 (2) | 6 (8) | 6 (3) | 2 (4) | 7 (11) |
|INH + RIF + STM | 1 (1) | 3 (4) | 3 (1) | 0 | 6 (10) |
|INH + RIF + EMB | 1 (1) | 3 (4) | 3 (1) | 2 (4) | 1 (2) |
|Resistant to all four drugs | 2 (2) | 3 (4) | 6 (3) | 2 (4) | 6 (10) |
|Multi-drug resistance (MDR) | 11 (11) | 11 (15) | 15 (7) | 4 (9) | 15 (25) |

* Testing was done on AFB smear positive cases only; while testing on cases for the other periods was done on isolates upon request. Decimals in percentages were rounded to the closest figure.
MOTT
Isolates of mycobacteria other than tuberculosis (MOTT), also known as non tuberculous mycobacteria (NTM) have been increasingly recovered, mostly from immunocompromised patients and those with underlying pulmonary diseases, locally and globally [23,24].

TB investigation carried out at the CML-AUBMC revealed a high proportion (30%-40%) of MOTT recovered among all specimens submitted for mycobacterial culture. However, this percentage didn’t reflect the percentage of MOTT in Lebanon among the smear-positive cases. In a TB nationwide survey conducted between 2002 and 2004, MOTT recovery was only 8% among all smear-positive cultured specimens [6].

The recovery of such isolates constitutes an ongoing concern, not only among immunocompromised patients, but also among the young who are heavy smokers of water-pipe “nergilleh” and tobacco [25].

MOTT speciation, by gene sequencing, carried out on 55 respiratory isolates recovered at AUBMC revealed the predominance of M. simiae (38%), among 11 other species, while M. marinum (53%) predominated among other 4 MOTT cutaneous isolates [26,27]. Recently, M. canariusense was recovered from breast prosthesis [28].

The reason behind the high proportion of M. simiae isolated in Lebanon is uncertain. The fact that this Mycobacteria sp. was recovered from the water supply of a hospital in Gaza, and mostly from individuals who lived near the coastal plains of Tel Aviv or in humid areas such as San Antonio, USA [29,30], may help explain its high recovery in Lebanon. This pathogen may also cause disseminated infections, as reported from Cuba, Hungary, Israel and USA [31]. In Lebanon, Balkis et al. reported a fatal disseminated M. simiae infection in a non-HIV patient [32].

MOTT recovery from respiratory specimen can entail significant potential for pathogenicity, and necessitates close follow-up and assessment of the patients especially in immunosuppressed individuals [33].

Reliable lab diagnosis
The rapid and reliable TB laboratory diagnosis and susceptibility testing has been emphasized all along using state-of-the-art automated instruments (first BACTEC TB and later the MGIT system) and standardized international protocols to detect both MTB and MOTT isolates [33,34].

Lately, TB Gene Xpert (Cephide) has been introduced as a rapid method (within 3h) for the detection of MTB (only) and resistance gene of rifampicin, primarily from smear-positive sputum specimen (sensitivity: 97%- 99%; specificity: 92%-100%) [35]. However, this test has low sensitivity (59%-75%) related to smear-negative sputa, extrapulmonary sites, inability to detect MOTT, limited susceptibility to one or two drugs, high cost, and lack of isolates retrieval for speciation or strain characterization. Moreover, it cannot distinguish between live and dead MTB. Therefore it cannot be used to confirm treatment success or failure or for the identification of relapse.

Thus, for an accurate and reliable diagnosis of mycobacterial infections, the simultaneous use of solid- and broth-based culture methods is mandatory. At AUBMC, both MGIT and TB Gene Xpert have been made available to facilitate early diagnosis and proper infection control and management.

CONCLUSION
Tuberculosis remains a major public health problem, representing the second leading cause of death from infectious diseases worldwide. National TB control necessitates prompt and accurate diagnosis, initiating and monitoring of effective treatment, and cessation of transmission [36].

Though Lebanon is ranked low in TB incidence compared with other countries, the fluctuating trends in incidence and increase in drug resistance may be worrisome given the increasing numbers of non-nationals and the influx of Syrian refugees. The close and ongoing collaboration among the NTP, HIV program, NGOs, private sector and the CML at AUBMC has strengthened program activities and constituted the leading dynamic driving force in the control and the elimination of TB infection in Lebanon.

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