Thinking in three dimensions: a web-based algorithm to aid the interpretation of tuberculin skin test results

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_____ S U M M A R Y

BACKGROUND: The tuberculin skin test (TST) is the most widely used test for detecting tuberculosis (TB) infection. Accurate interpretation of TST requires consideration of three dimensions—the size of the skin reaction, the positive predictive value (PPV) and risk of disease.
METHODS: We developed a web-based algorithm incorporating epidemiological, medical and radiographic risk factors to help in the interpretation of positive TST results in adults (http://www.meakins.mcgill.ca/meakins/ NEW TST Calculator/homeE.htm). We used summary estimates from published reviews on the prevalence of latent TB infection, the likelihood of false-positive TST and risk of active TB disease.
RESULTS: The algorithm calculations show that the most

important determinants of risk of active disease are the presence of medical and radiographic risk factors, while the size of the reaction is of modest importance. In persons who have received bacille Calmette-Guérin vaccination after infancy, the algorithm calculations show that the PPV will be low. In such persons, the risk of disease is predicted to be very low, unless there are medical or radiographic risk factors that increase the risk of reactivation.
CONCLUSIONS: Our web-based algorithm can generate clinically useful estimates of the annual and cumulative lifetime risk of developing TB in adults with a positive TST.
KEY WORDS: tuberculin skin test; latent TB infection; prediction rules; clinical decision aids; software

IN RECENT YEARS, new tests for the diagnosis of latent tuberculosis infection (LTBI) have been introduced, extensively evaluated[1] and recommended for adoption by some authorities.[2] Despite certain drawbacks, the tuberculin skin test (TST) remains in widespread use and, because of a number of advantages, is still recommended by many other authorities.[3,4] The TST is less expensive, simpler and hence more practical in many settings.

The most important advantage of TST is the availability of information regarding incidence of active tuberculosis (TB) among individuals with a positive TST result. This information has been established in different settings in numerous cohorts of persons who have undergone TST. This makes it possible to predict the likelihood of developing active TB in an individual with a positive TST result, which can be balanced with risks of LTBI treatment. However, predicting the risk of active TB is complex, as accurate interpretation requires consideration of TST reaction size, likelihood that the TST result may be false-positive or true-positive and risk of progression to active disease if truly infected. The likelihood that a positive test indicates true TB infection is influenced by age, the inci-

dence of TB in the population, other risk factors for TB exposure, plus causes of false-positive tests, particularly prior bacille Calmette-Guérin (BCG) vaccination and exposure to non-tuberculous mycobacteria (NTM). The risk of disease is affected by time since infection, presence of medical risk factors or therapy and chest X-ray findings.[5]

A recent survey of US medical residents has highlighted the lack of understanding regarding the interpretation and management of LTBI.[6] Web-based decision-support systems for applying American Thoracic Society/Centers for Disease Control and Prevention guidelines for TB preventive treatment have already been shown to be effective in improving the screening of high-risk LTBI patients.[7] Because clinicians and health providers often find it difficult to interpret the TST, the development of simplified computer-based decision aids may be helpful as they have been for other complex clinical situations, such as the calculation of medication dosages in renal failure.[8]

Our objective was to develop a computerised algorithm to calculate the risk of active TB disease for adults with positive TST using simple clinical and demographic information. We used information from a

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systematic review and meta-analysis of false-positive TST reactions due to BCG vaccination and NTM, which has been published elsewhere.[9] We also used information from a second literature review regarding the relative risk (RR) of reactivation associated with various medical and radiological risk factors.[10] This published information was then integrated into a predictive algorithm.

METHODS

Overview of the development of the algorithm

The algorithm was designed to calculate the predictive value of a positive TST based on size of reaction, the likelihood of false-positive reactions from exposure to NTM or BCG vaccination and the likelihood of true LTBI. The annual risk of development of active disease is then estimated, based on the annual incidence of disease in healthy general population samples and the RR of disease with various medical and radiographic risk factors. The annual risk of disease, multiplied by the positive predictive value (PPV) and then multiplied by the number of years of anticipated survival, provides a final calculated cumulative lifetime risk of TB disease.

Calculating the positive predictive value

The likelihood that a positive TST represents true TB infection:

$$\text{Positive predictive value (PPV)} = \frac{\text{TP } (= \text{prevalence of LTBI})}{\text{TP} + \text{FP } (= \text{FP-TST}_{BCG} + \text{FP-TST}_{NTM})}.$$

The rates of true positive (TP) TST from LTBI and false-positive (FP) TST from BCG and NTM were calculated as follows (and are summarised in Table 1).

Calculating the prevalence of LTBI

$$p\text{LTBI} = 1 - [(1 - c)(1 - \text{ARI})^{\text{age}}]$$

where pLTBI = prevalence of LTBI, c = prevalence of TB infection in contacts, and ARI = annual risk of infection in the general population.

As suggested by Styblo,[11] the ARI in the general population was calculated as the incidence of smear-positive pulmonary TB per 100 000 population divided by 49. The incidence of smear-positive TB was taken from World Health Organization (WHO) estimates.[12] The expected prevalence of infection among contacts was taken from published literature and a recent review.[13–18] If the person tested is not a contact, then $c = 0$. This results in the above equation being simplified to:

$$p\text{LTBI} = 1 - (1 - \text{ARI})^{\text{age}}.$$

Calculating the effect of BCG on TST reactions

In our previous review and meta-analysis,[9] the major determinant of the effect of BCG vaccination on TST reactions was age when vaccinated. We accordingly estimated the effect separately for subjects who were vaccinated in infancy (age 0–1 year), or after the age of 1 year (in practical terms this is usually in primary school, i.e., age 5–7 years). We compared the proportion of BCG-vaccinated and non-vaccinated individuals with TST reactions of 10–14 mm and ≥15 mm. For each TST size category, the difference between vaccinated and non-vaccinated was assumed to represent the percentage with false TST due to BCG (FP-TST$_{BCG}$). We estimated the average effect separately as a weighted average of all studies of individuals vaccinated in infancy, or vaccinated in older age.

Calculating the effect of NTM on TST reactions

In our previous review,[9] we identified 12 studies that performed dual testing with antigen from *Mycobacterium tuberculosis* (purified protein derivative) and from NTM. In these studies, if the reaction to one antigen was larger than the other, the smaller reaction was considered a cross-reaction[19–21] and hence considered a false-positive reaction. When the TST was 10–14 mm

Table 1 Summary of input parameters for algorithm calculation of positive predictive value

Parameters	Estimates	References
Prevalence of true-positive TST	$[1 - (1 - \text{ARI})^{\text{age}}] \times 100$	11
General population (country-specific)	AGE = age of patient	
	ARI = smear-positive TB/49	12
Contacts, %		
Close	40	13–18
Casual	8	
Prevalence of false-positive TST		
From BCG vaccination (by age last vaccinated), %		
Infancy (age 0–1 years)	8.5	9
Older (age ≥2 years)	41.8	9
From NTM sensitivity		
TST=10–14 mm, % false-positive if NTM-sensitive	2.7	Calculated
Prevalence NTM sensitivity, country-specific, %	2–58	
Prevalence false positive TST$_{NTM}$, country-specific, %	0.1–1.6	(from [9])

TST = tuberculin skin test; ARI = annual risk of infection; TB = tuberculosis; BCG = bacille Calmette-Guérin; NTM = non-tuberculous mycobacteria.

and the simultaneous NTM reaction was larger (dominant), then the TST reaction was considered a cross-reaction due to NTM sensitivity[19–21] and the TST was considered false-positive (FP-TST$_{NTM}$). However, if the TST was ≥15 mm, the subject was considered to have LTBI (true positive) regardless of the size of the NTM reaction.[19,20]

Using the 12 studies with dual testing, we estimated the rate of FP-TST$_{NTM}$; this rate was multiplied times the prevalence of NTM in different countries to estimate the absolute rate of false-positive TST related to NTM in different countries or world regions.

Calculating the risk of disease

Annual rate of disease (ARD) =

[PPV] × [baseline annual rate of disease if no risk factors are present] × [relative risk of disease, given the presence of specific risk factors].

The baseline annual risk of TB disease was taken from a large cohort of healthy TST-positive US military recruits followed up for 4 years.[22] The risks of disease relative to such healthy persons, associated with radiographic abnormalities or medical risk factors, are summarised in Table 2.

At age = *n*, up to age of 80:

Cumulative risk of disease = ARD × (80 − *n* years).

For computational simplicity, subjects were assumed to live to the age of 80.

Table 2   Summary of input parameters for algorithm calculation of relative and annual risks of active tuberculosis disease (adapted from Ref 23)

Medical or radiographic risk factor	RR	References	Annual risk, % per year
None (healthy or 'low-risk reactor')	1	22	0.1
Abnormal chest X-ray, granuloma	2	24, 25	0.2
Cigarette smoker (≥1 pack/day)	3	26	0.3
Underweight (<90% ideal body weight)	3	27	0.3
Diabetes mellitus	3.6	28–31	0.36
Infliximab (TNF-α inhibitor therapy)	4	32	0.4
Abnormal chest X-ray, fibronodular disease*	6	25, 33, 34	0.6
Recent TB infection (≤2 years)†	15	35, 36	1.5
Close contact	15	35, 36	1.5
Carcinoma of head and neck	16	37	1.6
Chronic renal failure (requiring hemodialysis)	25.3	38–41	2.5
Pulmonary silicosis	30	42, 43	3.0
HIV infection (all stages)	50	44–47	5.0
Transplantation (requiring immune-suppressant therapy)	74	48–51	7.4

* Lower estimate from Nolan of RR = 6.0,[33] and not the higher estimate of RR = 19 from Grzybowski.[34]
† Risk of disease elevated for first 2 years after infection, then falls to annual risk of 0.1% thereafter (close contacts should be considered to have recent infection in algorithm).
RR = relative risk; TNF-α = tumour necrosis factor-alpha; TB = tuberculosis; HIV = human immunodeficiency virus.

As this study did not directly involve human subjects, ethics approval was not needed.

RESULTS

In 24 studies involving 240 203 subjects who were BCG-vaccinated in infancy (age 0–1 year), 20 406 (8.5%) had a TST of ≥10 mm attributable to BCG, although only 56 of 5639 (1%) were TST-positive if tested ≥10 years after BCG. In 12 studies of 12 728 subjects vaccinated after their first birthday, 5314 (41.8%) had a false-positive TST of ≥10 mm and 191 of 898 (21.2%) had a false-positive TST after ≥10 years. Based on the 12 studies of 1 169 105 persons who underwent dual TST and NTM testing, for every 100 persons sensitised to NTM, 2.0 persons would have a false-positive TST of 10–14 mm. Using the five studies with 12 984 persons with detailed data, the rate of FP-TST$_{NTM}$ (of 10–14 mm) was 2.7 per 100 NTM sensitised persons. When this higher estimate of FP-TST$_{NTM}$ was multiplied by the prevalence of NTM sensitisation in 18 published surveys, the prevalence of FP-TST$_{NTM}$ ranged from 0.1% in Canada or France, to a maximum of 1.6% in India.[9]

The algorithm* estimates the PPV using the TST reaction size, country of origin (and state of birth if US-born), current age and age at immigration (in the case of migrants), BCG vaccination status and history of contact with TB. The annual and cumulative risk (to the age of 80) of disease is then calculated based on radiographic findings and medical history. See Figure 1 for an example screenshot of the parameters to be entered. Once all the relevant input parameters are entered, the algorithm computes the predictive value of a positive TST, as well as the annual and cumulative lifetime risk of disease. See example screen shot of algorithm output in Figure 2.

As seen in Table 3, the calculated cumulative risk of disease up to the age of 80 for a 35-year-old adult varies widely. The most critical determinants of risk of disease are country of origin, BCG vaccination and medical risk factors. The effect of TST size is relatively small, except in populations where the prevalence of NTM sensitivity is high and LTBI is uncommon—such as occurs in Southern USA. BCG vaccination has an important effect of reducing PPV and hence risk of disease, when expected prevalence of LTBI is low and BCG was routinely given to school-age children or

* The algorithm is accessible at: http://www.meakins.mcgill.ca/ meakins/NEW TST Calculator/homeE.htm. The screen should appear as Figure 1. Simply enter the demographic and clinical parameters, including TST size, for the patient, then 'Submit'. Results will appear as shown in Figure 2. Close that screen to re-enter new values for a different patient, etc. Software submitted, but not intended for direct publication, nor included in transfer of copyright to the IJTLD. Available freely as shared software upon request, or directly on website of authors.

Thinking in three dimensions:
An algorithm to aid interpretation of the tuberculin skin test
(Version 1.0 January 19,2006)

🎓 McGill

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The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of 10+mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5 TU PPDS, or 2 TU RT-23). Prevalence of tuberculosis infection is derived using the Styblo formula and incidence of smear positive TB in the country of origin (from WHO). The effects of NTM and BCG on TST positivity were compiled from a literature review as were the relative risks of various health conditions. For further information see references, or contact the authors.

Select:

1. TST reaction size:

    10-14 mm

2. Age: **Age at immigration if applicable:**

    35   0

3. Country of birth: **If Country of birth is the USA:**

    United States of America   Florida

4. BCG status:

    ◉ Never vaccinated or unknown
    ○ Vaccinated age < 2 years
    ○ Vaccinated age >= 2 years

5. Contact with active TB:

    ◉ None
    ○ Close Contact
    ○ Casual

6. Please select all the conditions that currently apply to the patient:

    ☑ Diabetes Mellitus
    ☐ Chronic renal failure/hemodialysis
    ☐ Transplantation (related to immune-suppressant therapy)
    ☐ Silicosis
    ☐ Carcinoma of head and neck
    ☐ Recent TB infection (TST conversion)
    ☐ Abnormal chest x ray fibronodular disease
    ☐ Abnormal chest x ray granuloma
    ☐ Underweight(< 90 percent of ideal body weight)
    ☐ Cigarette smoker(>1 pack/day)
    ☐ TNF-a blockers(Infliximab/Etanercept)
    ☐ HIV infection

    [Submit] [Reset]

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Figure 1   Screen shot of parameters to be entered in web-based algorithm.

adolescents. This was the practice in many European countries such as the UK, France and throughout Eastern Europe until quite recently.

DISCUSSION

Interpretation of a TST should take multiple factors into account. It is best to interpret the TST in three distinct stages or dimensions—size, PPV and risk of development of disease. To facilitate interpretation, we have developed a simple, web-accessible tool to calculate the likelihood that a TST is true-positive and the risk of active disease. These calculations are based on numerous studies published over the past 40 years—an important advantage of the TST. As demonstrated by the examples generated from this web-based programme, the cumulative risk of disease will be substantial in adults with important medical risk factors, particularly if the PPV of the test is >50%. These predictions are supported by a recent modelling study that emphasised the importance of medical conditions in determining the lifetime risk of TB.[52] However, in healthy low-risk adults, the cumulative risk of disease is low, even if the TST is almost certainly true-positive. This

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Your Results

For this patient with a TST reaction of 10–14 mm, 35 years of age, born in USA, Florida, whose BCG status is **Never vaccinated** or **unknown,** and with history of contact with TB of **None,** and characterized by:

- Diabetes Mellitus

Predicted risk of development of active tuberculosis is estimated to be:

The likelihood that this is a true positive test (PPV) is:
50.331%

The annual risk of development of active tuberculosis disease is estimated to be:
0.181%

The cumulative risk of active tuberculosis disease, up to age of 80, is:
8.153%

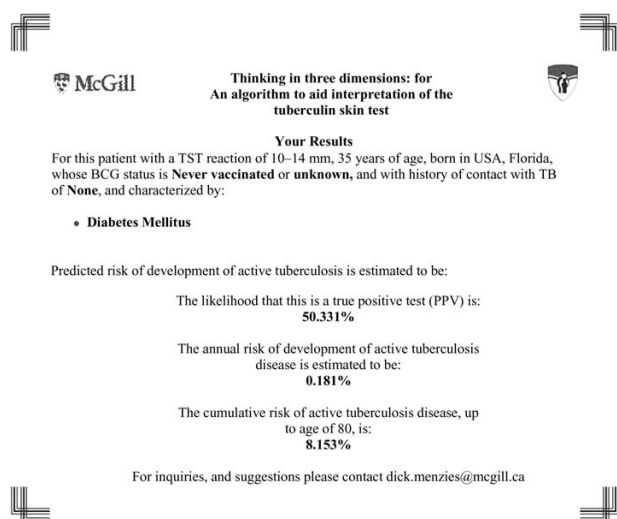For inquiries, and suggestions please contact dick.menzies@mcgill.ca

Figure 2 Screen shot of generated results from web-based algorithm.

reinforces the recommendation[10,53] to test only individuals who are at increased risk of disease in whom potential causes of false-positive TST can be ignored.

This computerised algorithm has a number of potential limitations. First, the current estimates of prevalence of true infection are based on currently available estimates of incidence of smear-positive TB from the WHO data. In some low-income countries, these estimates may be inaccurate due to limited case finding. However, as incidence tends to be very high in these countries, even if the actual incidence is 25% higher or lower than published estimates, this will have a relatively small impact on the estimated PPV as the estimated prevalence of true infection in adults will be high with all estimates. Furthermore, to estimate the annual risk of infection, the algorithm incorporates the Styblo formula. This formula has been criticised as it ignores the potential effect of transmission from smear-negative cases, which may account for 20–25% of all transmission,[54] thus potentially underestimating infection risk. However, Styblo based his formula on observed rates of disease and infection in countries that had, at the time, little or no capacity for diagnosis of smear-negative disease.[11] Hence the observed infection risk did account for all cases in the community at that time. The formula would be invalid now if the proportion of smear-negative to -positive cases had changed over the last two decades. This could have happened in countries with high human immunodeficiency virus (HIV) seroprevalence, as HIV-co-infected cases are more often smear-negative.[55] However, use of this formula is justified because it has

Table 3 Illustration of the algorithm calculations: cumulative risk (to the age of 80) of developing tuberculosis in 35-year-old adults with TST reactions of 10–14 or >15 mm

Country of origin	History of BCG vaccination	PPV		Cumulative risk of active TB disease	
		TST 10–14 mm %	TST ≥15 mm %	TST 10–14 mm %	TST ≥15 mm %
Healthy—no risk factor, normal chest X-ray					
Florida, USA	None*	50	100	2.3	4.5
Canada	None	93	100	4.2	4.5
	Infancy	18	19	0.8	0.8
	Older	3	3	0.1	0.1
Russia*	None	99.6	100	4.5	4.5
	Older*	41	41	1.8	1.8
Haiti*	None	99.5	100	4.4	4.5
	Infancy*	90	91	4.0	4.5
Diabetes					
Florida, USA	None	50	100	8.1	16.2
Canada	None	93	100	15.1	16.2
Russia†	Older	41	41	7	7
Haiti†	Infancy	90	91	14.5	15.1
Granuloma on chest X-ray and underweight					
Florida, USA	None	50	100	11.3	22.5
Canada	None	93	100	21	22.5
Russia†	Older	41	41	9.1	9.1
Haiti	Infancy	90	91	20.6	20.8
Healthy but recent contact with active TB					
Florida, USA	None	99	100	8.9	9.0
Canada	None	100	100	9.0	9.0
Russia†	Older	71	71	6.8	6.8
Haiti	Infancy	94	95	8.4	8.4

* Values of BCG vaccination most likely indicate BCG status in persons from that country.
† Immigrated to Canada at age 32.
TST = tuberculin skin test; TB = tuberculosis; BCG = bacille Calmette-Guérin; PPV = positive predictive value.

been validated, albeit many years ago, and there is no other formula available that does account for these factors and yet is simple enough to be incorporated into the algorithm.

A second limitation is that our NTM prevalence estimates for many countries were extrapolated from results in nearby countries with a similar climate.[9] However, the estimated effect of NTM is small[19–21] (even if somewhat greater than originally estimated),[56] so even moderate imprecision in these extrapolated estimates would have a trivial effect on the estimated PPVs.

Other limitations include that the algorithm will not identify false-negative tests, as it is designed only to assist the interpretation of a positive TST. The effects on TST reactions of BCG and NTM are derived from studies in non-HIV-infected persons, so may not be accurate in HIV-infected persons. However, because the risk of active TB is so high with HIV infection, imprecision regarding false-positive rates should have little impact on the estimated risk of disease, and current guidelines recommend that possible causes of false-positive TST, such as BCG, should be ignored in HIV-infected persons.[10,53] The values incorporated for each parameter were based on a thorough review of the literature, but there is no published information regarding how combinations of factors interact to affect likelihood of disease. The assumption that the presence of more than one risk factor will further increase risk is not based on published observations. It would be very difficult to validate the algorithm predictions in such patients, because such high-risk patients should receive treatment for LTBI.[10,53] One can thus only check whether the resultant estimates, such as those shown in Table 3, are clinically reasonable.

Finally, the current algorithm does not estimate PPV or risk of disease for TST reactions of 5–9 mm. This is because there is much less published information regarding prevalence of infection, relative risk and PPV in persons with TST reactions of this size. The algorithm also does not estimate risk for results of serial testing—again because there is less and inconsistent information regarding the occurrence and interpretation of serial TST testing in different populations. We acknowledge that this algorithm, like all software programmes, is work in progress. Readers and users are therefore invited to send comments or corrections to the authors.[*] We hope to develop updated versions with calculations for TST of 5–9 mm and for serial testing. Another possible development would be to adapt this for interpretation of the results of the newer interferon-gamma release assays (IGRAs). The algorithm would be simpler, as the PPV of IGRA should be uniformly high given that false-positive reactions are much less common.[1] There are, however, no published cohort studies of the follow-up of untreated populations with positive IGRA results. Estimates of risk of disease would therefore have to be based on older cohorts who were followed up after TST testing.

A key question is whether busy clinicians will use this tool. On the first occasion that colleagues in our institute tried the algorithm, they required about half a minute to launch the programme and another 15–20 seconds to input the data. If installed on a palm pilot, this could be even quicker and more accessible.

In conclusion, we believe that many of the limitations of TST interpretation can be overcome with this computer-based decision tool. A busy clinician can input a number of variables and estimate the risk of disease for patients in less than a minute. As demonstrated in our examples, individuals with medical risk factors for active TB or abnormal chest X-rays will have a high risk of developing active disease, even after accounting for potential false-positive tests. This reinforces an important advantage of the TST—the validity for prediction of disease risk. These findings also underscore the importance of performing the TST only in adults at increased risk to develop disease if infected, as they will benefit most from treatment of LTBI.

References

1 Menzies D, Pai M, Comstock G W. New tests for diagnosis of latent tuberculosis infection—areas of uncertainty and recommendations for research. Ann Intern Med 2007; 146: 340–354.
2 Mazurek G, Jereb J, LoBue P, et al. Guidelines for the investigation of contacts of persons with infectious tuberculosis—recommendations from the National Tuberculosis Controllers Association and CDC—guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR Morb Mortal Wkly Rep 2005; 54 [RR-15]: 49–55.
3 Royal College of Physicians. Tuberculosis: national clinical guidelines for diagnosis, management, prevention and control. London, UK: Royal College of Physicians, 2006.
4 Canadian Tuberculosis Committee. Interferon-gamma release assays for latent tuberculosis infection (an advisory committee statement). Canada Communicable Disease Report 2007; 33: 1–18.
5 Rieder H L. Epidemiologic basis of tuberculosis control. Paris, France: International Union Against Tuberculosis and Lung Disease, 1999.
6 Karakousis P C, Sifakis F G, De Oca R M, et al. US medical resident familiarity with national tuberculosis guidelines. BMC Infect Dis 2007; 7: 89.
7 Steele A W, Eisert S, Davidson A, et al. Using computerized

clinical decision support for latent tuberculosis infection screening. Am J Prev Med 2005; 28: 281.

8 Chertow G M, Lee J, Kuperman G J, et al. Guided medication dosing for in-patients with renal insufficiency. JAMA 2001; 286: 2839–2844.

9 Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests—what is the absolute effect of BCG and non-tuberculous mycobacteria? Int J Tuberc Lung Dis 2006; 10: 1–13.

10 Long R. Canadian Tuberculosis Standards. 6th ed. Ottawa, Canada: Canadian Lung Association, Public Health Agency of Canada, 2007.

11 Styblo K. The relationship between the risk of tuberculosis infection and the risk of developing infectious tuberculosis. Bull Int Union Tuberc Lung Dis 1985; 60 (3–4): 117–119.

12 World Health Organization. Global tuberculosis control: surveillance, planning, financing. WHO report 2004. WHO/HTM/TB/2004.331. Geneva, Switzerland: WHO, 2004.

13 Van Zwanenberg D. The influence of the number of bacilli on the development of tuberculous disease in children. Am Rev Respir Dis 1960; 82: 31–44.

14 Grzybowski S, Barnett G D, Styblo K. Contacts of cases of active pulmonary tuberculosis. Bull Int Union Tuberc Lung Dis 1975; 50 (1): 90–106.

15 Van Geuns H A, Meijer J, Styblo K. Results of contact examination in Rotterdam, 1967–1969. Bull Int Union Tuberc Lung Dis 1975; 50 (1): 107–121.

16 Karalus N C. Contact screening procedures for tuberculosis in Auckland. N Z Med J 1988; 101: 45–49.

17 Zaki M H, Lyons H A, Robins A B, Brown E P. Tuberculin sensitivity. NY State J Med 1976; 76: 2138–2143.

18 Greenaway C, Palayew M, Menzies D. Yield of casual contact investigation by the hour. Int J Tuberc Lung Dis 2003; 7 (Suppl 3): S479–S485.

19 Palmer C E, Edwards L B, Hopwood L, Edwards P Q. Experimental and epidemiologic basis for the interpretation of tuberculin sensitivity. J Pediatrics 1959; 55: 413–428.

20 Palmer C E, Edwards L B. Identifying the tuberculous infected. The dual-test technique. JAMA 1968; 205: 167–169.

21 Edwards L B, Acquaviva F A, Livesay V T. Identification of tuberculous infected: dual tests and density of reaction. Am Rev Respir Dis 1973; 108: 1334–1339.

22 Comstock G W, Edwards L B, Livesay V T. Tuberculosis morbidity in the US Navy: its distribution and decline. Am Rev Respir Dis 1974; 110: 572–580.

23 Long R. Canadian tuberculosis standards. Toronto, Canada: Canadian Lung Association, 2000.

24 Horwitz O, Wilbek E, Erickson P A. Epidemiological basis of tuberculosis eradication. Longitudinal studies on the risk of tuberculosis in the general population of a low-prevalence area. Bull World Health Organ 1969; 41: 95–113.

25 Grzybowski S, Fishaut H, Rowe J, Brown A. Tuberculosis among patients with various radiologic abnormalities, followed by the chest clinic service. Am Rev Respir Dis 1971; 104: 605–608.

26 Maurya V, Vijayan V K, Shah A. Smoking and tuberculosis: an association overlooked. Int J Tuberc Lung Dis 2002; 6: 942–951.

27 Comstock G W. Frost revisited: the modern epidemiology of tuberculosis. Am J Epidemiol 1975; 101: 363–382.

28 Kim S J, Hong Y P, Lew W J, Yang S C, Lee E G. Incidence of pulmonary tuberculosis among diabetics. Tubercle Lung Dis 1995; 76: 529–533.

29 Silwer H, Oscarsson P N. Incidence and coincidence of diabetes mellitus and pulmonary tuberculosis in a Swedish county. Acta Med Scand 1958; 161: 1–48.

30 Pablos-Mendez A, Blustein J, Knirsch C A. The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. Am J Public Health 1997; 87: 574–579.

31 Boucot K R. Diabetes mellitus and pulmonary tuberculosis. J Chronic Dis 1957; 6: 256–279.

32 Keane J, Gershon S, Wise R P, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001; 345: 1098–1104.

33 Nolan C M, Elarth A M. Tuberculosis in a cohort of South-east Asian refugees: a five-year surveillance study. Am Rev Respir Dis 1988; 137: 805–809.

34 Grzybowksi S, McKinnon N E, Tuters L, Pinkus G, Philipps R. Reactivations in inactive pulmonary tuberculosis. Am Rev Respir Dis 1966; 93: 352–360.

35 Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. Adv Tuberc Res 1976; 19: 1–63.

36 Sutherland I. The evolution of clinical tuberculosis in adolescents. Tubercle 1966; 47: 308.

37 Rieder H L, Cauthen G M, Comstock G W, Snider D E Jr. Epidemiology of tuberculosis in the United States. Epidemiol Rev 1989; 11: 79–98.

38 Malhotra K K, Parashar M K, Sharma R K, et al. Tuberculosis in maintenance haemodialysis patients. Study from an endemic area. Postgrad Med J 1981; 57: 492–498.

39 Lundin A P, Adler A J, Berlyne G M, Friedman E A. Tuberculosis in patients undergoing maintenance hemodialysis. Am J Med 1979; 67: 597–602.

40 Andrew O T, Schoenfeld P Y, Hopewell P C, Humphreys M H. Tuberculosis in patients with end-stage renal disease. Am J Med 1980; 68: 59–65.

41 Pradhan R P, Katz L A, Nidus B D, Matalon R, Eisinger R P. Tuberculosis in dialyzed patients. JAMA 1974; 229: 798–800.

42 Hong Kong Chest Service Tuberculosis Research Centre MB-MRC. A double-blind placebo-controlled clinical trial of three anti-tuberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Am Rev Respir Dis 1992; 145: 36–41.

43 Cowie R L. The epidemiology of tuberculosis in gold miners with silicosis. Am J Respir Crit Care Med 1994; 150: 1460–1462.

44 Antonucci G, Girardi E, Raviglione M C, Ippolito G, for the GISTA. Risk factors for tuberculosis in HIV-infected persons. A prospective cohort study. JAMA 1995; 274: 143–148.

45 Guelar A, Gatell J M, Verdejo J, et al. A prospective study of the risk of tuberculosis among HIV-infected patients. AIDS 1993; 7: 1345–1349.

46 Selwyn P A, Hartel D, Lewis V A, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 1989; 320: 545–550.

47 Wood R, Maartens G, Lombard C J. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with low or very high incidence of tuberculosis. J Acquir Immune Defic Syndr 2000; 23: 75–80.

48 Sakhuja V, Jha V, Varma P P, Joshi K, Chugh K S. The high incidence of tuberculosis among renal transplant recipients in India. Transplantation 1996; 61: 211–215.

49 Aguado J M, Herrero J A, Gavalda J, et al. Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain. Spanish Transplantation Infection Study Group, GESITRA. Transplantation 1997; 63: 1278–1286.

50 Miller R A, Lanza L A, Kline J N, Geist L J. Mycobacterium tuberculosis in lung transplant recipients. Am J Respir Crit Care Med 1995; 152: 374–376.

51 Meyers B R, Halpern M, Sheiner P, Mendelson M H, Neibart E, Miller C. Tuberculosis in liver transplant patients. Transplantation 1994; 58: 301–306.

52 Horsburgh C R. Priorities for the treatment of latent tuberculosis infection in the United States. N Engl J Med 2004; 350: 2060.

53 American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000; 161 (Suppl): S221–S247.

54 Behr M A, Warren S A, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative from acid-fast bacilli. Lancet 1999; 353: 444–449.

55 Page K R, Chaisson R E. Tuberculosis—HIV co-infection: epidemiology, clinical aspects and interventions. In: Raviglione M C, ed. Reichman and Hershfield's tuberculosis: a comprehensive, international approach. 3rd ed. New York, NY, USA: Informa Healthcare USA, 2006: 2 vols: pp 371–416.

56 Cobelens F G. False positive tuberculin reactions due to non-tuberculous mycobacterial infections [Letter]. Int J Tuberc Lung Dis 2007; 11: 934–935.

RÉSUMÉ

CONTEXTE : Le test cutané tuberculinique (TST) est le test le plus largement utilisé pour la détection de l'infection tuberculeuse. Une interprétation précise du TST exige la prise en compte de trois éléments : la dimension de la réaction cutanée, la valeur prédictive positive (PPV) et le risque de maladie.

MÉTHODES : Nous avons élaboré un algorithme basé sur le web et incorporant les facteurs de risque épidémiologiques, médicaux et radiologiques afin d'aider à l'interprétation d'un résultat positif du TST chez un adulte. Nous avons utilisé des estimations résumées dans des revues publiées sur la prévalence de l'infection TB latente dans diverses populations, sur la vraisemblance d'un test TST faussement positif provenant d'une vaccination par le bacille Calmette-Guérin (BCG) ou d'infections mycobactériennes non-tuberculeuses ainsi que le risque de tuberculose (TB) active lié à différents facteurs de risque médicaux et radiologiques.

RÉSULTATS : Les calculs de l'algorithme montrent que les déterminants les plus importants du risque de maladie active sont la présence de facteurs de risque médicaux ou radiologiques, alors que la taille de la réaction n'a qu'une importance modeste. Chez les personnes ayant reçu la vaccination par le BCG après la petite enfance, les calculs de l'algorithme montrent que la PPV d'un test positif sera faible particulièrement lorsque la probabilité d'une infection authentique est basse. Chez ces personnes, on peut prédire un risque très faible de maladie sauf s'il existe des facteurs de risque médicaux ou radiologiques qui augmentent le risque de réactivation.

CONCLUSIONS : Notre algorithme basé sur le web aide à clarifier les relations complexes entre la TB latente et la TB active et a le potentiel pour générer des estimations cliniquement utiles sur les risques annuels et les risques cumulatifs de développement d'une TB après un TST positif sur l'ensemble de la vie.

RESUMEN

MARCO DE REFERENCIA : La reacción cutánea a la tuberculina (TST) es la prueba más ampliamente utilizada en el diagnóstico de la infección tuberculosa. La interpretación exacta de la prueba precisa la consideración de tres aspectos : el tamaño de la reacción cutánea, el valor positivo de predicción (PPV) y el riesgo de enfermedad.

MÉTODOS : Se concibió un algoritmo con base en la web, que incorpora factores de riesgo epidemiológicos, médicos y radiográficos cuyo propósito es ayudar en la interpretación de un resultado positivo de la TST en el adulto. Se emplearon las estimaciones finales provenientes de reseñas publicadas sobre la prevalencia de infección tuberculosa latente en diversas poblaciones, la probabilidad de resultados positivos falsos debidos a la vacuna antituberculosa (BCG) o a infecciones por micobacterias diferentes a *Mycobacterium tuberculosis* y el riesgo de tuberculosis (TB) activa asociada con diversos factores de riesgo médicos y radiográficos.

RESULTADOS : Los cálculos con el algoritmo ponen en evidencia que los mayores determinantes del riesgo de enfermedad activa son la presencia de factores de riesgo médicos o radiográficos y que el tamaño de la reacción cutánea tiene escaso valor. En personas con antecedente de BCG después de la infancia, estos cálculos muestran que el PPV es bajo sobre todo cuando la probabilidad real de una infección es baja. En tales personas, se predice que el riesgo de enfermedad es muy bajo, a menos que existan factores de riesgo médicos o radiográficos que aumenten la probabilidad de reactivación.

CONCLUSIÓN : El algoritmo concebido con base en la web ayuda a aclarar la relación compleja entre TB latente y TB activa y puede contribuir a generar estimaciones con interés clínico sobre el riesgo anual y el riesgo acumulado durante la vida de presentar enfermedad tuberculosa tras un resultado positivo a la TST.