Annual risk of tuberculosis infection in Sri Lanka: a low prevalent country with a high BCG vaccination coverage in the South-East Asia Region

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ABSTRACT

Introduction: Despite its simplicity, efficiency and reliability, Sri Lanka has not used the Annual Risk of Tuberculosis Infection (ARTI) to assess the prevalence and efficiency of tuberculosis (TB) control. Hence, a national tuberculin survey was conducted to estimate the ARTI.

Materials and Methods: A school-based, cross-sectional tuberculin survey of 4352 children aged 10 years irrespective of their BCG vaccination or scar status was conducted. The sample was selected from urban, rural and estate strata using two-stage cluster sampling technique. In the first stage, sectors representing three strata were selected and, in the second stage, participants were selected from 120 clusters. Using the mode of the tuberculin reaction sizes (15 mm) and the mirror-image technique, the prevalence and the ARTI were estimated.

Results: The prevalence of TB estimated for urban, rural and estate sectors were 13.9%, 2.2% and 2.3%, respectively. The national estimate of the prevalence of TB was 4.2% (95% CI = 1.7-7.2%). ARTI for the urban, rural and estate sectors were 1.4%, 0.2% and 0.2%, respectively, and the national estimate was 0.4% (95% CI = 0.2-0.7%). The estimated annual burden of newly infected or re-infected TB cases with the potential of developing into the active disease (400/100 000 population) was nearly 10-fold higher than the national new case detection rate (48/100 000 population).

Conclusion: The national estimate of ARTI was lower than the estimates for many developing countries. The high-estimated risk for the urban sector reflected the need for intensified, sector-specific focus on TB control activities. This underscores the need to strengthen case detection. Repeat surveys are essential to determine the annual decline rate of infection.

Key words: Annual risk, prevalence, Sri Lanka, tuberculosis

INTRODUCTION

Annual Risk of Tuberculosis Infection (ARTI) is defined as the probability of acquiring new infection or re-infection over a period of 1 year. It is one of the simplest, most reliable, efficient and preferred indicators of the epidemiological situation of tuberculosis (TB).[1-3] ARTI can be computed from the disease prevalence estimated through well-planned cross-sectional tuberculin
surveys in a representative sample of children. It provides required information with a sufficient degree of accuracy. Furthermore, practical World Health Organization (WHO) guidelines on conducting tuberculin surveys and estimating ARTI are readily available.\cite{4} In contrast to cross-sectional disease burden surveys, conducting tuberculin surveys is less cumbersome, cost-effective and requires minimal skilled staff.\cite{4,5} ARTI expresses the overall impact of multiple factors influencing transmission of TB and the effectiveness of disease control measures in a given community.\cite{1-3}

Despite the feasibility and usefulness of estimating ARTI in low resource countries, this has not been conducted in Sri Lanka. Although Sri Lanka is considered as a low prevalent country in the South-East Asia region,\cite{6} around 9000 new TB cases are notified every year.\cite{7} Nearly 60% of these are smear-positive, pulmonary TB cases.\cite{7} Hence, conducting a nation-wide tuberculin survey to determine the prevalence of TB and the ARTI among Sri Lankan children, as an indicator of recent TB situation in the community, is timely and appropriate. This also helps determine whether there is an under-reporting of new cases through the routine disease surveillance system. Moreover, it would be a useful reference for future estimates, repeat tuberculin surveys to assess epidemiological trends and the impact of TB control activities in the country.

**MATERIALS AND METHODS**

**Study design**
A nation-wide, school-based, cross-sectional tuberculin survey.

**Study population and sampling**
Generally, un-vaccinated children or children without a BCG scar are enrolled for tuberculin surveys as BCG-induced tuberculin sensitivity could interfere with the interpretation of study results.\cite{8} However, given the very high BCG vaccination rates\cite{9} and the high rates of BCG scars among Sri Lankan children,\cite{10} enrolment of un-vaccinated children or children without a BCG scar in sufficient numbers is impracticable. Therefore, school-children aged 10 years (1999 birth cohort) irrespective of their BCG vaccination status and availability of a BCG scar enrolled in public and semi-public schools in Sri Lanka comprised the study population. All children with severe malnutrition, fever \(>38.5^\circ\text{C}\), known contraindications for tuberculin testing, immune-compromised conditions, skin rashes, eczema and those suffering from major viral infections, namely, measles, varicella, influenza and infectious mononucleosis at the time of tuberculin administration and those with exposure to live viral vaccines within 4 weeks preceding the date of tuberculin administration were excluded.\cite{11} The required sample size was estimated using the following formula\cite{12}:

\[
N = d \left(1.96 \right)^2 \left(1-P/\epsilon^2 \right) P
\]

where \(N\) = sample size, \(d\) = design effect, \(P\) = prevalence, \(\epsilon\) = relative precision

We considered a prevalence of 10% based on the results of a south Indian study among children aged 10 years with a BCG scar\cite{13} as no estimates for Sri Lanka were available. For a relative precision of 10%, level of significance of 5% and a design effect of 1.5, the estimated sample size was 5186. This estimated sample size was distributed proportionately among urban, rural and estate strata based on 2001 population census data.\cite{13} Accordingly, the number of study participants required from urban, rural and estate sectors were 936, 3978 and 272, respectively.

A two-stage sampling procedure was used to select the study sample. In the first stage, we listed all urban, rural and estate sectors in the country separately. These sampling frames were used to sample urban, rural and estate sectors for the study. Urban and rural sectors in the Northern Province were excluded from this sampling frame due to inaccessibility. The sector-categorization used in the national census of 2001 formed the basis for categorization. Guided by the WHO recommendation to select 5-25% of the total geographical units in a stratum based on the operational convenience and sample size,\cite{4} we selected 6 (35%) out of 17 sectors listed in the urban stratum, 8 (40%) out of 20 sectors listed in the rural stratum and 3 (20%) out of 15 sectors listed in the estate stratum. Overall, 12 (48%) districts in the country were represented in sectors selected under urban, rural and estate strata in the study.

In the second stage, the required number of clusters was selected from three individual strata. A ‘year 5’ class in a school was considered as a cluster. All ‘year 5’ classes in selected sectors, the total number enrolled in a class and the cumulative number of ‘year 5’ school-children were listed separately for all three strata. The required number of clusters within the respective stratum was selected probability proportionate to the size (PPS). The required number of clusters from a stratum was determined by the cluster size that depended on the median number of children in clusters within a stratum. Based on this, the total number of clusters that was required to select the estimated sample size was 120. Within a selected cluster, school-children who were eligible for the study with the parental consent were enrolled. When the number of eligible children in a selected cluster exceeded the required cluster size, the required numbers of participants were selected randomly.
Field procedure
In a cluster, after explaining the purpose of the study and obtaining the written parental consent, a medical officer appraised the eligibility of students. The Public Health Nursing Sister (PHNS) noted down the availability of a BCG scar in an eligible child. Then, a trained nursing officer administered 0.1 ml of tuberculin I (1 TU of PPD RT 23 stabilized with Tween 80), according to the standard protocol. The PHNS recorded this procedure as ‘satisfactory’ or ‘un-satisfactory’ using standard criteria. In 72 h after tuberculin administration, the test-reader measured the size of the tuberculin.

To determine the prevalence of infection, justifying the appropriateness of using the current batch of tuberculin and ensuring the comparability of results with other studies, Welisara Chest clinic administered tuberculin to 82 smear-positive TB patients within 1 week of diagnosis. With the expected frequency based on moving averages, the sensitivity of the batch of tuberculin used was 86.7% at 10 mm and 74.6% at 14 mm. Since these values were approximate to the sensitivity of 90% at 10 mm and 75-85% at 14 mm demarcation reported in different studies all over the world,[1,2,4] tuberculin PPD RT 23 was demonstrated to be appropriate for the field study.

While the study was in progress, due to death of a child recipient of rubella vaccine in the school programme, enrolment of study participants had to be limited to 103 clusters as all injection procedures were not permitted until a further notice by the Ministry of Education.

Statistical methods
The frequency distribution of reaction sizes in the form of a histogram was plotted from observed tuberculin reaction sizes. Depending on the form of the histogram, following scenarios were considered to determine the prevalence of infection. In the event of having a bi-modal graph showing two distinct modes and an easily definable anti-mode as seen in low prevalence of non-specific tuberculin sensitivity, frequencies of all reactions greater than the anti-mode were to be doubled. Then, the doubled frequencies were to be added to the frequency at the alternative mode to estimate the frequency of children assumed to be infected using the mirror-image technique.[4,16]

The following formula was used for estimating the prevalence (P) of TB infection[4]:

\[ P = \frac{\text{Number of children assumed to be infected}}{\text{Total number of children analysed}} \times 100 \]

As the number of test-read children was not uniform in each cluster, first, the proportion of children assumed to be infected in each cluster was calculated. After weights, equal to the inverse of initial probability of a cluster being selected (ratio of the population of \( i \)th cluster to the district stratum-specific population), were assigned, the proportions were pooled to estimate the proportion of children assumed to be infected in each district. The proportions of children assumed to be infected in a stratum were estimated by pooling the estimates of children assumed to be infected for each district using the proportion of district population to the stratum population as the weight. The stratum specific estimates were pooled to obtain the overall national estimate with the proportion of the stratum population to the total population of all strata as the weight.[1,4,5] Formulae used in this calculation process are given in Appendix I. This estimate of prevalence was used to calculate ARTI. The following formula, where \( P \) was the estimated prevalence while \( A \) was the mean age of test-read children, was used for the calculation[1,4,5]:

\[ \text{ARTI} = 1 - (1 - P)^{1/A} \]

RESULTS

Of the estimated sample size of 5186, only 4352 (84%) study participants were enrolled due to the death of a school-child following rubella vaccination. Overall, the enrolment rates in urban, estate and rural sectors were 73.0%, 98.5% and 85.6%, respectively. The number of children administered tuberculin satisfactorily was 4318 (99.2%). This consisted of 2346 (54.3%) girls and 1972 (45.7%) boys. The majority (\( n = 4238, 98.2\% \)) were vaccinated with BCG in infancy. The BCG scar was found in a great majority (\( n = 4039; 95.3\% \)). Of the children who were administered tuberculin, 4202 (97.3%) were test-read and analysed. The frequency distribution of tuberculin reaction sizes among children aged 10 years irrespective of the BCG scar and vaccination status is given in Figure 1. The proportion of children without a reaction was 57.1%.
A second mode of reactions potentially attributable to the infection with tubercle bacilli is distinguishable at 15 mm, although not distinctly clear. However, in this case, an anti-mode could not be identified. Therefore, the mode of reaction sizes of smear-positive Pulmonary Tuberculosis (PTB) cases was considered as the alternative mode of the frequency distribution of reactions sizes attributable to TB infection in the study participants [Figure 2]. The proportion without a reaction among smear-positive PTB patients was 7.4%.

Although this frequency distribution of tuberculin reaction sizes among smear-positive PTB cases is generally unimodal, in this series, we found two clearly visible modes at 15 mm and 20 mm. However, when accounted for the possible digit preference by smoothening data in terms of converting to two point moving averages, the mode was at 15 mm. This overlapped with the value of the suspected mode of reactions assumed to be attributable to the infection in the study participants. Hence, the frequency assumed to be TB among study participants was determined by doubling the frequency of tuberculin reactions larger than 15 mm and adding to the frequency at 15 mm (mirror-image technique). The estimated prevalence and ARTI based on this frequency assumed to be TB are indicated in Table 1.

The prevalence of TB and ARTI computed was similar among both the sexes. The prevalence among males and females were 4.2% (95% CI: 0-12%) and 4.1% (95% CI: 1.4-6.8%), respectively. The ARTI for males and females were 0.4% (95% CI: 0-1.2%) and 0.4% (95% CI: 0.1-0.7%), respectively. However, in contrast to the estate (2.3%, 95% CI: 0-6.4%) and rural sectors (2.2%, 95% CI: 0-5.7%), the prevalence was much higher in the urban sector (13.9%, 95% CI: 8.4-19.4%). The national prevalence was 4.2% (95% CI: 1.7-7.2%), while the ARTI was 0.4% (95% CI: 0.2-0.7%).

**DISCUSSION**

Although the estimation of ARTI is the simplest, most-efficient and reliable indicator of the epidemiological situation of TB, many developing countries still do not estimate ARTI.[16] The present study was the first national tuberculin survey that enabled estimation of the prevalence and the annual risk of TB in Sri Lanka. It provided baseline data to evaluate the impact of disease control and for future appraisals of epidemiological trends. One limitation of this study, performed in 2009, was its applicability of results to 2004 [2009 - the age of the study population/2). Assessing the trends in repeat surveys can minimize this limitation.

One general recommendation in planning surveys to determine ARTI is that national-level surveys are preferred in smaller countries, while, in larger nations, separate surveys are preferred at sub-national levels with adequate, separate sample sizes for each stratum.[4] We, as a small country, primarily planned for computation of a single-national estimate. In spite of this, we present separate estimates for urban, rural and estate sectors. However, over sampling in urban, rural and estate strata in this study or conducting independent surveys in different strata, including different socio-economic and age groups with adequate strata specific samples, would have given more precise strata-specific estimates of the ARTI. It could have resulted in better delineation of the disease prevalence and enhanced the understanding of the challenges of disease control and planning remedial actions.

![Figure 1: Frequency distribution of tuberculin reaction among 4202 test-read children](image1)

![Figure 2: Frequency distribution of tuberculin reaction among smear positive pulmonary tuberculosis patients](image2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence % (95% CI)</th>
<th>ARTI % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stratum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>13.9 (8.4-19.4)</td>
<td>1.4 (0.9-2.1)</td>
</tr>
<tr>
<td>Estate</td>
<td>2.3 (0-6.4)</td>
<td>0.2 (0-0.6)</td>
</tr>
<tr>
<td>Rural</td>
<td>2.2 (0-5.7)</td>
<td>0.2 (0-0.6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4.2 (0-12)</td>
<td>0.4 (0-1.2)</td>
</tr>
<tr>
<td>Female</td>
<td>4.1 (1.4-6.8)</td>
<td>0.4 (0.1-0.7)</td>
</tr>
<tr>
<td>Total</td>
<td>4.2 (1.7-7.2)</td>
<td>0.4 (0.2-0.7)</td>
</tr>
</tbody>
</table>

ARTI - Annual risk of tuberculosis infection
measures. Our total sample size was an under-estimate by about 60%, given the fact that we used 10% prevalence of TB based on south Indian estimates of the same age group as opposed to a figure closer to the national estimate (4.2%) derived in this study.

Generally, children with BCG scars are excluded from the analysis as the BCG-induced tuberculin sensitivity can interfere with interpretation of the study results and subsequent identification of natural infection. However, our finding of mere 5% of study participants without a BCG scar demonstrated that obtaining a sufficient population of children without BCG scar is operatively infeasible in Sri Lanka. In contrast, the BCG coverage is also very high in the country. In this context, we had to recruit children irrespective of their BCG vaccination status and BCG scar. Many studies have justified this approach by computing ARTI having enrolled children irrespective of the status of BCG vaccination and scar in settings with very high BCG coverage. These estimates were demonstrated to be comparable to that derived from unvaccinated children. The possible contamination due to BCG vaccination in skin test results also could be removed by applying mirror-image technique to the analysis.

We enrolled only 82.4% of the desired sample size, and we had to discontinue the study following the government circular temporarily stopping all injection procedures in schools following the death of the rubella vaccine recipient. This response rate (82.4%) was slightly above the 80% threshold recommended by Sackett to be considered internally valid. However, non-enrolment of 27% of children in the urban sector is indeed a great limitation to interpret the validity of the high estimate of ARTI for the urban sector.

Although not distinctly clear, the frequency distribution of tuberculin reaction sizes in the study appeared to be bimodal without an anti-mode. Similar distributions are observed in areas of low prevalence of infection and moderate to high prevalence of non-specific sensitivity that obscure a clear separation of reactions due to infection with tubercle bacilli from others. In contrast, the impact of environmental mycobacteria on interpretation of results cannot be determined due to non-availability of studies on the influence of environmental mycobacterium on the tuberculin reactivity in the country. Alternatively, the mode of reaction sizes among smear-positive pulmonary tuberculosis cases (15 mm) supplemented determination of the prevalence of TB by mirror-image technique.

Our national estimate of ARTI (0.4%, 95% CI: 0.2-0.7%) was low as compared with that of many developing countries. However, it is still higher than the ARTI, which is far below 0.05% in industrialized countries. One limitation for comparing ARTI estimates across studies is the non-uniformity in the methodology. Variability in dose, type of tuberculin used and the difference in cut-off points also play a role in different reported estimates. Nevertheless, extensive ARTI estimates in the range of 0.75-3% are available for several states in India, the neighbouring country. Among children aged 1-9 years in the eastern and western zones of India, the ARTI was 1.3% and 1.8%, respectively. The same in Orissa state of India was 1.7-1.8%. In the northern zone, among children of the same age, it was 1.9%. In the southern zone, ARTI among children aged 1-9 years was 1.0%. Observed high rates of transmission are expected in India as it contributes to one-third of the global burden of TB.

Although Indian estimates were generally high, ARTI estimates for children aged 10 years in Trivandrum in Kerala, India, which in terms of many health indicators is similar to Sri Lanka, was as low as 0.75%.

The estimate of ARTI for many other developing countries is in the range of 1-3%. While for Algeria, Egypt, the Republic of Korea, Kenya and United Republic of Tanzania, it was <2%. Thus, by the standards of developing countries, our estimate reflected the effectiveness of TB control activities in the country. However, no comments can be made on trend due to the non-availability of previous national estimates.

The national estimate of ARTI indicates that, on average, there are about 400 newly infected cases or re-infected cases with potential to progress to the disease per 100 000 population (95% CI: 200-700/100 000) every year. This is in contrast to the estimates of the incidence rates of all forms of TB and the nationally reported new case detection rates, which were 66 and 48 per 100 000 population, respectively, in 2009. Based on the parametric relationship derived by Styblo, the estimate of the annual incidence of new cases with smear-positive PTB cases derived from the present study was similar to the nationally reported figure of incidence of smear-positive cases for 2009 (20 per 100 000).

Like in many countries, a higher ARTI (1.4%; 95% CI: 0.8-2.1%) has been observed in the urban sector. The slightly wide confidence interval of the urban estimate indicates the small sample size, mainly due to pre-mature cessation of the study. Both estate and rural sectors have estimates suggestive of low transmission of TB infection. The higher risk of infection in the urban sector than in the rural and estate sectors may be due to high population density and poor socio-economic situation. Results underscore the need for paying greater attention to the urban sector and indicate possible weaknesses in the operation of the control programme in urban areas.

**CONCLUSION**

Our study concluded that the national estimate of
ARTI was lower than that reported in many developing countries. However, a relatively high risk was observed in the urban sector as compared with the estate and rural sectors. Although still far from the ideal, the relatively lower ARTI at the national level may reflect improving socio-economic status, the better and organized delivery of general healthcare as well as organized TB control activities. Despite this lower risk, nearly 10-fold low annual new case detection rate relative to the expected annual burden of newly infected and re-infected cases based on our study is a concern. Therefore, in the light of our findings, the National TB Programme needs to strengthen its efforts to detect newly infected or re-infected disease load capable of progressing to the disease. In addition, a fresh approach for a package of control activities in urban areas of the country is required.

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How to cite this article: Wijesinghe PR, Palihawadana P, De Alwis S, Samarawera S. Annual risk of tuberculosis infection in Sri Lanka: a low prevalent country with a high BCG vaccination coverage in the South-East Asia Region. WHO South-East Asia J Public Health 2013;2:34-40.

Source of Support: Global Fund for AIDS, Tuberculosis and Malaria(GFATM) Grant No : SRL/102G03/00. Conflict of Interest: None declared.

**APPENDIX - I**

The district estimates of prevalence in urban, rural and estate strata were calculated using the following formula:

\[
P_d = \frac{\sum w_i P_i / \cap}{\sum [1/\cap]}
\]

\(P_d\) - Prevalence of tuberculosis in the district

\(P_i\) - Proportion of infected children in the \(i^{th}\) cluster

\(\cap\) - Probability of selection of children (number of test read children/population of the \(i^{th}\) cluster)

Pooling of district estimates of a given stratum was done as shown below to obtain estimates for the urban, rural and estate sectors.

\[
P_s = \frac{\sum (w_i P_i)}{\sum w_i}
\]
$P_s$ - Prevalence of infection in the rural/urban/estate strata

$P_{di}$ - The proportion of infected children in the $i^{th}$ district

$w_i$ - The corresponding weight–the proportion of the district population to the population of the respective stratum

The stratum specific estimates were pooled to obtain the overall national estimates using the following formula:

$$P = \sum w_i P_i$$

$P_i$ - The prevalence in the urban/rural/estate strata

$w_i$ - The corresponding weight–the proportion of the stratum population to the national population

Standard error for stratum specific estimates was computed using the following formula:\cite{8,13}:

$$\sqrt{\sum w_i^2 (P_{di} - P_s)^2} / \sum (w_i)^2$$

$P_{di}$ - Prevalence for the district

$P_s$ - Prevalence for the stratum

$w_i$ - The corresponding weight–the proportion of the district population to the population of the respective stratum

Standard error for the pooled national estimate was computed using the following formula:

$$\sqrt{\sum V_i^2 S_i^2} / (\sum V_i)^2$$

$S_i$ - standard error for strata (urban, rural, estate)

$V_i$ - proportion of population in the respective area