

Tuberculosis in Malta: comparisons between the young and elderly in a low incidence country

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Abstract

Background: Malta has one of the lowest reported incidence rates of tuberculosis in Western Europe, and was approaching the elimination phase. It was observed that a disproportionate number of cases were occurring among persons of advanced age.

Objective: To investigate the epidemiology of tuberculosis in the elderly Malta-born population.

Methods: A retrospective review of national TB surveillance data from 1995 to 2005 with estimation of 11-year means. Age stratified comparisons between the general, the younger, and the elderly Malta-born populations were made.

Results: One hundred and seventeen Malta-born patients were included in the study; 99% of all notified cases. The mean stratified incidence rates of TB among the general population,

those less than 65 years of age, and the elderly (65 years and over) were 2.8, 1.6, and 10.6 per 100,000 person-years respectively. When the study sample was stratified into 15-year age groups, their mean TB incidence showed an exponential increase. All major age groups showed a fall in incidence, with the elderly group featuring the steepest decline of about 5% per year. The stratified incidence ratio of males to females, and pulmonary to extra-pulmonary TB was greatest in the elderly. Relapse occurred more commonly amongst elderly males.

Conclusion: Contrasting age-stratified differences in incidence, gender, site, relapse, and mortality rates were discovered between the two major age groups, with the elderly forming a sub-population with distinct TB-related characteristics. Thus, the elderly, even when living in very low TB-incidence regions, should receive particular consideration.

Introduction

Tuberculosis (TB) in Western Europe is characterised by an overall reduction in incidence rates in past years.^{1,2,3} If persons with HIV/AIDS are excluded, the elderly native population in these countries can be considered to be a high-risk group for developing TB.⁴ These countries have also experienced an increase in their elderly population, with an increase in both absolute and relative numbers.⁵ The Maltese islands are considered to be a low TB-incidence country,^{2,3} and while an increasing number of cases appear to be occurring among the elderly, no recent detailed epidemiological studies had investigated this phenomenon. The aim of this study is to describe the epidemiology of TB amongst the Malta-born elderly living in Malta; a very low TB incidence country.

Methods

A study period of eleven years, from 1995 to 2005 (both years included), was chosen. This period provided data which was reliable. The sample consisted of 117 new and 6 relapse cases, which is more than 99% of those notified during this period. The study sample included only those persons who were Malta-born and excluded foreign-born persons in order to obtain an unbiased picture of TB epidemiology in the native population. All new 'definite' and 'other than definite' cases diagnosed Malta-born population were included. Tuberculosis diagnosed in the elderly, was compared to that occurring among the general population and to those aged less than 65 years. Age

Keywords

Tuberculosis, elderly, Malta, low-incidence

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stratified comparisons regarding incidence, gender, site, and mortality were made.

All denominator populations were obtained from the official published Demographic Reviews of the National Statistics Office of Malta. The population of each year studied is the end of year Malta-born population.⁵ All case data were collected from the Chest Clinic and Chest Unit, which co-operate to ensure complete surveillance in Malta.

Eleven-year population averages and incidence rates were calculated, in order to smooth out trend instability due mainly to low case and population numbers. One case was excluded because of incomplete data.

Pulmonary TB is defined as disease involving the lung parenchyma, tracheo-bronchial tree and larynx, even when other sites are simultaneously involved. All TB disease involving other sites in isolation, are considered as extra-pulmonary.³ New cases were those treated for the first time with standard short-course chemotherapy. A low TB incidence country is defined as one with a rate of less than 20 per 100,000 person years. This study's definition of 'very low incidence area' is a country or area with an incidence of 5 or less per 100,000 person-years for three consecutive years. The elimination phase is reached when the incidence of all forms of active TB falls below 1 case per million population per year.¹ The elderly were defined as persons with an age of 65 years and over, while those assigned to the younger age group were less than 65 years of age.

Diagnosing physicians are required by law to notify all forms of TB. All patients, apart from those with HIV/AIDS, are treated and followed-up by the Chest Clinic, including those few patients who were diagnosed privately. Anti-TB medication cannot be obtained commercially, and the Chest Clinic is notified monthly of dispensation of such medication by state pharmacies. Free-of-charge anti-TB drugs can only be prescribed by designated senior physicians, and can only be dispensed by two particular state pharmacies. Patients' files were checked to confirm that bacteriological, histological, and/or other clinical evidence supported the diagnosis. TB cases included were those with a definite (bacteriologically confirmed) and 'other than definite' (histological, radiological and/or clinically confirmed) diagnosis, and were treated with standard short-course chemotherapy. It is laboratory policy to examine all samples obtained from suspected TB patients with the Ziehl-Neelsen stain and to culture on Lowenstein-Jensen medium for acid-fast bacilli (AFB). All cultures positive for AFB were referred for species identification and drug sensitivity testing to a national reference laboratory in the United Kingdom. DNA fingerprinting of positive cultures was not performed during the study period.

Results

Incidence: The mean Malta-born population for the 11-year study period was estimated at about 382,000. A total of 117 persons developed TB and were treated for the first time. The population was further sub-divided into a younger age group with a mean population of around 335,000; 62 of whom

developed TB, and an elderly population of around 47,000; 55 of whom developed TB (Table 1). The mean yearly incidence over eleven years for new cases of TB among the general, the younger, and the elderly population was 2.8, 1.6, and 10.6 per 100,000 person-years respectively.

The new Malta-born TB cases were also stratified according to age into one of six 15-year age categories. The mean yearly incidence over the 11 year was calculated for each of these six categories (Figure 1). The incidence of TB rises nearly exponentially with the increasing age of these groups. The greatest incidence amongst them was seen in the 75 to 90 age group, with an incidence of 14.9 per 100,000 person-years. There were only a few cases in the 0 to 15 year category; this was the lowest incidence rate at 0.8 per 100,000 person-years, also, between 2000 and 2005, no new cases were diagnosed among this group.

The TB incidence for each individual year of the study period, for both young and elderly, show a decreasing trend of 2.5, and 5% per year respectively (Figure 2).

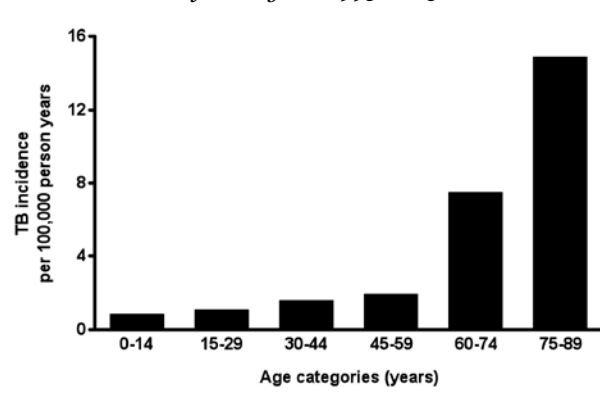
Gender ratio: In total, there were 81 (69%) male and 36 (31%) female cases of TB. The mean stratified incidence among males and females was 3.9 and 1.7 per 100,000 person-years respectively (Table 1) with a male to female incidence ratio of 2.3 to 1, a ratio very similar to that found among populations of Western Europe.³

Among the younger group, there were 41 (66%) male and 21 (34%) female cases of TB. The male and female stratified incidence was 2.2 and 1.2 per 100,000 person-years respectively, and the male to female incidence ratio in this younger group was the smallest at 1.8 to 1 (Figure 3 and Table 1).

Among the elderly, there were 40 (73%) male and 15 (27%) female TB cases. The incidence among elderly males and females was 18.3 and 5 per 100,000 person-years respectively; the incidence ratio, in this group, was the highest at 3.7 to 1 (Figure 3 and Table 2).

Site: There were 96 (82%) cases of pulmonary TB, making this the commonest site of infection. The second commonest site involved lymph nodes in 9 cases. There were 21 (18%) cases of extra-pulmonary TB, involving a variety of other sites (Table 2).

Figure 1: Mean incidence for 15-year age categories in those Malta-born for the years 1995-2005



The denominator populations, number of pulmonary and extra-pulmonary cases, their age stratified incidence, and incidence ratios according to major age groups is shown in Table 1.

Drug resistance: *Mycobacterium tuberculosis* complex was cultured in 38 (41.3%) patients with pulmonary TB. Drug resistance was discovered in only one new case; an elderly male and former dairy farmer, who had *Mycobacterium bovis* infection. This was expected as *M. bovis* is naturally resistant to pyrazinamide.

HIV/AIDS: Among new and relapsing cases, none of those tested were positive for HIV.

Treatment outcome: In the period studied, out of the 117 new cases treated, 106 (90%) were treated successfully, and 11 died before completing treatment (Table 2). There were no patients allocated to the other treatment outcome categories.

Relapses: There were 123 Malta-born TB cases, which included 117 (95 %) new and 6 (5%) relapse cases. None of the relapses were considered as re-infection. In the elderly group, of the 5 males who had relapsed, one eventually died during treatment. There was only one other relapse who had been originally diagnosed and treated as a new case during the study period. There was only one female, from among the younger group, who had relapsed. The relapse rates among the general, younger, and elderly age groups were 1.6, 0.3, and 10.6, per 100,000 person-years respectively.

Mortality: Malta's mortality rate was 0.26 per 100,000 person years. The percentage of deaths among TB cases in the general population, the younger group, and elderly was 9.4, 4.9, and 14.3% respectively.

Figure 2: Incidence of TB in major age groups in those Malta-born for individual years (1995-2005)

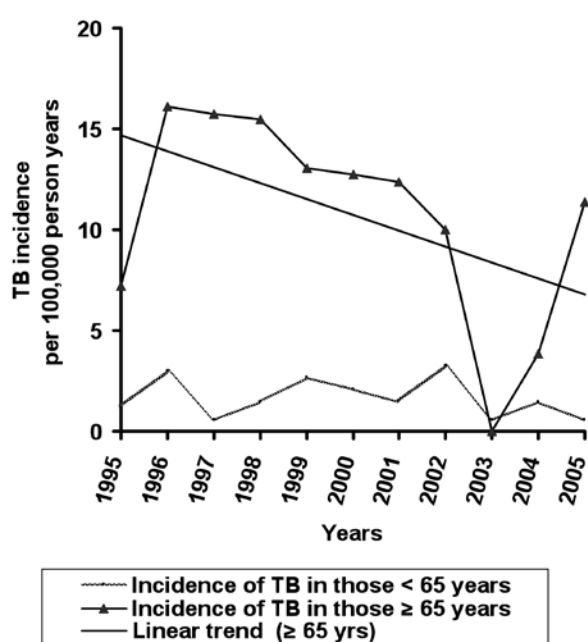


Figure 3: Incidence of TB by age and gender in those Malta-born for the years 1995-2005

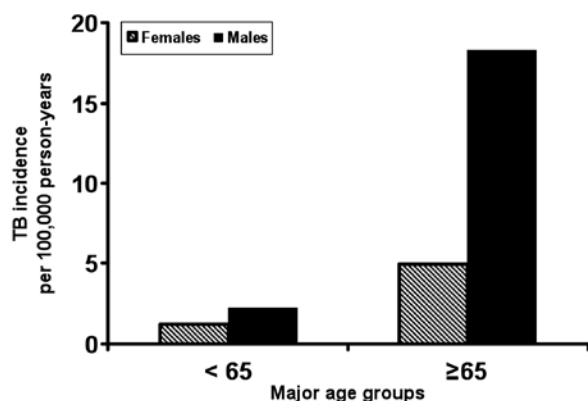


Table 1: Age stratified Malta-born data for the years 1995-2005. Mean population, cases, mean incidence, pulmonary and extra-pulmonary cases, incidence and mortality rates

Major age group	Malta-born population	Population < 65 years	Population ≥ 65 years
Mean population	382,393	335,021	47,374
New TB cases	117	62	55
Mean yearly incidence	2.8	1.6	10.6
Pulmonary TB cases	96	47	49
Mean pulmonary TB incidence	2.3	1.3	9.4
Extra-pulmonary TB cases during the study			
per 100,000 person years	21	14	7
Extra-pulmonary TB per 100,000 person years	0.5	0.38	1.3
Pulmonary to extra-pulmonary TB incidence ratio	4.6 to 1	3.4 to 1	7.2 to 1
Patients who relapsed over 11 years	6	1	5
Mean relapse rate per 100,000 person-years	0.14	-	1
Number of deaths over 11 years	11	3	8
% deaths among TB cases	9.4%	4.9%	14.3%
Mean mortality rate per 100,000 person-years	0.14	0.08	1.5

Table 2: New TB; case number and rate according to site in those Malta-born for years 1995 to 2005

Major site	Cases	Major site	New cases
Pulmonary (82 %)	96	pulmonary	96
Extra-Pulmonary (18 %)	21	lymph node	9
		pleural	2
		meninges	2
		skin	2
		urinary tract	2
		Digestive tract	1
		epididymis	1
		endometrium	1
		bone	1
Total	117		117

Discussion

Incidence: With a TB incidence of 4 times the national average, and 7 times that in the younger group, the elderly can be considered a high-risk group for TB among the Malta-born population. These findings are consistent with those obtained in other European populations.^{2,3,4}

In addition, over the 11 years studied, the mean incidence of TB rises nearly exponentially with 15-year age segments (Figure.1); a similar finding also observed among most populations in the EU when 2006 alone was considered.³ Elderly persons are considered to have an increased risk of developing tuberculosis due to reactivation of latent TB infection, occurring as a result of age-related changes in cell-mediated immunity.⁸ An impaired immune system resulting from conditions such as HIV/AIDS,⁹ diabetes, long-term steroid use, malnutrition, malignancy, lung fibrosis, silicosis⁹ and smoking,¹⁰ in combination with a higher incidence of latent TB infection acquired in youth, may lead to an increased risk of tuberculosis later on in life.¹

While the incidence has fallen across all age groups; the elderly have shown the greatest trend reduction at 5 % per year. In comparison, the drop among those below 65 years of age was 2.5 % per year, which finding is consonant with trends in Ireland, Italy, Norway and other countries where the incidence is also falling among the elderly.³ In the European Union, considering the two periods of 1998 to 2002, and 2002 to 2006, the fall in TB incidence in the general population was 1.3% and 4% respectively.³ These figures must be interpreted in the light of the significant enlargement of European Union. The above average fall in incidence among the Maltese elderly, may be the result of an effective National Tuberculosis Programme (NTP), and improvement of the socio-economic environment. Delayed patient referral, delayed and missed diagnosis, may lead to an under-estimation of TB among the elderly and a surreptitious fall in TB incidence.³ These factors may also hamper control measures, and contact screening, resulting in a longer period of infectiousness and transmission. There were no notifications of elderly patients with TB during 2003. This could also be due

to delayed notification, and the fact that no cases arose in that particular year as a result of year-to-year case fluctuations in a very low incidence country with a small population. Meanwhile, when incidence of tuberculosis is very low, a larger proportion of positive sputum smears are due to a relative increase of environmental mycobacterial infections, this usually occurring among elderly persons who were heavy smokers and/or have chronic respiratory disease. This can result in a false positive diagnosis being made if cultures are not grown.

A significant indicator of ongoing TB infection within a population is the incidence of TB in the 0-14 year old age group (Figure 1); this because young children (especially those from 0 to 5 years) are highly susceptible to TB infection and disease.³

The ultimate aim of all National TB Programmes is the elimination of TB in a country. It would appear that accurate and timely monitoring of stratified incidence, as the elimination phase is being approached, can give a clearer picture of the success or failure of tuberculosis control. This can indicate when and where specific interventions are warranted; interventions may include discontinuing routine vaccination programmes, screening of high-risk groups for infection and disease, and treatment of latent infection in these groups. Surveillance has always been one of the pillars of the Direct Observed Treatment Strategy (DOTS) as promulgated by the World Health Organization.⁸

Gender ratio: The difference in incidence, as regards gender, occurs in most countries,¹¹ and the situation in Malta is consonant with this recognised phenomenon, even when one takes into consideration the islands' small population, geographic isolation, relatively high socio-economic standards and free and easy access to all state health services. This marked difference between genders, not only exists among the general population, but was also found among younger and elderly age groups. The difference in gender incidence ratio, among the elderly, was found to be nearly double that found among the younger group. Explanations that may be considered include, differential exposure to smoking and airborne pollutants, differences in person-to-person interaction, work practices, and genetic differences.

Site: Pulmonary TB is much commoner than extra-pulmonary TB among the general population: a finding common to both elder and younger age groups. In Western Europe, 80% of cases in the general population are pulmonary in site.³ In Malta this proportion is 82% (Table 2). The pulmonary to extra-pulmonary TB incidence ratio in Malta was found to be twice as high among the elderly than in the young, with elderly males having the highest ratio (Table 2).

Drug Resistance: Drug resistance was not discovered among new or relapsed cases, thus reflecting favourably on the NTP. This sensitivity profile is clinically helpful in the empirical choice of initial anti-TB drug regimes in the Malta-born population. The NTP's DOT policy together with long-term nationwide socio-economic improvement has led to a reduction in TB incidence, and also kept drug resistance in abeyance.

HIV/AIDS: None of the cases discovered were found to be co-infected with HIV. Routine HIV testing on TB cases, was started from 2000; prior to this year all were offered screening but only those considered as having any increased risk of HIV/AIDS were strongly advised to undergo testing. During the period from 2000 to 2005, of the 63 new and relapse TB patients, 53 (85%) were screened for HIV, and none were found to be positive, whilst 15% had declined testing. There is no reason to believe that the incidence of HIV/AIDS in TB patients, including the elderly, will not follow trends similar to that found in other countries.⁵

Treatment outcome: Malta has exceeded the minimum 85% successful treatment outcome as recommended by WHO: even among the elderly group with the highest mortality rate.

Relapses: While the number of cases who relapsed was small, the elderly's tendency to relapse was observed to be much higher (35 times) to relapse than the younger group. Relapse occurred more commonly among the elderly: especially males, and was not found to be associated with reduced compliance, drug resistance, HIV/AIDS, or re-infection. One explanation may include the re-activation, of previously well treated disease, in a person with a progressively impaired immune system, occurring with age, and/or other co-morbidities. No DNA fingerprinting studies were carried out during the study. No drug resistance was discovered among cases who relapsed.

Mortality: The mortality in the EU for the period 2001-2006 was 0.7 and found to vary from 0 and 9.6 per 100,000 person-years.³ Malta's rate compares favourably at 0.26 per 100,000 person-years. During the study period, the mortality rate among the elderly was nearly 6 times greater than the mortality rate among the general population, and nearly 19 times greater when compared to the younger group.

Study limitations: The epidemiology of tuberculosis in those who were foreign-born was not taken into account for this study but this was accepted to obtain a clearer picture of TB among those who were Malta-born. Eleven years mean data were analysed in most cases as single year data were considered too small to be reliable. While the number of new Malta-born TB cases over eleven years was small (117) it was comprehensive as 99% of cases were included. The cases studied included both definite, and other than definite cases, therefore clinical, radiological, and histological over-diagnosis may have occurred. DNA fingerprinting was not performed prior to 2006; thus the possibility of cross-contamination of samples, which is known to occur universally, could not be excluded.

Conclusions

The study supports the initial observation that tuberculosis was occurring more often in the Malta-born elderly. This group as a whole, elderly males and the very old (75 to 85 years) are specific high-risk groups for TB, when compared to the general and younger populations. Very low incidence of TB among children (0-15 years) was discovered; this is a good indicator that

on-going TB infection among the native community was low. The findings of both low and falling trends in TB incidence among all age groups indicate the success of long-standing measures taken to control TB among the native population. The marked age-related differences discovered in gender, incidence, site, and mortality should continue to alert physicians, and public health specialists that the elderly form a sub-population with distinct TB-related characteristics, even when the population studied is small, the incidence of TB is very low and when the elimination phase is being approached.

Recommendations

1. Particular attention should be given to the challenge of tuberculosis amongst the elderly sub-group.
2. Increasing awareness among the population and health-care staff to reduce unnecessary delay in referral, investigation, diagnosis, and treatment of TB. The possibility of both under and over diagnosis should always be considered.
3. Treatment of latent TB among the elderly, especially those with radiological evidence of fibrotic changes compatible with old pulmonary TB, may be one way to further reduce reactivation of tuberculosis, and should be considered.^{1,6,7,8}
4. To investigate whether the discontinuation of the routine school BCG vaccination programme, due to very low incidence of TB, is indicated.
5. As all foreign-born TB patients were excluded, their impact on the health-care services, and on the local population should be investigated. The foreign-born populations' own particular epidemiology should be the subject of future studies.

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