

# Tuberculosis in Malta and the school BCG vaccination programme

Brian Farrugia, Victoria Sant'Angelo, Joseph Cacciottolo

## Abstract

**Background:** Malta has one of the lowest incidence rates of tuberculosis in Europe and a comprehensive free-of-charge health care system.

**Objective:** To investigate whether Malta satisfies the criteria recommended by the International Union Against Tuberculosis and Lung Disease (IUATLD) in order to consider the discontinuation of the present school BCG vaccination programme.

**Method:** Review of World Health Organization (WHO), and IUATLD guidelines for BCG use and discontinuation. Examination of surveillance data pertaining to tuberculosis in Malta, for the years 1979 to 2008.

**Findings:** Malta has a long-standing, well-developed surveillance, treatment and follow-up programme for tuberculosis. The average annual notification rate of smear positive pulmonary tuberculosis was about 2 per 100,000 person-years since 1990. This is well below rates recommended by the IUATLD for the discontinuation of routine BCG vaccination programs.

**Conclusion:** Malta satisfies established international criteria for discontinuation of the school BCG vaccination programme and therefore the programme should be re-considered.

## Keywords

Malta, tuberculosis, BCG vaccination, discontinuation.

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## Introduction

Routine mass immunisation with the Bacille Calmette-Guérin (BCG) vaccine has been a contentious issue since its inception. The BCG vaccine was first used in humans in 1921 but received a setback in 1930 following a disaster in Lübeck. Immediately after World War II, mass immunisation in many European countries was introduced as an emergency measures. However this was based on evidence which was far from clear. In addition, many studies on the efficacy of BCG vaccination have shown extensive variation compelling WHO to review the efficacy of the vaccine in 1959 and again in 1979. The WHO subsequently changed its recommendations in 1983.<sup>1</sup>

In the early 1950s, major trials were set up by the British Medical Research Council (MRC) and by the United States Public Health Service, to determine the efficacy of routine BCG vaccination. The procedure employed by the British MRC showed high efficacy against tuberculosis in early adulthood, in contrast to the American experience which did not. BCG vaccination was subsequently recommended as a routine procedure for tuberculin-negative adolescents in the UK, while in the USA, BCG vaccination was limited to certain high-risk populations.<sup>2-4</sup> The British MRC showed that the vaccine had a protective efficacy of 75–80% lasting 10–15 years. At that time, in the UK-born population, TB was commonest amongst those aged 15 to 29 years. Hence it was thought reasonable to vaccinate all tuberculin negative schoolchildren between the ages of 11-13 years to provide subsequent protection. Malta, then a British colony, followed suit as regards the adoption and timing of BCG immunisation. Even before 2005, the UK had satisfied the IAUTLD criteria for discontinuing the school BCG vaccination program, and this was subsequently stopped. The current UK guidelines recommend that vaccination efforts are targeted towards those most at risk, and discontinued in low-incidence and low-risk populations.<sup>5</sup> In the UK targeted use of the BCG vaccine is currently recommended because of evidence of its efficacy in infancy by reducing, pulmonary disease, disseminated and tuberculous meningitis, and mortality from TB.<sup>5</sup>

The epidemiological pattern of TB in Malta closely resembles that found in the UK today: very high rates in persons born in high TB-endemic regions, and very low levels in the native population. In addition, Malta has a lower national TB incidence rate and a lower annual risk of infection rate than in the UK.<sup>5,6</sup> In 2002, the Malta Tuberculosis Working Group called for

the reconsideration of the School BCG Programme in Malta as the IUATLD criteria had been reached. It was decided at the time to continue the vaccination program mainly because of uncertainties resulting from the changing epidemiological picture in Malta: in that year, an unusual number of irregular migrants from high TB and high HIV-incidence regions started to arrive in Malta. The UK had earlier on faced similar concerns.<sup>4</sup> To date, Malta has a routine school BCG vaccination program, for children between 11 and 12 years of age, who are Mantoux negative (0-4mm). This non-mandatory but highly recommended program is offered free-of-charge to all children, and has a coverage of more than 78 % (Table 1).

The incidence of TB in native-born populations of most western European countries, including Malta has been falling again since the early 1990`s.<sup>6</sup> In view of this favourable situation, school and neonatal BCG vaccination programmes in many of these countries have been reviewed, modified or discontinued.<sup>7</sup> The decision to discontinue mass vaccination in a given population and change to selective or targeted vaccination is based on criteria produced by the IUATLD as recommended by WHO. The criteria were produced to help national immunisation advisory bodies to examine local epidemiological data and reach a decision on the future of their routine immunisation programmes.<sup>8</sup>

The BCG vaccine is one of the most widely used vaccines, with a coverage of more than 80% in neonates and infants

in developing countries where it forms part of the national childhood immunisation programs, in accordance with WHO position documents.<sup>9</sup> This vaccine has a documented protective effect against tuberculous meningitis and disseminated disease in children, especially neonates. However, it neither prevents primary infection nor reactivation of latent pulmonary infection. It does not appreciably reduce the number of infectious persons, the principal source of airborne bacillary spread, and so the vaccine has a minimal role in lessening the incidence of TB at a community level.<sup>9</sup> BCG immunisation is thought to reduce post-primary mycobacterial haematogenous spread in young children and therefore reduces miliary or disseminated TB and TB meningitis. BCG immunisation can be life-saving in younger children since they have an increased risk of progression to active disease.<sup>10</sup> It has been shown that once infected, children under 12 months have a 43% increased risk of progression to acute disease, 1 to 5 year-olds have a 24% increased risk, while adolescents have a 15% increased risk of progression.<sup>11</sup>

The protection offered against adult forms of the disease is uncertain. Studies on BCG vaccination, from different areas of the world have shown variable efficacy rates ranging from 0 to 80%.<sup>10</sup> Exposure to and infection with environmental mycobacteria, more frequently found in hot climates, induces some immunity in the body.<sup>2</sup> The resulting increased immunity towards mycobacteria in general probably masks any protection BCG vaccination may provide.<sup>10</sup> Differences of human exposure to environmental mycobacteria is the most likely explanation for the wide range in efficacy of the various immunisation programmes. These inconsistent results have led to the adoption of diverse BCG vaccination programmes by different countries.<sup>2</sup>

The World Health Organization, through the Expanded Immunization Programme (EPI), recommends BCG vaccination for infants at birth (or as soon as possible thereafter) in high-risk and high-incidence populations.<sup>11</sup> High-risk regions include Eastern Europe, sub-Saharan Africa, South East Asia and the Middle East. Booster doses of BCG are not recommended by WHO, as there is no documented value in this policy.<sup>12</sup> BCG vaccination is contraindicated in persons with impaired immunity including known or suspected congenital immunodeficiency, leukaemia, lymphoma, generalised

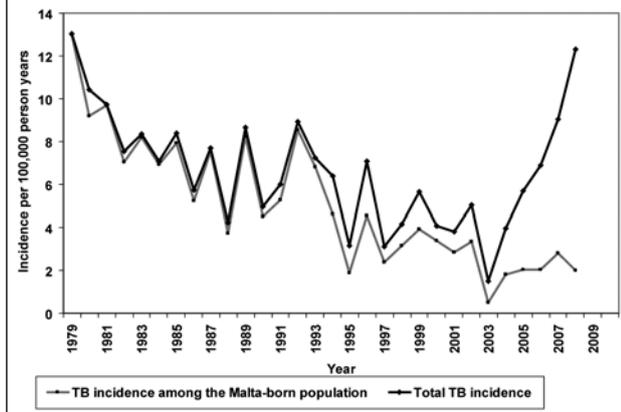
**Table 1:** Number and percentage vaccinated by scholastic year

Year	Total 11-12 year old population considered for vaccination	Population vaccinated	% vaccinated
2001-2	5517	4637	84
2002-3	5887	4810	82
2003-4	5716	4819	84
2004-5	5321	4392	83
2005-6	3403	2651	78
2006-7	7240	6076	84
2007-8	5287	4438	84

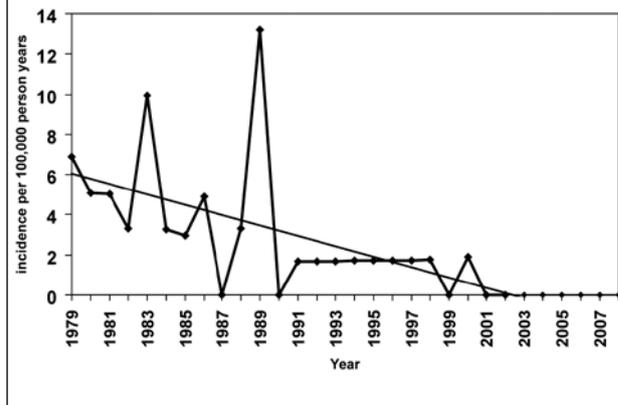
**Table 2:** Annual risk of infection (R) in children by scholastic year

Scholastic Year	Total population tested	Mantoux tested negative 0-4mm	Mantoux tested 5-9mm	Mantoux tested positive ≥ 10mm	Prevalence = positive (≥10mm) tested %	Annual risk of infection (R)
2001-2	4792	4641	107	44	0.918	0.188
2002-3	5135	4992	111	32	0.507	0.057
2003-4	4948	4819	100	29	0.586	0.071
2004-5	4609	4398	184	27	0.586	0.071
2005-6	2792	2672	102	18	0.645	0.083
2006-7	6428	6113	251	64	0.996	0.369
2007-8	4561	4446	90	25	0.548	0.064

**Figure 1: Incidence of tuberculosis: total and among the Malta-born population**



**Figure 2: Incidence of TB in the pre-vaccination Malta-born 0-10 year age group**



malignant disease, immunosuppressive therapy, pregnancy and in asymptomatic HIV-positive persons.<sup>13,14</sup> Countries with a low burden of TB may choose to limit BCG vaccination to neonates and infants of recognised high-risk groups for the disease. The routine use BCG vaccination for tuberculin-negative older children depends on the epidemiological situation found in specific communities. In some low-burden populations, BCG vaccination has been largely replaced by intensified case detection and supervised early treatment.<sup>9</sup>

In 1994, the IUATLD had suggested criteria under which it was reasonable for a country with low TB prevalence, to consider a shift from routine mass BCG vaccination programmes towards targeted vaccination of high-risk groups. A well-functioning National TB control programme with an efficient notification system had to be in place including one of the following conditions:

- The average annual notification rate of smear positive pulmonary tuberculosis is 5 per 100,000/year or less during the previous three years.
- The average annual notification rate of tuberculous meningitis in children under five years of age is less than 1 per 10 million population over the previous five years,
- The average annual risk of tuberculous infection is below 0.1%.<sup>8</sup>

## Methods

The IUATLD criteria for evaluation of National TB Control Programmes were considered as no other similar guidelines could be found.

All TB-related data were obtained from the Chest Clinic/ Unit which also functions as a TB surveillance unit for Malta. The number of smear (Ziehl–Neelsen stain) positive cases of pulmonary tuberculosis and the number of children less than five years of age notified with tuberculous meningitis were collected. Comprehensive TB-related medical care at this Clinic is free-of-charge; contact tracing is also performed and persons with latent TB infections are treated or advised accordingly. Diagnosing physicians are required by law to notify all forms

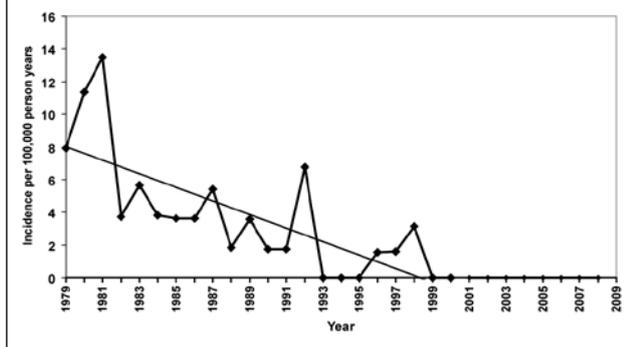
of tuberculosis. The few patients who were treated privately were identified, as anti-TB medications cannot be obtained commercially, and their prescription is restricted to specified physicians. Free-of-charge anti-TB medication is only dispensed by two state pharmacies and the Chest Clinic is notified regularly of all such medication dispensed in Malta. Almost all patients suffering from TB, including those diagnosed privately, were referred to the Chest Clinic, and those who were not, were still followed up by the Clinic. This Clinic also receives laboratory notification of all smear and culture positive results for TB, including those for environmental mycobacteria.

Information about the denominator populations for each specific age-group and for each year (end of year) investigated was derived from data provided in the National Statistics Office yearly demographic reviews.<sup>15</sup> These were used to calculate the incidence rates. TB cases included those with a *definite* (bacteriologically confirmed) and *other than definite* (histological, radiological and/or clinically confirmed) diagnosis, and who were treated with standard short-course chemotherapy.

It is a long-standing laboratory policy to screen all samples obtained from patients suspected of having TB 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 UK. TB cases used for estimation of incidence included all cases diagnosed in Malta *de novo* and relapses. New TB cases were included for estimation of national incidence and were separated into Malta-born and foreign-born. For estimation of sputum positive cases, native, foreign-born and relapse cases were combined as all these categories are deemed infectious.

The average annual risk of tuberculous infection is estimated by using tuberculin based population surveys. The results of Mantoux testing prior to school BCG vaccination, over seven consecutive scholastic years (2002–2008), in Malta were used (Table 2): transverse diameters of 0 to 4mm induration were considered as a negative result and eligible for vaccination,

**Figure 3:** Incidence of TB in the Malta-born 13-23 year age group



diameters of 5 to 9mm were considered as intermediate and not requiring vaccination, while diameters of 10mm and over were considered as positive and warranted further contact investigation. Children with the latter result were referred to exclude TB in both self and all other household members. The average annual risk of tuberculous infection was calculated by using the results of Mantoux testing (Table 2) and the equation  $R=1-(1-P)^{1/a}$ , where  $R$  stands for annual risk of infection,  $a$  is the average age at which prevalence is calculated and  $P$  the prevalence. This method to calculate the average annual risk of infection is derived from a formula by Nyboe,<sup>16</sup> and although it suffers from a number of shortcomings as shown by Rieder,<sup>17</sup> may be useful as a method of measurement. The prevalence  $P$  of TB infection was calculated by using the pre-vaccination numbers of positive Mantoux results. The value of  $a$  represents the average age of Mantoux screening: from their 11<sup>th</sup> to 13<sup>th</sup> birthday. High-risk indicates an incidence of at least 40/100,000 person-years and low-risk incidence is considered as 20/100,000 person-years or less.<sup>5</sup>

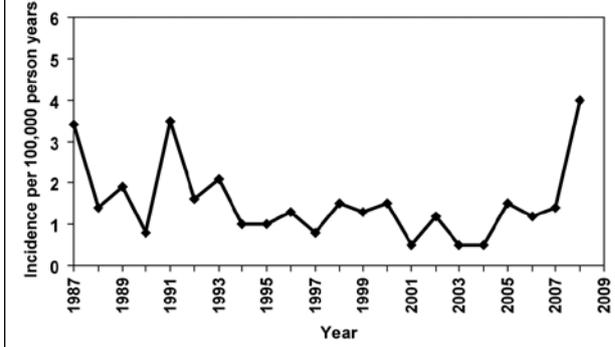
## Results

With a long-standing, well-developed surveillance, treatment and follow-up National TB programme, Malta has one of the lowest TB incidences in Western Europe. The downward trend in TB incidence in the Malta-born population has been maintained (Figure 1). Directly Observed Treatment, short-course chemotherapy, treatment outcome monitoring, good pharmaceutical services and consistent political support have helped to achieve WHO recommended targets. The absence of local drug-resistant TB is a good indicator of adequate local treatment.<sup>17</sup> The highest incidence of TB occurs amongst the elderly population and continues to fall.<sup>18</sup> There have been no notifications of TB in Malta-born children for at least 8 years (Figures 2 and 3).

The yearly average incidence of smear-positive pulmonary TB since 1990 was 2/100,000 person-years: this even includes cases of smear positive samples from which no organisms were cultured and could probably have included atypical mycobacteria (Figure 4). This satisfies IUATLD criterion *a*.

As regards meningeal tuberculosis, there was only one case

**Figure 4:** Total incidence, including relapses, of smear positive pulmonary TB in Malta



since 1979: a 5 year-old child notified in 1991. This rate, given the small size of the population, at around 410,000, is negligible: the latter and the time span satisfy criterion *b*.

The calculated average annual risk of tuberculous infection in 11 to 12 year old children over a seven-year period is 0.13%, or 0.089% if an anomalous scholastic year (2006/2007) is excluded (Table 1). Mantoux testing in the current circumstances of very low TB incidence is also expected to produce a high rate of false-positive results. In fact children who were pre-vaccination Mantoux-positive, were examined further and tested with the interferon gamma release assay (IGRA) available (QuantiFERON®TB Gold Test) with the result that approximately one third were subsequently found to be positive.<sup>19</sup> At such low prevalence rates even the IGRA itself could still be expected to produce a number of false positive results. The scholastic year 2005/2006 featured a lower than usual number of children considered for Mantoux screening due to an influenza epidemic which disrupted the service. The following scholastic year 2006/2007 showed a number of children carried over from the previous year and resulted in a higher number screened. The resultant higher annual risk of infection could represent an anomalous and biased result. The annual risk of infection  $R$  fell again to the usual range the following scholastic year (2007/2008).

## Discussion

The incidence of tuberculosis in Malta remains very low at less than 15 per 100,000 person years, in spite of the large influx of irregular immigrants and other foreign-born persons coming from high incidence countries, especially since 2002.

The incidence of smear positive pulmonary TB has been below 5 per 100,000/person - years since at least 1987. This finding provides evidence and is a good indicator of the small number of individuals in the community with the ability to infect other persons and maintain ongoing TB prevalence.

Children are more easily infected by the mycobacterium and more frequently go on to develop, often fatal, acute disease. The incidence of TB meningitis, in highly susceptible children under the age of five, gives a good indication of on-going TB infectious disease in the community and is approximately 1% of the annual risk of TB infection.<sup>10</sup> Children usually develop much less infectious forms of the disease because they rarely

produce sputum, and if samples are obtained, they are seldom smear-positive.<sup>20</sup> The likelihood of native children coming into contact with infectious TB in irregular migrants, a high-risk population, and becoming infected is unlikely. Children could be targeted for BCG vaccination at birth, if coming from high-risk groups. These would include children born in high TB-incidence countries or born in Malta where the provenance of at least one parent (or grand-parent) is from a region with a high incidence of tuberculosis.

The age (11-12 years) at which the vaccine is routinely offered in Malta, can certainly not provide any direct protection from TB in the most susceptible group: those less than 11 years of age. Despite the increased susceptibility, this age group had not shown any increase in miliary, meningeal, or pulmonary TB, moreover this group's estimated annual risk of infection was very low. Incidence of TB in this pre-vaccinated group showed a decline of approximately 4.3% per year from 1979 to 2000 and after this year there were no cases reported (Figure 2). These favourable findings indicate very low levels of ongoing TB infection in the community. Mantoux testing prior to school BCG vaccination (Table 2) did not show any marked or consistent increase in Mantoux positivity over the years 2002-2008, coincident with increased immigrant arrivals.

Consideration must also be given to the adverse effects of the vaccine; if the risk of disease is estimated to be much lower than the risk of serious vaccine adverse reactions, then a mass vaccine program should be reconsidered. Although the vaccine is known to be extremely safe, significant local reactions, such as extensive local ulceration and regional lymphadenitis occur in less than 1 per 1000 vaccinations. Other estimates per million vaccinations include a range of 1.7-72.9 cases of osteitis, and a range of 0.19-1.56 cases of disseminated BCG disease.<sup>10,21</sup> Considering these complication rates, Malta can expect at least one to two children developing a serious local adverse reaction each year. The risk of developing adverse events also varies by population, age, vaccine strain, dose, immune status, HIV status, site and depth of injection and technique of administration.<sup>2</sup> It would seem that the incidence of tuberculosis (figure 3) is now much less than the adverse reactions expected from the vaccine.

In conclusion, Malta satisfies the criteria proposed by the IUATLD to consider discontinuation of the routine mass BCG vaccination programme, and in turn it may no longer be reasonable, or even safe, to encourage routine school BCG vaccinations for the Malta-born, 11 to 12 year-old population. It may be recommended that a new policy document regarding targeted BCG immunization be drawn up and that surveillance should be continued to specifically monitor the effect of stopping the programme. Cost savings should be estimated and possibly diverted to strengthen other more pressing activities of the National TB Programme. One of the greatest threats to public health security is the very high incidence of TB in irregular immigrants coming to Malta from high-TB and high-HIV prevalence areas of the world. Any re-organisation of the National TB programme should take into account this changing demographic pattern in Malta.

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