

# International Controversies in Interpreting the Mantoux Test with Special Reference to Saudi Arabia

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من الملاحظ أن نسبة حدوث التدرن الرئوي انخفضت في الدول الغربية ولكن الإصابة بحُمة مرض نقص المناعة المكتسب زادت من نسبة حدوث التدرن الرئوي في البلدان التي تنتشر فيها هذه الحُمة بين المواطنين. وبالمقابل لا توجد مؤشرات لانخفاض التدرن الرئوي في الدول النامية.

إن إختبار مانتو يعتبر من أجمع الوسائل لتشخيص التدرن. والكتب الطبية والمقالات العلمية المنشورة في الدوريات الطبية تذخر بالاختلافات في تفسير نتيجة إختبار المانتو وماهو الحد الذي يمكن أن يعتبر بعده أن الإختبار موجبا.

إن الهدف من هذه المقالة المختصة هو إلقاء الضوء على هذه الإختلافات بين العلماء واقترح حد أدنى لاختبار مانتو لاستعماله في السعودية للمساعدة على تشخيص مرض التدرن وذلك بناء على مدى إنتشار عصابات التدرن البيئية في هذه البلاد.

أتضح من البحث في المقالات العلمية التي لها علاقة بالسعودية أن الباحثين استعملوا حدوداً مختلفة لتفسير ايجابية اختبار مانتو في زمن لم تكن درجة إنتشار عصابات التدرن البيئية غير معروفة قبل عام ١٩٩٣م حيث إتضح ان نسبة الانتشار لهذه العصابات هو ٣,٨ لكل ١٠٠٠ شخص (الرقم مأخوذ من مزرعة البصاق). وعليه فيُوصى أن يكون الحد الأدنى هو ٥م م يعتبر عنده أن إختبار مانتو إيجابي. خاصة عند الخاططين لمرضى بالتدرن أو من لديهم أعراض المرض أو يعانون من مرض نقص المناعة المكتسب. وهذا الحد يمكن مراجعته مستقبلاً ورفعته إلى ٨م م في حالة نقصان نسبة إنتشار التدرن الرئوي عما هو عليه حالياً مع إستمرارية النسبة التدرنية الحالية لإنتشار عصابات التدرن البيئية ولكن يبقى حد الـ ٥م م كما هو للمرضى المشار اليهم آنفاً.

الكلمات المرجعية: التدرن. عصابات التدرن البيئية. مانتو.

*There is a general decline in the incidence of pulmonary tuberculosis (PTB) in developed countries, but infection by HIV has increased the incidence of PTB in affected countries. There are no signs of a similar decline in the incidence of PTB in some developing countries. The Mantoux technique for tuberculin testing continues to be among the effective diagnostic tools. The medical literature and textbooks of medicine show disagreement as to what constitutes a positive (specific) tuberculin reaction. This short review was intended to cite some examples of these differences and suggest a cutting point for use in the Kingdom of Saudi Arabia (KSA) based on the prevalence of environmental mycobacteria (Mycobacteria other than M. tuberculosis, MOTT). From this review different researchers within the KSA used different cut-off points at a time that the prevalence of MOTT was unknown, until 1993 when it was reported to be as low as 3.8/1000 population (based on sputum culture) and that the Kingdom is categorised among the middle PTB prevalent countries. Consequently, it seems appropriate to have 5 mm as a cutting point (positive) in all unvaccinated patients, particularly for those who were in contact with an infectious case, or having symptoms compatible with PTB, and also patients who were immuno-compromised as in HIV infection. This cut-off point can be revised and raised to 8 mm provided that the prevalence of PTB becomes lower than the current reported rate and MOTT prevalence remains low, but the 5 mm cutting point should remain for the aforementioned categories of patients.*

**Key Words:** Tuberculosis, MOTT, Mantoux.

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## INTRODUCTION

Although the incidence of pulmonary tuberculosis (PTB) due to infection by *M. tuberculosis* is decreasing in western countries<sup>1-3</sup>, the efforts to control it are still keeping their strong momentum. This decline is accompanied by a decrease in the rate of specific, and a relative increase in the prevalence of non-specific reactions due to infection by mycobacteria other than *Mycobacterium tuberculosis* (MOTT). However, infection by HIV has increased the risk of infection by mycobacteria. Indeed, the notification rate in the U.K. for 1988 has increased one and a half fold since 1987<sup>4</sup>. On the other hand, there are no signs of a similar decline in the incidence of PTB in some developing countries<sup>1</sup>, but Saudi Arabia is an exception.<sup>5</sup>

Case finding remains the most important method of reducing the rate of transmission of PTB, and the Mantoux technique for tuberculin testing continues to be among the effective tools in this regard.<sup>3</sup> Some authors consider the Mantoux technique most accurate and reliable<sup>6</sup> though it may be time consuming.<sup>7</sup> On the other hand, the needles of the Tine test have varying degrees of coating of the tuberculin and therefore, give false negative reactions, while hepatitis B is a risk with the Heaf test.<sup>7</sup>

Children with uncomplicated primary PTB are asymptomatic in the majority of instances.<sup>8</sup> This latter situation emphasizes the need for routine tuberculin testing of children suspected to have this disease.

The medical literature and textbooks of medicine show great disagreements as to what constitutes a positive (specific) tuberculin reaction. The decision on a dividing line (cutting point) between significant and non-significant reactions is fraught with difficulties in countries with a high prevalence of cross-reactions from MOTT.<sup>9</sup>

The objective of this short review is to cite

some examples of these differences and suggest a cutting point for use in the Kingdom of Saudi Arabia (KSA) and countries with a similar prevalence of tuberculosis and environmental mycobacteria. This review was not at all meant to be an exhaustive search of the literature, but rather to highlight controversies in the interpretation of the Mantoux test.

## REGIONAL AND WORLD LITERATURE.

### CUTTING POINT OF:

#### 2 - 5 mm.

In Vietnam, 1035 children aged 7 - 19 years from three cities were skin tested with a battery of 15 tuberculins, and an induration of 2 mm or more was the cut-off point.<sup>10</sup> Lunn and Johnson<sup>11</sup>, from the U. K., studied two groups of volunteers in 1979 and 1980. Both groups received 5 TU PPD and, according to the recommendations of the National Tuberculosis and Respiratory Diseases Association, a 5 mm induration was the cutting point. It is worth noting that the prevalence of MOTT in England was less than 30.0%.<sup>12</sup>

The prevalence of *M. intracellulare* in Montreal and Sherbrooke, Canada, was reported to range from 3 to 20.0% and 0.0 to 9.6%, respectively, while *M. Kansaii* was much less in both areas.<sup>13</sup> Because of this low prevalence of MOTT at least in some parts of Canada and for "a more realistic evaluation" of the extent of infection with *M. tuberculosis*, the investigators recommended a fixed 5 mm induration as positive, rather than the 10 mm adopted at the time of their study.

#### 6 - 8 mm.

In Spain, where infection with MOTT was considered not to be significant, a large community-based study involving 38,665 individuals used a cut-off point of 6 mm to 5 TU of PPD.<sup>14</sup>

The incidence of infection with *M. tuberculosis* in Sweden was so low that routine vaccination with BCG is no longer practiced. In

that country an induration of 6 mm or more was considered as the cut-off point.<sup>15</sup> Great differences in the prevalence of non-specific reactions was demonstrated between coastal urban and inland rural areas.<sup>16</sup> A larger proportion of the studied school children reacted to *M. scrofulaceum* (32%) than to *M. avium* (25%) in the urban area while the corresponding figures for the rural area were 13.9% and 9.7%. Even with this moderate rate of reactions to MOTT in the urban area the cut-off point to PPD was kept at 6 mm.

In Singapore, where BCG coverage for children is 100%, the results of tuberculin testing with the usual 1 TU PPD adopted in that country are interpreted with a "special consideration".<sup>17</sup> An induration of 8 mm or more was considered as positive.

#### **10 mm or more:**

In a study from Kuwait 260 persons were Mantoux tested with 5 TU. A 10 mm induration was considered as a positive reaction while less than 5 mm was negative.<sup>18</sup> Another report from the same country used 2 TU and children with a reaction of less than 10 mm induration were revaccinated.<sup>19</sup> Presumably this was considered a negative reaction and an indication of lack of immunity. Prevalence of MOTT did not appear in the two reports.

Fox and Lepow<sup>20</sup> assessed the tuberculin reaction in 14 Vietnamese children with a history of BCG vaccination and compared them with 36 unvaccinated children of a similar age group. Five TU were used and a 10 mm reaction or more was the cutting point. Mantoux reactions in BCG-vaccinated healthy children are usually weak, but the authors stated no reason for a joint cutting point. A recent study of 741 male and female Vietnamese refugees in the Philippines determined the prevalence of tuberculosis by an induration of 10 mm or more to 5 TU PPD.<sup>21</sup>

To study the prevalence of tuberculosis infection among Afghan refugees' children in

Pakistan a cluster sample of 4108 males was investigated.<sup>22</sup> A cut-off point of 10 mm induration gave a prevalence rate of 13.8%. Another report from Pakistan on 181 patients with tuberculosis and Mantoux tested with 1 TU did not specify a cutting point but rather divided the reactions into 0 - 4, 5 - 9, 10 - 14, 15 - 19, 20 - 24, and 25 - 30 mm of induration.<sup>23</sup> However, the authors found the Mantoux test useful as a diagnostic aid as well as for epidemiologic purposes.

In a report involving the use of 5 TU PPD in 370 children, Hsu considered an induration of more than 10 mm as indicative of infection by *M. tuberculosis*.<sup>24</sup>

More than 600 Indochinese refugees were screened by Morse and associates in Monroe County, NY, using 5 TU PPD.<sup>25</sup> Mexican Americans in San Antonio, Texas, with and without tuberculosis were also skin tested by Cox and colleagues with the same dose of PPD.<sup>26</sup> In both studies only reactions of 10 mm or more were considered as positive. However, the American Thoracic Society (ATS) recently recommended a different cutting point depending on specific risk factors.<sup>27</sup>

Two studies from Chile involving in the first a group of 40 six-years-old children<sup>28</sup> and in the second 208 first-year medical, nursing and medical technology students<sup>29</sup>, recorded the reaction as positive when it was 10 mm or more. The authors of the latter study mentioned that infection by MOTT was not the cause of the positive reactions since the students were city dwellers, and as such not exposed to MOTT, the prevalence of which was not cited in their paper.

#### **SAUDI LITERATURE**

The available literature relevant to the subject in the KSA was also found to have this controversy. In this country a large sector of the adult population is unvaccinated with BCG. However, BCG together with DPT, polio., hepatitis B, and measles vaccines are compulsory

before a birth certificate can be issued.

There is a rapid overall decline of all communicable diseases in the KSA, and PTB is no exception; thanks to the Ministry of Health (M O H) for its concerted efforts in this regard.<sup>5</sup> According to reports from within and outside this country the rate (incidence) of new reported cases of tuberculosis dropped from 327 (all forms) per 100,000 population in 1976/77<sup>30</sup> to 243(PTB)/100,000 population in the year 1398H (1978G) and 38(PTB)/100,000 population in 1406H (1986 G).<sup>5</sup> From 1987 to 1992 the rate of PTB decreased from 30.5 to 14.7/100,000 population.<sup>31</sup> However, there is a discrepancy in the number of reported cases for the three years' period 1986-1988 between the 1408H and the 1412/1413H annual health reports. The rate for the year 1408H (1988G) appeared as 78.5/100,000 population in the 1408H report<sup>32</sup>, while it was 23.8 in the 1412/1413H report.<sup>31</sup> We believe that this might be a misprint since the figures for the years 1980 to 1985 were similar in the two reports.

According to Froude and Kingston<sup>33</sup>, tuberculosis in Saudi Arabia is the most important communicable disease. In their well designed nationwide community based study, Al-Kassimi and associates reported the prevalence rate of a positive reaction in unvaccinated children (5-14 years old) as 6.0%  $\pm$  1.8, thus categorizing the KSA among the middle prevalence countries.<sup>34</sup>

In addition to vaccination at birth there are extensive efforts to reduce the incidence to the minimum, and particular attention is being paid to expatriates arriving from high prevalence areas.

#### **CUT-OFF POINT OF: 5 mm.**

Rowlands surveyed a Saudi military school population to determine the prevalence of tuberculin sensitivity in that population.<sup>35</sup> The Tine test was used, and the Mantoux (1 TU and

re-tested with 10 TU) was a confirmatory test. An induration of 5 mm or more was the cutting point.

#### **10mm or more:**

Froude and Kingston<sup>33</sup> reviewed 162 patients with extra-pulmonary tuberculosis and they considered an induration of 10 mm following 5 TU PPD as the lower limit for a positive reaction. Another group of investigators<sup>36,37</sup>, reporting the results of an epidemiologic community-based survey of Mantoux testing, classified the reactions in response to 5 TU of PPD into positive (10 mm or more), intermediate (5 - 9 mm), and negative (0 - 4 mm). The significance of the intermediate reaction was not indicated. The unvaccinated subjects in the first study gave an overall positive rate of 19.0% with a peak (58.0%) in the age group 65 years and above (mostly males) while the 5 - 14 year age group had a rate of 4.0%.<sup>36</sup> In the second study the unvaccinated Saudi children aged 5 - 14 years had a reactivity rate of 2.7% (4 out of 150) which was much less than that for the corresponding age group among the Non-Saudis (10.5%, 2 out of 19).<sup>37</sup>

In a report cited earlier the rate among the former age group (65 years and above) in the Kingdom (all nationalities) was 55.0%  $\pm$  6.6 and in the latter (5-14 years) 6%  $\pm$  1.8.<sup>34</sup> The rate for Saudi children among this age group was 4.5%, and 54% for the age group 45-64.

Teklu and Al-Wabel investigated the tuberculin reactivity in 75 Saudi and Yemeni patients admitted to a chest hospital.<sup>38</sup> Their cut-off level was 10 mm; and 17.3% of the patients had indurations less than this.

Personal contacts with some hospitals in the Kingdom revealed no consistent policy; some used the 5 mm criterion others 10 mm as the lower limit with 0 - 4 mm as negative and 5 - 9 mm doubtful.

#### **UNSPECIFIED CUTTING POINT:**

Al-Hajjaj and colleagues reviewed

retrospectively 1,566 medical records of patients with pulmonary tuberculosis. Subjects with negative sputum results were considered to have the disease if they had typical clinical and roentgenographic findings in addition to a "positive tuberculin test" and a good response to chemotherapy.<sup>39</sup> Unfortunately, the authors did not qualify this positive tuberculin test and the dose of the tuberculin was not mentioned.

In another retrospective review of 47 Saudis with different forms of tuberculosis the tuberculin test was not mentioned as one of the diagnostic tools.<sup>40</sup> In that report the peak prevalence was in the age group 20 - 59 years. Similarly, Al-Sulaimani<sup>41</sup> in his case report of tuberculous pyloric stenosis with a negative "tuberculin test" specified neither the technique and dose of PPD nor did he explain what constituted a positive/negative result.

#### **REFERENCE AND TEXTBOOKS OF MEDICINE:**

The books of medicine available in our medical libraries also have this kind of disagreement.

##### **5 mm:**

Two books<sup>42-43</sup> recommended a 5 mm or more as a positive result. Both were published in the United Kingdom (U.K.)

##### **10 mm:**

The dates of publications of the books recommending this limit ranged from 1976 to 1990<sup>12, 44-50</sup> and all recommended 10 mm as the cutting point, except one<sup>12</sup> where the cutting point was more than 10 mm. This latter reference book was published in 1987 in the U.K. This limit is not in agreement with the two others mentioned above, one published in 1984<sup>42</sup> and the other<sup>43</sup> in 1987. However, most if not all of these books were published before the last ATS recommendations.<sup>27</sup>

Unfortunately, the latest editions of these books are not available to the author.

#### **DISCUSSION:**

The Kingdom of Saudi Arabia has adopted Primary Health Care (PHC) as a means of delivering efficient health services to the population. PHC physicians must have a role in the diagnosis and management of tuberculosis if we are to reduce the burden on secondary health care facilities. It is imperative that standard diagnostic and treatment protocols be developed and adopted, and a cut-off point for the Mantoux test needs to be defined. The size of a positive induration following the Mantoux technique requires careful consideration in areas where the exact prevalence of MOTT is unknown.

The Prevalence of MOTT in the KSA was reported to be 3.8/1000 population (29 positive sputum and saliva specimens obtained from 7721 subjects<sup>34</sup>), which was, according to the authors, lower than the rates reported from other countries. The authors attributed this low rate to the prevailing type of climate in the country. In a recent report of a pilot study in Urban and Rural Gizan, KSA, sensitivity to MOTT was demonstrated among children aged 6-12 years but no exact figures were quoted for the area.<sup>51</sup>

In countries with little or no cross-reactions the distribution of the size of the tuberculin reaction is bimodal, with a high proportion of the population having small reactions.<sup>1</sup> It follows that a cutting point anywhere between 3 and 10 mm, in unvaccinated populations, would very well distinguish between the two groups (infected and uninfected) with few patients being misclassified.<sup>1</sup> Others recommended between 5 and 10 mm.<sup>52</sup>

On the other hand, when tuberculosis is less than non-tuberculous mycobacterial infections a cutting point of 10 mm is considered more reasonable.<sup>1,9</sup> Referring to the rates quoted from Al-Kassimi et al<sup>34</sup> it is apparent that the prevalence of MOTT was lower than for M. tuberculosis as judged by the Mantoux reaction in unvaccinated children and adults.

The prevalence of MOTT was 80% in some parts of Asia and India while it was less than 10.0% in Denmark and North America, and less than 30.0% in England.<sup>12</sup> About 10% of tuberculosis in the South-Eastern USA was due to infection by *M. avium-intracellulare* group while in England and Wales, the rate was much less (about 1.5%).

The ATS<sup>27</sup> recent recommendations for the diagnosis of tuberculosis are primarily meant for the USA, but they can certainly be applied to developing countries. However, the recommendation for the general classification of the tuberculin reaction cannot be accepted without reservations, so long as the prevalence of cross-reactions in Saudi Arabia remains low. The cutting point of 5 mm certainly applies to (a) the symptom group (b) the close contacts of patients known to have open pulmonary tuberculosis and (c) those with HIV infection or who are immunocompromised. But for the other groups in this country, Saudis and non-Saudis alike, a cutting point of 10 mm might well misclassify tuberculosis patients with indurations less than this as non-tuberculous if the prevalence of MOTT turns out to be low in the country of origin of the expatriate as it is now in Saudi Arabia.

There is no reason, so far, to believe that the distribution of *M. tuberculosis* (MT) follows directly or indirectly the distribution of MOTT. It follows that the distribution of these mycobacteria in any one country or region will be one of the following four possibilities (disregarding the moderate levels).

1. High MT, high MOTT
2. High MT, low MOTT
3. Low MT, low MOTT
4. Low MT, high MOTT

Since it might be risky to miss a patient with PTB particularly if infectious, it would be better to have a cutting point of 5 mm for countries having the first and second possibilities, 8 mm for the third, and 10 mm for the fourth.

In countries where the extent of cross-reactions remains to be determined, a cutting point of 5 mm would be appropriate. For Saudi Arabia it is, therefore, suggested to have 5 mm as a cutting point in all patients particularly in the case of PTB contacts, HIV positives, and those with symptoms compatible with PTB. If in the future the prevalence of environmental mycobacterial infection proved to be much higher than the reported rate of 3.8 per thousand<sup>34</sup>, then this limit can be raised to 8 mm provided that the prevalence of PTB becomes lower than the current rate reported by Al-Kassimi et al.<sup>34</sup> But the 5 mm cutting point should remain for the aforementioned categories of patients.

Dual testing with sensitins (prepared from MOTT) and tuberculin is, according to some researchers, neither practicable nor of value as a diagnostic tool especially in areas where the prevalence of cross-reactions might be high.<sup>53</sup> However, others did find the contrary, particularly when the reaction to sensitin is larger by 4 or 5 mm which indicates an infection by MOTT.<sup>16</sup>

In conclusion, it seems that the current practice in most hospitals in Saudi Arabia of having an induration of 10 mm or more as signifying a positive (specific reaction) needs to be reviewed in the light of the evidence regarding the low prevalence of MOTT and that the Kingdom is considered among the middle prevalence countries for PTB. An induration of 5 mm following 5 TU PPD is recommended if we are to avoid the probability of misclassifying patients with tuberculosis as non-tuberculous. A nationwide survey to determine the magnitude of non-specific reactions due to MOTT using sensitins has much to commend it.

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