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Research Article

Prevalence of Latent *Mycobacterium tuberculosis* among School Children in Lebanon

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Abstract

Aim: This study aimed to determine the prevalence of LTBI among Lebanese healthy school children and to compare the result with a previous study done in Lebanon in 2004 which showed a prevalence of 7.5%.

Methods: A self-administered questionnaire, including demographic characteristics, time of prior Bacillus Calmette-Guérin (BCG) vaccine, known household contact with tuberculosis as well as parents' characteristics and living conditions were administered. Purified protein derivative (PPD) testing was performed on selected school children aged between 3 and 19 years of age. Schools were selected from 4 Governorates of Lebanon (Beirut, Bekaa, South and North). We measured PPD reactivity. LTBI cases were defined by positive PPD test. Chest radiographs were obtained as part of the evaluation for children with positive PPD.

Results: Of the 5858 distributed questionnaires, 2805 school children entered into our final data analysis. 2688 (95.8%) had negative PPD test, and 117 (4.2%) had positive PPD test. None of the participants demonstrated TB-related abnormality on Chest X-ray. The highest prevalence was in Bekaa (4.9%) followed by Beirut (4.6%), South (4.3%), then North (1.9%) (P = 0.033). The prevalence of LTBI was higher among non-Lebanese population (P = 0.007). Of 33% of children who were BCG vaccinated, 4.3% had positive PPD test, and from the remaining 67% who were non-BCG vaccinated children, 4% had positive PPD test, with no statistically significant P-value (P = 0.443).

Conclusion: Our prevalence of LTBI among school children is 4.2% which indicates a decrease in the prevalence in our country over the last 10 years. This data support the recommendation to screen for tuberculosis even for vaccinated children to reach the WHO End TB Strategy by 2030.

Keywords: *Latent Tuberculosis; PPD; BCG; Induration*

Introduction

Mycobacterium tuberculosis (MTB) is still currently one of the leading causes of death worldwide with 1.5 million deaths in 2014 and 1.4 million in 2015, making it as lethal as HIV as a major cause of death (1.2 million death) [1]. Initial infection with MTB leads to Latent Tuberculosis Infection LTBI in 95% of the time. These patients, if left untreated, have a 5 - 10% for reactivating their MTB infection with pulmonary or extra pulmonary manifestations [2]. An important strategy to reduce the transmission is the early identification of LTBI to prevent its progression to active disease [3]. In the year 2014, *Mycobacterium tuberculosis* has claimed the life of 140,000 children and remains of the top 10 causes of death amongst children worldwide [4]. The diagnosis of TB is more difficult to diagnose in children due

to non-specific or complete absence of symptoms and difficulty in confirming the diagnosis microbiologically with children suffering more from extra pulmonary and disseminated disease than adults [5]. Pediatric tuberculosis is a public health concern not only because children suffer worse outcomes but because it is also a marker of recent transmission (CDC). In 2004, Sleiman., *et al.* reported the first epidemiological data for the prevalence of tuberculosis among school age children in Lebanon reporting a prevalence of 280 per 100,000 for active tuberculosis and a 7.5% prevalence of LTBI [6]. Since 2011, Lebanon's neighbor Syria has been suffering from civil war causing massive internal and external population displacements giving rise to the worse refugee crisis in the 21st century [7]. With the loss of a structured healthcare system, TB monitoring instance poses a huge concern in terms of disease monitoring and emergence of drug resistance in case of forceful discontinuation of medication. This mixing of the two populations raises concerns for MTB infection control given the increased risk of infection in the displaced population [8].

Objective of the Study

Our objective was to conduct a study to determine the prevalence of LTBI among Lebanese healthy school children and to compare the result with a previous study done in Lebanon in 2007 which showed a prevalence of 7.5%.

Materials and Methods

After we obtained approval from the Makassed General Hospital Institutional Review Board, a population based cross sectional study was conducted during a 9-month period between June 2016 till February 2017. It included children with dissimilar levels (primary, intermediate, and secondary), aged between 3 and 19 years. It covered four governorates of Lebanon (South, North, Beirut, Bekaa), with wide range of socioeconomic status and demographic characteristics.

We excluded children who did not complete the questionnaires, did not sign the consent, data of participants whose skin induration diameter was not measured between 48 - 72 hours, had chronic disease or on immunosuppressive medication, those with previous or current TB or with a previous severe reaction to TST did not have a TST performed, in order to prevent severe allergic reactions.

The study was divided into two phases:

- Phase 1 started from first of June till end of September, during this period we arranged meeting in the schools included in our study, to explain the concept of the study to the parents. Consents were distributed. Signed informed consent was obtained from parents for eligible children aged 3 to 16 years and from both parents as well as participants aged 16 years and above. Those who signed the consent were included in the study and then questionnaires were distributed. It included name, gender, age, nationality, demographic characteristics, medical history pertaining to signs and symptoms of TB disease, smoking habit, history of household contact with a TB patient, exposure to anyone with TB disease, close contact with a person with positive skin test, traveling history, presence of servant at home from endemic area. The self-administered questionnaire was completed by all participants' parents.

- Phase 2 started from first October till end of February. After collecting the questionnaires, a study team consisted of 3 pediatric physicians visited these schools and performed a full physical examination including height, weight, oral temperature, presence of BCG scar, examination of oral cavity, cervical lymph nodes, chest and heart auscultation.

Purified protein derivative (PPD) test was performed using 10 IU (Pasteur Merieux, Paris, France) equivalent to 5 units of PPD-S that served as the standard material in the United States. Insulin syringes (0.3 x 8 mm) were used for intradermal injection. The PPD test was performed at the flexor surface of the left forearm with the needle bevel pointing upward. Evaluation of the technique was done by one of the study group who considered a raised area at the injection site (a 6- to 10-mm wheal) as a marker of good technique. The test was repeated immediately in the other forearm if no wheal was formed or if a wheal was less than 6 mm. After 48 to 72 hours, schools were

visited again by the same study team, the transverse diameter of the induration was demarcated with ballpoint pen technique, measured and recorded in millimeters.

Induration size of the tuberculin test was interpreted as follows:

- An induration of 5 or more millimeters is considered positive in: HIV-infected persons, a recent contact of a person with TB disease, persons with fibrotic changes on chest radiograph consistent with prior TB, patients with organ transplants, persons who are immunosuppressed for other reasons (e.g. taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists).

- An induration of 10 or more millimeters is considered positive in: Recent immigrants (< 5 years) from high-prevalence countries, injection drug users, residents and employees of high-risk congregate settings, mycobacteriology laboratory personnel, persons with clinical conditions that place them at high risk, children < 4 years of age, Infants, children, and adolescents exposed to adults in high-risk categories.

- An induration of 15 or more millimeters is considered positive in any person, including persons with no known risk factors for TB [9].

Chest radiographs were obtained as part of the evaluation for children with a positive skin test. Pulmonary TB was defined as a positive PPD with the presence of compatible findings on chest radiography. Criteria of radiologic TB were hilar adenopathy, hilar calcification, primary complex, pleural calcified plaques, granuloma and cavity. LTBI was defined as MTB infection in a person who has positive PPD result, no physical findings of disease and normal chest radiograph [9].

Statistical analysis

The Statistical Package for Social Sciences (SPSS, version 21) program will be used for data entry, management, and analyses. A p-value of < 0.05 will be used to indicate statistical significance.

Categorical variables will be presented as number and percent. Bivariate analysis will be carried out by using the chi square for comparing categorical variable.

Results

Enrolment of participants

A total of 5858 questionnaires were distributed for this survey and 2805 children were entered into the final data analysis with response rate 48%. Reasons for excluding children are shown in figure 1.

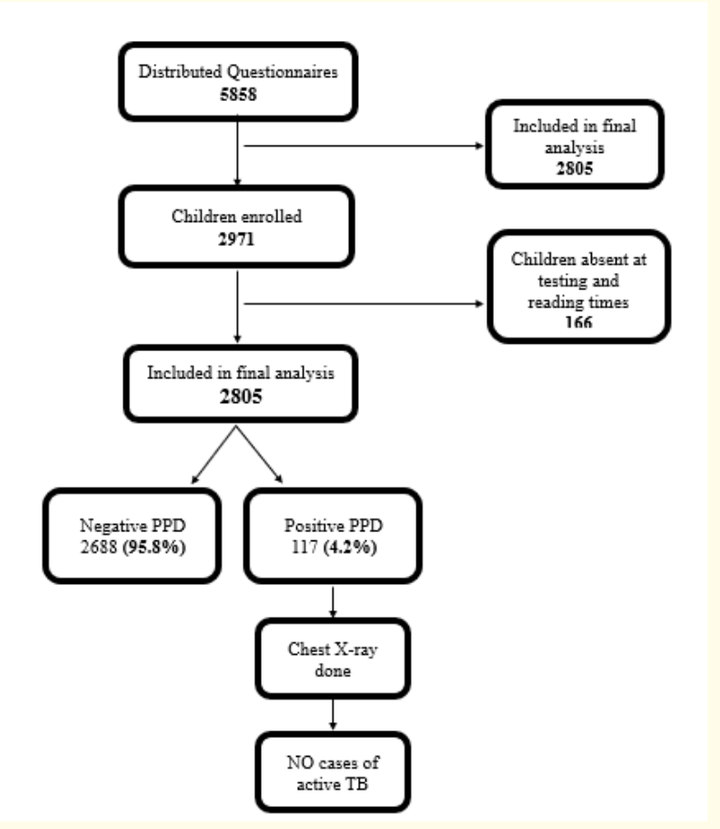

Figure 1: *Flow chart of PPD reactivity.*

Characteristics of participants

As shown in table 1, 410 children (15.4%) were below 5 years, and 2254 (84.6%) were above 5 years. 1416 (50.5%) out of 2805 children included were males and 1389 (49.5%) were females. 865 children (31%) were from Bekaa, 560 (20%) from North, 228 (8%) from South, and 1152 (41%) from Beirut. 2236 (80%) of children were Lebanese, and the remaining 531 (20%) were non-Lebanese. The mothers were illiterate in 194 (7%) of children and the fathers were illiterate in around same frequency 174 (6.3%). Concerning the housing conditions, 967 children (35%) lived in 3 rooms or less, and 1794 children (65%) lived in more than 3 rooms. 1979 (71%) did not share bed while 806 (29%) share beds. All the children were students from diverse schools. 2494 children (89.2%) lived in sun exposure house and the remaining 303 (10.8%) lived in house not exposed to Sun. 2596 children (93%) lived in non-aerated house and only 201 (7.2%) lived in aerated. 2633 (94%) did not have foreign worker while only 164 (6%) did have. The most frequently reported monthly family income was above 675,000 LL (1768: 65.7%).

			PPD		
Characteristics		**Total N = 2805**	**Positive N = 117**	**Negative N=2688**	**P-Value**
Age	≤ 5 years	410 (15.4%)	10 (9.7%)	400 (15.6%)	0.1
	> 5 years	2254 (84.6%)	93 (90.3%)	2161 (84.4%)	
Gender	Male	1416 (50.5%)	57 (48.7%)	1359 (50.6%)	0.697
	Female	1389 (49.5%)	60 (51.3%)	1329 (49.4%)	
Nationality	Non-Lebanese	531 (19.2%)	33 (28.9%)	498 (18.8%)	0.007
	Lebanese	2236 (80.8%)	81 (71.1%)	2155 (81.2%)	
Mother Illiterate	Yes	194 (7.0%)	5 (4.3%)	189 (7.1%)	0.251
Father Illiterate	Yes	174 (6.3%)	4 (3.4%)	170 (6.4%)	0.202
Monthly income	≤ 675,000 L.L	925 (34.3%)	32 (29.6%)	893 (34.5%)	0.292
	> 675,000 L.L	1768 (65.7%)	76 (70.4%)	1692 (65.5%)	
House not exposed to sun	Yes	303 (10.8%)	13 (11.2%)	290 (10.8%)	0.895
TB Infected Housemate	Yes	31 (1.1%)	2 (1.7%)	29 (1.1%)	0.372
Housemaid	Yes	164 (5.9%)	6 (5.9%)	158 (5.9%)	0.816
Exposure to Smoking	Yes	781 (28.1%)	31 (27.4%)	750 (28.1%)	0.879
History of travel	Yes	431 (17.3%)	19 (20.9%)	412 (17.2%)	0.362
Time of last BCG dose	< 1 year	174 (21.5%)	8 (22.2%)	166 (21.4%)	0.108
	1 - 5 years	373 (46.0%)	11 (30.6%)	362 (46.7%)	
	> 5 years	264 (32.6%)	17 (47.2%)	247 (31.9%)	

Table 1: *Demographic characteristics of studied population.*

Prevalence of latent TB infection

The overall prevalence of LTBI was 4.2% using the PPD as a screening tool (Figure 1).

The distribution of positive PPD reactivity of all tested school children was significantly different between Lebanese districts with the highest prevalence in Bekaa 43 children (4.9%) followed by Beirut 53 children (4.6%), South 10 children (4.3%), then North 11 children (1.9%) (P = 0.033) (Table 2).

Region	Number of children tested (%)	Frequency of positive PPD	Frequency of negative PPD
Bekaa	865 (30.8%)	43 (36.8%)	822 (30.6%)
North	560 (20.0%)	11 (9.4%)	549 (20.4%)
South	228 (8.1%)	10 (8.5%)	218 (8.1%)
Beirut	1152 (41.1%)	53 (45.3%)	1099 (40.9%)

Table 2: *Prevalence of PPD reactivity among Lebanese districts.*

The prevalence of LTBI was higher among non-Lebanese population versus Lebanese (P = 0.007).

None of the studied factors (gender, age, parents' education, smoking, number of rooms, aerated house, TB infected housemate, foreign worker and traveling history, time of last BCG vaccine and PPD reactivity, monthly family income) had any associations with positive test results.

PPD reactivity according to BCG vaccination status

931 children (33%) were BCG vaccinated: 891 of vaccinated children (95.7%) had negative PPD test and 40 of them (4.3%) had positive test. 1874 children (67%) were not BCG vaccinated: 1797 of non-vaccinated children (95.8%) had negative PPD test and 77 of them (4.2%) had positive test (P = 0.443) (Figure 2).

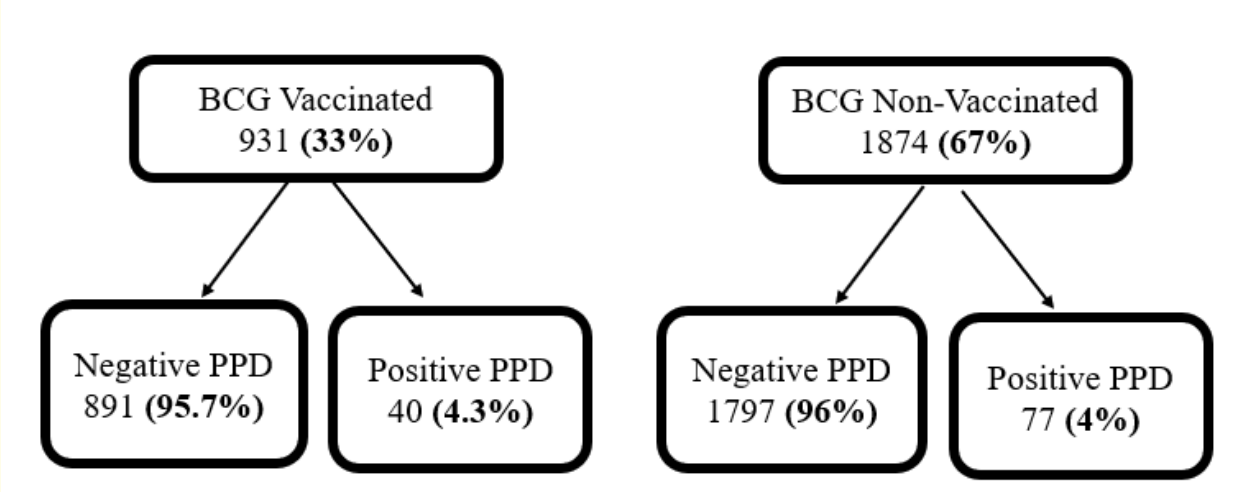

Figure 2: *Positive PPD reactivity among vaccinated and non-vaccinated children.*

Positive PPD reactivity among vaccinated and non-vaccinated children

There was no difference in millimeter of induration among both vaccinated and non-vaccinated groups (P = 0.101) (Figure 3).

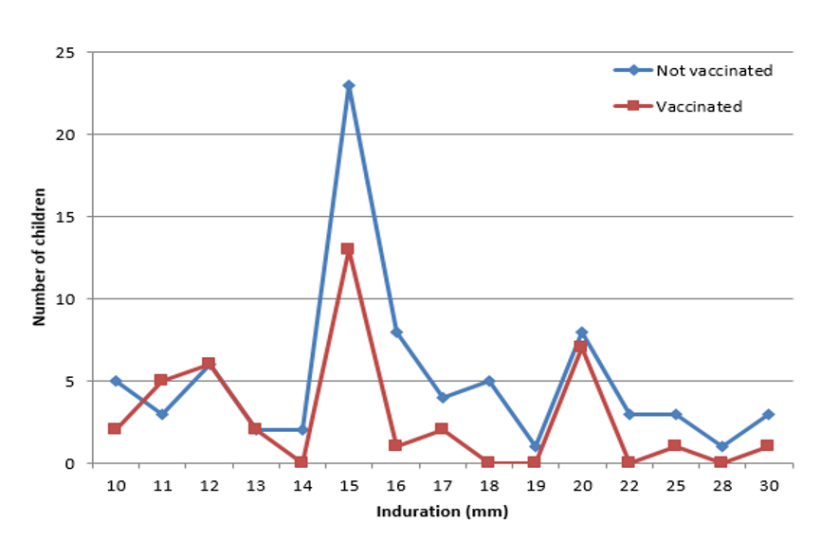

Figure 3: *PPD reactivity among vaccinated and non-vaccinated children.*

Discussion

Knowledge of LTBI among children is essential in understanding the long-term trend of TB. It remains a key indicator in reflecting the severity of TB transmission in population [10].

There have been Worldwide studies of LTBI in school-aged children with different rate: Gopi., *et al.* (2006, India) with 7.8%, Sleiman., *et al.* (2004, Lebanon) with 7.5%, Garcia-Sancho., *et al.* (2006, Mexico) with 12.4%, Serane., *et al.* (2001, India) with 18.6%, and Escobar., *et al.* (2004, Brazil) with 32%.

The present study detected a low positive rate of LTBI in school-aged children of 4.2%, which is closest to that found in the Gholam Sefidgaran., *et al.* (2006, Iran) with a rate of 2.2% [11].

Regarding the prevalence of TB among children in Lebanon, Araj., *et al.* (2016) reported decreased prevalence from 10.8% to 5.2% of all TB cases (1999 - 2011) [12]. however regarding the prevalence of LTBI among school children, Sleiman., *et al.* (2004) was the first effort in a nationwide representation of its study sample [6]. Our study which protocol mimics that of the aforementioned study shows a rate of LTBI of 4.2% using the PPD test as a screening tool.

This decrease of prevalence of LTBI over the last years may indicate more awareness of using PPD which leads to early detection and treatment of latent TB cases, in addition to the lower circulation rate of the bacteria and better infection control measure from the Health Department over the last 10 years, and the big effort from the Ministry Of Public Health in Lebanon to allow the medications more available and more easy to be delivered, and through mixing the anti-TB drug in a pill we may find more compliance to the treatment [3].

The distribution of positive PPD reactivity of all tested school children was significantly different between Lebanese districts with the highest prevalence in Bekaa (4.9%) followed by Beirut (4.6%) (P = 0.033) (Table 1), in contrast to the study of Sleiman., *et al.* which showed the high prevalence in Beirut (13.3%). This may be contributed to the increased crowdedness due to external displacement in Bekaa. Table 1 also shows children diagnosed with LTBI among Lebanese districts.

The prevalence of LTBI was higher in non-Lebanese population compared to the Lebanese-population (P = 0.007), so as reported by World Health Organization report 2015 [13].

TB has long been thought to be associated with overcrowding and poverty in communities, and several studies worldwide in children support this [14].

Not only is poverty associated with increased risk of a child being exposed to TB, it also influences the risk of becoming infected and also of then developing disease [15].

In this study, the monthly family income did not affect the PDD reactivity result consistent with Sleiman., *et al.* study [6].

The age of the child will influence their risk of TB exposure. Older children are more at risk due to the risk of exposure to infectious cases of TB in the community however younger children interact with fewer adults, and generally come into contact with adults only in their family units [15]. In this survey, no significant difference between age group.

The disease occurs in males more frequently than in females. This observation has also been noted in previous studies in Lebanon and in several Arab countries.

This great difference in the ratio of male to female patients could be partly explained by multiple factors such as: biological factors (occurrence of symptoms, severity of disease); health care system factors (availability of health care service, accessibility of service, quality of service); and socio-economic and cultural factors (poverty, social stigma, isolation, cultural behavior and belief) [16]. In this survey, there was no difference in gender.

Previous studies emerged showed a conflicting results on tuberculin sensitivity patterns among BCG-vaccinated children [17-20].

Many studies in other countries have demonstrated the usefulness of the TST for screening for TB infection regardless of BCG status [21-23]. There is persistent reluctance, however, to agree that BCG vaccination induces sensitivity to tuberculin that might interfere with interpretation of TST results [6,24,25]. The present study showed that more than 95% of BCG vaccinated children had no reaction to the PPD test.

Sleiman., *et al.* (2004, Lebanon) and Gholam., *et al.* (2006, Iran) reported no reaction to PPD with a rate of 72.7% and 82% respectively [11].

This may indicate that PPD positivity in the school children was related to natural infection rather than previous vaccination.

Based on our survey findings, PPD test is a useful test to identify children infected with TB independently of whether or not they had received BCG. These results are consistent with the conclusion of Sleiman., *et al.* which showed that BCG vaccination does not confound the interpretation of PPD (Figure 3).

Strengths and Limitations

The strengths of this study were the relatively large number of the study participants. The inclusion of the main four geographic governorates of Lebanon. The use of clinical history coupled with radiological investigation to exclude active TB among participants.

There are several limitations to this study as we did not use Interferon Gamma Release Assay and we were unable to differentiate and exclude positive TST reactions due to non- tuberculous *Mycobacterium* infection, so this can lead to the increase prevalence rate of LTBI. Also we did not test the HIV status for our population because as we know HIV infection can attenuate the cell mediated immune reaction so can lead to false negative.

It was a cross sectional design, so we were not able to detect causal relationship with risk factors. This study included selected Makassed School Children so the current findings should be generalized cautiously to the other population in Lebanon. We did not measure the Population-based annual risk of TB infection (ARTI) in our population so we could not estimate the change in TB transmission in our population.

Conclusion

Our prevalence of LTBI is 4.2% which indicate a decrease in the prevalence in our country over the last 10 years. Routine diagnosis for LTBI is crucial intervention for TB disease control in our country. PPD test is a valuable diagnostic test for latent TB screening in childhood. BCG vaccination has no remarkable effect on the interpretation of PPD reactivity.

Future studies are needed to study TB genetics in well-defined pediatric populations and to characterize the strain differences in pathogenicity and induction of immune responses in children.

Our data support the recommendation to screen for tuberculosis even for vaccinated children to reach the goal to end TB by 2030 which is part of the UN Sustainable Development Goals and the WHO End TB Strategy.

Bibliography

1. WHO. Global tuberculosis report (2016).
2. Powell DA and Hunt WG. "Tuberculosis in children: an update". *Advances in Pediatrics*. 53 (2006): 279-322.
3. Lebanese Ministry of Public Health. "National Guidelines for Tuberculosis Prevention, Care and Elimination in Lebanon National TB Program– 2017".
4. S Swaminathan S and Rekha B. "Pediatric tuberculosis: global overview and challenges". *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 50.3 (2010): S184-194.
5. Loeffler AM. "Pediatric tuberculosis". *Seminars in Respiratory Infections* 18.4 (2003): 272-291.
6. Sleiman R., *et al*. "Interpretation of the tuberculin skin test in bacille Calmette-Guerin vaccinated and nonvaccinated school children". *The Pediatric Infectious Disease Journal* 26.2 (2007): 134-138.
7. United Nations High Commissioner for Refugees: Syria regional refugee response (2014).
8. Cookson ST., *et al*. "Impact of and response to increased tuberculosis prevalence among Syrian refugees compared with Jordanian tuberculosis prevalence: case study of a tuberculosis public health strategy". *Conflict and health* 9 (2015): 18.
9. Red book 30th edition. Mycobacterium Tuberculosis (2015).
10. Hu Y., *et al*. "Prevalence of latent tuberculosis infection and its risk factors in schoolchildren and adolescents in Shanghai, China". *European Journal Of Public Health* 23.6 (2013): 1064-1069.
11. Alavi SM and Sefidgaran GH. "Tuberculin survey among school-aged children in Ahvaz, Iran, 2006". *International Journal of Infectious Diseases: IJID: official publication of the International Society for Infectious Diseases* 12.4 (2008): 406-409.
12. Araj GF., *et al*. "Tuberculosis Burden in Lebanon: Evolution and Current Status". *Le Journal medical libanais The Lebanese Medical Journal* 64.1 (2016): 1-7.

13. WHO. Global tuberculosis report (2015).

14. Walls T and Shingadia D. "Global epidemiology of paediatric tuberculosis". *The Journal of Infection* 48.1 (2004): 13-22.

15. Seddon JA and Shingadia D. "Epidemiology and disease burden of tuberculosis in children: a global perspective". *Infection and Drug Resistance* 7 (2014): 153-165.

16. Diwan VK and Thorson A. "Sex, gender, and tuberculosis". *Lancet* 353 (1999): 1000-1001.

17. Wang L., *et al*. "A meta-analysis of the effect of Bacille Calmette Guerin vaccination on tuberculin skin test measurements". *Thorax* 57.9 (2002): 804-809.

18. Chee CB., *et al*. "Interpretation of the tuberculin skin test in Mycobacterium bovis BCG-vaccinated Singaporean schoolchildren". *American Journal of Respiratory and Critical Care Medicine* 164.6 (2001): 958-961.

19. Almeida LM., *et al*. "Use of purified protein derivative to assess the risk of infection in children in close contact with adults with tuberculosis in a population with high Calmette-Guerin bacillus coverage". *The Pediatric Infectious Disease Journal* 20.11 (2001): 1061-1065.

20. Gounder CR., *et al*. "Tuberculin testing and risk of tuberculosis infection among New York City schoolchildren". *Pediatrics* 111.4 (2003): e309-e315.

21. Raharimanga V., *et al*. "Tuberculin reactivity in first-year schoolchildren in Madagascar". *Tropical Medicine and International Health* 17.7 (2012): 871-876.

22. Gulnar SB and Bulut BU. "Influence of BCG vaccination on tuberculin reactivity in healthy Turkish school children". *Acta Paediatrica* 86.5 (1997): 549.

23. Mudido PM., *et al*. "The effect of bacille Calmette-Guerin vaccination at birth on tuberculin skin test reactivity in Ugandan children". *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease* 3.10 (1999): 891-895.

24. Lohiya GS., *et al*. "Interpretation of the tuberculin skin test". *Journal of the National Medical Association*. 101.3 (2009): 282-283.

25. Kiwanuka JP. "Interpretation of tuberculin skin-test results in the diagnosis of tuberculosis in children". *African Health Sciences* 5.2 (2005): 152-156.

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