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Trends in the annual risk of tuberculous infection in India

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SUMMARY

SETTING: Twenty-four districts in India.

OBJECTIVES: To evaluate trends in annual risk of tuberculous infection (ARTI) in each of four geographically defined zones in the country.

STUDY DESIGN: Two rounds of house-based tuberculin surveys were conducted 8–9 years apart among children aged 1–9 years in statistically selected clusters during 2000–2003 and 2009–2010 (Surveys I and II). Altogether, 184 992 children were tested with 1 tuberculin unit (TU) of purified protein derivative (PPD) RT23 with Tween 80 in Survey I and 69 496 children with 2TU dose of PPD in Survey II. The maximum transverse diameter of induration was measured about 72 h after test administration. ARTI was computed from the prevalence of infection estimated using the mirror-image method.

RESULTS: Estimated ARTI rates in different zones varied between 1.1% and 1.9% in Survey I and 0.6% and 1.2% in Survey II. The ARTI declined by respectively 6.1% and 11.7% per year in the north and west zones; no decline was observed in the south and east zones. National level estimates were respectively 1.5% and 1.0%, with a decline of 4.5% per year in the intervening period.

CONCLUSION: Although a decline in ARTI was observed in two of the four zones and at national level, the current ARTI of about 1% in three zones suggests that further intensification of TB control activities is required.

KEY WORDS: tuberculosis; infection; risk; trends; India

INDIA CONTINUES to have the highest tuberculosis (TB) burden in the world.[1] To address the problem, a National TB Programme (NTP) was implemented in 1962.[2] Following a review of the NTP, the Revised National TB Control Programme (RNTCP), adopting the DOTS strategy, was launched in 1997 and extended in phases to achieve complete population coverage by 2006.[3,4]

To evaluate the impact of the RNTCP, two rounds of tuberculin surveys were carried out during 2000–2003 and 2009–2010 (Surveys I and II). For this purpose, the country was divided into four geographic zones, north, south, east and west, with the objective of estimating the annual risk of tuberculous infection (ARTI) and its trends in each zone. ARTI denotes the proportion of persons in a community who become (re-) infected within 1 year.[5] It depends not only on the incidence of infectious TB cases but also on the efficiency of the programme.[6] In all the zones, high rates of treatment success (⩾80%) among diagnosed TB patients have been achieved since the introduction of the RNTCP, and notification rates among new smear-positive TB cases have shown consistent improvement over the years, reaching 50 per 100 000 population in the south, east and west zones and 60/100 000 in the north zone in 2010.[4]

MATERIAL AND METHODS

Study population

House-based surveys were carried out among children aged 1–9 years. Survey I was planned to estimate the ARTI primarily among children without bacille Calmette-Guérin (BCG) vaccination (referred to as non-vaccinated children).[7] However, children with BCG scar (referred to as vaccinated children) encountered during the process of registering non-vaccinated children were also tuberculin-tested. Analyses revealed that the ARTI rates estimated by including vaccinated children were not different from those based exclusively on non-vaccinated children.[8,9] Survey II was therefore carried out to estimate ARTI

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among 'all children' (including non-vaccinated, vaccinated and those with a doubtful BCG scar).

Sampling

The sample size for both surveys in each zone was calculated to estimate the prevalence of tuberculosis infection within 10% of true value at a 5% level of significance and with a design effect of 2 to account for cluster sampling. In Survey I, the sample size for non-vaccinated children in each zone was estimated at 11 045, arbitrarily considering the expected prevalence of infection at 10%. In Survey II, the expected prevalence of infection among all children in each zone was estimated considering a decline of 5% per year from the prevalence of infection estimated in Survey I. The sample size thus estimated for each zone was as follows: north 13 600, west 16 800, east 20 000 and south 25 000.

In each zone, the estimated sample size was equally allocated to 600 clusters in Survey I and 300 clusters in Survey II. Numbers of clusters were allocated in ratio of population size to six districts selected by population proportion to size (PPS) sampling. Numbers of clusters allocated to individual districts were further allocated to rural and urban areas in proportion to population; clusters were selected by PPS sampling.

Field procedures

Three visits were made to each cluster for planning, registration and testing, and reading. During planning, community leaders were apprised of the purpose of the surveys. A sketch of the cluster, including hamlets and lanes, was made and the lane to start fieldwork was selected using a random number table.

On the day of testing, children were registered on individual data cards, starting from the first house of the selected lane. Contiguous houses were visited in a clockwise direction until the cluster size was achieved. Tuberculin skin tests (TSTs) were performed at a temporary centre set up by trained testers after obtaining informed written consent from the parent/guardian. Each child was injected intradermally on the anterior aspect of the left forearm with 0.1 ml of ready-to-use dilution containing PPD RT23 with Tween 80 (Statens Serum Institute, Copenhagen, Denmark). 1TU dose was used in Survey I and 2TU in Survey II. Each test was recorded as 'satisfactory' if it raised a flat pale wheal with clearly visible pits and well demarcated borders, and 'unsatisfactory' in case of leakage or subcutaneous injection. Presence/absence of BCG scar was recorded after examining both shoulders; scars not characteristic of BCG were recorded as 'doubtful'. Children with fever, history of skin rash or anti-tuberculosis treatment during the previous 6 months were excluded from testing.

Reactions were read approximately 72 h after test administration. Trained readers identified the margins of induration by careful palpation and measured the maximum transverse diameter of induration in mm. Most reactions in a given zone were read by a single reader; only in the event of his/her absence did a second trained reader perform the reading.

Children suspected to have TB (based on symptoms, contact history and TST result) were further investigated and treated at the nearest government health centre.

In Survey II, 150 new smear-positive TB patients also underwent a TST in each zone to facilitate a comparison with tuberculin sensitivity patterns among the truly infected children at the time of analysis.

Statistical methods

Data were double-entered into Epi Info™ 3.5.3 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and verified. Analyses were performed using SPSS 15.0 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA) and *R* software 2.5.1 (R Software Computing, Vienna, Austria), in addition to an in-house programme written in Microsoft Foxpro version 9.0 (Microsoft, Redwoods, WA, USA).

The reaction sizes of all children aged 1–9 years were arrayed in frequency distributions to identify the mode of tuberculous reactions. In the event of failure to identify a clear mode, frequency distributions were plotted and examined for subsets of study population in the following order sequentially until decisions could be made on mode (and also anti-mode, applicable to non-vaccinated children only):

1 Non-vaccinated children aged 1–9 years
2 Non-vaccinated children aged 5–9 years
3 Non-vaccinated children aged 5–9 years of age from urban areas

Non-vaccinated children are more likely to portray bimodality due to absence of contamination by BCG-induced tuberculin sensitivity, and also an anti-mode that separates tuberculosis reactions from cross-reactions. Each of the above subsets has a greater likelihood of throwing up mode/anti-mode than the previous subset, due to a higher prevalence of true tuberculous infection.[7–11]

In Survey II, in the event of continued uncertainty, the mode of the tuberculous reactions was identified after fitting normal distribution to the frequencies of tuberculin reaction sizes among new smear-positive patients who had undergone a TST.

The mode seen in any of the above distributions was applied to all children (tuberculous reactions were assumed to be normally distributed around the same mode, irrespective of age group, BCG vaccination status and presence/absence of TB disease[8,9,12–18]).

Prevalence of infection was estimated using the mirror image (MI) method, in which the proportion of reactions larger than the mode of TB reactions is doubled and added to the proportion at the mode.[19]

To reduce the influence of digit preference, estimations were made using frequencies of tuberculin reaction size at each millimetre, as obtained by moving averages (5-point).[20]

In each zone, prevalence and standard deviation (SD), which measures the spread of data about the mean infection, with standard error (SE), as $SD/\sqrt{c}$, where c is the number of clusters, were first estimated separately for urban and rural areas. Weighted prevalence of infection for zone (PZ) was obtained as $\Sigma w_s p_s / \Sigma w_s$, where p_s is prevalence in urban/rural area and w_s is weight corresponding to proportion of population (all age groups) of the total zonal population. The SE for zonal level prevalence was estimated using the pooled variance method.[21]

Zonal estimates of infection prevalence were pooled to obtain the weighted national-level estimate; the weight corresponded to the proportion of population in the zone of the total population in the country. The SE for national-level prevalence was estimated as follows:

$$\sqrt{\Sigma w_i^2 s_i^2 / (\Sigma w_i)^2}$$

where w_i and s_i represent the weight and SE for the ith zone. 95% confidence intervals (CIs) were derived as prevalence of infection ± 1.96*SE. ARTI was computed from the estimated prevalence of infection using the following formula:[22]

$$R_{b+a/2} = 1 - (1 - P_{b+a})^{1/a}$$

where b = the median year of birth of the children test-read, a = the mean age of the children, $R_{b+a/2}$ = the ARTI at the mid-point in calendar time between the median year of birth and the period of the survey, and P_{b+a} = the prevalence of infection at the time of the survey.

Estimation was also carried out separately for non-vaccinated and vaccinated children by the MI method using the same mode obtained as above. In addition, estimation among non-vaccinated children was also carried out by the anti-mode (if observed) method, in which reactions greater than or equal to the anti-mode are attributed to tuberculous infection.[19] This method was not applied to all children or vaccinated children due to the greater likelihood of overlap between true tuberculous reactions and cross-reactions around the anti-mode. For comparisons, the χ^2 test with continuity correction was used for test of significance; $P < 0.05$ was considered significant.

Using *R* software, changes in ARTI rates and CIs were computed by the beta distribution function, with input as ARTI rates, the SEs in Surveys I and II and the intervening time period in years, by simulating the number of response vectors to 50 000 iterations.

Analysis was also undertaken by the mixture model using R software and scripts available at www.tbrieder.org.[23] As the model did not generate a good fit in either zone, the results of mixture analysis are not presented here.

RESULTS

The numbers of children registered and satisfactorily test-read in each zone in Surveys I and II are given in Table 1. The number of children for whom data were available for analysis was much larger than the estimated sample size for Survey I, as explained under 'Study population'.

Zone-wise frequency distributions of reaction sizes for 'all children' aged 1–9 years did not reveal clear bi-modality in either zone (Figure 1). Distributions for subsets of children that revealed maximum clarity of mode/anti-mode during Survey I are presented in Figure 2. Distributions of reaction sizes among TB patients in Survey II are presented in Figure 3. In the north zone, a mode at the same reaction size as in TB

Table 1 Numbers of children investigated by zone, Surveys I and II

	Children registered n	Excluded from testing n (%)*	Children tested		No. read of those satisfactorily tested		
			Satisfactory n (%)†	Unsatisfactory n (%)	BCG− n	BCG+ n	All‡ n (%)§
North zone							
Survey I	55433	3728 (6.7)	51380 (87.7)	325	25816	21869	48323 (94.1)
Survey II	15175	1524 (10.0)	13309 (94.2)	342	4286	7684	12535 (94.2)
South zone							
Survey I	52951	327 (0.6)	52300 (98.8)	324	17811	32549	50533 (96.6)
Survey II	25 704	2137 (8.3)	23343 (90.8)	224	6201	15577	22059 (85.8)
East zone							
Survey I	44165	883 (2.0)	42836 (97.0)	446	17861	19488	37854 (88.4)
Survey II	20969	1326 (6.3)	19563 (93.3)	80	6058	12678	19159 (97.9)
West zone							
Survey I	55366	3434 (6.2)	51733 (93.4)	199	22258	25114	48282 (93.3)
Survey II	16800	540 (3.2)	16 065 (95.6)	195	3770	11868	15743 (98.0)

* Proportion excluded from testing of those registered.
† Proportion satisfactorily tested of those registered.
‡ Includes non-vaccinated and vaccinated children and children with doubtful BCG scar.
§ Proportion of all children read of those satisfactorily tested.
BCG = bacille Calmette-Guérin; − = negative ; + = positive.

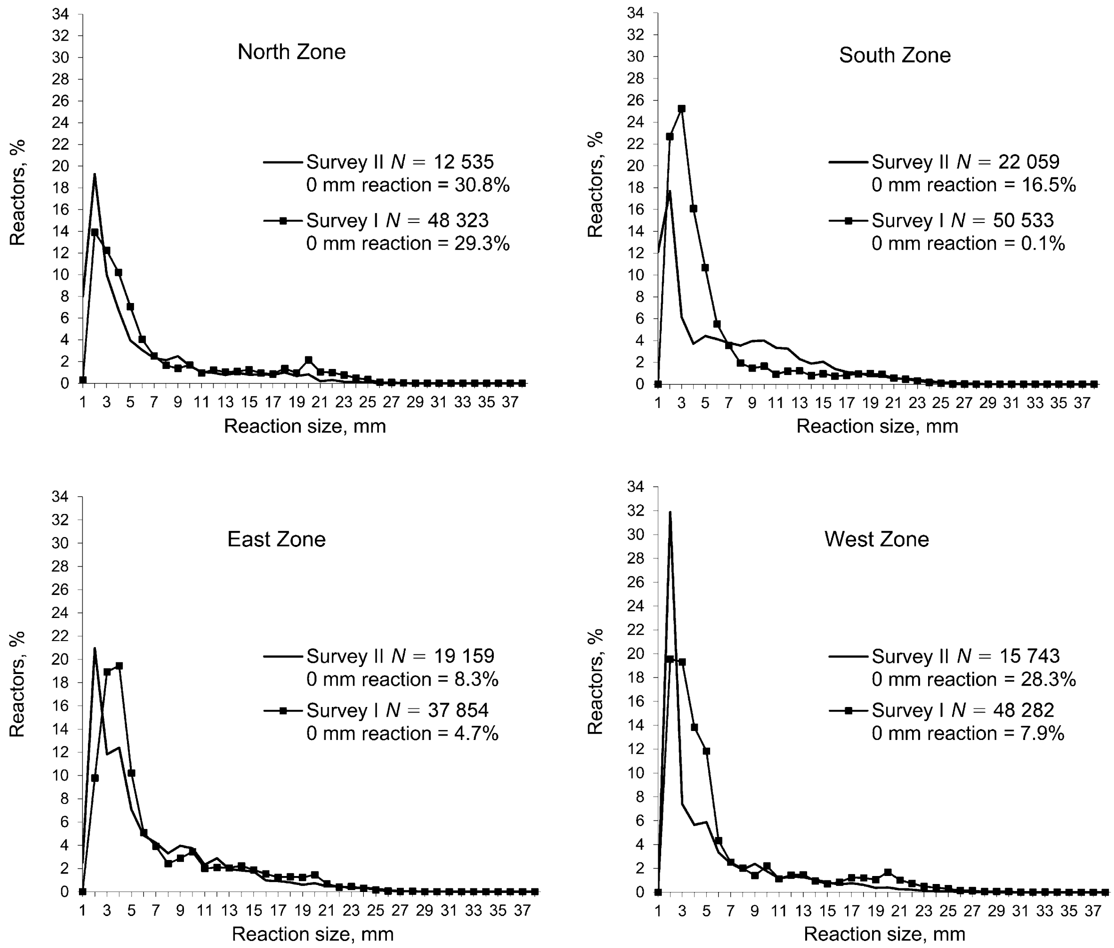

Figure 1 Frequency distributions of reaction sizes for all children aged 1–9 years, irrespective of BCG status, rural and urban populations combined. BCG = bacille Calmette-Guérin.

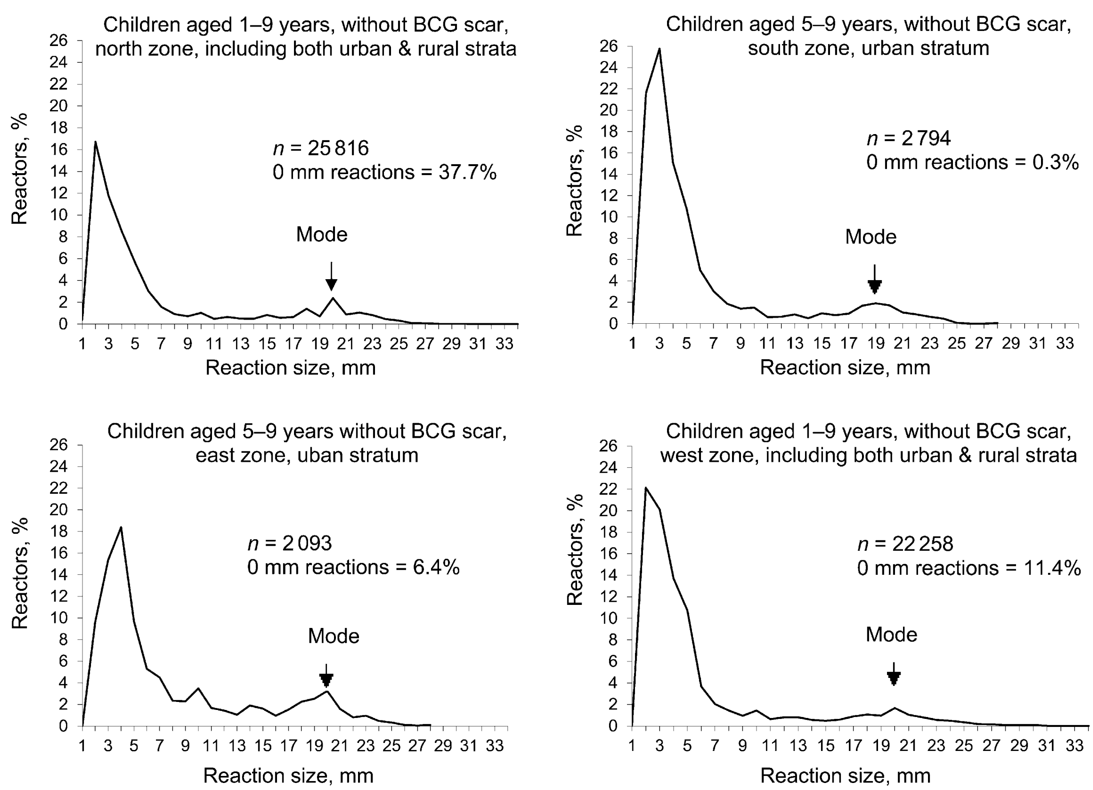

Figure 2 Frequency distribution of tuberculin reaction sizes for selected subgroups, Survey I. BCG = bacille Calmette-Guérin.

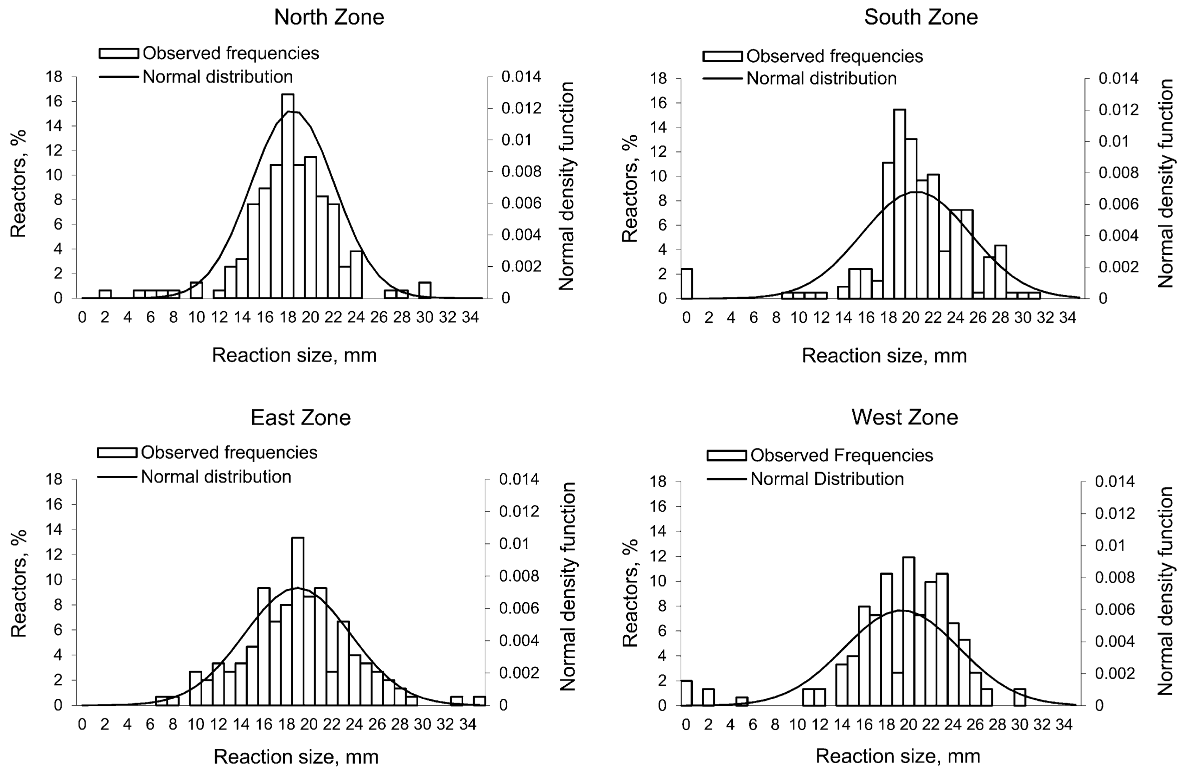

Figure 3 Frequency distribution of reaction sizes among smear-positive TB patients by zone, Survey II. TB = tuberculosis.

patients and an anti-mode at 13 mm was seen among non-vaccinated children aged 1–9 years (data not shown); none of the subgroups of children in the other zones revealed a mode/anti-mode in Survey II. Based on these distributions, the modes/anti-modes used for estimations are given in Table 2.

The estimated prevalence of infection with computed ARTI rates among all children in Surveys I and II and the average per year change in ARTI are presented in Table 3. Considering the mean age of the test-read children and mid-points of surveys in individual zones, the ARTI rates in Survey I corresponded to the year 1998 for the north, south and west zones and 1999 for the east zone, and 2007 for all zones in Survey II. ARTI rates declined by respectively 6% and 11.7% per year in the north and west zones; there was no change in the south and east zones. ARTI rates at the national level declined by 4.5% per year between 1998 and 2007.

Infection prevalence estimates were lower in vaccinated children than in non-vaccinated children in most of the surveys (Table 4); the estimated ARTI rates were similar between the two subgroups.

Table 2 Mode and anti-mode used for estimating prevalence of infection by zone, Surveys I and II

	Mode		Anti-mode	
Zone	Survey I	Survey II	Survey I	Survey II
North	20	18	14	13
South	19	20	14	—
East	20	19	16	—
West	20	19	15	—

DISCUSSION

The estimated ARTI rates among all children aged 1–9 years varied between 1.1% and 1.9% in Survey I

Table 3 Estimated prevalence of infection and ARTI by zone, Surveys I and II

	Survey I		Survey II		
Zone	Prevalence % (95%CI)	ARTI % (95%CI)	Prevalence % (95%CI)	ARTI % (95%CI)	Change in ARTI/year % (95%CI)
North	10.1 (9.1–11.1)	1.9 (1.7–2.1)	5.9 (4.7–7.0)	1.1 (0.8–1.3)	−6.1 (−8.8 to −3.6)
South	6.1 (5.4–6.7)	1.1 (1.0–1.2)	5.3 (4.5–6.0)	1.0 (0.8–1.1)	−1.0 (−3.0 to +0.8)
East	6.2 (5.5–7.0)	1.2 (1.0–1.3)	6.5 (4.8–8.2)	1.2 (0.9–1.5)	−0.1 (−3.2 to +3.0)
West	8.7 (7.7–9.6)	1.7 (1.5–1.9)	3.0 (2.3–3.7)	0.6 (0.4–0.7)	−11.6 (−14.7 to −8.7)
National level	7.8 (7.3–8.2)	1.5 (1.4–1.6)	5.2 (4.6–5.8)	1.0 (0.8–1.1)	−4.5 (−6.3 to −2.8)

ARTI = annual rate of tuberculous infection; CI = confidence interval.

Table 4 Estimated prevalence of infection and ARTI by BCG scar status

	Survey I			Survey II		
	Non-BCG-vaccinated % (95%CI)	BCG-vaccinated % (95%CI)	*P* value*	Non-BCG-vaccinated % (95%CI)	BCG-vaccinated % (95%CI)	*P* value*
North zone						
Test read, *n*	25816	21869		4286	7684	
MI method						
Prevalence	10.9 (9.7–12.1)	9.5 (8.3–10.7)	<0.001	6.7 (4.1–9.3)	5.4 (4.0–6.8)	0.004
ARTI	2.0 (1.8–2.2)	1.8 (1.6–2.0)		1.1 (0.7–1.6)	1.0 (0.7–1.3)	
AM method						
Prevalence	11.4 (10.5–12.3)	—†	—†	7.6 (5.8–9.5)	—†	—†
ARTI	2.1 (1.9–2.2)			1.3 (1.0–1.6)		
South zone						
Test read, *n*	17811	32549		6201	15577	
MI method						
Prevalence	6.6 (5.6–7.5)	5.7 (5.0–6.4)	<0.001	5.2 (3.9–6.4)	5.1 (4.2–5.9)	0.67
ARTI	1.2 (1.0–1.3)	1.1 (0.9–1.2)		0.9 (0.7–1.2)	1.0 (0.8–1.1)	
AM method						
Prevalence	7.1 (6.4–7.8)	—†	—†	—†	—†	—†
ARTI	1.2 (1.1–1.4)					
East zone						
Test read, *n*	17861	19488		6058	12678	
MI method						
Prevalence	6.6 (5.7–7.6)	6.0 (5.2–6.2)	0.02	7.7 (5.0–10.3)	5.7 (4.2–7.3)	<0.001
ARTI	1.2 (1.0–1.4)	1.2 (1.1–1.3)		1.3 (0.8–1.8)	1.1 (0.8–1.4)	
AM method						
Prevalence	7.7 (6.8–8.6)	—†	—†	—†	—†	—†
ARTI	1.4 (1.3–1.6)					
West zone						
Test read, *n*	22258	25114		3770	11868	
MI method						
Prevalence	9.6 (8.5–10.7)	7.8 (6.5–9.2)	<0.001	2.9 (1.7–4.1)	3.0 (2.2–3.7)	0.77
ARTI	1.8 (1.6–2.0)	1.5 (1.2–1.8)	—†	0.5 (0.3–0.7)	0.6 (0.4–0.7)	
AM method						
Prevalence	9.9 (9.0–10.7)	—†	—†	—†	—†	—†
ARTI	1.9 (1.7–2.0)					
National level						
Test read, *n*	83746	99020		18400	47807	
MI method						
Prevalence	8.4 (7.9–9.0)	7.3 (6.7–7.8)	<0.001	5.7 (4.6–6.7)	4.8 (4.2–5.4)	<0.001
ARTI	1.5 (1.4–1.6)	1.4 (1.3–1.5)		1.0 (0.8–1.2)	0.9 (0.8–1.0)	
AM method						
Prevalence	9.0 (8.6–9.5)	—†		—†		—†
ARTI	1.7 (1.6–1.8)					

* *P* values are for test of significance between the estimated prevalence among children with BCG scar and those without BCG scar.
† Due to non-identification of anti-mode, estimates of prevalence of infection and *P* values were not available.
ARTI = annual risk of tuberculosis infection; BCG = bacille Calmette-Guérin; MI = mirror-image; AM = anti-mode method.

and 0.6% and 1.2% in Survey II in the different zones. Variable trends in ARTI were observed in the different zones during the intervening period of roughly 8–9 years, which coincided with the expansion phase of the RNTCP.[3,4] While significant declines in ARTI rates were estimated for the north and west zones, no such decline was noticed in the south and east zones. This was contrary to expectations, as uniform progress in RNTCP implementation should have reduced transmission rates in all of the zones. It was perhaps easier for the RNTCP to bring down the level of infection from relatively higher levels during Survey I in the west and north zones, where the estimated ARTI rates were respectively about 1.7% and 1.9% compared to respectively 1.1% and 1.2% in the east and south zones. However, this incongruence could also be attributed to limitations of the methods available to segregate true tuberculous infections from cross-reactions and subjectivity in measuring TST reaction size. It may not be naïve to say that while significant declines in the transmission of infection were observed in two zones, similar declines were not observed in the other zones due to limitations of the survey tool. It would also be improbable to segregate the impact of control efforts from improvements in socio-economic conditions, as seen in the significant increase in gross domestic product (GDP) in all the Indian states.

Although the surveys were not designed (with respect to sample size) to estimate ARTI and trends by area (rural, urban) or by age group, the ARTI was higher in urban than in rural areas in all the zones in both rounds of surveys. Estimated ARTI rates were similar among the 1–4 year and 5–9 year age groups, which may be due to the fact that estimates in the latter group included the exposure experienced in the younger age group, thus masking the actual size of the difference and making it undetectable.

The pooled national-level estimates of ARTI were respectively 1.5% and 1.0% in Surveys I and II, with a decline in the intervening period of 4.5% per year. It has been estimated that if at least 70% of incidence cases of smear-positive pulmonary TB are detected every year and 85% of them are cured, ARTI rates would decline by 7–11% per year.[23] Declines of 10–15% per year have been observed under good programme conditions in some Western countries.[22,24–26]

An important difference between the two surveys was that while 1TU PPD was used during Survey I, its non-availability during Survey II prompted the use of 2TU, which is now recommended as the standard dose.[12] Differences between these two doses usually show up in the intermediate range of reaction sizes and are therefore not likely to influence the estimates, particularly those made using the MI method.[27]

To evaluate the effect of BCG vaccination, if any, estimations were also carried out separately for non-vaccinated and vaccinated children using the MI method. Estimated ARTI rates were found to be similar between vaccinated and non-vaccinated children in most of these surveys. However, the prevalence of infection was generally lower among the former due to their lower mean age. This was due to a decline in the proportions of vaccinated children with age, supporting the phenomenon of scar disappearance with age in a proportion of children.[28,29] In addition, estimations among children without BCG scar were also carried out using the anti-mode method to ascertain any gross variation between estimates using the MI method in all children when compared to the estimates using the anti-mode method in non-vaccinated children. These differences were not found to be pronounced.

None of the data sets among all children showed clear bimodal patterns. On examining the data subsets by BCG status and age group, only mode or anti-mode could be discerned in some of them. Such identified modes of tuberculous reactions were not far askew from the normal pattern one would expect in a group of infected individuals, and were generally in line with tuberculin distributions seen among TB patients. Nevertheless, challenges faced in segregating true tuberculous reactions from cross-reactions suggest that future tuberculin surveys should be restricted to high-risk populations.

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RÉSUMÉ

CONTEXTE : Vingt-quatre districts en Inde.

OBJECTIF : Déterminer les tendances du risque annuel d'infection tuberculeuse (ARTI) dans chacune des quatre régions géographiquement définies du pays.

SCHÉMA : On a mené deux séries d'enquête tuberculinique basées sur le domicile à 8–9 ans d'intervalle chez les enfants âgés de 1 à 9 ans dans des grappes statistiquement sélectionnées au cours des périodes 2000–2003 et 2009–2010 (Enquêtes I et II). Au total, 184 992 enfants ont été testés au moyen d'une unité internationale de tuberculine purifiée (PPD) RT23 avec Tween 80 lors de l'Enquête I et 69 496 enfants au moyen d'une dose de 2 unités de PPD lors de l'Enquête II. Le diamètre transversal maximal de l'induration a été mesuré environ 72 h après l'administration du test. On a comparé l'ARTI à partir des prévalences d'infection estimées au moyen de la méthode des images en miroir.

RÉSULTATS : Les taux d'ARTI estimés dans les différentes zones ont varié entre 1,1% et 1,9% lors de l'Enquête I et entre 0,6% et 1,2% lors de l'Enquête II. L'ARTI a diminué de 6,1% et 11,7% par année respectivement dans les zones du nord et de l'ouest ; on n'a observé aucune diminution dans les zones du sud et de l'est. Les estimations nationales du niveau ont été respectivement de 1,5% et 1%, avec une diminution de 4,5% par année dans la période concernée.

CONCLUSION : Bien qu'un déclin de l'ARTI ait été observé dans deux des quatre zones ainsi qu'au niveau national, le niveau actuel d'ARTI d'environ 1% dans trois zones suggère la nécessité d'une intensification future des activités de lutte contre la tuberculose.

RESUMEN

MARCO DE REFERENCIA: Veinticuatro distritos en la India.

OBJETIVOS: Evaluar las tendencias del riesgo anual de infección tuberculosa (ARTI) en cuatro zonas del país definidas geográficamente.

MÉTODOS: Se llevaron a cabo dos sesiones de encuestas de tuberculina en los hogares con un intervalo de 8 a 9 años, en niños de 1 a 9 años de edad, en un muestreo por conglomerados del 2000 al 2003 y del 2009 al 2010 (Sesiones I y II). En total, se practicó la prueba tuberculínica a 184 992 niños con 1 unidad tuberculínica purificada (PPD) RT23 y polisorbato 80 en las encuestas de la Sesión I y a 69 496 niños con 2 unidades tuberculínicas (TU) PPD en las encuestas de la Sesión II. El diámetro máximo de induración se midió 72 h después de la administración de la tuberculina. El ARTI se obtuvo a partir de la prevalencia de infección, calculada mediante el método de la imagen especular.

RESULTADOS: El índice del ARTI en las diferentes zonas osciló entre 1,1% y 1,9% en las encuestas de la Sesión I y entre 0,6% y 1,2% en las encuestas de la Sesión II. El ARTI disminuyó a 6,1% por año en la zona norte y a 11,7% por año en la zona occidental. No se observó ninguna disminución en las zonas sur y oriental. A escala nacional, el ARTI fue 1,5% al norte y 1,0% al occidente, con una disminución de 4,5% por año, durante el período de la intervención.

CONCLUSIÓN: Si bien se observó una disminución del ARTI en dos de las cuatro zonas estudiadas y a escala nacional, este criterio que fue cercano a 1% en tres zonas justifica una mayor intensificación de las actividades del control de la tuberculosis.