Prevalence of tuberculous infection and incidence of tuberculosis; a re-assessment of the Styblo rule

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Objective To evaluate the validity of the fixed mathematical relationship between the annual risk of tuberculous infection (ARTI), the prevalence of smear-positive tuberculosis (TB) and the incidence of smear-positive TB specified as the Styblo rule, which TB control programmes use to estimate the incidence of TB disease at a population level and the case detection rate.

Methods Population-based tuberculin surveys and surveys on prevalence of smear-positive TB since 1975 were identified through a literature search. For these surveys, the ratio between the number of tuberculous infections (based on ARTI estimates) and the number of smear-positive TB cases was calculated and compared to the ratio of 8 to 12 tuberculous infections per prevalent smear-positive TB case as part of the Styblo rule.

Findings Three countries had national population-based data on both ARTI and prevalence of smear-positive TB for more than one point in time. In China the ratio ranged from 3.4 to 5.8, in the Philippines from 2.6 to 4.4, and in the Republic of Korea, from 3.2 to 4.7. All ratios were markedly lower than the ratio that is part of the Styblo rule.

Conclusion According to recent country data, there are typically fewer than 8 to 12 tuberculous infections per prevalent smear-positive TB case, and it remains unclear whether this ratio varies significantly among countries. The decrease in the ratio compared to the Styblo rule probably relates to improvements in the prompt treatment of TB disease (by national TB programmes). A change in the number of tuberculous infections per prevalent smear-positive TB case in population-based surveys makes the assumed fixed mathematical relationship between ARTI and incidence of smear-positive TB no longer valid.

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. .الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة

Introduction

The formulation of the Millennium Development Goals (MDGs) in 2000 was a landmark step taken by 189 countries in their commitment to "meet the needs of the world's poorest."[1] A projected target within goal number 8 (combat HIV/AIDS, malaria and other diseases) is to "stop the increase and start reversing the incidence of tuberculosis (TB) by 2015". The Stop TB Partnership has translated this goal into targets to be met by national TB control programmes (NTPs). These targets are to detect at least 70% of the incident smear-positive TB cases and to successfully treat 85% of these.[2]

To be able to assess whether the detection target is met, information about the incidence of smear-positive TB in the general population is needed. This information is not readily available, because studies to measure disease incidence are rarely conducted due to the logistical problems and costs involved.[3] Two population surveys assessing prevalence of TB disease must be conducted within a limited time frame and with an adequate surveillance system to monitor TB disease in persons emigrating or dying between the two surveys. Incidence estimates based on prevalence of disease and duration of illness as measured in population-based surveys, or on TB-specific death rates from routine health system or vital registration data, are often imprecise due to measurement errors and misclassifications.[3,4] Using the number of notified TB cases within a country as a proxy for incidence of TB disease is in general not a valid approach. The passive reporting underlying notification data makes them dependent, among others, on NTP performance, the population's access to health care, diagnostic service quality and the social stigma surrounding TB. Notification data can be relied on as a proxy for incidence of TB only when their quality and completeness are assured through the presence of a well-established surveillance system.

The Styblo rule

A method often used to estimate the incidence of TB disease in the general population is to assess the annual risk of tuberculous infection (ARTI) in the general population and apply the Styblo rule.[5] The ARTI denotes the proportion of persons in a community who become (re-)infected within one year and is estimated in large-scale tuberculin skin test (TST) surveys in the general population. The Styblo rule assumes a fixed mathematical relationship between the incidence of smear-positive TB, the prevalence of smear-positive TB and the ARTI. For the quantification of the rule, Styblo used estimates of the incidence of TB disease derived from three different sources. Directly measured incidence in the general population was used in the Netherlands (routine notifications to the health system were used,

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Table 1. **Original data as reported by Styblo[5]**

Source	Period	Disease parameter	ARTI (%)	Ratio between ARTI (%) and mortality[a]	incidence[a]	prevalence[a]
Netherlands	1921–1928	Mortality	2.7–6.0	**19**	38	–
Netherlands	1951–1976	Incidence	0.038–0.4	–	**37**	–
Developing countries	1956–1961	Prevalence	2.0–8.0	–	40–60	**80–120**
Alaska	1948–1951	Mortality	25	**26**	52	–
India	1961–1968	Prevalence	1.5	–	53	**106**
India	1969–1971	Prevalence	4.1	–	51	**102**

ARTI, annual risk of tuberculous infection.
[a] per 100 000 population.
The **bold** figures indicate data from source documents used by Styblo; the other figures are the estimates that Styblo derived using his assumptions.

but notification was deemed complete). Data on TB mortality were used in the Netherlands and Alaska (United States of America). Data on measured prevalence of disease were used for India and 12 other developing countries. The original data are reproduced in Table 1.

Since only the data from the Netherlands were based on measured disease incidence (complete notification), assumptions were made to arrive at an estimate for the incidence of smear-positive TB from the other data sources. These assumptions were: 1) the mortality is half the disease incidence, and 2) the number of prevalent cases at a given point in time is twice the number of incident cases in one year, assuming a duration of disease of two years. By doing so, Styblo calculated that 50–60 new cases per 100 000 population per year of smear-positive TB corresponded to 1% ARTI (Fig. 1). In the data from 10 of the 13 developing countries, the ratio between the number of new infections (per 100 000 per year), as derived from the ARTI, and the number of prevalent smear-positive TB cases (per 100 000) ranged from 8 to 12.

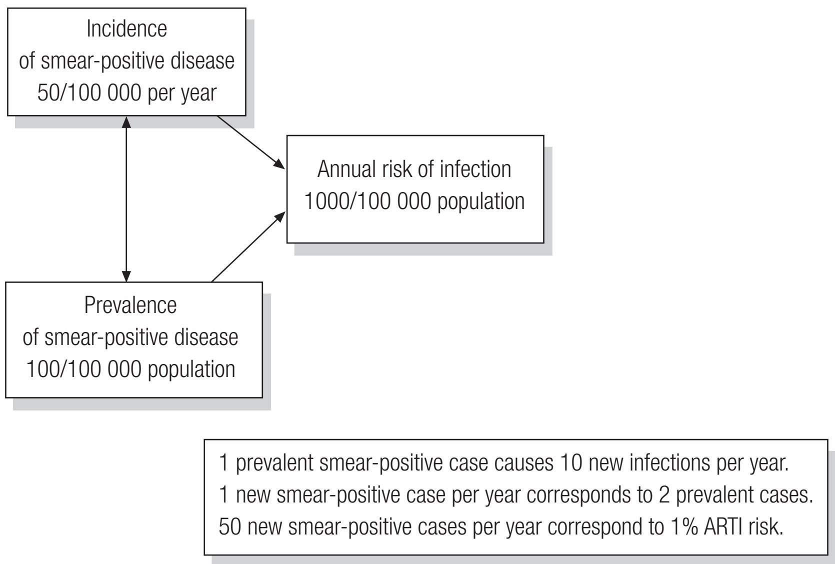
The data used by Styblo were from an era without established TB control programmes and efficacious TB treatment regimens, and before the emergence of the HIV epidemic. In the current situation where, in general, control measures are in place, efficacious treatment is available, and HIV prevalence is high in many countries, it is likely that the fixed mathematical relationship does not hold. Identification of smear-positive TB cases through control programmes and treatment of the cases with effective drug regimens will reduce the duration of infectiousness, and as a consequence interrupt ongoing transmission. Furthermore, HIV-associated TB becomes symptomatic faster than TB in HIV-negative individuals, which may lead to earlier detection and treatment with interruption of transmission. With any interruption in transmission, the number of new tuberculous infections per prevalent smear-positive TB case will be lower than originally reported by Styblo. As a consequence, the incidence of smear-positive TB must in these circumstances be higher to establish an ARTI of 1%. Therefore, using the Styblo rule for calculating the incidence of smear-positive TB might not be a valid approach in a situation where interventions that interrupt transmission are available.

We use recent national surveys on prevalence of tuberculous infection among schoolchildren and smear-positive TB cases in the general population to answer two questions. Does the Styblo rule, with an estimated 8–12 new tuberculous infections per year per prevalent smear-positive case of TB disease, still hold? If this is not the case, is there any other fixed mathematical relationship that can be defined either universally or within a specific country?

Methods

The starting point of our study was to identify TST surveys performed on a national scale. Surveys conducted after 1975 were added to identified TST surveys in a previous conducted review by Cauthen et al.[6] To identify the new surveys, we performed a literature search in Medline and Embase with the major subject headings tuberculosis and prevalence, and the simple term tuberculin.

Fig. 1. **Mathematical relationship between ARTI, and prevalence and incidence of smear-positive TB according to the Styblo rule**



ARTI, annual risk of tuberculous infection; TB, tuberculosis.

Table 2. **Number of tuberculous infections and smear-positive TB cases per 100 000 population, by country and year[a]**

Country	Year[a]	Infections	Smear-positive TB	Infection-to-disease ratio	95% CI of ratio
Republic of Korea[7,8]	1975	1780	480	3.7	2.9–4.5
	1980	1240	310	4.0	2.7–5.3
	1985	1120	240	4.7	3.5–5.9
	1990	60	144	3.2	1.6–4.8
China[9]	1979	640	187	3.4	Not done[b]
	1985	590	156	3.8	Not done[b]
China[10]	1990	638	134	4.8	Not done[b]
	1996	700	121	5.8	Not done[b]
Philippines[11]	1982	2480	950	2.6	Not done[b]
	1994	2300	525	4.4	3.9–4.9

CI, confidence interval; TB, tuberculosis; TST, tuberculin skin test.

[a] The year for the number of infections is derived from the midpoint between the birth of the cohort and the year of the actual tuberculin survey.

[b] Not done due to missing information of denominator in TST survey.

We reviewed titles and abstracts to identify eligible articles. Surveys reporting only data from specific populations, like health care workers, prison inmates or immigrants, were excluded. An exception was made for army recruits in countries with mandatory military service, since this group can be seen as a representative sample of the male population. The bibliographies of the identified articles were searched for additional surveys not included in the original retrieved documents. The compiled list was sent to experts in the field of TST surveys for review of its completeness. From all identified TST surveys (in the review by Cauthen et al. and newly identified), we selected those from countries for which at least two TST surveys were available, making it possible to construct a trend line. The surveys were included if data on the prevalence of smear-positive TB also was present (in the same or other documents) for at least two different points in time and within the same time frame as the ARTI data.

For each country, the number of new tuberculous infections per year as estimated from ARTIs derived from TST surveys were plotted against time, together with data on the prevalence of smear-positive TB per 100 000 population.

The prevalence of smear-positive TB was plotted in the calendar year the actual survey was conducted. The ARTI was plotted at the midpoint of the mean of the time between the birth year and the survey year for children in the survey cohort, because tuberculous infections found in TST surveys are accumulated over the total years of an individual's life. From these two plotted estimates, we calculated the number of tuberculous infections per prevalent smear-positive TB case per year. When one of the estimates was not present at a specific year, we inferred it from the trend line. The variance around the ratio of the number of infections and number of smear-positive TB cases was calculated with the formula:

$$\frac{(N^2 * \mathrm{var}(T)) + (T^2 * \mathrm{var}(N))}{N^4}$$

where N is the proportion of smear-positive cases in the survey, and T the proportion of tuberculous infections in the survey. The standard error of the proportion of smear-positive cases was estimated using a Poisson distribution, while the standard error of the proportion of tuberculous infections was calculated using the formula:

$$\sqrt{\frac{p(1-p)}{N}}$$

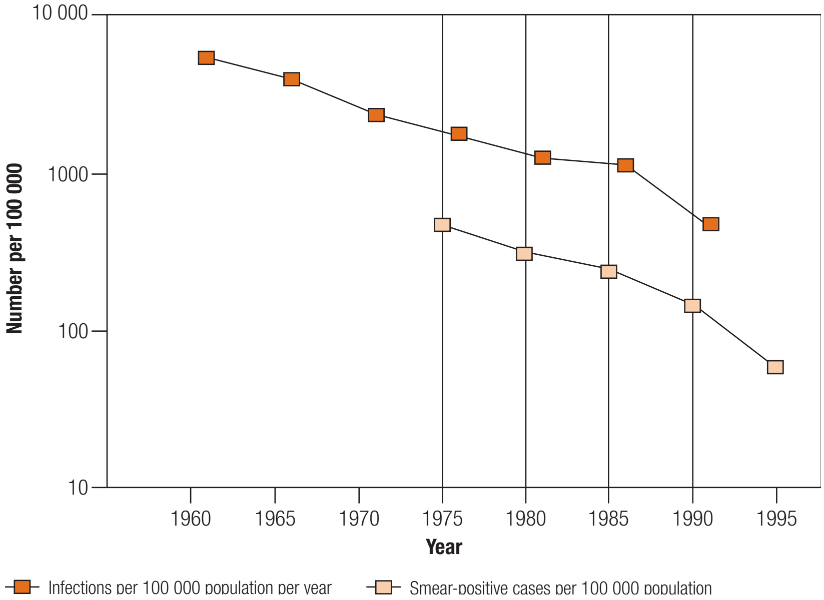
where p is the proportion of infections, and N is the sample size of the TST survey.

Results

The initial database search identified 359 titles. These included articles from 21 countries from which data of at least one national tuberculin survey conducted after 1975 was available in the public domain. National surveys from four additional countries were identified through experts in the field from non-public sources. Four large-scale regional surveys (from three different countries) were included, bringing the number of countries to 28. Of these, four were excluded because the reports could not be retrieved. From the remaining 24 countries, five had no published earlier national tuberculin surveys for comparison, leaving 19 countries (16 national, three regional) with data on prevalence of tuberculous infection over time. Of these only three national surveys (China, the Philippines and the Republic of Korea) had information on prevalence of smear-positive TB in comparable time frames as the data on prevalence of tuberculous infection. These were included in the current analyses. Two regional surveys had information on the prevalence of TB disease in appropriate time frames, but these data were based on culture-positive TB without sufficient information to estimate the prevalence of smear-positive TB.

In the Republic of Korea, the prevalence of smear-positive TB was 480/100 000 in 1975 and declined steadily to 144/100 000 in 1990 (Fig. 2). The corresponding ARTI was 1.78% in 1976 (survey 1980), 1.24% in 1981 (survey 1985), and 1.12% in 1986 (survey 1990).[7,8] The number of infections per prevalent smear-positive TB case was 3.7 [95% confidence interval (CI): 2.9–4.5] in 1975, increased slightly to 4.7 (95% CI: 3.5–5.9) in 1985, and then declined to 3.2 (95% CI: 1.6–4.8) in 1990 (Table 2). In China, the prevalence of smear-positive TB declined steadily from 187/100 000 in 1979 to 121/100 000 in 1996. The corresponding ARTI estimates showed a decline between 1979 (0.64%) and 1985 (0.59%), but increased again to 0.64% in 1990 and 0.7% in 1996 (Fig. 3).[9,10] The number of infections per prevalent TB case was 3.4 in 1979 and increased steadily to 5.8 in 1996. The reports of the TST surveys did not indicate the denominator for the survey, making it impossible to calculate a confidence interval around the ratio. In the Philippines, the prevalence of smear-positive TB was 950/100 000 in 1982 and declined to 525/100 000 in 1994. The ARTI did not change much in this time interval (2.48% and 2.30%, respectively; Fig. 4).[11] The number of infections per prevalent TB case in these years was 2.6 and 4.4 (95% CI: 3.9–4.9), respectively. The confidence interval for the ratio in 1982 could not be calculated due to an absent denominator for the TST survey.

Fig. 2. **Number of tuberculosis infections and smear-positive TB cases, the Republic of Korea**



TB, tuberculosis.

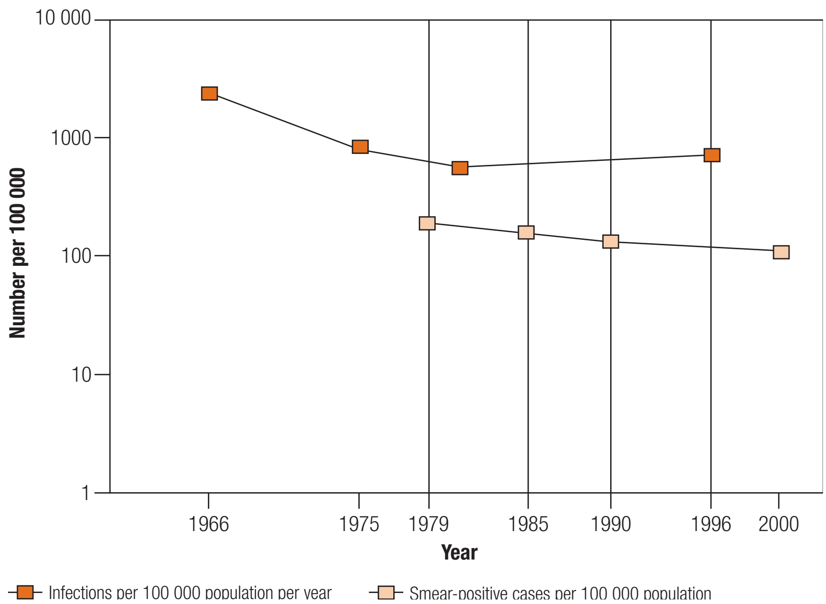
Discussion

The present study showed that the number of tuberculous infections per prevalent smear-positive TB case ranged from 2.6 to 5.8 in surveys from China, the Philippines and the Republic of Korea (Fig. 5). These ratios were consistently lower in each country and each time point than estimated earlier by Styblo. Using the Styblo rule for estimating the incidence of smear-positive TB in these countries therefore seems no longer valid.

A similar finding of a lower ratio between tuberculous infections and prevalence of smear-positive TB was reported by Trunz et al. in their study on bacille Calmette–Guérin-efficacy.[12] The authors report a number of tuberculous infections per prevalent smear-positive TB case between 5.7 and 7.2 for China, between 3.8 and 7.4 for the Philippines, and between 4.8 and 7.9 for the Republic of Korea. These numbers are in general higher than reported in the present study. In the study by Trunz et al., the year at which the number of tuberculous infection was plotted corresponded with the year of the survey. As mentioned, we plotted this number at the year at the midpoint between the mean birth of the survey cohort and the actual survey. With a general decline in the prevalence of tuberculous infection, plotting this prevalence at the year of the survey overestimates the prevalence slightly, resulting in a higher number of tuberculous infections per prevalent smear-positive TB case.

In contrast, a recent study by Gopi et al. in Tiruvallur district, south India, reported an incidence of 51 new smear-positive cases per 1% ARTI, an estimate that is similar to the one given by Styblo.[13] The study comprised of two prevalence surveys for TB disease; one in 1999–2001 and the other in 2001–2003. At the same time, two TST surveys were conducted in children below the age of 10 years. The incidence of new TB cases was assessed by identifying new cases in the repeat survey. However, there was no follow-up of the population between the two surveys, which is a crucial step in an incidence study. Instead the authors relied on passive notification of TB cases in this period between the surveys. When notification is incomplete, this

Fig. 3. **Number of tuberculosis infections and smear-positive TB cases, China**



TB, tuberculosis.

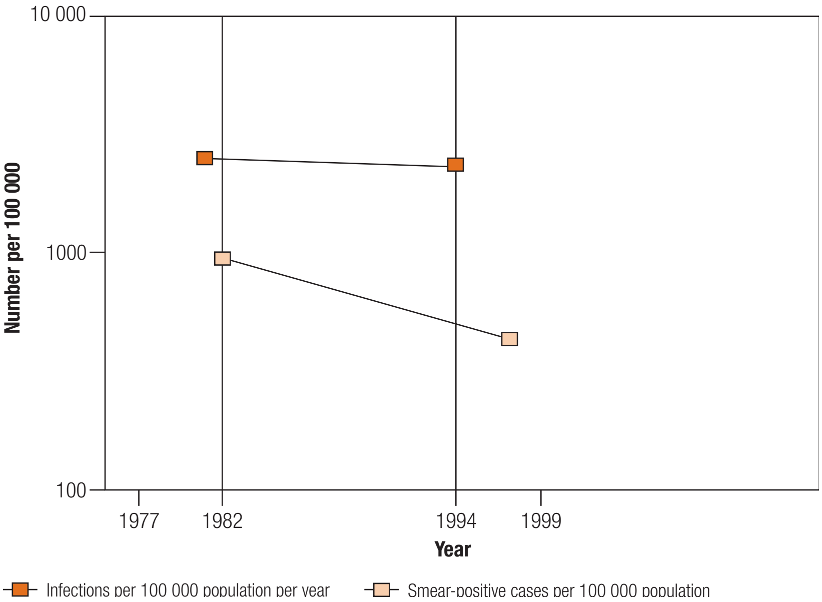
methodology will underestimate the number of incident smear-positive TB cases and consequently overestimate the number of tuberculous infections per incident smear-positive TB case.

The point estimates of the ratios between infections and cases in the three countries range between 2.6 and 5.8, which is more than a factor of two. Although the confidence intervals around the ratios in the Philippines and the Republic of Korea overlap, it is not possible to say that their mean value could reflect a new common fixed mathematical relationship, given the very limited amount of data in this study. In our opinion, the differences in ratios indicate that a universal application of any fixed mathematical relationship between the prevalence of tuberculous infection, the prevalence of smear-positive TB and the incidence of smear-positive TB is not feasible. This concurs with the opinion of WHO's Strategic and Technical Advisory Group that, in its meeting in June 2006 in Geneva, endorsed the recommendation of a WHO working group to no longer use the Styblo rule to estimate the incidence of smear-positive TB.

The explanation for the lower ratio compared to the one described by Styblo probably lies in improved TB control through DOTS programmes. Most of the data evaluated date from before the onset of the HIV epidemic. Even the data after the onset of the HIV epidemic are from settings with a limited HIV epidemic at the time of measurement. Therefore, the effect of HIV, through more rapid detection and treatment, and subsequent interruption of transmission, is not a major explanation for the lower infection-to-disease ratios. Finally, a changing pattern of social mixing would change TB epidemiology and the ratio of infection to disease. Increased mixing of social or age groups due to increased mobility or population growth will lead to higher chances of TB transmission and an increased infection-to-disease ratio. Unfortunately, there is no information on this parameter to be found in the analysed surveys. A detailed assessment of possible changing social mixing patterns was beyond the scope of the study.

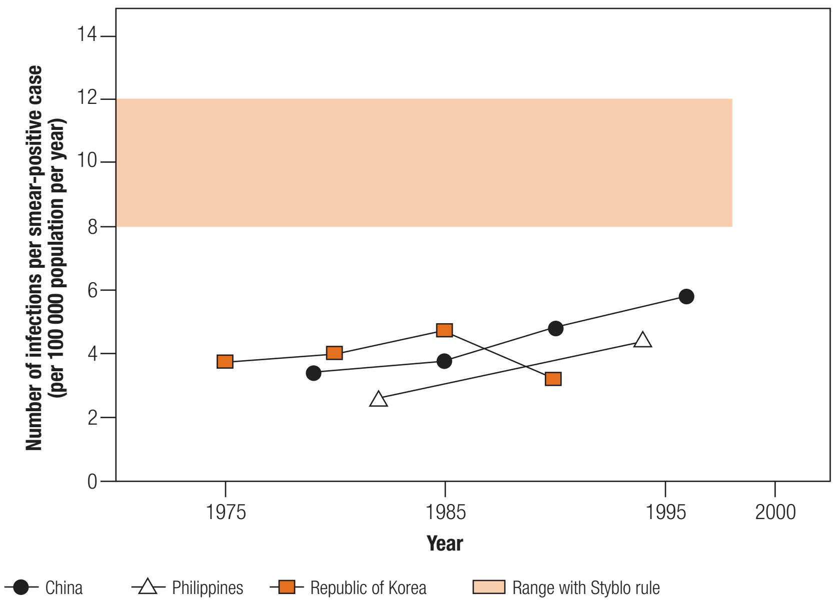
The observation that the number of tuberculous infections per prevalent smear-positive TB case remained relatively stable over time within a single country suggests a potentially useful role for regularly repeated TST surveys. Repeated TST surveys are logistically and financially easier to perform than population surveys for smear-positive TB. With a valid ARTI estimate from these studies and a known infection-to-disease ratio, the TST surveys can be used to describe the trends in the prevalence of smear-positive TB in a country. However, TST surveys have some inherent methodological difficulties. These include the effect of bacille Calmette–Guérin vaccination and environmental mycobacteria on the TST induration, the presence of digit preference in TST measurements, and the difficulties in obtaining a useful and valid cut-off point to distinguish those infected and those not.[14] These issues and the limited amount of data in the present study make this approach

Fig. 4. **Number of tuberculosis infections and smear-positive TB cases, the Philippines**



TB, tuberculosis.

Fig. 5. **Number of tuberculosis infections per prevalent smear-positive TB cases**



TB, tuberculosis.

speculative. It is to be hoped that in the design and implementation of new prevalence surveys for TB disease, data will concurrently be collected on the prevalence of tuberculous infection.

Conclusions

The case detection rate is an important indicator in current TB control efforts. Not only is it used as a target under the MDGs, it is also an indicator that NTPs use to monitor and evaluate their efforts in controlling TB. It is therefore important that the case detection rate can be accurately estimated from estimates of the incidence of new smear-positive TB cases. We showed that the ratio between the number of patients with tuberculous infections and the number of smear-positive TB cases is markedly lower in the surveys in China, the Philippines and the Republic of Korea than previously reported by Styblo, making a universal application of the Styblo rule no longer a valid approach. Surveys to estimate TB prevalence in countries with a high and intermediate TB burden are currently the best tools to capture information that can be used for measuring the progress in TB control towards the MDGs so long as adequate routine TB surveillance systems are not available. ■

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Résumé

Prévalence de l'infection tuberculeuse et incidence de la tuberculose : réévaluation de la règle de Styblo

Objectif Evaluer la validité de la relation mathématique fixe, appelée règle de Styblo, entre le risque annuel d'infection tuberculeuse (RAIT), la prévalence de la tuberculose (TB) à frottis positif et l'incidence de la TB à frottis positif, utilisée par les programmes de lutte antituberculeuse pour estimer l'incidence de la TB à l'échelle d'une population et le taux de détection des cas.

Méthodes Des enquêtes tuberculiniques en population et des enquêtes sur la prévalence de la TB à frottis positif depuis 1975 ont été identifiées par une recherche dans la littérature. Pour ces enquêtes, on a calculé le ratio entre le nombre d'infections tuberculeuses (d'après les estimations du RAIT) et le nombre de cas de TB à frottis positif et on l'a comparé au ratio de 8 à 12 infections tuberculeuses par cas prévalent de TB à frottis positif, fourni par la règle de Styblo.

Résultats Trois pays disposaient pour plus d'une date de données nationales en population à la fois sur le RAIT et la prévalence des TB à frottis positif. En Chine, le ratio considéré allait de 3,4 à 5,8, aux Philippines, de 2,6 à 4,4 et en République de Corée, de 3,2 à 4,7. Tous ces ratios étaient notablement inférieurs à ceux fournis par la règle de Styblo.

Conclusion D'après des données nationales récentes, il y a habituellement moins de 8 à 12 infections tuberculeuses par cas prévalent de TB à frottis positif et les variations notables du ratio d'un pays à l'autre restent inexpliquées. Cette baisse du ratio par rapport à la valeur fournie par la règle de Styblo est probablement liée aux progrès dans le traitement rapide des malades tuberculeux (par les programmes nationaux de lutte contre la TB). Une telle variation du nombre d'infections tuberculeuses par cas prévalent de TB à frottis positif invalide la relation supposée fixe entre le RAIT et l'incidence de la TB à frottis positif.

Resumen

Prevalencia de la infección tuberculosa e incidencia de tuberculosis: reevaluación de la regla de Styblo

Objetivo Evaluar la validez de la relación matemática fija entre el riesgo anual de infección tuberculosa (RAIT), la prevalencia de la tuberculosis (TB) bacilífera y la incidencia de la TB bacilífera establecida por la regla de Styblo, utilizada por los programas de lucha contra la TB para calcular la incidencia de la enfermedad en la población y la tasa de detección de casos.

Métodos Mediante una búsqueda bibliográfica se identificaron las encuestas poblacionales tuberculínicas y sobre la prevalencia de la TB bacilífera llevadas a cabo desde 1975. Con los datos de esas encuestas se calculó la razón entre el número de infecciones tuberculosas (basado en estimaciones del RAIT) y el número de casos de TB bacilífera, y se comparó con la razón de 8 a 12 infecciones tuberculosas por caso prevalente de TB bacilífera obtenida con la aplicación de la regla de Styblo.

Resultados Tres países tenían datos poblacionales nacionales sobre el RAIT y la prevalencia de TB bacilífera obtenidos en más de un momento. En China la razón osciló entre 3,4 y 5,8, en Filipinas entre 2,6 y 4,4, y en la República de Corea entre 3,2 y 4,7. Todas estas razones fueron considerablemente menores que la obtenida con la regla de Styblo.

Conclusión Según datos recientes de algunos países, normalmente hay menos de 8 a 12 infecciones tuberculosas por caso prevalente de TB bacilífera, pero no está claro si esta razón varía de forma significativa de un país a otro. Esta disminución de la razón en comparación con la obtenida con la regla de Styblo probablemente esté relacionada con mejoras en el tratamiento rápido de la TB por los programas nacionales de lucha contra la TB. La variación del número de infecciones tuberculosas por caso prevalente de TB bacilífera en las encuestas poblacionales hace que la relación matemática fija generalmente aceptada entre el RAIT y la incidencia de TB bacilífera haya dejado de ser válida.

ملخص

انتشار عدوى السل ووقوعاته: إعادة تقييم قاعدة ستايبلو

الغرض: تقيـيم مصدوقية العلاقة الرياضية الثابتة بين معدل الاختطار السنوي لعدوى السل، ومعدل انتشار حالات السل الإيجابية اللطاخة، ووقوع حالات السل الإيجابية اللطاخة، المعروفة باسم قاعدة ستايبلو، التي تستخدمها برامج مكافحة السل لتقدير وقوعات مرض السل على مستوى قطاع سكاني معين، ومعدل اكتشاف الحالات.

الطريقة: تم التعرُّف على المسوحات السكانية الخاصة بالتوبركولين، ومسوحات انتشار السل الإيجابي اللطاخة، التي أجريت منذ 1975، من خلال البحث في الدراسات المنشورة. وقد حُسبت النسبة بين عدد حالات العدوى السلِّية (تأسيساً على تقديرات الاختطار السنوي لعدوى السل)، وعدد حالات السل الإيجابية اللطاخة، وفقاً لهذه المسوحات، وقورنت مع نسبة 8 إلى 12 الخاصة بحالات العدوى السلية لكل حالة سل منتشر إيجابية اللطاخة، وذلك في إطار قاعدة ستايبلو.

النتائج: كانت لدى ثلاثة من البلدان معطيات سكانية المرتكز عن كل من معدل الاختطار السنوي لعدوى السل، وانتشار حالات السل الإيجابية اللطاخة، لأكثر من فترة زمنية واحدة. ففي الصين تـراوحت النسبة بين 3.4 و5.8، وفي الفلبين بين 2.6 و4.4، وفي جمهورية كوريا بين 3.2 و4.7. وكانت كل النسب أقل، بشكل ملحوظ، من النسبة التي جاءت في إطار قاعدة ستايبلو.

الاستنتاج: وفقاً للمعطيات الحديثة بالبلدان، فإن حالات العدوى السلِّية لكل حالة سل منتشر إيجابية اللطاخة كانت دائماً أقل من نسبة 8 إلى 12. ويظل من غير الواضح ما إذا كانت هذه النسبة تـتفاوت تفاوتاً يُعتد به إحصائياً بين البلدان، وربما كان النقص في النسبة، بالمقارنة مع قاعدة ستايبلو، راجعاً للتحسينات التي طرأت في مجال المعالجة الفورية لمرض السل (من خلال البرامج الوطنية لمكافحة السل). وإن حدوث تغيُّر في عدد حالات العدوى السلِّية نسبة إلى حالات السل الإيجابية اللطاخة في المسوحات السكانية المرتكز، يجعل العلاقة الرياضية التي يفتـرض أنها ثابتة بين معدل الاختطار السنوي ووقوع حالات السل الإيجابية اللطاخة لم تعد صحيحة.

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