Population-Based Tuberculin Skin Testing and Prevalence of Tuberculosis Infection in Afghanistan

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Abstract

Objective. A tuberculin skin-test survey was conducted in eight provinces of Afghanistan to estimate the prevalence and annual risk of tuberculosis infection among the Afghan population.

Methods. A cluster survey in eight Afghan provinces, chosen based on population density and geographic distribution, was carried out between October and February 2006. Interviews were conducted and tuberculin skin tests were administered and read.

Findings. 11,413 individuals participated in the study. Using the international standard cut-off of ≥10 mm, tuberculosis prevalence and annual risk of infection in the population were 15% (CI: 14.4–15.7) and 0.80 (CI: 0.76–0.84), respectively. Tuberculosis prevalence was higher in rural than in urban areas. Other risk factors included age, prior tuberculosis treatment or contact, productive cough or cough >3 weeks, no prior bacille Calmette Guérin (BCG) vaccination and a cooking fire in the sleeping room.

Conclusions. The survey documented a lower prevalence and risk of tuberculosis infection than the 1978 national survey and a substantially lower estimate of incidence of new smear-positive tuberculosis cases than World Health Organization estimates. However, other findings suggest that active tuberculosis may remain widespread and undiagnosed, and indicate a need for both additional research and continued investment in tuberculosis treatment and prevention, and in health infrastructure.

Introduction

Tuberculosis is a leading infectious cause of morbidity and mortality globally, resulting in an estimated 1.7 million deaths annually, and disease burden is expected to increase as a consequence of interaction with the HIV epidemic (World Health Organization [WHO] 2006). Afghanistan is among the 25 countries with the greatest tuberculosis burden and has the highest number of cases in Asia: the WHO estimates the annual tuberculosis incidence is 333/100,000/year, and tuberculosis mortality is 92/100,000/year (WHO 2004). During three decades of instability in Afghanistan, the health system has deteriorated, though substantial improvements have occurred since 2002. In spite of recent changes, facilities providing tuberculosis diagnosis and treatment are unevenly distributed and are concentrated in urban areas (Management Sciences for Health 2006).

Tuberculin skin testing is a method commonly used to estimate prevalence of tuberculosis infection and annual risk of tuberculosis infection (ARTI) and is suitable for populations receiving bacille Calmette Guérin (BCG) vaccinations (Salanipioni et al. 2004; Shashidhara et al. 2004; Norval et al. 2004). The last national tuberculin skin-test survey in Afghanistan was conducted in 1978 and estimated prevalence of tuberculosis infection at 46% and ARTI at 3.53% (Japan International Cooperation Agency [JICA] 1978). More recently, a tuberculin skin-test survey among 6575 school-age children in Kabul noted a 4.3% prevalence of tuberculosis infection, with a corresponding ARTI of 0.62% (Dubuis 1999).

Available data do not provide a clear picture of current tuberculosis infection prevalence or disease incidence in Afghanistan. WHO estimates are based on the 1978 survey and data from those currently on tuberculosis treatment (WHO 2004). With the global tuberculosis pandemic and the increasing prominence of multiple-drug-resistant (MDR) tuberculosis, quantification of the epidemic in high-prevalence areas such as Afghanistan is essential for adequate management. The present study aimed to determine prevalence of tuberculosis infection and ARTI in selected provinces of Afghanistan using population-based survey methods.

Methods

Sample-size calculations were performed at the province level and with the objective of determining a sample sufficient to detect a 10% change in the proportion of skin-test-positive individuals from a hypothesized 1978 rate of 46% (95% CI: 41–51) with 80% power and alpha = 0.05 (JICA 1978). Sample size was doubled to 390 per province to account for loss of efficiency in the cluster survey design. Allowing for a 10% loss to follow-up after the skin test, and a design effect of 2, required 906 individuals per province or 7246 in total. To account for potentially underestimating differences between urban and the other, predominantly rural, sites, an additional 1812 persons were included to increase specificity of urban estimates, yielding a minimum sample of 9058. A sample of 11,970 was planned to allow for variation in household size and potential loss or inaccessibility of clusters due to lack of security. Each cluster contained five households, and average household size was assumed to be seven, so cluster size was approximated at 35 individuals (Asscfa et al. 2001). Based on estimated cluster-size and sample-size calculations, 329 clusters were required and 342 clusters were planned. Rural clusters were equally distributed among the eight provinces (n = 36 clusters per province), and urban clusters (n = 54) were apportioned according to the relative size of the urban population centres.

Of Afghanistan's 34 provinces, eight (Bamiyan, Herat, Jawzjan, Kandahar, Kapisa, Khost, Kunduz and Wardak) were selected as representative of the country on the basis of population density, geographic location and accessibility (Figure 1). Sampling employed a probability proportional to size methodology that was modified for use in conflict settings where insecure districts were excluded from the sampling frame; within each province, districts were eligible to be sampled only if security was adequate. Within each district, rural villages or urban neighbourhoods were randomly selected as cluster sites using probability-based sampling that employed pre-census data from the Central Statistics Office (CSO) as the reference population (Central Statistics Office 2005). Cluster numbers in both urban and rural areas were adjusted after the first month of enrollment to accommodate variability in cluster sizes in each province.

Once an area was identified as a cluster site, the survey team met with community leaders to obtain permission to approach households. The community centre, usually the mosque, was used as the starting point for cluster identification. The survey team then proceeded in a random direction numbering houses and then randomly selected five households to participate. Permission from the household head was obtained prior to approaching household members for enrollment. Household members were defined as those who slept in the same dwelling and shared at least one meal per day. Few households refused to participate, though this information was inconsistently recorded. For consenting households, all members older than 1 year of age were eligible. Parental consent was obtained for all members under the age of 18 years, and subject assent was secured for children aged 7 and older.

Figure 1. Map of Afghanistan provinces and survey area

The survey was conducted between October 2005 and February 2006. After consent had been given and questionnaires administered, tuberculin dosing was performed according to WHO/IUATLD recommendations, where 1 mL of PPD RT23/Tween 80 (Statens Serum Institute, Copenhagen, Denmark) was administered to people 1 year or older who were not pregnant. Transverse and vertical induration widths were measured within 48 to 72 hours to the nearest millimeter using metal calipers, and recorded. Prior to the survey, study teams completed competency-based training in administering and interpreting tuberculin skin tests. Supervisors and field managers conducted routine spot checks to assess accuracy of placement and induration measurement using standard messages from the Afghanistan National Tuberculosis Program (NTP). People with symptoms suggestive of active tuberculosis disease were referred to the nearest tuberculosis clinic for evaluation.

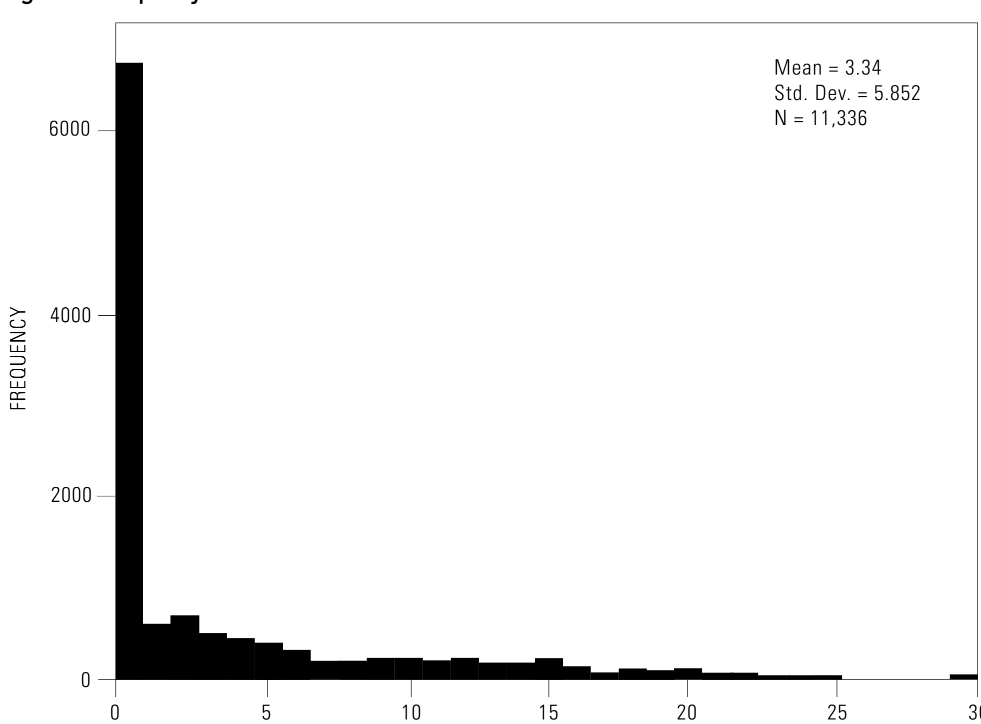
Data analysis was performed using Excel, STATA Version 8.0 (College Station, TX), and SPSS Version 14.0 (Chicago, IL). The design effect from cluster sampling was calculated at 1.97 such that confidence intervals did not subsequently need to be adjusted. Risk factors for tuberculosis were assessed using chi-square tests and logistic regression. Nagelkerke R2 was used to examine the proportion of variance accounted for by predictors in multivariate models, and the Hosmer–Lemeshow test was used to assess goodness-of-fit. Prevalence of tuberculosis infection was estimated based on a transverse induration diameter of ≥10 mm, a criterion commonly used to determine latent or active tuberculosis in high-prevalence countries. The cut-off is applicable to all age groups and has been used in multiple international settings in population-based studies to approximate tuberculosis prevalence (American Thoracic Society 2000). Annual risk of tuberculosis infection is a mathematical calculation used to indicate the proportion of the population that will be primarily infected or re-infected with tubercle bacilli in 1 year. The trend in change of risk of infection is calculated based on prevalence of infection rates using the standard of ≥10 mm to classify a person as positive (Reider 1999; Spinaci et al. 1989).

Ethical review and approval was obtained from review boards of the Ministry of Public Health of the Islamic Republic of Afghanistan, the University of California at San Diego and Johns Hopkins School of Public Health prior to data collection.

Results

The sample comprised 11,413 individuals, and skin-test results were recorded for 11,336 or 99.3% of subjects. The sample population was 55.5% male and 44.5% female and had the following age distribution: 0–4 years, 13.8%; 5–9 years, 20.3%; 10–14 years, 15.2%; 15–19 years, 10.5%; 20–29 years, 13.0%; 30–39 years, 10.6%; and 40+ years, 16.5%. Of participants, 52.2% (CI: 51.2–53.1) had received a BCG vaccination, and 13.3% (CI: 12.7–14.0) reported prior tuberculosis treatment or contact with an individual with active disease.

Figure 2. Frequency of induration size



Induration Characteristics

The distribution of induration width among participants is presented in Figure 2. Of all participants, 60% (95% CI: 59–61) had a reaction of 0–5 mm to the tuberculin skin test. The distribution of induration was: 78% negative reaction (0–5 mm); 7% some reaction (6–9 mm, defined by the WHO as a negative reaction and by the manufacturer as a weak positive reaction); 7% positive reaction (10–14 mm); and 8% strong positive reaction (15+ mm). Among those with any induration (n = 4564), mean and median transverse diameters were 8.3 mm (standard deviation [SD] = 6.6) and 6.0 mm, respectively, and the distribution was somewhat skewed as reflected by the 25th and 75th percentile values of 3 mm and 13 mm, respectively. In general, induration size increased with age: diameter increased on average 0.14 mm (95% CI: 0.13–0.15) per year ($p < .001$).

Prevalence of Tuberculosis Infection and Annual Risk of Infection

At the standard 10 mm cut-off, prevalence of tuberculosis infection was 15% (95% CI: 14.4–15.7) and ARTI was 0.80 (95% CI: 0.76–0.84) for the survey population. Prevalence of tuberculosis infection rates by sex, age, prior BCG vaccination, urban/rural residence and province are presented in Table 1. Prevalence of tuberculosis infection was similar between the two sexes. Skin-test positivity increased with age and was significantly greater among those without prior BCG vaccination. Prevalence of infection varied widely between provinces, with the lowest in Wardak (5%) and the greatest in Kandahar and Bamiyan (25%). While Bamiyan and Kandahar had the highest prevalence rates, the odds of having BCG scars differed appreciably between the two areas, at 1.9 (95% CI: 1.6–2.2) and 0.5 (95% CI: 0.5–0.6), respectively. Prevalence of infection was significantly greater in rural than in urban areas, although there was no significant difference in BCG vaccination rates between urban and rural areas ($p = .202$).

The ARTI is the proportion of the population that will be primarily infected or re-infected with tubercle bacilli in 1 year and is usually expressed as a percentage. The risk of contracting tuberculosis may change over time; thus, ARTI represents the midpoint in time between the year the cohort was born and the year of the survey. Annual risk of infection by age, sex, BCG status, urban/rural residence and province are presented in Table 1. The risk of infection is directly related to prevalence, and a higher prevalence of infection is associated with a greater ARTI. For the eight provinces surveyed, ARTI was 0.80% (CI: 0.76–0.84).[1] ARTI was similar for men and women, and higher among those without prior BCG vaccination. In general, ARTI increased with age; however, the greatest ARTI was observed in two groups, those 0–5 years and 30–39 years of age, where the point estimate for ARTI in both groups was 1.0%. ARTI varied widely by province and was significantly higher in rural areas.

Risk Factors for Tuberculosis Infection

Risk factors for tuberculosis infection assessed included location (province, urban/rural residence); demographic characteristics (age, sex); tuberculosis prevention, exposure and symptoms (prior BCG vaccination, history of TB treatment or contact with infected individual, cough >3 weeks in duration and productive cough); and environmental risk factors (crowding, defined by the number of people sleeping per room and presence of a cooking fire in the sleeping room). The odds and adjusted odds of tuberculosis infection for risk factors are presented in Table 2. All predictors were significantly associated with tuberculosis infection in univariate models, and, with the exception of sex and crowding, the observed relationships remained statistically significant in multivariate models.

The adjusted odds ratio of tuberculosis infection was 1.56 (CI: 1.29–1.87) times greater in rural than in urban areas and varied between provinces. An age-dependent increase in risk of 1.47 (CI: 1.42–1.52) was associated with each additional 10 years of age. The adjusted odds ratio of tuberculosis infection was significantly greater among those with prior TB treatment or exposure (13.3%, CI: 12.7–14.0; OR = 2.46, CI: 2.10–2.88), cough greater than 3 weeks in duration (17.1%, CI: 16.4–17.8; OR =2.36, CI: 1.95–2.87) and productive cough (10.1%, CI: 9.5–10.6; OR = 2.84, CI: 2.27–3.54). A BCG scar was noted in 52% (CI: 51.3–53.1) of subjects and was protective against tuberculosis in the univariate model; however, in the adjusted model this finding was reversed, and those with no prior BCG vaccination were significantly less likely to be identified as having tuberculosis infection (OR = 0.86, CI: 0.75–0.99). A positive association between the presence of a BCG scar and age was observed and is a potential confounder.

Table 1. Prevalence and annual risk of tuberculosis infection

	Prevalence of infection (transverse diameter ≥ 10 mm)		Annual risk of tuberculosis infection			
	n	Percent (95 CI)	Point Estimate	95 % CI		
Overall (*n* = 11,336)	1701	15.0 (14.4–15.7)	0.80	0.76	–	0.84
By sex						
Males (*n* = 5023)	714	14.2 (13.3–15.2)	0.76	0.71	–	0.82
Females (*n* = 6306)	987	15.7 (14.8–16.6)	0.83	0.78	–	0.88
By age						
0–4 yrs (*n* = 1569)	42	2.8 (1.9–3.6)	1.01	0.68	–	1.30
5–9 yrs (*n* = 2310)	110	4.8 (3.9–5.7)	0.72	0.58	–	0.86
10–14 yrs (*n* = 1730)	140	8.1 (6.9–9.5)	0.71	0.60	–	0.84
15–19 yrs (*n* = 1194)	144	12.1 (10.3–14.0)	0.77	0.65	–	0.90
20–29 yrs (*n* = 1470)	255	17.3 (15.4–19.4)	0.80	0.71	–	0.91
30–39 yrs (*n* = 1194)	341	28.6 (26.0–31.2)	1.01	0.91	–	1.12
40 + yrs (*n* = 1869)	669	35.8 (33.6–38.0)	0.86	0.80	–	0.93
By BCG status						
Prior BCG (*n* = 5934)	723	12.2 (11.4–13.0)	0.73	0.68	–	0.78
No BCG (*n* = 5402)	978	18.1 (17.1–19.2)	0.86	0.81	–	0.91
By location						
Urban (*n* = 1919)	232	12.1 (10.7–13.6)	0.66	0.58	–	0.74
Rural (*n* = 9417)	1469	15.6 (14.9–16.3)	0.83	0.79	–	0.87
By province						
Bamiyan (*n* = 1076)	264	24.5 (22.0–27.2)	1.26	1.11	–	1.42
Herat (*n* = 2313)	277	12.0 (10.7–13.4)	0.65	0.58	–	0.74
Jawzjan (*n* = 1491)	214	14.4 (12.6–16.2)	0.68	0.59	–	0.78
Kandahar (*n* = 1566)	399	25.5 (23.3–27.7)	1.52	1.37	–	1.68
Kapisa (*n* = 1191)	161	13.5 (11.6–15.6)	0.69	0.59	–	0.81
Khost (*n* = 1213)	142	11.7 (10.0–13.7)	0.70	0.59	–	0.82
Kunduz (*n* = 1153)	176	15.3 (13.2–17.5)	0.75	0.64	–	0.86
Wardak (*n* = 1333)	68	5.1 (4.0–6.4)	0.28	0.28	–	0.35

Discussion

The present study of eight provinces represents the first population-based tuberculosis skin-test survey in Afghanistan since the national survey of 1978. Although smaller studies have been conducted in the interim, there are few reports with which to compare results. The distribution of induration diameters in the present survey was similar to that previously observed in Afghanistan (Reider 1999). Using a 10 mm standard for induration, the prevalence of tuberculosis infection was 15.0% (CI: 14.4–15.7) and ARTI 0.80 (CI: 0.76–0.84). These are substantially lower than the national prevalence of infection of 46% and ARTI of 3.53 observed in 1978 (JICA 1978). A recent tuberculin skin-test survey among children 7–8 years of age in Kabul estimated the prevalence of tuberculosis infection at 4.3% and ARTI at 0.34 (CI: 0.23–0.54) (Dubuis et al. 2004). If the cut-off used in the Kabul study (8 mm) in children 7–8 years of age were applied in the current study, tuberculosis prevalence across the eight provinces surveyed would be 8.3% and ARTI 1.15, both greater than the rates recently observed in Kabul. These comparisons should be made with caution because of the pronounced geographic variation in prevalence of infection (where infection rates appear to be higher in rural areas) and because Kabul was not included in our survey.

The 2004 WHO estimates place Afghan active tuberculosis disease prevalence and incidence, respectively, at 661/100,000 and 333/100,000/year with a constant incidence rate (i.e., a trend in incidence rate change of 0.0% per year) (WHO 2006). To compare WHO figures and survey data, Styblo's rule was applied, where a 1% annual risk of infection corresponds to an incidence rate of 50/100,000/year (CI: 39–59) new smear-positive tuberculosis cases (Styblo 1985). Using the ARTI estimate of 1.01 for the youngest age group (0–4 years) as a measure of current risk, the corresponding annual incidence rate would be 50/100,000/year, which is considerably less than WHO estimates. This could suggest that estimated prevalence of tuberculosis infection documented in the survey is biased toward lower values or that the Styblo rule may not apply in Afghanistan.

A primary cause of false-positive tuberculin skin tests is BCG vaccination (Menzies and Vissandjee 1992). Because of the large proportion of the population with BCG scars (52%), there was concern that tuberculosis prevalence rates may have been overestimated. Some prior surveys calculate prevalence and annual risk of infection only for the population that has not received BCG. However, in our study, mean induration size was significantly smaller among those with a vaccination, suggesting they were less likely to be categorized as a false positive. Among children who received BCG in infancy, almost all will have a reaction of less than 10 mm in diameter after 2 years of age; among those who received BCG between primary school age and adolescence, 15–25% have positive reactions up to 20 years later (Menzies and Vissandjee 1992; Jonson et al. 1995; Joncas et al. 1975). In most Asian countries and in other regions where tuberculosis infection is frequent, tuberculosis is a more likely cause of a positive skin test than BCG vaccination (Menzies et al. 1992; Menzies et al. 1999).

Another major cause of false-positive tuberculin skin tests is infection with nontuberculous mycobacteria, which is commonly present in soil and water in tropical and subtropical climates. Sensitivity is common among people in these areas, and cross-reaction may produce a false-positive tuberculin test. Nontuberculous mycobacteria are relatively rare in cold environments, such as mountainous areas of Afghanistan with their cold winters, and more common in tropical and subtropical climates (Menzies et al. 1999). In most of Afghanistan, nontuberculous mycobacteria are expected to occur rarely and are not likely to be an important cause of false positives; however, an exception might be the southern provinces bordering Pakistan, where mean annual soil temperature is 15°C or greater (United States Department of Agriculture 2001). The only southern province surveyed was Kandahar, which had the highest prevalence of infection of all provinces; continued conflict has limited access to health facilities in Kandahar, and this could also be associated with elevated infection rates.

Our survey found that risk of tuberculosis infection was 1.56 (CI: 1.29–1.87) times greater in rural than in urban settings. In contrast, higher prevalence of tuberculosis infection is anticipated in urban areas, where opportunity of exposure and risk of contracting infection are presumed greater due to increased population density (Reider 1999). Larger household size, lower rates of care seeking, and more treatment failures may be associated with higher tuberculosis infection prevalence in rural areas.

Table 2. Risk factors for tuberculosis infection

Predictor variables	Unadjusted		Adjusted (all predictors included)	
	Odds (95 % CI)	*p*	Odds (95 % CI)	*p*
Location variables				
Bamiyan	6.05 (4.57–8.01)	<.001	5.57 (4.03–7.69)	<.001
Herat	2.53 (1.92–3.33)	<.001	2.76 (2.01–3.77)	<.001
Jawzjan	3.12 (2.35–4.14)	<.001	5.08 (3.65–7.06)	<.001
Kandahar	6.36 (4.86–8.33)	<.001	12.63 (9.12–17.48)	<.001
Kapisa	2.91 (2.17–3.91)	<.001	3.24 (2.34–4.49)	<.001
Khost	2.47 (1.83–3.33)	<.001	3.40(2.44–4.74)	<.001
Kunduz	3.35 (2.50–4.49)	<.001	3.05 (2.19–4.23)	<.001
Wardak (reference)	1.00		1.00	
Rural area (reference: urban)	1.34 (1.16–1.56)	<.001	1.56 (1.29–1.87)	<.001
Individual characteristics				
Age (per 10-year increase)	1.59 (1.54–1.63)	<.001	1.47 (1.42–1.52)	<.001
Male sex (reference: female)	0.89 (0.80–0.99)	.033	0.91 (0.80–1.03)	.117
Prior TB treatment / contact	3.33 (2.94–3.77)	<.001	2.46 (2.10–2.88)	<.001
No BCG scar	1.59 (1.43–1.77)	<.001	0.86 (0.75–0.99)	.003
Cough >3 weeks' duration	6.42 (5.73–7.20)	<.001	2.36 (1.95–2.87)	<.001
Productive cough	9.29 (8.14–10.60)	<.001	2.84 (2.27–3.54)	<.001
≥ 7 people sleeping / room	0.85 (0.74–0.98)	.023	0.88 (0.73–1.05)	.142
Cooking fire in sleeping room	1.50 (1.25–1.80)	<.001	0.81 (0.64–1.03)	<.001
	Nagelkerke R^2		.316	
	Hosmer Lemeshow		.109	

There are a number of limitations to this survey. First, the survey encompassed eight of 34 provinces, when a survey of all provinces would have been ideal considering the paucity of data on tuberculosis in Afghanistan. Although efforts were made to select representative provinces, there is no assurance that the eight are indeed representative of the country. Second, survey teams were unable to cover all districts in some provinces due to security concerns; this was particularly true in Kandahar. Populations in insecure areas may have restricted access to health services as well as higher infection rates than those in areas with better access; conversely, isolation may protect populations from infections entering from other areas. Third, the smear-positive incidence rates derived from Styblo's rule are unexpectedly low, and there is a discrepancy between survey findings and anticipated incidence rates that suggests the survey may have underestimated the extent of tuberculosis in Afghanistan. False negatives, resulting from poor nutrition, improper storage of PPD, or incorrect application or reading of skin tests, could have biased survey findings toward lower prevalence rates. Lastly, the distribution of induration width shows no clear cut-off for classification of tuberculosis based on size of induration, thus it is possible that employing a 10 mm cut-off may have increased specificity. However, some true infections may have been misclassified as false negatives where other noninfections could have been classified as positives. This is an unavoidable problem that the authors attempted to address by providing prevalence rates and ARTI by multiple classification criteria.

Conclusions

The present eight-province survey documented a lower prevalence of tuberculosis infection and lower annual risk of infection compared to the 1978 national survey. The annual incidence of smear-positive tuberculosis cases calculated from survey data was also lower than disease incidence rates estimated by the WHO. These findings suggest that poor infrastructure coupled with several decades of instability may not have adversely affected the epidemiological situation; however, prevalence of tuberculosis infection as measured in the skin-test survey cannot be directly compared with prevalence of active disease reported by the WHO. Several other study outcomes, notably the high proportion of individuals reporting prior TB treatment or exposure and current TB symptoms, are causes of concern and suggest that active tuberculosis disease may remain relatively widespread and undiagnosed, despite increasing trends in diagnosis and treatment. While this is not unexpected in a country that has the greatest estimated tuberculosis burden in Asia, it illustrates the need for additional efforts to update national tuberculosis statistics and continued and expanded investment in the National Tuberculosis Program and reconstruction of the Afghan health system.

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Notes

[1]When the international standard cut-off of 10 mm is applied.