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Determination of the Prevalence of Infection with *Mycobacterium tuberculosis* among Persons Vaccinated against Bacillus Calmette-Guérin in South Korea

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The prevalence of tuberculous infection was estimated among 12,032 persons with a Bacillus Calmette-Guérin (BCG) vaccination scar and 7,788 persons without such a scar who participated in a nationwide tuberculin skin test survey conducted in the Republic of Korea in 1975. The analysis was built upon mixture models that captured the heterogeneity of indurations arising from tuberculous infection, cross-reactions due to infection with environmental mycobacteria, and BCG vaccination. The three distributions were allowed to vary by age, sex, and BCG vaccination status in the Bayesian manner, according to the prior opinion of the authors. Estimated prevalences of tuberculous infection were similar among persons with a BCG scar and persons without one: 7.5% (95% credibility interval (CI): 3.1, 12.5) and 5.2% (95% CI: 4.2, 6.3), respectively, at age 0–4 years and 87.3% (95% CI: 84.0, 90.2) and 84.0% (95% CI: 81.9, 85.8), respectively, at age 25–29 years. From this analysis it can be concluded that mixture models allow investigators, for the first time, to estimate the prevalence of tuberculous infection not only in unvaccinated persons but also in the BCG-vaccinated population. Mixture models are a versatile tool for analyzing diagnostic test data and more general classification problems of considerable complexity. *Am J Epidemiol* 2002;155:654–63.

Bayes theorem; BCG vaccine; mixture model; *Mycobacterium bovis*; prevalence; tuberculin test; tuberculosis

Estimation of the prevalence of infection with *Mycobacterium tuberculosis* by means of tuberculin skin testing is difficult in situations where sensitization with environmental mycobacteria or *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) is prevalent (1). BCG vaccination is a well-recognized cause of nonspecific reactions to tuberculin, leading to a distribution closely similar to that due to *M. tuberculosis* infection in the period shortly after vaccination (2), but the degree of postvaccinal tuberculin sensitivity may vary with the strain of BCG (3). BCG may also induce cross-reactions for a prolonged time after vaccination (4). For this reason, persons with a BCG vaccination scar have usually been excluded from the analysis of tuberculin skin test surveys (5–9). However, BCG vaccination coverage has increased in many regions of the world. Therefore, results of analyses of tuberculin skin test indurations limited to children without prior BCG vaccination (i.e., without a BCG scar) may be increasingly nonrepresentative for the population at large. New methods of analyzing tuberculin skin test survey data in BCG-free individuals have recently been introduced and have been applied to surveys in the Republic of Korea (10). These methods rely on mixture modeling, a statistical approach designed for situations with inherent structural heterogeneity that is unobserved but of crucial interest for the problem under scrutiny. For tuberculin skin testing in BCG-free individuals, such heterogeneity consists of the two types of indurations arising from infection with *M. tuberculosis* and cross-reactions due to infection with environmental mycobacteria, where primary interest is centered around the prevalence of the former, although two-component mixture models also provide valuable insight into the distributions of both reactions.

The analysis presented here goes a step further. To our knowledge, it is the first attempt to estimate prevalence of infection for BCG-vaccinated individuals, a group that has hitherto been considered out of analytical reach because of the problem of cross-reactions arising from prior BCG vaccination. This additional source of heterogeneity necessitates the use of three-component mixture models that are more complex than two-component mixture models used in the population of unvaccinated individuals. Moreover, BCG reactions are particularly disturbing, because they are usually larger and more prevalent shortly after vaccination and fade away later. A further assumption is that BCG vaccination does not prevent infection but protects against the consequences of

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Abbreviations: BCG, Bacillus Calmette-Guérin; PPD, purified protein derivative; PPD-S, purified protein derivative standard; TU, tuberculin units.

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infection (11). However, because of the considerable overlap between the distribution of BCG reactions and those resulting from *M. tuberculosis* infection, it might be unrealistic to assume that an analysis of the vaccinated population alone would provide useful estimates of infection prevalence. In this article, we put forward an alternative and more promising framework that borrows information from the group of unvaccinated individuals. It consists of a simultaneous analysis of both the vaccinated and unvaccinated populations, where in the latter, estimation of the distributions of infections due to *M. tuberculosis* and cross-reactions due to environmental mycobacteria turns out to be successful (10); it further assumes that the two distributions are similar in vaccinated and unvaccinated individuals. The latter assumption's being fulfilled seems to be a necessity in order to make an estimation of the third mixture component (distribution of cross-reactions) feasible. However, if this assumption is not valid, or if the size of the unvaccinated population is too small for estimating the distributions of cross-reactions and infections, estimation of the three-component mixture distribution in the vaccinated population is hardly possible, meaning that prevalence and mixture component estimates would be unstable or too imprecise to be of practical value.

For a population in which assignment of BCG vaccination is close to random, the suggested methodology will be regarded as successful if the ratio of the infection prevalence in the BCG-vaccinated population to the prevalence in the unvaccinated population is close to 1. The South Korean survey of 1975 provided us with a good opportunity to validate the chosen methodology, because both groups (persons with and without a BCG scar) were fairly large, lending credibility to the hypothesis of similar infection prevalences in both groups. Furthermore, if the proposed methodology is considered successful, it can also be applied in populations with high BCG coverage wherein the vaccinated and unvaccinated might differ in terms of the prevalence of tuberculous infection. This would also allow much more cost-effective conduct of such surveys.

MATERIALS AND METHODS

Survey methodology

Between 1965 and 1995, the Korean National Tuberculosis Association conducted seven tuberculosis and tuberculin skin test surveys at 5-year intervals. The survey methodology has been described elsewhere in detail (12). Briefly, all surveys were based on multistage stratified cluster sampling. A total of 190 clusters were sampled, using as a sample unit a modified enumerating district, defined according to the census. Two thirds of the clusters were in an urban stratum and one third were in a rural stratum, all clusters having the same sampling fraction. Enumeration districts with special mass accommodations (such as military bases, dormitories, or hospitals) were excluded.

For this analysis, we selected the survey conducted in 1975, because our interest was in the analysis of the estimated prevalence of *M. tuberculosis* infection at a time when BCG coverage was sufficiently high to allow meaningful analysis of BCG-vaccinated individuals.

Tuberculin skin testing

The dose of international standard tuberculin was calibrated. It was established to be 5 tuberculin units (TU) of purified protein derivative (PPD) standard (PPD-S) (13, 14). Subsequently, the introduction of a stabilizing agent (a polyoxyethylene derivative of sorbitan mono-oleate) demonstrated that the number of units of tuberculin PPD RT-23 (Statens Serum Institut, Copenhagen, Denmark) could be reduced to 2 TU to achieve a response that was bioequivalent to 5 TU of PPD-S (15). International recommendations for the dosage using tuberculin PPD RT-23 have changed over time (16), which complicates the issue further. For this reason, the Korean Institute of Tuberculosis opted to use the dosage of 1 TU of PPD RT-23 originally recommended by the World Health Organization throughout all of the surveys to ensure comparability of the data. Thus, in addition to clinical, radiographic, and bacteriologic examinations, individuals under 30 years of age were tuberculin-tested by trained personnel with 1 TU of PPD RT-23 in all seven surveys. Approximately 72 hours after application of the test, the diameter of induration of the reaction was measured transversely to the long axis of the arm. The number of reactors by exact millimeter of induration was recorded up to a reaction size of 29 mm. Persons with indurations of 30 mm or more were recorded as having indurations of 30 mm.

BCG vaccination policy in South Korea

Before 1952, there was no systematic BCG vaccination program in South Korea. Subsequently, systematic vaccination targeting primary school, junior high school, and high school students was implemented. Coverage was fairly low until 1963, when the scheme was expanded to include preschool children. From 1966 onward, vaccination policy was altered, and preschool children were vaccinated without prior tuberculin testing, while schoolchildren were only vaccinated (or revaccinated) if they had a negative tuberculin skin test result. From 1967 onward, vaccination without prior tuberculin testing was extended to first graders if they had no visible BCG scar, but for sixth graders, BCG vaccine was given in the presence of a negative tuberculin skin test irrespective of the presence or absence of a BCG scar. This scheme remained unaltered until 1997. In 1975, when the population of South Korea was 35 million, 2.5 million doses of BCG vaccine were given (Korean Institute of Tuberculosis, unpublished data).

Data set for the current analysis

The population surveyed in 1975 was stratified by 5-year age group (0–4, 5–9, 10–14, 15–19, 20–24, and 25–29 years), by sex, and by the presence or absence of a BCG scar upon physical inspection (table 1). A total of 19,820 individuals with recorded tuberculin skin test results were included in the 1975 tuberculin skin test survey. Of these, 12,032 (60.7 percent) had a BCG scar and 7,788 (39.3 percent) did not (17).

TABLE 1. Distribution of individuals in a tuberculin skin test survey, by age, sex, and the presence or absence of a BCG* scar, South Korea, 1975

Age (years)	No BCG scar present			BCG scar present			Total		
	Males	Females	Total	Males	Females	Total	Males	Females	Total
0–4	975	886	1,861	915	831	1,746	1,890	1,717	3,607
5–9	580	592	1,172	1,671	1,445	3,116	2,251	2,037	4,288
10–14	490	512	1,002	1,751	1,632	3,383	2,241	2,144	4,385
15–19	623	634	1,257	1,115	1,033	2,148	1,738	1,667	3,405
20–24	426	642	1,068	433	603	1,036	859	1,245	2,104
25–29	642	786	1,428	291	312	603	933	1,098	2,031
Total	3,736	4,052	7,788	6,176	5,856	12,032	9,912	9,908	19,820

* BCG, Bacillus Calmette-Guérin.

Analysis by mixture models

The statistical analysis was based on mixture models (18) that captured the heterogeneity of indurations arising from infection with *M. tuberculosis*, cross-reactions due to infection with environmental mycobacteria, and reactions due to BCG vaccination. The distributions of these three types of reactions, together with their relative weights, were the building blocks of the mixture model (table 2). It was assumed that the distribution of indurations in the group of individuals with a BCG scar was a mixture of three components: a distribution of infections with *M. tuberculosis* (f), a distribution of cross-reactions due to environmental mycobacteria (g), and a distribution of BCG reactions (h) due to prior vaccination. In the group without a BCG scar, only the distributions of *M. tuberculosis* infections (f') and cross-reactions (g') needed to be considered. The prevalences of *M. tuberculosis* infection were q_1 in the group with a BCG scar and p_1 in the group without a BCG scar. Because of the possibility of multiple reactions, it was further assumed that an individual's reaction to *M. tuberculosis* infection always dominates the other two reactions (in the sense of being larger in size than the other two). As a consequence, q_2 (p_2) and q_3 cannot be interpreted as the prevalences of cross-reactions and BCG reactions, respectively, since a reaction due to *M. tuberculosis* infection never excludes the possibility of a smaller (unobserved) cross-reaction or BCG reaction. The mixture component distributions were assumed to be Weibull, lognormal (both parameterized by their 25 percent and 75 percent quantiles), or gamma distributions (parameterized by mean and standard deviation). Hence, the two mixture distributions $m(x)$ and $m'(x)$ comprise 15 unknown model parameters (five mixing weights and 10 quantile parameters).

It was assumed that sex and age not only affect the prevalences (mixture weights) but might have an influence on the mixture component distributions (f, g, h, f', g') as well. When taking these covariates into account (12 strata), the full model would consist of 180 free parameters. However, this model would unrealistically assume that the mixture component distributions are completely unrelated to each other with regard to the different covariate strata. For exam-

TABLE 2. Model structure for mixture components and mixture distributions in a tuberculin skin test survey, South Korea, 1975

Distribution	Notation
BCG scar present*	
Infections†	$f(x)$
Cross-reactions‡	$g(x)$
BCG reactions§	$h(x)$
Mixture distribution¶	$m(x) = q_1 f(x) + q_2 g(x) + q_3 h(x), (x > 0)$ $m(0) = 1 - q_1 - q_2 - q_3$
No BCG scar present	
Infections†	$f'(x)$
Cross-reactions‡	$g'(x)$
Mixture distribution#	$m'(x) = p_1 f'(x) + p_2 g'(x), \quad (x > 0)$ $m'(0) = 1 - p_1 - p_2$

* BCG, Bacillus Calmette-Guérin.
† Reactions due to infection with *Mycobacterium tuberculosis*; x denotes induration in millimeters.
‡ Cross-reactions due to infection with environmental mycobacteria.
§ Reactions due to vaccination with BCG.
¶ Distribution composed of infection due to *M. tuberculosis*, cross-reactions due to infection with environmental mycobacteria, and reactions due to vaccination with BCG.
# Distribution composed of infection due to *M. tuberculosis* and cross-reactions due to infection with environmental mycobacteria.

ple, the distribution of infections for males aged 10–14 years with a BCG scar—$f_{M3}(x)$, for example—is likely to be close to 1) the distribution of infections for males aged 5–9 years, $f_{M2}(x)$, and males aged 15–19 years, $f_{M4}(x)$; 2) the distribution of infections for females aged 10–14 years, $f_{F4}(x)$; and 3) the distribution of infections for males aged 10–14 years without a BCG scar, $f'_{M3}(x)$. On the other hand, assuming that the component distributions are not affected at all by sex, age, and BCG scar status might also be questionable. Therefore, a compromise driven by knowledge of the subject matter and the observed data seems reasonable, where the former has to be included in the statistical model as external knowledge and the latter enters the analysis automatically during the process of statistical estimation.

Since the analysis was conducted in a Bayesian way (19, 20), subject-matter knowledge was included in the form of prior opinion. Noninformative (uniform) prior distributions were used for all prevalence parameters (mixture weights), whereas prior opinion about the relations between the parameters (25 (75) percent quantiles) of the component distributions was specified in the form of constraints (intervals) for the ratios of related parameters. Uniform distributions were assumed within these intervals. Elicitation of prior opinion among the authors led to the following constraints for the ratios of the 25 (75) percent quantiles (table 3):

- Differences of quantiles with regard to sex were assumed to be, at most, 10 percent for all distributions.
- Differences of quantiles between subsequent age classes were assumed to be, at most, 10 percent for the distribution of *M. tuberculosis* infections and, at most, 15 percent for the distribution of cross-reactions. For the distribution of BCG reactions, a decrease of 10–25 percent between subsequent age classes was assumed.
- Differences of quantiles between the distributions of *M. tuberculosis* infections in the groups with and without a BCG scar (f vs. f') were assumed to be, at most, 10 percent. The same assumption was made for the distributions of cross-reactions (g vs. g').

The posterior distribution of all model parameters was obtained by combining the likelihood function (given by the mixture distributions $m(x)$ and $m'(x)$ for all covariate strata) and the prior distribution via Bayes' theorem. Because of the complexity of the model, computation of the posterior distribution was analytically intractable, but Markov chain Monte Carlo methods (21, 22) offered a feasible alternative. The simulations were done by a random-walk Metropolis algorithm, with a burn-in period of 100,000 and a sample size of 500,000 iterations. All posterior quantities were extracted from a thinned sample comprising 2,000 values. Convergence of the algorithm was good; we checked for it by comparing runs starting from different initial values.

TABLE 3. Prior specifications (uniform distributions) for ratios of 25 (75) percent quantiles of related mixture component distributions in a tuberculin skin test survey, South Korea, 1975

Relation	Distribution	Quantile interval for ratios
Males to females	Infections*	0.90, 1.10
	Cross-reactions†	0.90, 1.10
	BCG‡ reactions§	0.90, 1.10
Current age class to previous age class	Infections*	0.90, 1.10
	Cross-reactions†	0.85, 1.15
	BCG reactions§	0.75, 0.90
Group without BCG scar to group with BCG scar	Infections*	0.90, 1.10
	Cross-reactions†	0.90, 1.10

* Reactions due to infection with *Mycobacterium tuberculosis*.
† Cross-reactions due to infection with environmental mycobacteria.
‡ BCG, Bacillus Calmette-Guérin.
§ Reactions due to vaccination with BCG.

RESULTS

Analysis of the class of mixture models based on Weibull, lognormal, and gamma distributions suggested a best model with Weibull distributions for *M. tuberculosis* infections and BCG reactions and lognormal distributions for cross-reactions (table 4). The log-likelihood values showed that the second-best model (with lognormal distributions instead of Weibull distributions for BCG reactions) might be a reasonable choice as well. However, since the posterior odds in favor of the first model were overwhelming (independent of the model selection criterion used), the results of the final analysis were based on the Weibull-lognormal-Weibull model. Posterior predictive model checks were done by comparing observed induration frequencies for seven intervals (0, 1–2, 3–7, 8–12, 13–17, 18–22, and >22 mm) and 24 covariate strata with their 95 percent prediction intervals. An observed frequency falling outside of its prediction interval was considered a predictive failure. The model showed a predictive failure rate of approximately 5 percent, and we thus concluded that calibration of the model was reasonably good. Examples of observed induration frequencies and model estimates are displayed in figures 1 and 2 by age, sex, and vaccination status.

For the 1975 tuberculin skin test survey in South Korea, the model supported the assumption that the mean induration size of reactions due to *M. tuberculosis* infection varied by age, sex, and the presence of a BCG scar (table 5). Mean values were consistently higher (by 0.5–1 mm) among females than among males across all age groups, and they were somewhat lower among persons with a vaccination scar as compared with those without one. On the other hand, mean induration sizes of cross-reactions due to environmental mycobacteria seemed fairly constant with regard to sex and BCG vaccination status and showed only a slight increase over age (2–2.5 mm). The mean values for reactions due to BCG vaccination were smaller than those for *M. tuberculosis* infection and decreased with increasing age (and time elapsed since vaccination), from approximately 11 mm to 5 mm (see figures 1 and 2).

TABLE 4. Model selection and model checks in a tuberculin skin test survey, South Korea, 1975

Distribution of infections	Distribution of cross-reactions	Distribution of BCG* reactions	Log-likelihoods†	Posterior predictive failure rate‡
Weibull	Weibull	Weibull	−785.5	15/168 = 0.089
Weibull	Weibull	Lognormal	−781.0	16/168 = 0.095
Weibull	Lognormal	Weibull	−661.2	9/168 = 0.054
Weibull	Lognormal	Lognormal	−668.6	13/168 = 0.077
Lognormal	Weibull	Weibull	−1,279.0	49/168 = 0.292
Lognormal	Weibull	Lognormal	−1,344.5	58/168 = 0.345
Lognormal	Lognormal	Weibull	−936.4	41/168 = 0.244
Lognormal	Lognormal	Lognormal	−999.2	45/168 = 0.268

* BCG, Bacillus Calmette-Guérin.
† Log-likelihood values at posterior means.
‡ Proportion of predictive failures (observed frequency outside the 95% prediction interval) for seven induration intervals (0, 1–2, 3–7, 8–12, 13–17, 18–22, and >22 mm) of 24 covariate strata given by sex, age, and BCG status. Models involving gamma distributions were generally worse (results not shown).

The prevalence of *M. tuberculosis* infection increased rapidly with age, from an average of 5 percent in the youngest age group (0–4 years) to almost 90 percent in the oldest age group (25–29 years) (table 6). The credibility intervals were wide in the youngest age group of BCG-vaccinated individuals. This finding was due to the very low prevalence of *M. tuberculosis* infection and the fact that the highest mean value for reactions due to BCG vaccination appeared in this age group. The total prevalence of tuberculous infection (BCG-vaccinated and unvaccinated individuals combined) is shown in figure 3.

When comparing the prevalences of tuberculous infection in the BCG-vaccinated and unvaccinated populations, the ratio of the two prevalences was close to 1, with the excep-

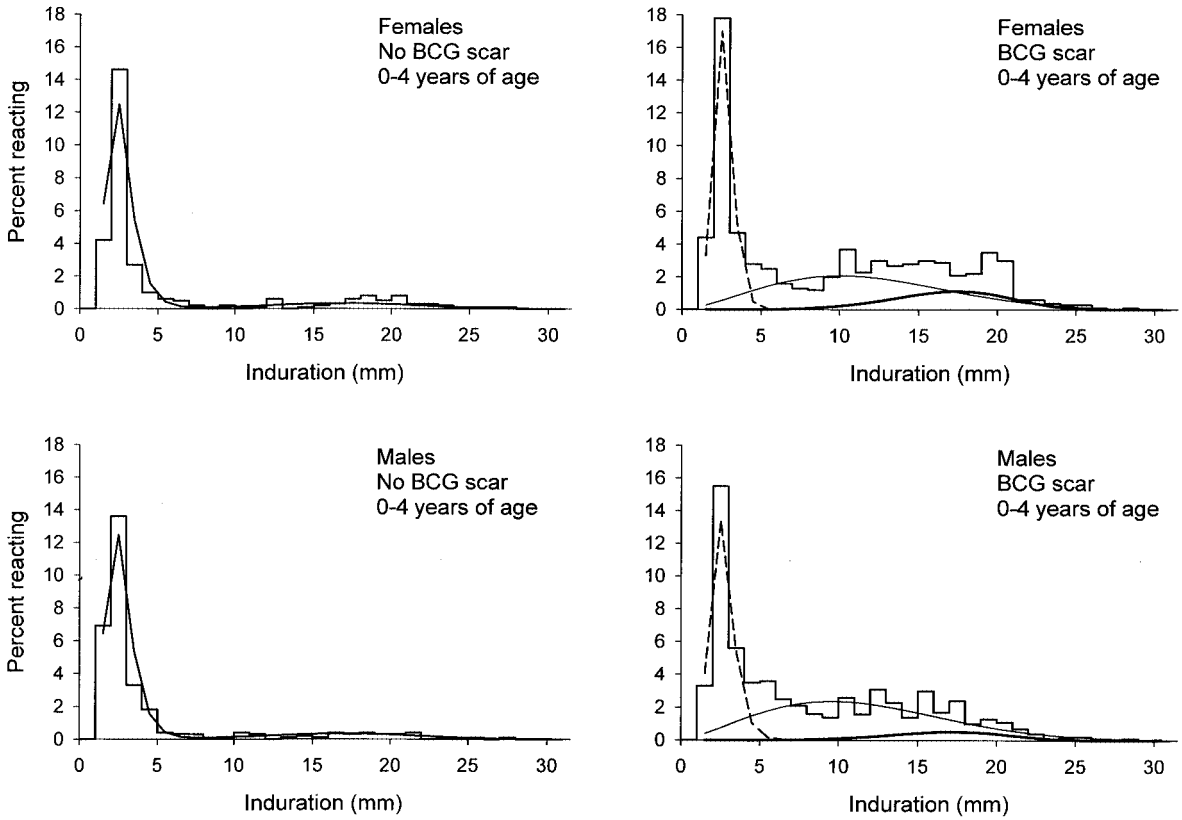

FIGURE 1. Observed distribution of tuberculin skin test induration sizes (histograms), mixture distribution (solid line on left panel), distribution due to infection with *M. tuberculosis* (solid thick line on right panel), distribution due to Bacillus Calmette-Guérin (BCG) vaccination (solid thin line on right panel), and distribution due to infection with environmental mycobacteria (dashed line on right panel) among children aged 0–4 years, by sex and presence or absence of a BCG scar, tuberculin skin test survey, South Korea, 1975.

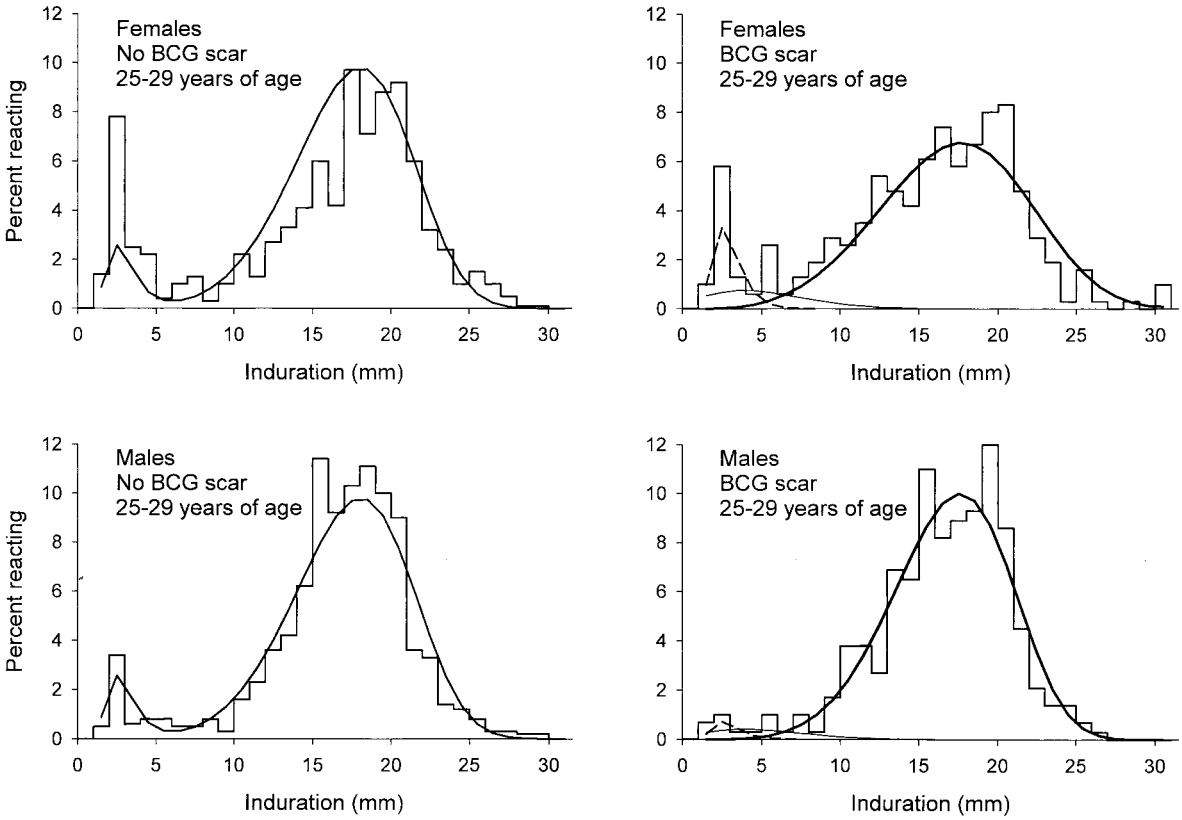

FIGURE 2. Observed distribution of tuberculin skin test induration sizes (histograms), mixture distribution (solid line on left panel), distribution due to infection with *M. tuberculosis* (solid thick line on right panel), distribution due to Bacillus Calmette-Guérin (BCG) vaccination (solid thin line on right panel), and distribution due to infection with environmental mycobacteria (dashed line on right panel) among persons aged 25–29 years, by sex and presence or absence of a BCG scar, tuberculin skin test survey, South Korea, 1975.

tion of the youngest age group, which had a highly uncertain ratio (figure 4). Moreover, the results for the unvaccinated population were very similar to those obtained in a previous analysis of unvaccinated individuals only (10). Both findings support the conclusion that the chosen methodology based on mixture models allows one to estimate prevalences of tuberculous infection in the population of BCG-vaccinated and unvaccinated individuals.

DISCUSSION

The extent of transmission of *M. tuberculosis* in the community is obviously important, since it influences the extent to which future cases of tuberculosis will emerge. Styblo et al. (23) have proposed utilizing a determination of the average annual risk of *M. tuberculosis* infection in the community as an index of transmission. This average annual risk of infection can be derived algebraically, under suitable conditions, from the prevalence of *M. tuberculosis* infection (23, 24). The approach is hampered by the limitations of the operating characteristics of the tuberculin skin test (1) and the high BCG coverage in most societies, precluding a representative ascertainment of the prevalence of *M. tuberculosis* infection. Thus, limiting the estimation of tuberculous infection to persons without a BCG scar (as a proxy for vaccination) becomes increasingly questionable with increasing BCG coverage; furthermore, it would require ever-increasing sample sizes in tuberculin skin test surveys. It would therefore be desirable to identify a method that would allow estimation of the prevalence of tuberculous infection irrespective of prior BCG vaccination.

The opportunity to investigate the new method arose in studying the surveys conducted systematically and regularly in South Korea (17, 25–30). While all surveys provided information on the existence or absence of a scar resulting from BCG vaccination, the 1975 survey data allowed us to estimate the prevalence of tuberculous infection among both persons with a scar and persons without a scar at a time when BCG coverage was high but not yet great enough to make either the vaccinated group or the unvaccinated group obviously unrepresentative of the Korean population. The 1975 survey fell into a period when approximately 60 percent of the surveyed population had been vaccinated. Thus, we expected that the prevalences of *M. tuberculosis* infection would be similar in the vaccinated and nonvaccinated populations. The estimated ratio of infection prevalences (BCG-vaccinated:unvaccinated) was highly uncertain in the

TABLE 5. Mean (expected) values (in mm) for distributions of *Mycobacterium tuberculosis* infections, cross-reactions due to environmental mycobacteria, and BCG* reactions due to prior vaccination in a tuberculin skin test survey, South Korea, 1975

Age (years)	Males		Females	
	Posterior median of mean (mm)	95% CI†	Posterior median of mean (mm)	95% CI
	Infections‡			
	No BCG scar present			
0–4	16.2	15.4, 17.3	16.7	15.9, 17.6
5–9	16.5	15.9, 17.1	16.9	16.4, 17.4
10–14	17.2	16.8, 17.5	17.8	17.5, 18.2
15–19	17.0	16.7, 17.3	18.2	17.9, 18.6
20–24	16.9	16.6, 17.1	18.4	18.1, 18.6
25–29	16.8	16.5, 17.1	17.4	17.1, 17.7
	BCG scar present			
0–4	16.1	15.2, 17.2	16.3	15.4, 17.3
5–9	16.2	15.5, 16.7	16.2	15.6, 16.9
10–14	15.8	15.5, 16.2	16.4	16.0, 16.7
15–19	15.6	15.3, 15.9	16.7	16.4, 17.0
20–24	15.7	15.4, 16.0	17.0	16.8, 17.3
25–29	16.4	16.0, 16.8	16.7	16.3, 17.2
	Cross-reactions§			
	No BCG scar present			
0–4	2.2	2.0, 2.3	2.1	2.0, 2.2
5–9	2.2	2.1, 2.3	2.1	2.0, 2.2
10–14	2.2	2.1, 2.3	2.1	2.0, 2.3
15–19	2.3	2.2, 2.4	2.3	2.2, 2.4
20–24	2.4	2.3, 2.6	2.5	2.3, 2.6
25–29	2.5	2.3, 2.7	2.5	2.3, 2.7
	BCG scar present			
0–4	2.2	2.1, 2.3	2.1	2.0, 2.2
5–9	2.1	2.0, 2.2	2.1	2.0, 2.2
10–14	2.1	2.0, 2.2	2.1	2.0, 2.2
15–19	2.2	2.1, 2.3	2.2	2.1, 2.3
20–24	2.4	2.2, 2.5	2.3	2.2, 2.5
25–29	2.5	2.2, 2.7	2.5	2.3, 2.7
	BCG reactions¶			
	BCG scar present			
0–4	11.1	10.0, 12.0	11.3	10.1, 12.4
5–9	9.6	8.7, 10.4	9.7	8.7, 10.7
10–14	8.3	7.5, 9.2	8.5	7.5, 9.4
15–19	7.1	6.3, 8.0	7.2	6.4, 8.1
20–24	6.0	5.2, 6.8	6.1	5.3, 6.9
25–29	5.0	4.2, 5.7	5.0	4.3, 5.8

* BCG, Bacillus Calmette-Guérin.
† CI, credibility interval.
‡ Reactions due to infection with *Mycobacterium tuberculosis*.
§ Cross-reactions due to infection with environmental mycobacteria.
¶ Reactions due to vaccination with BCG.

TABLE 6. Prevalence (%) of infection with *Mycobacterium tuberculosis*, by age and sex, in a tuberculin skin test survey, South Korea, 1975

Age (years)	Males		Females		Total	
	Posterior median of prevalence	95% CI*	Posterior median of prevalence	95% CI	Posterior median of prevalence	95% CI
			No BCG scar present*			
0–4	4.2	3.0, 5.6	6.3	4.8, 8.1	5.2	4.2, 6.3
5–9	18.6	15.6, 22.0	18.6	15.5, 21.9	18.6	16.5, 21.0
10–14	50.4	45.8, 54.8	55.7	51.3, 60.1	53.2	50.0, 56.3
15–19	74.7	71.1, 78.1	72.5	68.9, 76.0	73.6	71.0, 76.0
20–24	86.2	82.6, 89.4	77.9	74.4, 81.0	81.2	78.7, 83.5
25–29	92.0	89.7, 94.0	77.4	74.4, 80.2	84.0	81.9, 85.8
			BCG scar present			
0–4	4.7	0.5, 10.3	10.5	4.1, 17.3	7.5	3.1, 12.5
5–9	17.3	13.0, 22.2	21.2	15.7, 27.0	19.2	15.1, 23.4
10–14	51.4	46.6, 55.7	56.2	51.4, 60.5	53.7	50.0, 57.2
15–19	63.8	59.2, 68.1	62.6	57.9, 66.9	63.2	59.7, 66.6
20–24	82.3	77.1, 86.5	70.0	65.6, 74.1	75.1	71.6, 78.2
25–29	94.2	90.6, 96.8	81.0	75.5, 85.7	87.3	84.0, 90.2

* CI, credibility interval; BCG, Bacillus Calmette-Guérin.

youngest age group (with documented recent vaccination) but close to 1 for the remaining age groups. This supports the conclusion that the chosen methodology was successful in estimating the prevalence of tuberculous infection in both BCG-vaccinated and unvaccinated individuals.

The statistical inference of tuberculous infection prevalences was based on mixture modeling. Mixture models provide the appropriate inferential framework in situations where heterogeneity (subpopulations) in an outcome variable is present and where the subpopulation to which an individual belongs is unknown. Quantities of interest can be the distributions of the subpopulations (mixture components), the prevalences of the subpopulations (mixture weights), or quantities related to them (e.g., individual classification probabilities). Mixture models offer great flexibility (number of components, types of component distributions) in describing epidemiologic applications. In the context of tuberculin skin test results, the population of persons with a BCG scar can be described reasonably well by a three-component mixture representing infection with *M. tuberculosis*, cross-reactions due to environmental mycobacteria, and BCG reactions due to prior vaccination.

Even though the mixture models merely capture the indispensable characteristics of tuberculin skin testing, their complexity is, relative to the information provided by the data, already high. For example, when assuming that prevalences and mixture components are affected by sex and age

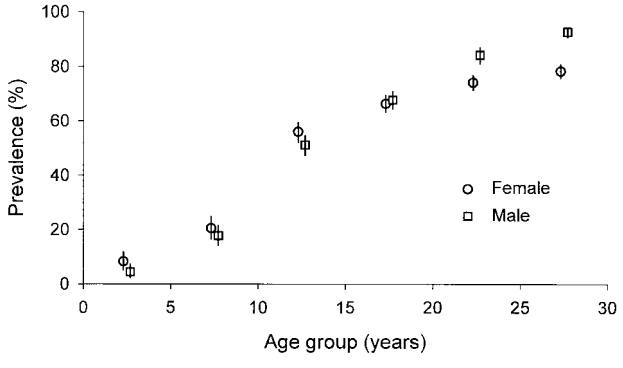

FIGURE 3. Estimated prevalence of infection with *M. tuberculosis*, combined for individuals with and without a Bacillus Calmette-Guérin scar, by age and sex, tuberculin skin test survey, South Korea, 1975. Symbols, posterior medians; lines, 95% credibility intervals.

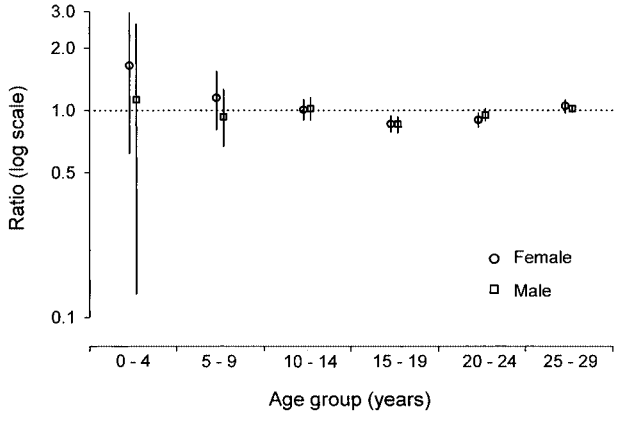

FIGURE 4. Estimated ratio of the prevalence of tuberculous infection among those with and those without the presence of a Bacillus Calmette-Guérin scar, by age and sex, tuberculin skin test survey, South Korea, 1975. Symbols, posterior medians; lines, 95% credibility intervals.

(12 covariate strata), induration data for a specific sex/age stratum may hardly be informative enough to estimate the nine parameters of the three-component mixture (group with a BCG scar) or the six parameters of the two-component mixture (group without a BCG scar).

In general, estimation of parameters in mixture models can be difficult if the number of mixture components is large, and even more difficult if the component distributions overlap to a great extent. In the extreme case of complete overlap of component distributions, mixture weights (prevalences) are no longer identifiable. In practical situations, identifiability problems can arise to an extent that depends both on the complexity of the model and on the available data, and that is reflected in imprecise parameter estimates. When applying mixture analysis to tuberculin skin test data, we experienced problems of identifiability mostly in situations with aggregated data. Improved estimates can generally be obtained whenever covariate information is available and 1) mixture component distributions are similar or even identical (in location and spread) in the different covariate strata and 2) some covariate strata are particularly informative with regard to one of the mixture component distributions. The latter is typically the case if prevalences in some of the subpopulations are large. For example, in the Korean data on nonvaccinated persons, stratification with regard to the important covariate "age" turned out to be advantageous: It showed large prevalences of cross-reactions in the very young and large prevalences of infection in the elderly, revealing valuable information on the distribution of cross-reactions and infections, respectively. If we had ignored age and pooled the data from the subpopulations, information on the component distributions would have been obscured and estimation of mixture parameters made more difficult (less precise).

For the Korean data, a mixture model was chosen (among several competing models) that was flexible enough to incorporate covariate information (age, sex) while imposing reasonable constraints on the similarity of the mixture component distributions over the covariate strata. Moreover, the distributions of cross-reactions and infections were assumed to be similar for vaccinated and unvaccinated persons as well. The degree of similarity was introduced in the form of prior opinion that was agreed upon by the authors. No formal assessment of prior opinion was done, however.

For the statistical analysis of the mixture models (including prior opinion), we took the Bayesian stance, a statistical paradigm that has been shown to be not only theoretically sound (a long-recognized feature) but also versatile and generally practicable (31). Bayesianism (full probability modeling) puts forward a general framework of statistical thinking that is based on a probability model for the data, the likelihood function, and a prior distribution for the unknown parameters of this model. Once these parts are specified, the approach is fully automatic, since there is no ambiguity in the estimation process (computation of the posterior distribution), which relies exclusively on the laws of probability (an axiomatic system). However, specification of the model and assessment of prior knowledge are not as straightforward because of their being heavily dependent on the epidemiologic problem (32), and both are open to discussion, but primarily by epidemiologists, not statisticians. Since the focus of the inferential process is thereby shifted away from statistics to epidemiology, more realistic and better calibrated inference statements are likely to result.

The methodology adopted here demonstrates that the prevalence of infection with tubercle bacilli can be estimated successfully in persons with and without prior BCG vaccination. The distribution of reaction sizes is importantly affected by the amount of time elapsed since vaccination (2), which is reflected by the diminishing size of BCG-attributable indurations with increasing age. The vaccine strain used may also affect the rapidity with which reactions due to BCG vaccination wane (3). Nevertheless, this analysis—to our knowledge, the first of its kind—suggests that tuberculin skin-test survey data from both vaccinated and unvaccinated populations might be utilized. This would be important in the most commonly prevailing situation, where BCG coverage is high and an analysis restricted to the nonvaccinated might seriously hamper an unbiased assessment of the epidemiologic situation in a community.

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