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Tuberculosis epidemiological trend in Sousse, Tunisia during twenty years (2000–2019)

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ABSTRACT

Describe the epidemiology of tuberculosis in the last two decades (2000–2019) in the East region of Tunisia (city of Sousse). This was a descriptive retrospective analysis of notified incident cases of tuberculosis from 2000 to 2019 in Sousse Governorate, Tunisia. The data collection was done via the regional registry of tuberculosis. Stata software was used to characterize the socio-demographic and clinical profile of tuberculosis, to calculate its incidence, mortality and fatality rates and to determine predictive factors of mortality. R software was used to analyze the chronological trend of tuberculosis incidence and mortality. A total of 2606 incident cases of tuberculosis were declared from 2000 to 2019 in Sousse. The mean age was 39 ± 19 years with a sex ratio (male/female) of 1.19. Only one case was HIV positive among the total 2606 incident cases. Extra-pulmonary tuberculosis was the most recorded (1,534 cases, 58.9%). The mean annual case notification and deaths were 130 and four respectively. After adjusting for confounders, individuals with pulmonary tuberculosis were 1.9 significantly more likely to die from tuberculosis compared to those suffering from extra-pulmonary tuberculosis. There was a trend of increasing mortality with increasing age. The association was statistically significant only for those above 60 years' old who had 12.5 times higher odds of dying compared to those below 60 years. After adjusting for age and gender, with every year there was an increase in the total incidence rate (+0.35 per 100,000) with p = 0.005 and in the extra-pulmonary incidence (+0.27 per 100,000), with p = 0.001. This study demonstrated the increasing trend of tuberculosis in Sousse, Tunisia from 2000 to 2019. The national program against tuberculosis should enhance community knowledge and centralize the national and regional epidemiological information for better epidemiological surveillance.

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1. Introduction

Tuberculosis is an infectious disease caused by the bacillus Mycobacterium tuberculosis [1]. It affects the lungs usually, but it might affect other organs and sites (urinary tract, ganglionic, cutaneous, etc.) [1]. The transmission of pulmonary tuberculosis is facilitated by expelling bacteria into the air [2]. Tuberculosis has existed for centuries and remains a public health problem globally. In 2015, it was one of the leading causes of death in the world, beating HIV-AIDS as one of the leading causes of death from infectious diseases with 1.4 million deaths. In the same year, there were 10.4 million new cases and 480,000 multidrug resistance tuberculosis cases [3]. As a global response, the World Health Organization (WHO) has led global initiatives to fight tuberculosis with the recent one being the End Tuberculosis Strategy to reduce deaths by 95% and new infections by 90% between 2015 and 2035 [4].

Tunisia is no exception in terms of tuberculosis infection as the country has intermediate endemicity [5]. The efforts to fight tuberculosis started since the independence in 1956, with screening campaigns in certain areas. Then in 1978, the National Tuberculosis Control Program was created and it integrated three main interventions: mandatory BCG vaccine for school-aged children, systematic screening for those consulting Primary Healthcare Centers (PHCs) with suspected symptomatology, and finally free treatment in PHCs for all confirmed cases till complete healing [5]. From 1978 to 2018, the tuberculosis incidence rate dropped from 48.8/100 000 to 35/100 000 population [6] with the goal to ultimately achieve the WHO's recommendations and to obtain an incidence of one case per one million populations by 2050 [5].

Despite the implementation of the national program, the burden of tuberculosis is inequitable across the country. A recent analysis of tuberculosis disease

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Supplemental data for this article can be accessed here.

burden in Southern Tunisia revealed a recent increase in incidence in this region and suggested regional heterogeneity in infection burden [7]. The data on tuberculosis burden and other epidemiological indicators had not been analyzed for the other regions of Tunisia. Therefore, to assess the performance of control strategies, the description of the epidemiological trend and profile of the disease over time and in other geographical areas is fundamental. This research project aimed to understand the epidemiology of tuberculosis in the last two decades (2000–2019) in the city of Sousse, Tunisia.

2. Methodology

This study is an epidemiological description of tuberculosis incidence in the city of Sousse. It was based on a descriptive retrospective analysis of all notified cases of tuberculosis from 2000 to 2019 in Sousse, Tunisia. The data collection was done via the regional registry of tuberculosis which included cases notified from both private and public institutions. The regional registry of tuberculosis is an epidemiological surveillance support and it is maintained by the Regional Healthcare Service. Proper agreement for accessing and using the data from the regional registry of tuberculosis was made with the Regional Directorate of Health and the Basic Health Group of Sousse (ethical approval number 7047). For the purposes of the study, we included notified new tuberculosis cases (incident cases) independently of the site (pulmonary, extra-pulmonary). According to the National tuberculosis guidelines and in alignment with the WHO diagnosis criteria [8], the confirmation of cases was done via bacteriological or histological evidence, or alternatively, via clinical and radiological evidence and amelioration under treatment [5]. Relapsed cases were not included, to be able to calculate the incidence rate. A relapsed case of tuberculosis was defined as the occurrence of a new episode of tuberculosis in an already treated and cured patient [9]. Statistical analysis was done using STATA, except for the trend analysis, which was done in RStudio software.

We used Pearson's Chi-Square test and the independent t-test to compare the socio-demographic and clinical profile of cases (pulmonary and extra-pulmonary). We also calculated for every year from 2000 to 2019 using the corresponding formulas. The total population size of the city of Sousse in each year was extracted from the Tunisian National Institute of Statistics [10]. We then analyzed predictors of mortality using logistic regression controlling for all variables statistically associated with the outcome at the bivariate level at $p < 0.2$. Finally, we analyzed the chronological trends of tuberculosis incidence and mortality rates through R software using simple and multiple linear regression adjusting for gender (expressed as the % male in each year) and age (expressed as the average age each year), adding the R-squared (R2) ranging from 0 to 1 which indicates how much of the variation of the incidence is explained by the chronological trend. Significance was set at $p < 0.05$ at 95% confidence interval.

Table 1. Comparison of basic characteristics between pulmonary and extra-pulmonary tuberculosis cases in Sousse, Tunisia, 2000–2019, n (%).

	Pulmonary tuberculosis N = 1072	Extra-pulmonary tuberculosis N = 1534	Total cases N = 2606	p
Demographic characteristics				
Gender				
Male	799 (74.5)	619 (40.4)	1,418 (54.4)	$<10^{-3}$
Female	273 (25.5)	915 (59.6)	1,188 (45.6)	
Age groups				
<60	885 (82.6)	1293 (84.3)	2178 (83.6)	0.24
≥60	186 (17.4)	240 (15.7)	426 (16.4)	
Management				
Patient transferred from				
Not mentioned	670 (62.5)	816 (53.2)	1,486 (57.0)	<0.001
Public institution	355 (33.1)	587 (38.3)	942 (36.2)	
Private institution	47 (4.4)	131 (8.5)	178 (6.8)	
HIV Test				
Not done	929 (86.7)	1,267 (82.6)	2,196 (84.3)	–
Negative	143 (13.3)	266 (17.3)	409 (15.7)	
Positive	0 (0.0)	1 (0.1)	1 (0.0)	
Antibiotics				
Bi therapy	34 (3.4)	84 (6.1)	118 (5.0)	
Tri therapy	20 (2.0)	50 (3.6)	70 (2.9%)	0.01
Quadric therapy	937 (94.6)	1253 (90.3)	2,190 (92.1)	
Outcome				
Loss of follow-up	53 (5.0)	65 (4.3)	118 (4.6)	0.001
Cured	964 (90.4)	1,416 (93.7)	2,380 (92.3)	
Deceased	49 (4.6)	31 (2.1)	80 (3.1)	

3. Results

From 2000 to 2019, there were 2,606 incident cases of tuberculosis in all sites combined in Sousse Governorate. The mean age was 39 years ± 19 years with a sex ratio (male/female) of 1.19. Extra-pulmonary tuberculosis was the most recorded with 1,534 cases (58.9%). Table 1 compares basic demographic characteristics, management of cases, and patient outcome between pulmonary and extra-pulmonary tuberculosis. Table 2 showcased the mean incidence of tuberculosis in the different areas within Sousse.

Over the study period, a mean number of 130.2 tuberculosis cases and 4 deaths were reported per year (Table 3) with a mean tuberculosis incidence rate equal to 21.23, 95%CI [20.33, 22.14] (per 100,000 population). A total of 80 tuberculosis death cases were reported over the 20 years of the study in Sousse governorate (Table 4). After adjusting for confounders, individuals with pulmonary tuberculosis were 1.9 significantly more likely to die from tuberculosis compared to those suffering from extra-pulmonary tuberculosis. There was a trend of increasing mortality with older age group. The association was statistically significant for those above 60 years' old who had 12.5 times higher odds of dying compared to those below 60 years old (95%CI [7.5, 21.0]) (Table 4).

The trend of the total tuberculosis incidence (all sites combined) from 2000 to 2019 was increasing (Figure 1A). Each year, there was an increase in the total tuberculosis incidence rate by 0.27 per 100,000, and it was significant with $p = 0.01$, and in extra-pulmonary incidence rate by +0.25 per 100,000 with $p < 0.001$ (Figure 1B). The increase in pulmonary tuberculosis incidence was much smaller and not significant (Figure 1C) (+0.02 per 100,000, $p = 0.7$).

When adjusting for age and gender, every year there was an increase in the total incidence rate by +0.35 per 100,000 and it was significant ($p = 0.005$, and adjusted $R^2 = 0.29$) and the increase in the extra-

Table 2. Mean incidence rate of Tuberculosis per delegation, in Sousse, Tunisia, from 2000 to 2019.

Delegation	Population in 2009	Frequency N	Incidence/ 1000	95% Confidence Interval
Prison	1178	29	246.18	[243.24, 249.12]
Sousse medina	29,271	541	184.82	[182.16, 187.48]
Hamam sousse	38,474	207	53.80	[52.36, 55.24]
Sousse Riadh	79,206	421	53.15	[51.72, 54.58]
Hergla	8309	43	51.75	[50.35, 53.15]
Kalaa sghira	31,342	131	41.80	[40.53, 43.07]
Enfidha	45,607	158	34.64	[33.49, 35.79]
Sidi abdelhamid	53,783	174	32.35	[31.24, 33.46]
Jawhra	73,286	235	32.07	[30.96, 33.18]
Kalaa kbira	53,692	172	32.03	[30.92, 33.14]
Sidi bou ali	18,596	58	31.19	[30.10, 32.28]
Kondar	12,245	35	28.58	[27.54, 29.62]
Akouda	28,244	78	27.62	[26.59, 28.65]
Msaken	90,168	229	25.40	[24.41, 26.39]
Bouficha	25,161	51	20.27	[19.39, 21.15]
Sidi el heni	11,871	21	17.69	[16.87, 18.51]
Others		23		

Table 3. Tuberculosis incidence and mortality rates in Sousse Governorate by year from 2000 to 2019.

Year	Total population	Incident cases	Death cases	Fatality rate (%)	Incidence rate / 100,000	Mortality rate /100,000
2000	492,500	99	2	2 [1.72, 2.28]	20.10 [19.22, 20.98]	0.41 [0.28, 0.53]
2001	501,200	87	3	3 [2.66, 3.34]	17.36 [16.54, 18.17]	0.60 [0.45, 0.75]
2002	510,100	87	3	3 [2.66, 3.34]	17.06 [16.25, 17.86]	0.59 [0.44, 0.74]
2003	536,300	96	9	9 [8.41, 9.59]	17.90 [17.07, 18.73]	1.68 [1.42, 1.93]
2004	545,800	82	3	4 [3.61, 4.39]	15.02 [14.26, 15.78]	0.55 [0.40, 0.69]
2005	557,100	131	8	6 [5.52, 6.48]	23.51 [22.57, 24.46]	1.44 [1.20, 1.67]
2006	568,200	110	5	5 [4.56, 5.44]	19.36 [18.50, 20.22]	0.88 [0.70, 1.06]
2007	579,000	114	7	6 [5.52, 6.48]	19.69 [18.82, 20.56]	1.21 [0.99, 1.42]
2008	590,100	146	4	3 [2.66, 3.34]	24.74 [23.77, 25.72]	0.68 [0.52, 0.84]
2009	608,624	138	6	4 [3.61, 4.39]	22.67 [21.74, 23.61]	0.99 [0.79, 1.18]
2010	621,778	159	4	3 [2.66, 3.34]	25.57 [24.58, 26.56]	0.64 [0.49, 0.80]
2011	600,382	124	3	2 [1.72, 2.28]	20.65 [19.76, 21.54]	0.50 [0.36, 0.64]
2012	648,706	120	2	2 [1.72, 2.28]	18.50 [17.66, 19.34]	0.31 [0.20, 0.42]
2013	662,487	154	4	3 [2.66, 3.34]	23.25 [22.30, 24.19]	0.60 [0.45, 0.76]
2014	677,501	140	3	2 [1.72, 2.28]	20.66 [19.77, 21.55]	0.44 [0.31, 0.57]
2015	690,715	155	3	2 [1.72, 2.28]	22.44 [21.51, 23.37]	0.43 [0.31, 0.56]
2016	703,646	187	5	3 [2.66, 3.34]	26.58 [25.57, 27.59]	0.71 [0.55, 0.88]
2017	715,744	143	1	1 [0.80, 1.20]	19.98 [19.10, 20.85]	0.14 [0.07, 0.21]
2018	726,867	161	3	2 [1.72, 2.28]	22.15 [21.23, 23.07]	0.41 [0.29, 0.54]
2019	737,027	173	2	1 [0.80, 1.20]	23.47 [22.52, 24.42]	0.27 [0.17, 0.37]
2000–2019		2606	80	3 [2.66, 3.34]	20.03 [20.14, 21.93]	0.67 [0.52, 0.83]

Table 4. Predictive factors of Tuberculosis deaths, in Sousse Governorate, Tunisia, from 2000 to 2019, n (%).

	Cured N = 2380	Dead N = 80	p	Crude OR 95%CI	Adjusted OR 95%CI
Gender					
female	1,105 (97.4)	29 (2.6)		-	-
Male	1,275 (96.2)	51 (3.8)	0.07	1.5 [0.4, 1.]	1.5 [0.9, 2.4]
Age groups					
<60	2029 (98.7)	26 (1.3)			
≥60	349 (86.6)	54 (13.4)	**<0.001**	**12.1 [7.5, 19.5]**	**12.5 [7.5, 21.0]**
Tuberculosis site					
Extra-pulmonary	1,416 (97.9)	31 (2.1)		-	-
Pulmonary	964 (95.2)	49 (4.8)	**<0.001**	**2.3 [1.5, 3.7]**	**1.9 [1.1, 3.3]**
Antibiotherapy					
Two antibiotics	103 (96.3)	4 (3.7)		-	-
Three antibiotics	63 (92.6)	5 (7.3)	0.30	2.0 [0.5, 7.9]	2.9 [0.7, 12.4]
Four antibiotics	2,004 (97.0)	62 (3.0)	0.67	0.8 [0.3, 2.2]	0.8 [0.3, 2.4]

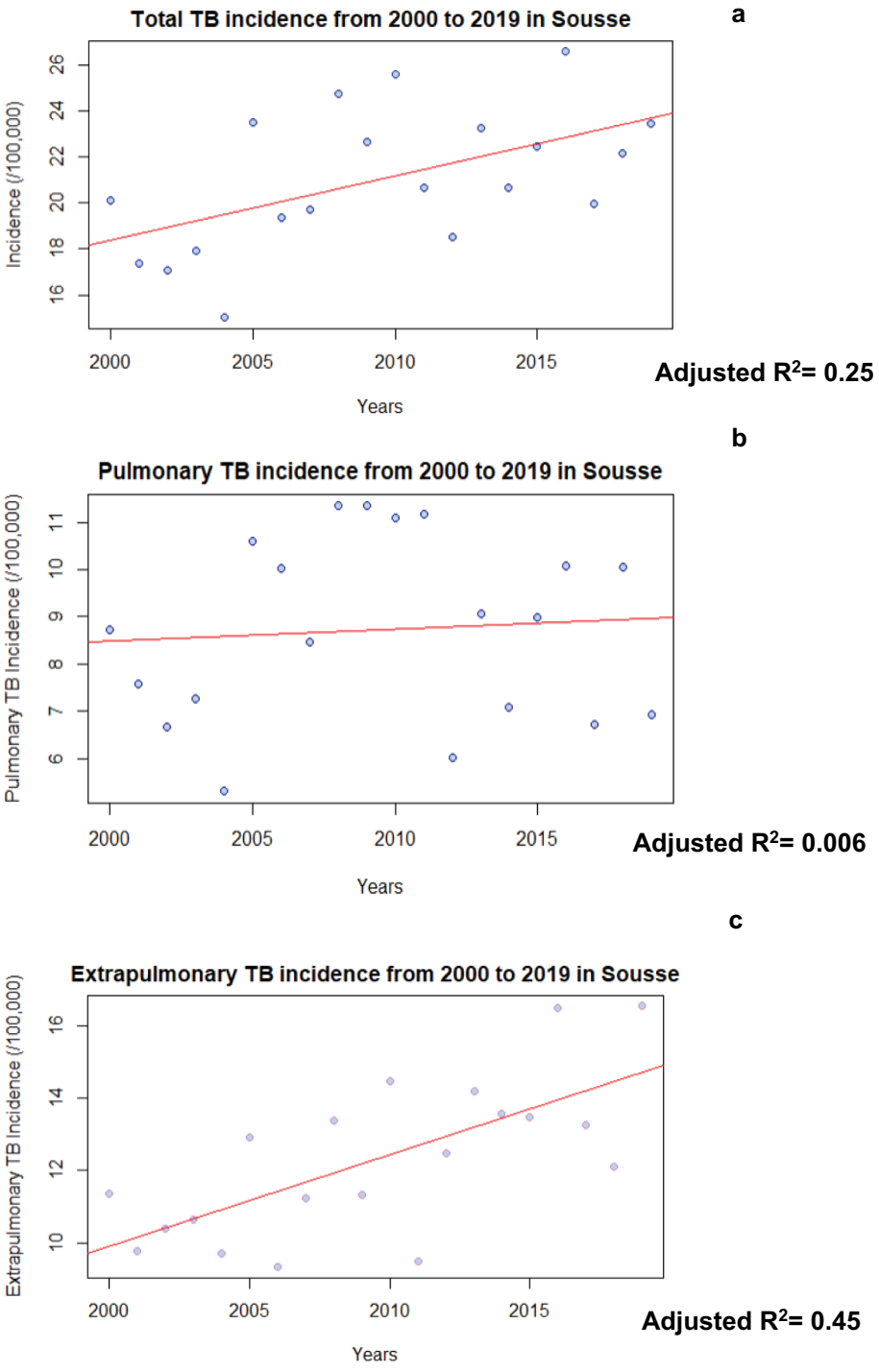

Figure 1. Incidence Trend of tuberculosis (TB) from 2000 to 2019 in Sousse Governorate, Tunisia.

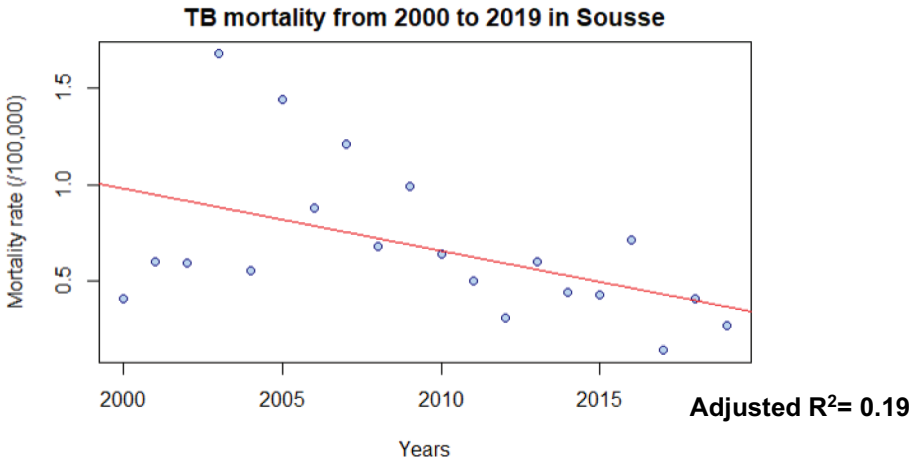

Figure 2. Mortality rate trend of tuberculosis (TB) from 2000 to 2019, in Sousse governorate, Tunisia.

pulmonary incidence (+0.27 per 100,000) remained significant (p = 0.001 and adjusted R^2 = 0.40).

There was a decreasing mortality rate trend (−0.03 per 100,000 each year), and it was statistically significant with p = 0.02 (Figure 2). However, it was not significant when adjusting for age and gender (p = 0.08).

4. Discussion

In the early 90s, the WHO declared tuberculosis as a global health emergency, and since then, prominent efforts to address it have been put in place. Currently ending tuberculosis is a target under the Sustainable Development Goals (target 3.3). The global incidence of tuberculosis is decreasing globally by 2% per year with a cumulative reduction of 9% between 2015 and 2019 [11]. The End Tuberculosis Strategy defines targets for reduction in tuberculosis cases (80% reduction in the tuberculosis incidence rate) and deaths (90% reduction in the number of tuberculosis deaths) [11]. In Tunisia, efforts to fight tuberculosis started more than 60 years ago and the incidence has decreased from 48.8 to 22.5 per 100,000 habitants from 1978 to 2007 [12] and then increased to 35 per 100,000 in 2018 [6].

5. Increasing trend of Tuberculosis

Our study showcased a linear increasing trend of tuberculosis incidence over the past 20 years (from 2000 till 2019) with a slope equal to +0.35 per year when adjusting for age and gender. This incidence found in our study, even though below the national rate, remains above the threshold set by the office of the WHO Eastern Mediterranean to classify countries of low incidence which is 20/100,000 population [12]. The increasing trend of tuberculosis can be the result of socio-economic deprivation, which may lead to poor living conditions, overcrowding, and malnutrition especially in prisons where there is a higher incidence of tuberculosis compared to the general population [13–16] which was objective also in our study. These factors increase tuberculosis exposure risk, and individual vulnerability. According to the literature, unhealthy lifestyle habits are also implicated in the genesis of tuberculosis, for example, active or passive tobacco smoking are risk factors for latent tuberculosis cases and enhance the progression to active disease, same for alcohol use [17,18]. Moreover, the lack of social support can lead to non-compliance and poor treatment outcomes [19]. Also, demographic factors characterized by aging can lead to an increase in tuberculosis incidence. A study in China found that tuberculosis incidence increased for those above 45 years old [20]. Other studies have associated this increase to the degradation of the immune system over time due to other comorbidities or drugs [21–23]. Among these comorbidities, diabetes has been linked to increased risks and adverse tuberculosis treatment outcomes [18,24,25]. Environmental factors have been also incriminated in the tuberculosis genesis such as air pollution [26] and seasonality [14,15,27]. In Sousse, Tunisia, the tuberculosis incidence increasing trend can also be explained by the above-described factors, as the population is aging [28], and there is a quite high prevalence of smoking and diabetes [17,29–31]. Other studies done in Tunisia, have also have objectified this rise in incidence whether in the South of Tunisia [7] and Monastir governorate [32].

6. Rise of Extra pulmonary cases

Our results showed a much higher proportion of extra-pulmonary tuberculosis with 58.9% of the total tuberculosis cases from 2000 to 2019 of which the majority was females (59.6%) and with a younger age compared to pulmonary cases. The predominant extra-pulmonary sites were lymph nodes, pleura, and digestive system. This increase in extra-pulmonary cases could be the results of a multitude and complex risk factors such as immunological factors (HIV infection), socio-demographic factors (female sex, younger age, and non-white race) comorbidities, and lifestyle

behaviors (diabetes, liver diseases, and consumption of unpasteurized raw milk) and genetic factors [33–38] and also the evolution and amelioration of diagnostic tools [39]. Worldwide, out of the 6.3 million new cases of tuberculosis recognized in 2017, 16% were extra-pulmonary with an incidence rate ranging from 8% in the Western Pacific Region to 24% in the Eastern Mediterranean Region [24]. Extra-pulmonary cases represented 20% of all tuberculosis cases in Korea [40], 33% in China [24], 49% in both Morocco and Ethiopia [37,39] and reached 51% in India [41]. In the European Union and the European Economic Area, more than 150,000 cases of extra-pulmonary tuberculosis were declared in the 30 member states from 2002 to 2011 which accounted for 19.3% of all cases [42]. In Tunisia, the proportion of extra-pulmonary tuberculosis exceeded 50%, both in Monastir governorate (51%) [43] and in the south region of Tunisia (68%) [7]. This increase in tuberculosis incidence in Tunisia may be partially due to sociodemographic factors, comorbidities, and especially lifestyle factors dominated by the consumption of unpasteurized milk [5,44,45]. However, it can be the result of progress made in screening-diagnosis tools and the improvement of surveillance, policy, and programming of tuberculosis management.

The Tunisian efforts to fight tuberculosis started after the independence, and the latest version of the National Guide was published in 2018 [46]. This edition is, still, more oriented toward pulmonary tuberculosis which may be due to the contagious nature of pulmonary tuberculosis compared to the extra-pulmonary form. Currently, there is a need to be more, or at least, equally focused on both pulmonary and extra-pulmonary tuberculosis. Incidence of tuberculosis were found to be much higher in prison settings which need to be addressed by the public health authorities. Moreover, there is a national necessity to enhance the community's knowledge about tuberculosis and especially about the extra-pulmonary form. Ben Salah et al. [47] highlighted the knowledge disparity and heterogeneity. They stated that coughing was the main alarming symptom for people, with a variety between regions, educational status, and gender. They highlighted the importance of mass media such as televisions and radios as they were the main two sources of information stated by the population of the study [47]. Also, it is time to digitalize and computerize the regional and national registry of tuberculosis. This will allow the centralization of both national and regional epidemiological information at the ministerial level, thus, better knowledge about the distribution of important epidemiological parameters using geographical information systems and per consequence identifying high-risk zones and intervene effectively and efficiently.

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