Correspondence

Table 1. Results of tuberculin skin testing conducted in 2007.

Age group	Age, mean years	No. of participants	No. of participants with a positive tuberculin skin test result	Prevalence, %	Annual risk of infection, %
5–8 Years	7.8	233	61	26.2	3.8
9–11 Years	10.4	222	70	31.5	3.6
12–13 Years	13.0	237	107	45.1	4.5
14–17 Years	15.1	139	311	52.5	4.8

NOTE. Adapted from [1].

On the Relationship between Age, Annual Rate of Infection, and Prevalence of *Mycobacterium tuberculosis* in a South African Township

To the Editor—A recent article [1] reported a very high prevalence of infection due to *Mycobacterium tuberculosis* among children 5–17 years of age in a South African township. The results are based on tuberculin skin tests performed in 2007 for 829 children 5–17 years of age and are listed in table 1. From such age-specific prevalences, it was possible to estimate the mean annual risk of infection experienced by each cohort.

Let q_x denote the proportion of children aged x with a negative tuberculin skin test result. If these children experienced a constant annual risk of infection a throughout their life, then q_x would be given by $q_x = (1-a)^x$, so $a = 1 - q_x^{1/x}$.

In Middelkoop et al. [1], the value a was computed for 4 different age groups. All of the results were close to 4%. From this analysis, it could be argued that the annual risk of infection may indeed have remained relatively constant in the recent past (e.g., during the past 15 years).

The surprising thing is that the tuberculosis notification rate in the adult population has increased by ~5-fold over the same period because of the rapid increase in HIV infection [2]. If the sources of *M. tuberculosis* have increased, why do the available data not show a corresponding increase in the annual risk of infection? A possible explanation is that HIV-positive individuals with tuberculosis remain infectious in the community for a much shorter time than do HIV-negative individuals with tuberculosis.

A comment by Rieder [3] on the article by Middelkoop et al. [1] pointed out that one should be careful when concluding that the annual risk of infection has remained constant. Rieder [3] assumed, on the contrary, that the annual risk of infection had increased each year by 10%, starting with an annual risk of infection of 1% in 1991. He claimed that this assumption gave a good fit with the data presented in table 2 in the article by Middelkoop et al. [1].

Here, we use a probabilistic model to show that one cannot conclude from the data presented in [1] whether the annual risk of infection has remained constant (as suggested in [1]), has increased (as suggested in [3]), or has decreased. However, we show that a decreasing annual risk of infection is the most likely possibility.

Let $a(n)$ be the annual risk of infection in year n. The probability for an individual x years of age in 2007 to have escaped infection is

$$q_x = [1 - a(2006)] \times [1 - a(2005)] \times \cdots \times [1 - a(2006 - x + 1)] .$$

If c_m is the size of the cohort born in year m, then the probability that i will be infected in 2007 is

$$\binom{c_m}{i} (q_x)^{c_m - i} (1 - q_x)^i ,$$

where $x = 2007 - m + 1$. We use each cohort c_m (table 2) of the prevalence data instead of the specific cohort groupings used in table 2 from Middelkoop et al. [1].

Figure 1*A* shows the binomial distribution of the number of infected individuals for a cohort aged 7 years in 2007, assuming a constant annual risk of infection of 4%. Using $a(n) = a(2007) \times r^{(n-2007)}$, where r is the annual increase or decrease, we can construct a confidence region for values of $a(2007)$ and r. For each choice of $a(2007)$ and r, we impose the condition that, for each age group, the observed number of infected individuals should not decrease below the 2.5 percentile or increase to above the 97.5 percentile, thereby excluding 5% of each distribution.

Another approach is to give equal

Table 2. Tuberculin skin test results, by age.

Tuberculin skin test result	No. of patients, by age in years												
	5	6	7	8	9	10	11	12	13	14	15	16	17
Negative	1	27	66	78	62	47	43	65	63	45	15	5	1
Positive	0	9	18	34	30	24	16	42	65	40	19	9	5

NOTE. Data were obtained from the Desmond Tutu HIV Centre, Institute of Infectious Diseases, Department of Medicine, University of Cape Town, Cape Town, South Africa.

weight to all groups and to exclude the same amount y from each of the 13 distributions, to exclude 5% overall. Using $1-(1-y)^{13}=0.05$ to find $y=0.004$, we see that the observed number of infected individuals should not decrease to below the 0.2 percentile or increase to above the 99.8 percentile. The boundary of the first type of confidence region is shown by the narrow (inner) dashed contour in figure 1*B*. The boundary of the second type of confidence region is shown by the wide (outer) dashed contour in figure 1*B*.

Also shown in figure 1*B* is the likelihood of observing the data set (table 2), calculated as follows: $L=q_5^{n_5}\times(1-q_5)^{p_5}\times\cdots\times q_{17}^{n_{17}}\times(1-q_{17})^{p_{17}}$, where n_x and p_x are the number of children aged x with negative and positive tuberculin skin test results, respectively. The likelihood is normalized so that the maximum value is 1, and the contour $L=0.05$ is shown in figure 1*B*.

The results show that, although a decreasing annual risk of infection is more likely, given the prevalence data, a constant or even increasing annual risk of infection cannot be ruled out. It does, however, rule out the possibility of the annual risk of infection increasing by 10% per year, starting from 1% in 1991 (and reaching 4.6% in 2007), as suggested by Rieder [3].

Additional prevalence surveys are needed to verify actual trends in the annual risk of infection. Estimating trends from this particular survey may be influenced by details of the histories of children participating in the survey. We have assumed that all children were equally susceptible to the sources of infection throughout their lives. However, children were eligible for the survey if they merely resided in the town and were registered at the local school at the time of the survey. Such uncertainties about the detailed cumulative exposure to the sources of infection add to uncertainty in the analysis.

In addition, an age-dependent annual risk of infection may have been acting in the community, which may account for a relatively constant annual risk of infection in an environment of increasing exposure to *M. tuberculosis*. Notice that, according to table 1, the annual risk of infection is lower for young children. It is unfortunately not possible to disentangle time-dependent and age-dependent effects when estimating the annual risk of infection from a single prevalence survey.

The analysis improves our understanding of the annual risk of infection and serves to calibrate parameters in HIV and tuberculosis coinfection models [4]. This, in turn, helps to predict the possible consequences of interventions.

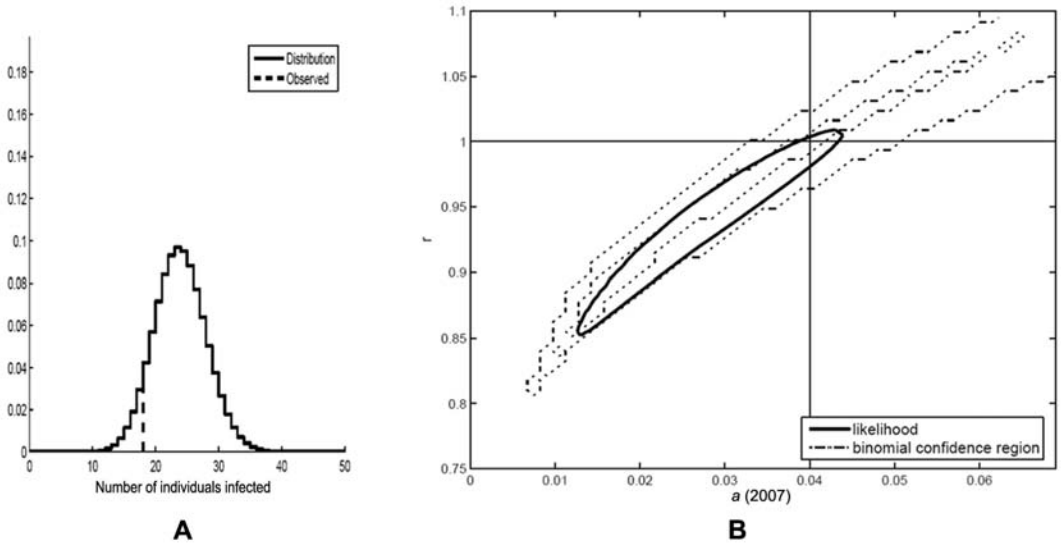

Figure 1. *A*, Probability distribution of the number of infected children in a cohort born in 2000, assuming a constant annual risk of infection of 4%. *B*, Constant annual risk of infection of 4%, as indicated by lines $a(2007)=4\%$ and $r=1$. A decreasing annual risk of infection is more compatible with the prevalence data, but a constant or increasing annual risk of infection is also within the confidence region and cannot be ruled out.

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Reply to Pretorius et al.

To the Editor—I note with satisfaction that the gauntlet that I dared to throw in a recent commentary [1] on an article published in *Clinical Infectious Diseases* on the risk of children in Cape Town, South Africa, becoming infected with *Mycobacterium tuberculosis* [2] has been picked up. The senior author of the original article [2] has joined forces with experts who recognize that it is not directly possible to disentangle age, period, and cohort effects in a single cross-sectional survey, even if that survey spans several age groups [3]. Nevertheless, the sophistication introduced in the reanalysis suggests that my incredulity at an observation that seemingly runs against all intuition—namely, that an unprecedented and continued increase in the sources of infection in the community would have no impact whatsoever on disease transmission to children—must be fundamentally flawed. Indeed, the authors even go a step further and venture to postulate that there is a higher likelihood of a decrease in transmission risk to children when sources of infection have simultaneously been growing exponentially in the same community. Perhaps, if you hear hoof beats, you should look for zebras; after all, this is an observation from Africa.

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Comparison of the Effectiveness of Zanamivir and Oseltamivir against Influenza A/H1N1, A/H3N2, and B

To the Editor—Both our influenza study group [1–5] and Sugaya et al. [6] have reported that oseltamivir is clinically less effective than zanamivir against influenza B in analyses of the duration of fever and viral shedding; our group and Sugaya and colleagues have also reported that zanamivir is almost equally effective for both influenza A and B. Recently, Sugaya et al. [7] compared the clinical effectiveness of oseltamivir with that of zanamivir against influenza A/H1N1, A/H3N2, and B, and they reported that both drugs were equally effective in children. However, no study of these viruses has been reported that compares the effectiveness of zanamivir with that of oseltamivir among large numbers of adult patients, including elderly adults. We analyzed the duration of fever after administration of the first dose of zanamivir or oseltamivir in 858 patients for whom influenza A/H1N1, A/H3N2, or B was diagnosed by virus isolation over the 5 consecutive influenza seasons from 2003–2004 through 2007–2008.

Zanamivir was administered to 411 patients (mean age ± SD, 22.1 ± 14.7 years; range, 5–68 years), of whom 70 had influenza A/H1N1, 193 had influenza A/H3N2, and 148 had influenza B. Oseltamivir was administered to 447 patients (mean age ± SD, 30.9 ± 22.1 years; range, 9–94 years), of whom 79 had influenza A/H1N1, 177 had influenza A/H3N2, and 191 had influenza B. The duration of fever after the first dose of zanamivir or oseltamivir was calculated according to the method reported in our previous studies [2, 5].

For patients with influenza A/H1N1, the mean duration (±SD) of fever was almost the same in patients who received zanamivir therapy (32.0 ± 20.6 h) as it was in those who received oseltamivir therapy (32.8 ± 19.2 h). For patients with influenza A/H3N2, the mean duration