Original Article

Tuberculosis in Malta: Thirty-five years of epidemiological trends in the native population

Brian Farrugia, Charmaine Gauci, Julian Mamo, Wafaa Ahmed, Joseph Cacciottolo

Abstract

Background: Malta, the smallest island state in Europe, with an approximate population of 400,000, has one of the lowest reported incidence rates for tuberculosis (TB) in its native-born population.[1] Long-term trends for TB among this population were investigated.

Methods: A period of 35 years (1979-2013) for the Malta-born population was investigated using single-age population numbers for each year, retrospective, and partly prospective analysis of notified TB cases. Mean five-yearly populations were then used to calculate 5-yearly incidence rates for birth-cohorts, age-groups, major site and gender. Annual reported TB incidence rates were also calculated.

Results: In the Malta-born population, over the 35-year period, reported yearly TB incidence shows a downward, albeit decelerating trend. Consecutive follow-up of 5-year age-cohorts and 5-year age-groups confirms that incidence has fallen, with the highest rates being observed in progressively older age-groups. A falling trend in TB incidence according major site and gender was also observed.

Conclusion: TB is being successfully controlled among the Malta-born population, and confirmed to be slowly approaching the elimination phase.[2]

Keywords

Malta-born population, low incidence, epidemiology, tuberculosis.

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Introduction

While tuberculosis is a worldwide pandemic, incidence varies enormously across populations, geographical regions, countries and even within cities.[3,4] The highest reported incidence rates are still seen in sub-Saharan Africa, while most cases originate from South-East Asia (35%). Although global TB incidence has been gradually falling since 2002, absolute cases numbers had continued to rise until 2006, and are only, until recently, recognized to have been falling since that year.[5]

The European Centre for Disease Control (ECDC) publishes yearly national data on reported TB cases and incidence in country populations but not on incidence rates in foreign-born populations;[1] this may be partly due to difficulties in determining a constantly changing or unknown denominator population to calculate the incidence rate in foreign-born persons.

In 2009, Europe representing 5.6% of the global TB burden, and is divided into three main geo-political regions. These include the European Union (EU) including European Economic Area (EEA) countries, the Balkans, and the East (former Soviet Union countries and Russia). Malta forms part of the former region which has the lowest incidence rates of the three; EU rates are approximately 15.8 per 100,000 person-years.[1] Reported TB incidence in Malta remains among the lowest in Europe, at about 13/100,000 person-years

during 2009[5], despite the increase in absolute number of cases diagnosed in Malta after 2001. A relatively large influx of irregular migrants, led to a proportional increase in the number of cases diagnosed among the sub-Saharan population.[1,6]

In 1930, the Norwegian Kristian Ardvord was the first physician to perform longitudinal cohort analysis using country-wide retrospective mortality data to investigate epidemiology, using data pertaining to TB. He presented a classical study using 5-year aggregate data, his discoveries revealed a pattern, enabling him to make accurate predictions on future TB mortality rates among the populations studied.[7]

This study was our investigation of trends in reported incidence rates in a small island population similarly using 5-year aggregate data, over the period 1979 - 2013. Fortunately, TB mortality rates have fallen drastically over the years and could not be used, as in the study by Ardvord, leading us to investigate a number of 5-year mean incidence rates in isolation.

Methods

Thirty five years of data, from 1979 to 2013 pertaining to all TB notification for those native-born were available and investigated. All data was collected from cases seen at the Chest (TB) Clinic at the main hospital, including notifications made centrally by physicians to Public Health, and cover the whole population of Malta. This data was considered highly reliable because TB remains a mandatory notifiable infection by law, nearly all (98%) patients were followed up medically by one Chest Clinic, the number of prescribing consultant physicians were strictly limited and controlled, anti-TB drugs were cost free for all patients and could not be bought on the free market, in addition TB drugs are only dispensed by two designated government pharmacies. These pharmacies in turn inform both Public Health and the Chest Clinic every month of anti-TB medications dispensed. The data set included all cases considered previously as definite and other-than-definite, and nowadays referred to as confirmed, probable and possible. A TB case specifically refers to new reported cases, diagnosed in Malta, among those Malta-born, and commenced on standard anti-TB treatment. The denominator populations used to calculate all 5-year mean reported incidence rates were estimated using the mid-year population values obtained from the yearly produced single-year tables. These tables provided population numbers for each specific age for each year. The source of this population data was the official state publication; The Yearly Demographic Review of the National Statistics Office of Malta.[8]

The original population values for years 1978 to 1984 were revised in 2000 (following the 1995 census), these were considered more accurate than earlier estimated values, and were thus used.[9] Four cases notified in 2003, they were excluded from the official data following a request for declassification from the diagnosing physician. In retrospect, there was a near certainty that their positive cultures were cross-contaminated, as they were asymptomatic on starting treatment and had normal chest x-rays.

The thirty five years under review were apportioned into seven consecutive 5-year periods, because both denominator populations and yearly case numbers were small. The 5-year periods were 1979-1983, 1984-1988, 1989-1993, 1994-1998, 1999-2003, 2004-2008, and 2009-2013. Each of these 5-year periods were further sub-divided according to 5-year age-groups, specifically birth to 4 years of age, 5 to 9 years, 10 to 14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90-94, and 95 to 99 years. The mean reported TB incidence for each of the separate age-groups in each of the seven 5-year periods was calculated using mid-year population numbers and 5-year aggregate data. Seven 5-year cross-sectional studies were produced and merged (figure 2). The calculated mean TB incidence for 5-year age cohorts, for each of the 5-year periods, was successively followed over the 35 years. Similarly, mean incidence trends for 5-year age-groups for each of the seven 5-year periods were followed. Finally, mean 5-year TB incidence was estimated according to major site and gender over the study period.

Results

During the study period there were a total of 566 new cases; 368 males and 198 females which included 378 and 188 cases of pulmonary and non-pulmonary TB respectively.

The yearly trend in TB incidence (Figure 1) among those born in Malta show yearly fluctuations but has fallen throughout the thirty five years, resulting in an overall pattern resembling that of exponential decay.

The combined seven 5-year cross-sectional plots, according to 5-year age-groups, of reported TB incidence show that incidence has fallen in nearly all age-groups and that the higher incidence rates tended to occur among progressively older age-groups (Figure 2). The resulting composite figure of seven 5-year cross-sectional plots reveals a general shift downwards and to the right.

Five-year birth cohorts (Figure 3a and 3b) were followed over the study period and show a clear fall in reported incidence over time, with the exception of the 1989-1993 period. Five-year reported incidence in all age-groups (Figure 4) also show a fall over the same period. Five-year reported incidence rates over the 35 years for both gender and major site reveal a clear downward trend (Figure 5).

***Figure 1**: Yearly TB incidence for the Malta-born population (1979-2013)*

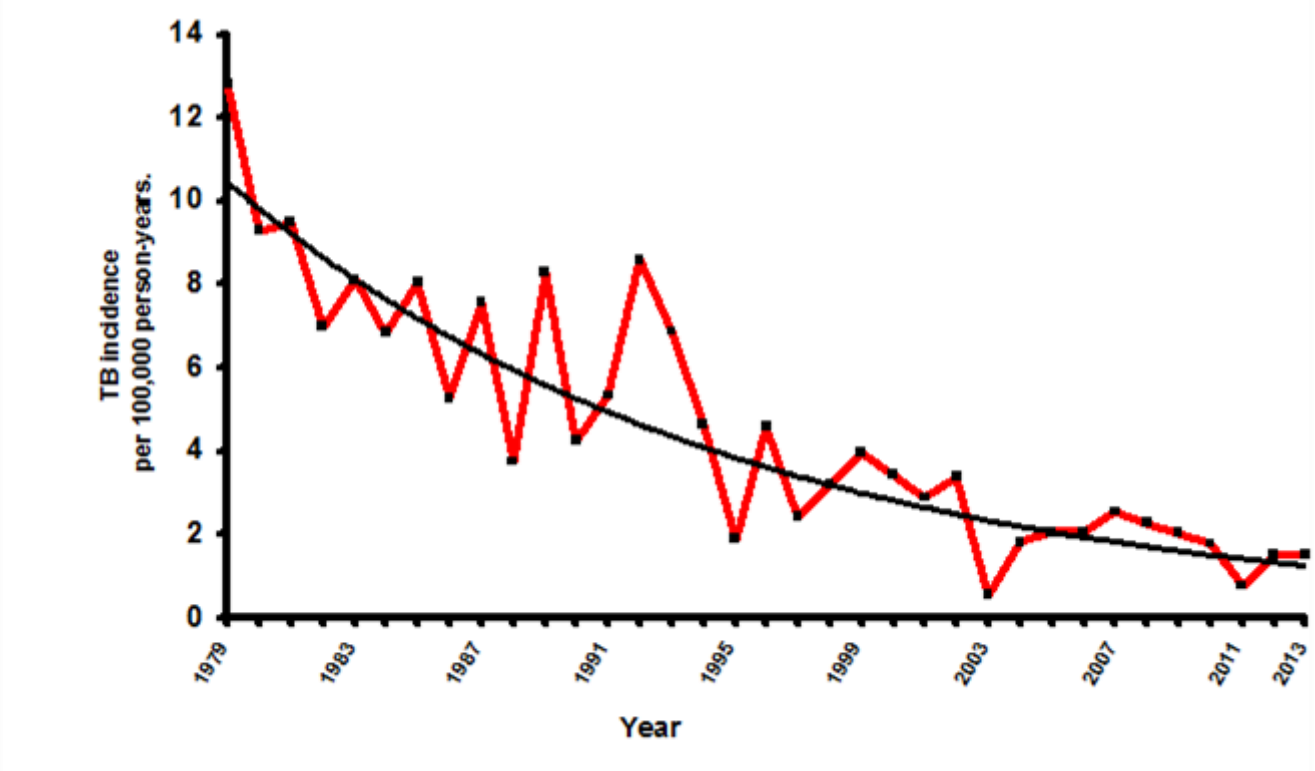


***Figure 2**: Combined plot of TB incidence for 5-year age-groups for each of the seven 5-year periods (Malta-born 1979-2013)*

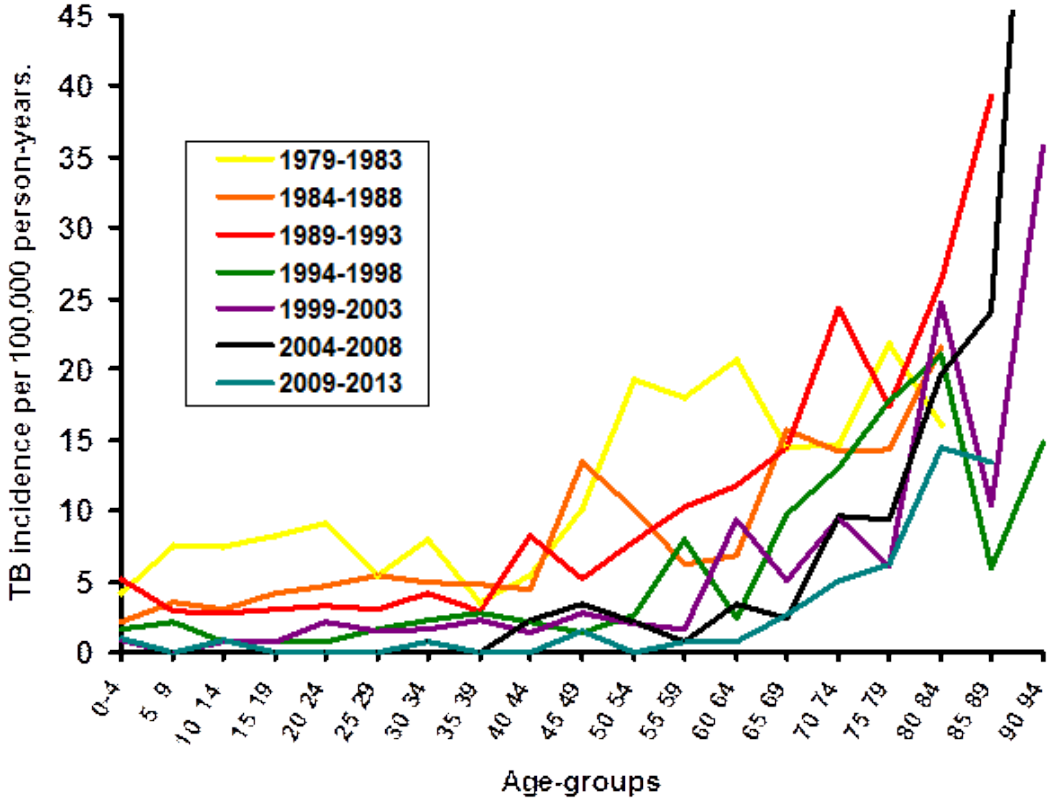


***Figure 3a**: Mean 5-year TB incidence for 5-year birth cohorts for 1979-1983 followed at 5-year intervals (Malta-born from 0 to 44 years)*

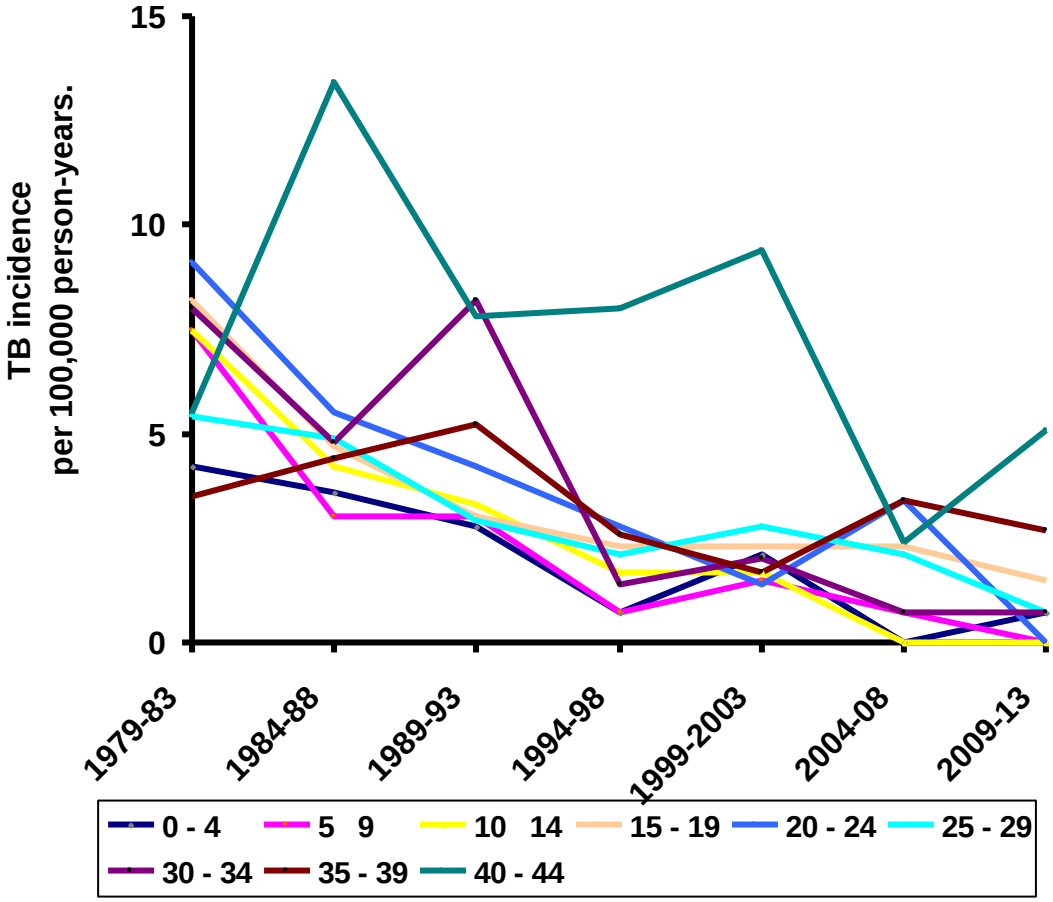


***Figure 3b**: Mean 5-year TB incidence for 5-year birth cohorts for 1979-1983 followed at 5 year intervals. (Malta-born 45 to 94 years)*

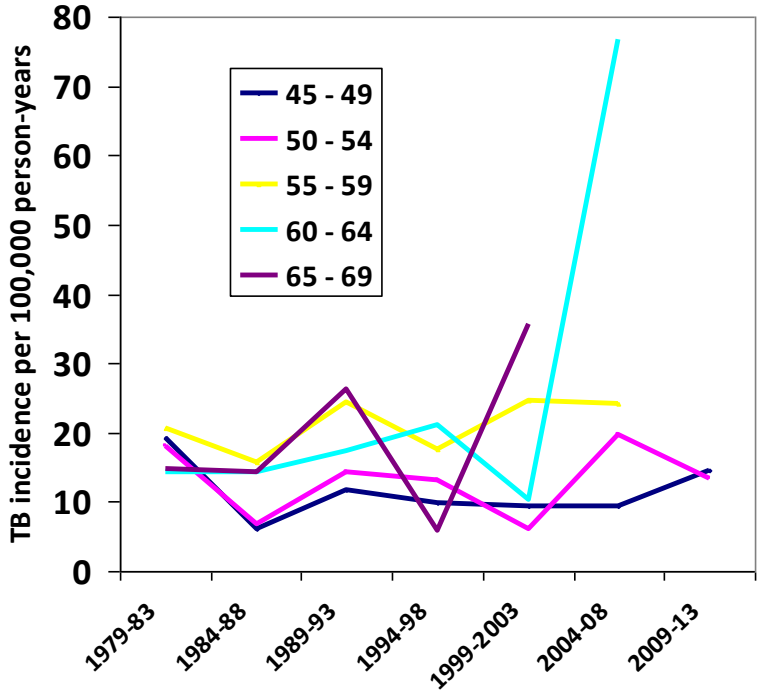


Figure 4: *Mean 5-year TB incidence for 5-year age-groups for each 5-year period (Malta-born 1979-2013)*

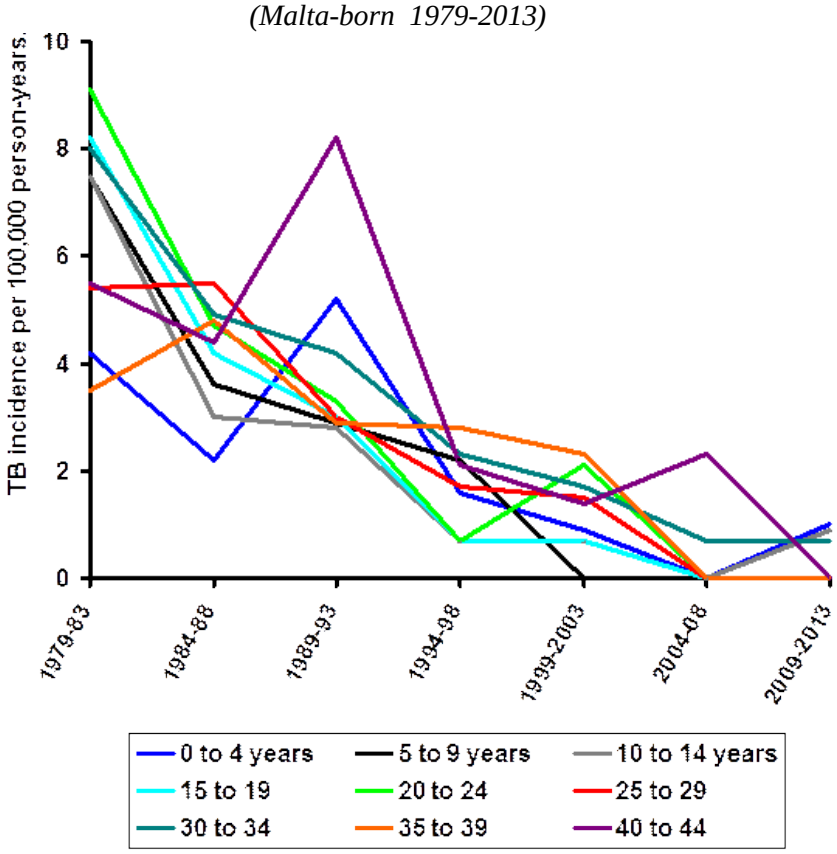
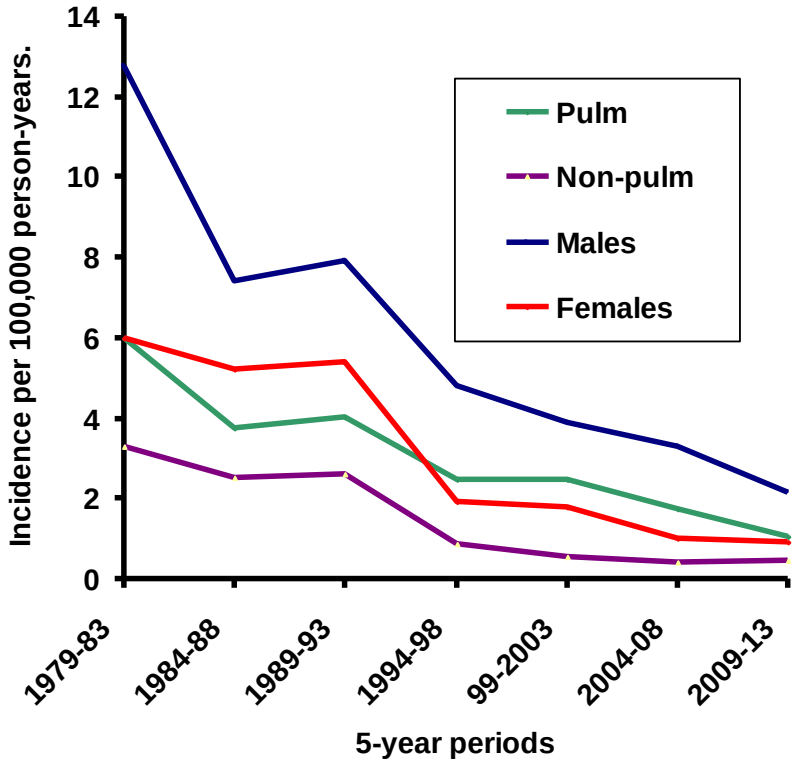


Figure 5*: Mean 5-year TB incidence according to major site and gender. (Malta-born: 1979-2013)*



Discussion

Longitudinal studies examine how data pertaining to specific birth cohorts behave over time, and while prospective studies are preferred, they are often prohibitive due to financial and temporal restraints. In contrast, retrospective studies, less hampered by these obstacles, are useful when data collection is considered reliable, even more so if considered nearly complete, as in our case. Analysis of incidence data for specific age-groups and birth cohorts, which are followed up over time, may give a comprehensive picture of changing epidemiological trends. The patterns may reveal the progression of a disease in a population, and when specific interventions might be indicated, they have also been shown to possess predictive value.[7] In contrast, cross-sectional studies examine variables in a population, or representative sample, over a specific time period.

The elimination of tuberculosis is the ultimate goal of all National TB Programmes (NTPs). The global aim (Millennium Development Goal 6) being the reduction of TB prevalence and mortality to half that of 1990 by 2015, and TB elimination by 2050.[7] The first objective has been achieved for the Malta-born population. Success, in this long-term endeavor in a particular population may well be feasible through the consistent work of a well-functioning NTP, in conjunction with public health and socio-economic measures aimed at improving environmental living conditions and elimination of poverty.[10] WHO had taken the initiative through the STOP TB Partnership in launching a new global STOP TB strategy for 2011-2015, focusing on high quality DOTS expansion and enhancement, control of HIV/TB and multi-drug resistance. It also addresses the needs of poor and vulnerable populations, strengthening of primary health care systems, engaging all care providers, and empowering patients and communities. The publication also gives an indication of the funding required to achieve these goals. It high-lights the development and timely adoption of new technologies and the need for enabling and promoting local research.[11] In Malta`s case, the strategy used in the past consisted of adopting strategies developed by WHO and other larger Western countries, although more recently, an official national strategy for Malta has been produced.[12]

For epidemiological purposes, a population can be considered to be made up of both foreign and native-born persons; both groups exhibit a host of differing dynamics and require appropriate approaches and action. Considering that by definition, the national reported TB incidence is a combined value of disease arising in both native and new entrant populations, elimination of TB, even in developed countries is challenging, if not impossible to achieve. This is simply because no country has complete control over newly-entrant foreign-born persons, legal or otherwise, arriving from high-incidence countries harbouring either latent or active TB, from crossing national borders. In addition, there are no interventions which can completely prevent reactivation in persons with latent TB. It is recognized that in high-risk new entrant populations, higher TB reactivation rates will occur, similar, if not higher, to rates found in their countries of origin. This is highest in the first 2-3 years from entry, and will continue for many years thereafter, albeit at a much lower level.[1-2,13] One of the main factors pivotal to the success of TB control include the political decision to declare the elimination of both TB as a national health and social priority. In contrast, the greatest danger to TB control is complacency which can occur at any and all levels, from patients to health-care workers to politicians. In addition, falling TB incidence can easily tempt administrators to cut on funding and prematurely scale down resources with dire consequences for TB control. The history of TB control in the United States is a case in point.[14]

Figure 1 shows wide fluctuations in reported yearly TB incidence, this is probably due to both low case and population numbers. This finding is consistent with that found in other countries with small populations, including Andorra, Iceland, Liechtenstein, Luxemburg, and San Marino in contrast to larger populations which do not show such large yearly fluctuations.[1] Moreover, as prevalence falls, one would expect a relative increase in non-tuberculous mycobacterial infections,[15-16] and an increase in the proportion of misdiagnosed TB cases relative to actual TB cases. This fact may in part explain the reduced rate of decline seen in Figure 1.

When comparing incidence, for each of the age-groups in the seven 5-year periods (Figure 2, and 4), this falls consistently over time for the younger age-groups. TB among the paediatric age-group is a very good indicator (indicator population) of on-going TB infection in the community, as they have immature immune systems and thus more easily infected and more liable to develop disease.[17] Analysis in the less-than-19 year age-group indicates that TB incidence had fallen consistently and is similarly low – both being indicators of successful national TB control and the actual low levels of TB in the community at large. The higher reported TB incidences rates shift to the right, indicating that over time TB is being mostly diagnosed in older age-groups (Figure 2, and 3b). It is recognised that, in the older population immune-senescence causes reactivation and is the usual cause of TB in the vast majority of cases.[18] For epidemiological purposes, a population can be considered to be made up of both foreign and native-born persons; both groups exhibit a host of differing dynamics and require appropriate approaches and action.

Analysis of trends (Figure 1, 3a,3b, 4, and 5)

showed an unexpected peak during the 1989-1993 period. Examination of yearly incidence (Figure 1) indicates that this was a result of unusually high incidence occurring in 1992 and 1993 and thus influenced data in the 5-year period of 1989-93. This may have been due to a combination of factors including changes in personnel and case ascertainment, mode of diagnosis (clinical, radiological, histological or microbiological), cross contamination, a micro-epidemic situation or the effect of HIV. It does not seem to have been related specifically to major site or gender (Figure 5), further investigation is indicated. The past and present success seen in Malta in reducing TB is multi-factorial, the main reasons may include, reduction in poverty, improvement in housing, centralisation of both clinical and pharmaceutical services, standardisation of treatment regimes, investigation, drug treatment, follow-up, compliance, and close contact screening, all of which were and still remain cost free for all. In addition, anti-TB drugs were and remain unavailable on the private market, thus eliminating the problem of unrecorded diagnosis and treatment of cases. It must be noted that no increase in incidence occurred after 2001, when the massive influx of new irregular entrant cases started. Investigating the epidemiology of foreign-born TB was not an objective of the present study, and was specifically excluded to obtain a clearer epidemiological picture prevailing in the local population.

Limitations of the study

Data collection was mainly retrospective, and case numbers and populations were both small, although the data was considered nearly complete and reliable for reasons alluded to above. The cases studied included confirmed, probable and possible cases, thus clinical, radiological, histological and microbiological over diagnosis, may have occurred. This was strongly suspected to have occurred at least in 2003 and involved four cases. DNA fingerprinting in Malta was not performed prior to 2006, thus, the possibility of cross-contamination of samples before this date should be considered. In addition, a number of cases which were diagnosed with TB from smear positive but negative culture results may have actually had an environmental mycobacterium infection. In fact, in recent years, approximately 75 % of positive cultures in smear positive cases were non-tuberculosis in origin.

Further study

The high number of cases which occurred in 1992 and 1993 should be investigated further. As prevalence continues to fall, the proportion of false positive diagnoses may increase, moreover the impact of imported TB with often drug resistance, on the native population and the increase of non-tuberculous mycobacterial infections will require particular attention and continued epidemiological monitoring.

Conclusion

It has been shown that trends in TB epidemiology, in small populations with very low levels of TB, can still be investigated using 5-year aggregate data. Trends in TB incidence in the native population in Malta, continues to fall, albeit at a slower rate, while TB is being diagnosed more often in progressively older patient cohorts. TB elimination in Malta, at least in the native population, despite rising national incidence, still remains an achievable goal.

Key points

- Epidemiological portraits were produced using 5-year aggregate data.
- An alternative methodology (compared to analysis of yearly data) concerning TB epidemiological dynamics in small populations with very low incidence, approaching the elimination phase has been described.
- It was possible to show falling trends for 5-year age-groups, birth cohorts, major site, and gender among a whole native population with very low TB incidence.

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