INT J TUBERC LUNG DIS 16(10):1315–1319

http://dx.doi.org/10.5588/ijtld.12.0098

Trend in tuberculosis infection prevalence in a rural area in South India after implementation of the DOTS strategy

C. Kolappan, R. Subramani, V. Chandrasekaran, A. Thomas

National Institute for Research in Tuberculosis, Indian Council of Medical Research, Chetput, Chennai, India

SUMMARY

SETTING: Three tuberculin surveys were conducted at intervals of 5 years following the implementation of a DOTS-based programme in 1999 in Tiruvallur District, South India.

OBJECTIVE: To estimate the trend in the prevalence of tuberculosis (TB) infection among children and to evaluate the impact of the DOTS strategy.

METHODS: Children aged 1–9 years in the sample for each survey were registered and administered 1 tuberculin unit of purified protein derivative RT 23 with Tween 80 by intradermal injection on the volar aspect of the left forearm. The induration diameter of the reaction was measured in mm after 72 h (3 days) and the prevalence of TB infection estimated.

RESULTS: The induration data of bacille Calmette-Guérin (BCG) vaccinated and non-vaccinated children were analysed using the mixture model. The estimated prevalence of TB infection among non-BCG-vaccinated children in the three tuberculin surveys were respectively 19.4%, 13.8% and 11.4%, with an average annual decline of 5.2% (95%CI 3.6–6.8). The prevalence of TB infection among BCG-vaccinated children decreased, with an average annual decline of 5.4% (95%CI 10.0–18.6).

CONCLUSION: A significant declining trend in the prevalence of TB infection among children was observed following the implementation of the DOTS strategy in the area.

KEY WORDS: DOTS; surveys; infection; trend in prevalence

ONE THIRD of the world's population is latently infected with the *Mycobacterium tuberculosis* bacillus, which causes tuberculosis (TB). In 2002, there were nearly 9 million new cases of TB; one person with active TB will infect on average 10–15 persons every year.[1]

Tuberculin surveys among a particular age group of children are used to measure the prevalence of TB infection. The prevalence of TB infection is the proportion (expressed as percentage) of children of a particular age group infected with *M. tuberculosis*. Repeated tuberculin surveys at reasonable intervals (preferably ⩾5 years) can be used to measure the epidemiological trends and impact of the intervention strategies.[2] The National Institute for Research in Tuberculosis (formerly Tuberculosis Research Centre) had a unique opportunity to assess the impact of the DOTS strategy through a series of tuberculin surveys and disease prevalence surveys carried out concurrently from 1999 to 2009 in Tiruvallur District, South India, in a predominantly rural study population. Further details on the study area and the 1999–2006 survey findings are available in earlier reports published by this Institute.[3–5] This paper reports the findings from three serial tuberculin surveys repeated at 5-yearly intervals on the trend in TB infection prevalence among children aged 1–9 years after DOTS implementation in 1999.

MATERIAL AND METHODS

Three tuberculin surveys were carried out in random samples of children aged 1–9 years in a sub-district of Tiruvallur, South India, as part of an assessment of the epidemiological impact of the DOTS strategy implemented in 1999. The first tuberculin survey was undertaken during the period 1999–2001, while the second and third tuberculin surveys were conducted in 2004–2005 and 2009–2010. All the surveys were conducted in a mutually exclusive sample of villages randomly selected from target villages in the study area.

Sampling

Assuming a bacille Calmette-Guérin (BCG) vaccination coverage of 40–50% in this area and an annual risk of TB infection (ARTI) of the order of 2% in children, the sample size required to detect an annual decline of 3%, with 80% power at the 5% significance level, was estimated and a sample of 26 748 children aged 1–9 years was registered for the 1999–2001 survey. For the 2004–2005 survey, a sample of

Correspondence to: Aleyamma Thomas, National Institute for Research in Tuberculosis, ICMR, Chetput, Chennai 600 031, India. Tel: (+91) 44 2836 9600. Fax: (+91) 44 2836 2528. e-mail: aleyammat@trcchennai.in

Article submitted 2 February 2012. Final version accepted 8 May 2012.

25 391 children of the same age group was registered assuming a BCG coverage of 63% and a prevalence of infection of 8%, with 10% accuracy and at 5% significance level. For the third survey in 2009–2010, the BCG vaccination status was not considered for two reasons: first, earlier studies had reported similar prevalence rates among non-vaccinated children, and the children were sampled irrespective of BCG vaccine status.[6,7] Second, BCG vaccination coverage among children in the Tiruvallur District was increasing steadily (in 2009 it was 99%),[8] which made it impossible to enrol non-vaccinated children representative of the target population. Assuming an infection prevalence rate of 6% with a precision of 20% and at 5% significance level, a sample of 3461 children aged 1–9 years, irrespective of BCG scar, was registered.

Table 1 Coverage of children aged 1–9 years with tuberculin skin tests and reaction measurements in the surveys

Survey period, BCG vaccination status	Tested *n*	Measured *n* (%)
1999–2001		
Non-BCG-vaccinated children	12 408	12 106 (98)
BCG-vaccinated children	12 536	12 241 (98)
Total	24 944	24 347 (98)
2004–2005		
Non-BCG-vaccinated children	7 840	7 636 (97)
BCG-vaccinated children	15 797	15 372 (97)
Total	23 637	23 008 (97)
2009–2010		
Non-BCG-vaccinated children	1 011	974 (96)
BCG-vaccinated children	2 425	2 359 (97)
Total	3 436	3 333 (97)

BCG = bacille Calmette-Guérin.

Methodology

A team consisting of census takers, tuberculin testers, readers and supervisory staff visited each village and registered all children aged 1–9 years in the study sample. After the purpose of the study had been explained, written consent for undergoing a tuberculin skin test (TST) was obtained from the parent or guardian of every child. Before testing, the upper third of each arm was examined for the presence or absence of a BCG scar. All children with or without a BCG scar were given 1 tuberculin unit (TU) of purified protein derivative (PPD) RT 23 with Tween 80 (Statens Serum Institute, Copenhagen, Denmark) by intradermal injection on the volar aspect of the left forearm, inducing a pigmented weal of 5–6 mm above the skin level with pits and clear follicles. The induration diameter of the reaction was measured in mm after 72 h (3 days). In case of intervening holidays or exigencies, it was read after 48 h (2 days) or after 96 h (4 days). By palpating the edges of the reaction (to demarcate, not to measure), the maximum transverse diameter of the induration was demarcated and measured in mm with a transparent scale. In all the three surveys the same set of readers was used to measure the reactions. Quality control of the TST was performed by direct observation, while as quality control for reading, a supervisor independently measured a random sample of 5% of measurements, and corrective measures were undertaken.

The institutional ethics committee of the National Institute for Research in Tuberculosis approved the surveys.

Data management and analysis

All data were double-entered and verified using the data entry package MicroPro DataStar (MicroPro International Corp, San Rafael, CA, USA). In the 1999–2001 TST survey, 24 347 children with recorded TST results were included, of whom 12 106 (49.7%) had no BCG scar. In the 2004–2005 TST survey, 23 008 children with recorded TST results were included, of whom 7636 (33.2%) had no BCG scar. In the 2009–2010 TST survey, 3333 children with recorded TST results were included, of whom 974 (29.4%) had no BCG scar. The prevalence of infection among children with and without BCG vaccination were estimated by applying the mixture-model components using the Bayesian approach and programme codes for the R software used for this analysis.[9,10]* The mixture model considered the Weibull distributions for *M. tuberculosis* infections and BCG reactions, and lognormal distributions for cross-reactions, and predicted the results for the induration data. These distributions were not allowed to vary by sub-age groups and sex due to errors that occurred with initial values of the parameters defined in the model while executing the R programme. The mixture analysis was restricted to all children aged 1–9 years and both sexes only in all the surveys.

RESULTS

TST coverage and measurement of TST reaction were consistently >90% for all three surveys (Table 1).

Using mixture model analysis, the mean induration values due to *M. tuberculosis* infection were not different in BCG-vaccinated and non-vaccinated children, or from survey to survey (Table 2). The mean values of cross-reactions due to environmental mycobacteria varied by <1 mm only from survey to survey, and the values were not different in BCG-vaccinated and non-vaccinated children. The mean values of reactions due to BCG vaccination were smaller than those for TB infection (Figures 1, 2 and 3).

Table 3 shows that the prevalence of TB infection among non-BCG-vaccinated children decreased from 19.4% (95% confidence interval [CI] 18.3–20.5) in the first survey, to 11.4% (95%CI 9.37–14.0) in the last survey with an average annual decline of 5.2% (95%CI 3.6–6.8). Similarly, the prevalence of infection among BCG-vaccinated children decreased, with an average decline of 5.4% (95%CI 10.0–18.6).

* The R software can be downloaded for free from the R homepage: http://lib.stat.cmu.edu/R/CRAN

Table 2 Mean induration values in mm for distributions of TB infection cross-reactions and BCG vaccination in the three tuberculin skin test surveys among children aged 1–9 years using mixture analysis*

Survey period	BCG vaccination status in infections and reactions	Posterior median of mean mm (95%CI)
TB infections†		
1999–2001	Non-BCG-vaccinated	10.9 (10.6–11.2)
2004–2005	Non-BCG-vaccinated	11.2 (10.1–12.3)
2009–2010	Non-BCG-vaccinated	11.0 (9.97–12.0)
Cross-reactions‡		
1999–2001	Non-BCG-vaccinated	3.22 (3.20–3.25)
2004–2005	Non-BCG-vaccinated	2.48 (2.46–2.50)
2009–2010	Non-BCG-vaccinated	2.61 (2.58–2.65)
BCG reactions§		
1999–2001	BCG-vaccinated	6.19 (5.98–6.38)
2004–2005	BCG-vaccinated	7.51 (4.77–9.89)
2009–2010	BCG-vaccinated	5.31 (4.69–5.95)

*The results for BCG-vaccinated children for TB infection and cross-reactions are the same as for non-BCG-vaccinated children in all the surveys.
†Reactions due to infection with *Mycobacterium tuberculosis.*
‡Cross-reactions due to infection with environmental mycobacteria.
§Reactions due to BCG vaccination.
TB = tuberculosis; BCG = bacille Calmette-Guérin; CI = confidence interval.

The 95%CIs were wide in the BCG-vaccinated children in the 2004–2005 survey due to the low prevalence of TB infection compared to findings from other surveys.

The extended mixture model, considering sub-age groups and sex, was not used for the induration data measured. However, the basic mixture model was used, as it allowed us to estimate TB prevalence in both BCG-vaccinated and non-vaccinated children aged 1–9 years. The basic mixture model yielded predictive failure rates of respectively 53.3%, 70% and 23.3%, corresponding to the non-BCG data of the three surveys; the corresponding findings for BCG data were respectively 33.3%, 66.7% and 16.7%.

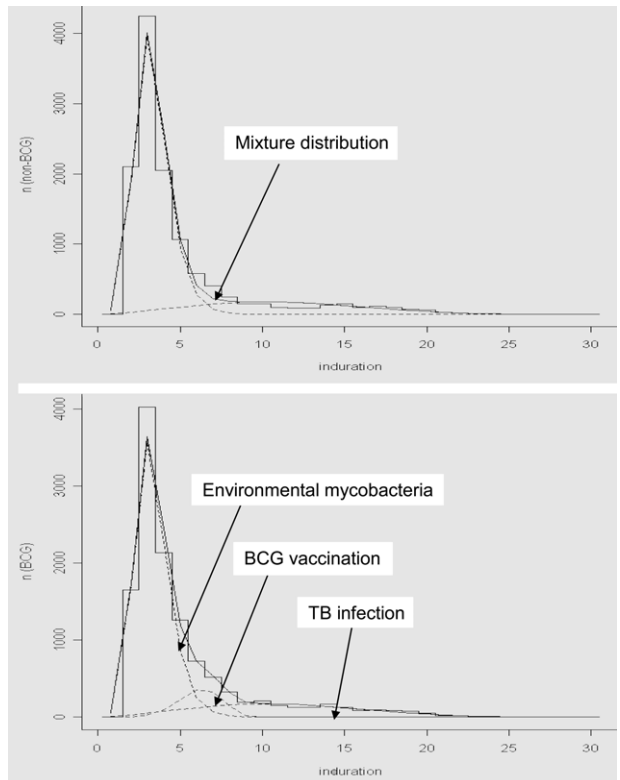

Figure 1 Observed distribution of TST induration sizes (histograms) in the 1999–2001 TST survey. ----- = mixture distribution; – – – = distribution due to infection with environmental mycobacteria; - - - - = distribution due to BCG vaccination; ▬▬ = distribution of TB infection among children aged 1–9 years. BCG = bacille Calmette-Guérin; TB = tuberculosis; TST = tuberculin skin test.

DISCUSSION

Three successive tuberculin surveys were conducted at intervals of 5 years with different sample sizes. In the first two surveys, the sample sizes were larger because they were calculated to analyse data on non-BCG-vaccinated children only, in which the sample sizes were dependent on vaccination coverage and were proportionately boosted to obtain the required number of non-vaccinated children. However, in the third survey, the sample size was smaller and was not dependent on vaccination coverage, as it was decided to include all children, irrespective of vaccination status, in the analysis for reasons mentioned earlier. This strategy resulted in a large reduction in the required sample size, thereby saving considerable cost and valuable time. As per Arnadottir et al.'s recommended sample size of at least 3000–5000 non-vaccinated children in high-prevalence countries,[11] a sample size of 3461 children for the third survey was considered adequate, although it was much smaller than in the earlier two surveys. In 2006, Kumar et al. used a sample size of only 4821 children in Kerala to estimate TB infection prevalence.[12] Similarly, Gopi et al. used a sample size of only 7098 children in Chennai City to estimate TB infection prevalence among non-vaccinated children.[13] Furthermore, the sample sizes of the first two surveys were much larger than the recommended size due to the stringent assumptions mentioned in the Methods. However, the increased sample size in the first two surveys yielded estimates that were more precise.

In this report, we analysed data from all three surveys to study infection prevalence trends among children aged 1–9 years over a period of 10 years. All children with or without a BCG scar were given 1 TU of PPD RT 23 with Tween 80 in all three surveys.

Histograms depicting the frequency distributions of reaction sizes of all three surveys did not show the classical bimodal distribution, and the definition of distinct antimode or cut-off points was not clear in all three distributions (data not shown). A declining trend of 5.2% (95%CI 3.6–6.8) per annum in the prevalence of infection among non-BCG-vaccinated children was observed in the mixture-model analysis, which allowed us to separate cross-reactions due to infection with environmental mycobacteria from BCG vaccination. The use of the mixture-model method could be justified if the ratio of infection prevalence

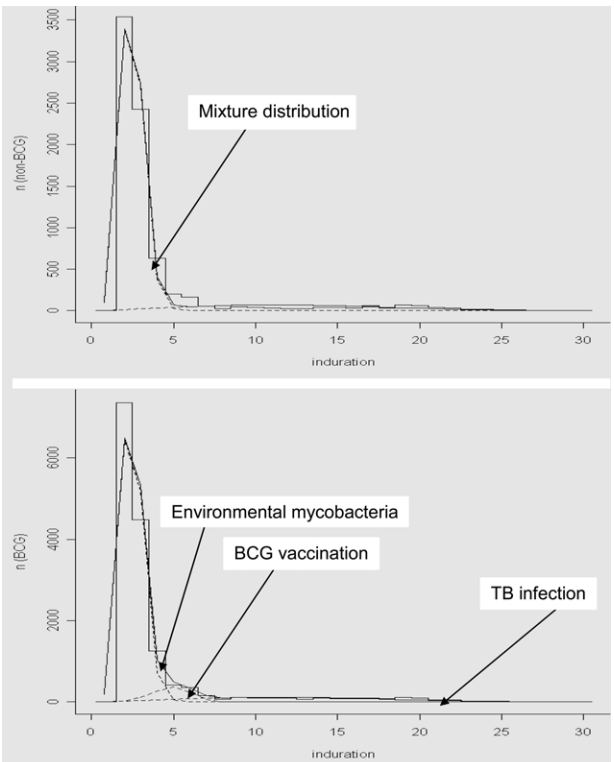

Figure 2 Observed distribution of TST induration sizes (histograms) in the 2004–2005 TST survey. ----- = mixture distribution; – – – = distribution due to infection with environmental mycobacteria; - - - - = distribution due to BCG vaccination; ▬▬ = distribution of TB infection among children aged 1–9 years. BCG = bacille Calmette-Guérin; TB = tuberculosis; TST = tuberculin skin test.

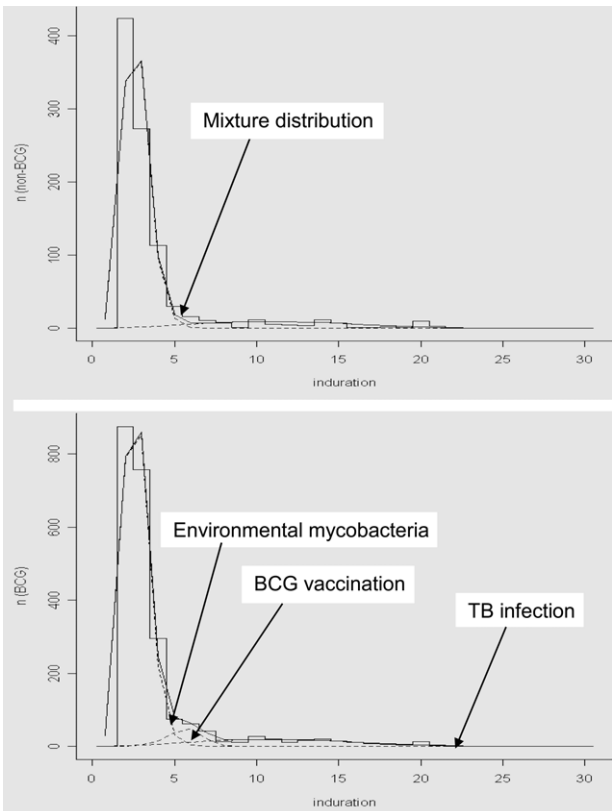

Figure 3 Observed distribution of TST induration sizes (histograms) in the 2009–2010 TST survey. ----- = mixture distribution; – – – = distribution due to infection with environmental mycobacteria; - - - - = distribution due to BCG vaccination; ▬▬ = distribution of TB infection among children aged 1–9 years. BCG = bacille Calmette-Guérin; TB = tuberculosis; TST = tuberculin skin test.

in the BCG-vaccinated population to that in the non-vaccinated population is close to 1.[9] In this study, the estimated ratios were respectively 1.1 and 1.1 in the first and third surveys, and 1.9 in the second survey. The basic mixture model showed predictive failure rates of respectively 53.3%, 70% and 23.3%, corresponding to the non-BCG data of the three surveys, whereas those for BCG data were respectively 33.3%, 66.7% and 16.7%. Induration measurements recorded with digit preferences may be one of the reasons for the high predictive failure rates. TB infection prevalence can be estimated precisely and predictive failure rates can be minimised if the extended mixture model (including sub-age groups, sex and BCG status) works for the induration data measured in the surveys. The study findings suggest that these analysis issues should be considered when planning future studies with appropriate sampling procedure, selection of sample size and measurement of reaction size. However, the basic mixture model was used because it allowed us to separately estimate infection prevalence in both BCG-vaccinated and non-vaccinated children aged 1–9 years.

Prevalence estimates in the three earlier surveys conducted in 1969, 1979 and 1984 (pre-DOTS era) in the same study area were respectively 9.0%, 10.2% and 9.1%.[14] There was no change in infection prevalence over the 15-year period. Two more tuberculin surveys conducted in a smaller population during 1991–1996 also showed no difference in prevalence of infection.[15] These earlier findings were estimated using conventional cut-off points or the mirror method by plotting induration data, and could have been different from the findings from the mixture

Table 3 Prevalence of infection with *Mycobacterium tuberculosis* in tuberculin skin test surveys among children aged 1–9 years using mixture analysis

Survey period, BCG vaccination status	Posterior median of infection prevalence % (95%CI)	Average annual decrease %
1999–2001		
Non-BCG-vaccinated	19.4 (18.3–20.5)	Non-BCG-vaccinated: 5.2 (3.6–6.8)
BCG-vaccinated	18.3 (17.3–19.5)	BCG-vaccinated: 5.4 (10.0–18.6)
2004–2005		
Non-BCG-vaccinated	13.8 (12.7–14.9)	
BCG-vaccinated	7.12 (0.24–11.5)	
2009–2010		
Non-BCG-vaccinated	11.4 (9.37–14.0)	
BCG-vaccinated	10.5 (8.71–12.5)	

BCG = bacille Calmette-Guérin; CI = confidence interval.

method, if this method had been used. No other studies assessed infection trends in any other part of India during the same period. The substantial annual decline of 5.2% reported in the current series of tuberculin surveys can be attributed to some extent to the impact of DOTS implementation in the study area in 1999, although there may have been other contributing factors, such as improved socio-economic conditions, greater awareness about TB among patients, better nutritional status among children and an improved health care delivery system.

The DOTS strategy, which includes an initial 2 months of intensive treatment with four first-line anti-tuberculosis drugs, generally results in the conversion of sputum-positive cases to sputum-negative. This drastic reduction in the number of infectious cases in the community, in a short span of 2 months, would also have contributed to a sharp decline in the occurrence of new infection among children aged 1–9 years in the study population.

Limitations

The sample sizes for the three surveys were estimated using different assumptions and methodology, necessitated by a change in methods used in similar surveys elsewhere. There are inherent limitations in the tuberculin survey, such as the selection of standardised tuberculin, the technique of administration, and intra-reader variation in reading reaction sizes. The absence of clear-cut antimode or cut-off points and modes in all three surveys made it impossible to estimate the ARTI, and the data could be used only to estimate trends in TB infection. Although the induration data showed no clear-cut bimodal distribution for non-infected and infected children the first time, we attempted to analyse the data using the mixture-model approach. However, this approach, with sub-age groups and sex, and with consideration of the initial values of parameters in the extended model, could not be carried out due to errors that occurred while executing the R programme. The posterior predictive failure rate was high in the basic model data; its possible impact on the estimation of TB prevalence could therefore not be measured. Another reason for noisy frequency distributions might be the result of digit preference in recording induration measurements, which was not identified at the time of the quality check.

CONCLUSION

The implementation of the DOTS strategy led to a considerable reduction in TB infection prevalence among children aged 1–9 years in contrast to no reduction in infection prevalence over a 15-year period in the pre-DOTS era. Anti-tuberculosis treatment using the DOTS strategy under the Revised National Tuberculosis Control Programme should therefore be continued for TB control.

Acknowledgements

The authors thank the field staff for data collection, the Statistics Division staff for data verification and computerisation and the electronic data processing staff for data entry and management; and the Government of Tamil Nadu and district officials for carrying out the surveys. The survey was supported in part by the World Health Organization, with financial assistance from the United States Agency for International Development under the Model DOTS Project. Finally, they are greatly indebted to the referee for suggesting the mixture-model techniques employed for analysis.

References

1 UN Millennium Project 2005. Investing in strategies to reverse the global incidence of TB. Task Force on HIV/AIDS, Malaria, TB, and Access to Essential Medicines. New York, NY, USA: UN, 2005.
2 World Health Organization, Regional Office for South East Asia. Generic guidelines for the estimation of the annual risk of tuberculosis infection (ARTI). New Delhi, India: WHO, 2006.
3 Gopi P G, Subramani R, Radhakrishna S, et al. A baseline survey of the prevalence of tuberculosis in a community in South India at the commencement of a DOTS programme. Int J Tuberc Lung Dis 2003; 7: 1154–1162.
4 Subramani R, Radhakrishna S, Frieden T R, et al. Rapid decline in prevalence of pulmonary tuberculosis after DOTS implementation in a rural area of South India. Int J Tuberc Lung Dis 2008; 12: 916–920.
5 Gopi P G, Subramani R, Narayanan P R. Trend in the prevalence of TB infection and ARTI after implementation of a DOTS programme in South India. Int J Tuberc Lung Dis 2006; 10: 346–348.
6 Chadha V K, Jagannatha P S, Kumar P. Can BCG-vaccinated children be included in tuberculin surveys to estimate the annual risk of tuberculous infection in India? Int J Tuberc Lung Dis 2004; 8: 1437–1442.
7 Gopi P G, Subramani R, Kolappan C, Venkatesh Prasad V, Narayanan P R. Estimation of annual risk of tuberculosis infection among children irrespective of BCG scar in the south zone of India. Indian J Tuberc 2006; 53: 7–11.
8 Kuruvilla T A, Bridgitte A. Timing of zero dose of OPV, first dose of hepatitis B and BCG vaccines. Indian Pediatr 2009; 46: 1013–1015.
9 Neuenschwander B E, Zwahlen M, Kim S J, Lee E G, Rieder H L. Determination of the prevalence of infection with *Mycobacterium tuberculosis* among persons vaccinated against bacillus Calmette-Guérin in South Korea. Am J Epidemiol 2002; 155: 654–663.
10 Neuenschwander B E, Zwahlen M, Kim S J, Engel R R, Rieder H L. Trends in the prevalence of infection with *Mycobacterium tuberculosis* in Korea from 1965 to 1995: an analysis of seven surveys by mixture models. Int J Tuberc Lung Dis 2000; 4: 719–729.
11 Arnadottir T, Rieder H L, Trébucq A, Waaler H T. Guidelines for conducting tuberculin skin test surveys in high-prevalence countries. Tubercle Lung Dis 1996; 77 (Suppl 1): 1–20.
12 Kumar S, Radhakrishna, Chadha V K, et al. Prevalence of tuberculous infection among school children in Kerala. Indian J Tuberc 2009; 56: 10–16.
13 Gopi P G, Venkatesh Prasad V, Vasantha M, et al. Annual risk of tuberculosis infection in Chennai City. Indian J Tuberc 2008; 55: 157–161.
14 Mayuranath S, Vallishayee R S, Radhamani M P, Prabhakar R. Prevalence study of tuberculosis infection over fifteen years, in a rural population in Chingleput District (South India). Indian J Med Res 1991; 93: 74–80.
15 Tuberculosis Research Centre, Chennai, India. Trends in the prevalence and incidence of tuberculosis in South India. Int J Tuberc Lung Dis 2001; 5: 142–157.

RÉSUMÉ

CONTEXTE : Trois enquêtes tuberculiniques ont été menées à des intervalles de 5 ans après l'application de la stratégie DOTS en 1999 dans le district de Tiruvallur, Inde du Sud.

OBJECTIF : Estimer la tendance de la prévalence de l'infection tuberculeuse (TB) chez les enfants et évaluer l'impact de la stratégie DOTS.

MÉTHODES : Pour chaque enquête, les enfants de l'échantillon âgés de 1 à 9 ans ont été enregistrés et soumis à un test tuberculinique par la protéine purifiée dérivée RT 23 avec Tween 80 sous forme d'une injection intradermique sur la face antérieure de l'avant-bras gauche. Le diamètre de l'induration de la réaction a été mesuré en mm après 72 h (3 jours) et on a estimé la prévalence de l'infection TB.

RÉSULTATS : On a analysé avec un modèle de mélanges les données concernant les indurations chez les enfants non-vaccinés et vaccinés par le bacille Calmette-Guérin (BCG). Dans les trois enquêtes tuberculiniques, la prévalence estimée de l'infection TB parmi les enfants non-vaccinés par le BCG été respectivement de 19,4%, 13,8% et 11,4%, avec une diminution annuelle moyenne de 5,2% (IC95% 3,6–6,8). Parallèlement, la prévalence de l'infection TB parmi les enfants vaccinés par le BCG a diminué d'une moyenne annuelle de 5,4% (IC95% 10,0–18,6).

CONCLUSION : On a noté une tendance significative à la baisse de la prévalence de l'infection TB parmi les enfants après l'application de la stratégie DOTS dans la région.

RESUMEN

MARCO DE REFERENCIA: Después de la introducción de la estrategia DOTS en el distrito de Tiruvallur al sur de la India en 1999, se han llevado a cabo tres encuestas tuberculínicas con intervalos de 5 años.

OBJETIVO: Calcular la tendencia de la prevalencia de infección tuberculosa en los niños y evaluar la repercusión de DOTS.

MÉTODOS: En la muestra de cada encuesta se registraron niños entre 1 y 9 años de edad y a cada uno se aplicó una unidad tuberculínica de PPD RT 23 con polisorbato 80, por inyección intradérmica en la cara anterior del antebrazo izquierdo. Después de 72 h (3 días) se midió el diámetro de la reacción de induración y se calculó la prevalencia de infección tuberculosa.

RESULTADOS: Los datos sobre el diámetro de la induración en los niños con antecedente de vacunación por el bacille Calmette-Guérin (BCG) y sin vacunación se evaluaron mediante un análisis de modelos mixtos. La prevalencia calculada de infección tuberculosa en los niños sin vacunación antituberculosa en las tres encuestas tuberculínicas fue respectivamente 19,4%, 13,8% y 11,4%, con un promedio de disminución anual de 5,2% (IC95% 3,6–6,8). De manera análoga, la prevalencia de infección tuberculosa en los niños con antecedente de vacunación por el BCG disminuyó con un promedio anual de 5,4% (IC95% 10,0–18,6).

CONCLUSIÓN: Después de la introducción de la estrategia DOTS en esta región, se observa una tendencia decreciente significativa de la prevalencia de infección tuberculosa en los niños.