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Research Article

Comparative Sensitivity of the Test With Tuberculosis Recombinant Allergen and Tuberculin Skin Test in Children and Adolescents with Newly Diagnosed Tuberculosis

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A B S T R A C T

Background: This article emphasizes the importance of detecting latent tuberculosis infection in children aged 17 years or younger. This study examined the effectiveness of two contemporary diagnostic methods: the traditional Mantoux tuberculin skin test (TST) using 2 TE of PPD-L and a test that utilizes recombinant TB allergen (ATR).

Materials and Methods: The sensitivity of ATR and TST with 2 TE of PPD-L was compared in family medicine centers in the Bishkek and Chui regions for children and adolescents aged 1-17 years. A total of 4,899 tests were conducted in these areas.

Results: The infiltrate measurement for 43.4% of the children fell within the range of 5-14 mm, and 47.2% had at least 15 mm when using 2 TE of PPD-L for TST. Among the 3581 children aged 7-14 years, 2371 (66.2%) tested negative, 1210 (33.8%) tested positive, and 558 (46.1%) showed hyperergic reactions. In comparing TST and ATR tests for adolescents, 11 (11.0%) cases showed positive reactions to both, 4 (7.8%) had hyperergic reactions, and 419 (76.9%) tested negative.

Conclusions: ATR was more effective than TST with 2 TE PPD-L in eliminating post-vaccinal allergies in children under 6 years of age for the diagnosis of latent tuberculosis infection (8 times more often; 78.3% vs. 9.4%, p < 0.05).

Keywords: Tuberculosis, Mantoux Tuberculin Skin Test, Recombinant TB Allergen, ESAT-6 Protein, CFP-10 Protein

Introduction

According to the World Health Organization estimates, around 10.6 million people, including 1.3 million children, were diagnosed with tuberculosis (TB) globally in 2022.[1] TB is a major cause of disease and death in people worldwide. Extrapulmonary TB is a condition that can be caused by Mycobacterium tuberculosis (MTB), which predominantly causes TB in the lungs (pulmonary TB).[2–4] The high prevalence of TB in adults is the reason for the high rates of TB in children. Although more than one-third of the global population is infected, they do not exhibit symptoms related to the infection and are still at risk of developing it. The emergence of latent TB infection is the cause of this condition.[5,6]

Currently, tuberculin diagnosis using the intradermal Mantoux tuberculin skin test is the primary method of identifying latent tuberculin in children and adolescents. TSTs have been used worldwide for more than 100 years, but they have some problems, such as cross-sensitisation with non-tuberculous mycobacteria and the vaccine strain M. bovis Bacillus Calmette-Guérin (BCG). Due to the high rate of false-positive responses, particularly those brought on by using the BCG vaccination strain, the specificity of TST is limited.[5,7,8]

Two interferon-gamma release assays (IGRAs) have been developed worldwide: QuantiFERON and interferon (IFN)-γ release assay (T-SPOT. TB). The high cost of the new tests, the requirement for laboratory supplies, the necessity of handling the research data (blood) to preserve lymphocyte viability, and the in vitro testing requirement (which makes it challenging to use this method for examining children) are its drawbacks.[9–11]

This study aimed to compare the effectiveness of two modern immunological diagnostic methods in children. The tests being examined were the traditional Mantoux tuberculin skin test (TST) with 2 TE of PPD-L and the test with recombinant TB allergen (ATR).

Materials and Methods

Table 1.Distribution by Gender and Age Composition of Children and Adolescents up to 17 Years of Age

Age (Years)	Boys	Girls	Total
	n (%)	n (%)	N (%)
1–6	287 (5.9)	308 (6.3)	595 (12.1)
7–10	935 (19.1)	938 (19.1)	1873 (38.2)
11–14	825 (16.8)	883 (18.0)	1708 (34.9)
15–17	358 (7.3)	365 (7.5)	723 (14.8)
Total	2405 (49.1)	2494 (50.9)	4899 (100.0)

This cross-sectional study enrolled 4899 children and adolescents, including 2405 boys (49.1%) and 2494 girls (50.9%) (Table 1). Preschool-aged children were recruited from the City Tuberculosis Control Center in Bishkek, and consisted of children with positive TST results and those who had been in contact with TB (high-risk groups). School-aged and teenaged children underwent concurrent intradermal testing, with one group receiving a TST with 2 TU of PPD-L and the other group tested with ATR.

Among the 595 preschool-aged children, 121 (20.3%) had contact with proven TB, 97 (16.3%) had close family contact, and 27 (22.3%) had contact with PTB/ MDRTB. Of the 1873 children aged 7–10 years, 97 (5.2%) had contact, including 79 (4.2%) with family and 21 (21.6%) with PTB/ MDRTB. Of the 1708 children aged 11–14 years, 108 (6.3%) had confirmed contact. Among the 723 teenagers aged 15–17 years, 115 (15.9%) had contact, 551 (76.2%) were rejected, and 57 (7.9%) were not established. In total, 4043 (82.5%) participants had BCG vaccine scars ranging from 4 to 8 mm, 420 (8.6%) had no scars, and 436 (8.9%) had evidence of BCG vaccination.

Children in healthcare organisations were classified into four groups: Group I consisted of individuals with active pulmonary and extrapulmonary TB who responded well to anti-TB medicines; Group II was a high-risk group for TB; Group III A included children who tested positive in the TST; and Group III B comprised healthy children exposed to a patient with active TB.

Children and adolescents whose parents declined immunodiagnosis during infectious diseases or other illnesses, as well as those with epilepsy or allergic reactions, were excluded from the study. The study analysed immunodiagnostic findings using an electronic database of children and adolescents and medical records of preventive vaccinations. The sensitivities of ATR and TST with 2 TE of PPD-L were compared to detect TB in family medicine centres in the Bishkek and Chui regions. A total of 4,899 tests were conducted on children and adolescents aged 1–17 years in these regions.

The City TB Center in Bishkek enrolled preschool children in a group that had undergone follow-up examinations. These children belonged to high-risk categories, including those who tested positive for TST and those with a history of TB contact. A continuous approach is employed in this study.

Immunological tests were performed by specially trained nursing personnel in family medicine centres located in the Bishkek and Chui regions. Additionally, a paediatric TB doctor and trained nurse participated in tests conducted in schools situated in these areas. TST was used for testing. Transverse induration was measured 72 h after intradermal administration of two tuberculin units of allergen TB. The TST was conducted in accordance with the clinical protocol

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"Tuberculosis in Children," which was authorised by the Kyrgyz Republic's Ministry of Health's directive No. 482 dated August 22, 2014. A child's TST result was considered negative if there was an infiltrate of 0–4 mm. If the TST was positive, regardless of the infiltrate size, it was considered positive for children with HIV infection, eating disorders, and contact with patients with TB. Additionally, when the TST was positive, regardless of the infiltrate size, it was considered positive for vesiculonecrosis in other children. The evaluation was performed by a paediatric TB specialist with extensive expertise in interpreting the outcomes of the immunological tests.

ATR (Diaskintest®) was administered intradermally using the TST technique at a dosage of 0.2 µg/0.1 ml (Generium Pharmaceuticals, Russia). The test was considered negative if there was no infiltrate present, positive if any size of infiltrate was present, and uncertain if only hyperaemia was present. The same method and interpretation were used for both the TST and intradermal testing with ATR. At the Scientific and Production Association, "Preventive Medicine" of the Ministry of Health of the Kyrgyz Republic, parents provided informed consent for their children to participate in the study, and the researchers obtained ethical approval from the committee based on study protocol No. 2, dated March 18, 2015.

The statistical analysis of the study results involved calculating proportions and 95% confidence intervals for these proportions as well as comparing them using the Z-test in the SPSS programme, version 16.0.

Results

Efficacy of ATR and TST with 2 TE PPD-L for Screening of TB Infection in Preschool Children from Risk Groups Among the preschoolers from risk groups in Bishkek, a comparative study was carried out to evaluate the efficacy of the two immunologic tests. There were 595 children aged 0–6 years in the study. The majority of children (586, 98.5%) had some BCG vaccine remaining on them. Twenty-one (10.3%) children who had contact with TB patients developed drug-resistant TB. The results of TST with 2 TE of PPD-L showed that the infiltrate was in the range of 5–14 mm in 43.4% of children and ≥ 15 mm in 47.2% of cases. There were no statistically significant changes in the results based on the age of the participants ($p > 0.05$). In 1.3% of cases, there was an unclear outcome, and in 8.1% of cases, there was a bad result (8 children). With a 95% confidence interval (CI) of 0.114 (0.09–0.14), there was a statistically significant difference between the comparative test results ($p < 0.05$) (Figure 1).

When the ATR test was performed, the majority (66.7%) of patients got a negative result ($p < 0.05$). An uncertain outcome was seen in 69 (11.6%) cases ($p < 0.05$). In comparison with TST with 2 TE of PPD-L, positive and hyperergic findings were seen in 58 (9.7%) and 71 (11.9%) instances, respectively ($p < 0.05$). This is nearly four times fewer cases. An ATR skin test indicates a genuine TB infection and helps rule out post-vaccinal and other positive results. The findings of this study demonstrated the prevalence of infection in preschool-aged children in the risk category, with 21.6% (n = 129) of cases having positive results from two immunologic tests.

Regarding the effectiveness of vaccinations, out of all the children with postvaccinal scars measuring 4 mm or more, 35 (41.7%) tested positive on the TST 2 TE PPD-L test, and 43 (51.2%) tested hyperergic. Just six children (7.1%) received negative immunology test results. The percentage of positive and hyperergic samples was only 5.9% (5 people) and 5.9% (5 people), respectively, and the frequency of negative reactions was 88.1%, which is statistically significant ($p < 0.05$) (83 out of 93 children). These are very significant data points that were observed while analysing the ATR results in the mentioned children's category. It was demonstrated that the ATR skin test can accurately determine whether the child has been infected with MTB.

Almost half (59, 48.8%) of the children had a combination of positive reactions to the TST and the ATR tests (coincidence of immunologic samples). It was found that among children aged 0–6 years who were in family contact with a TB patient, the state of TB infection was 48.8% (Figure 2).

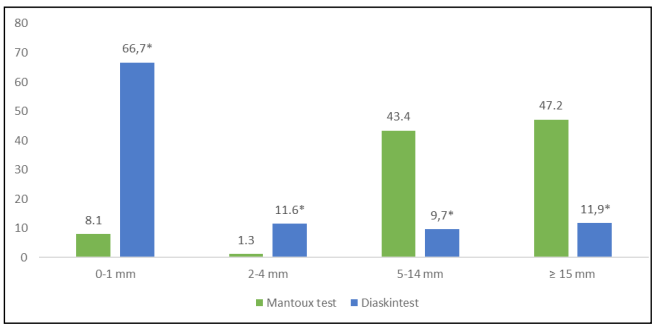

Figure 1.Results of the TST and the ATR Test in Preschool Children
*Statistically significant in relation to TST, $p < 0.05$

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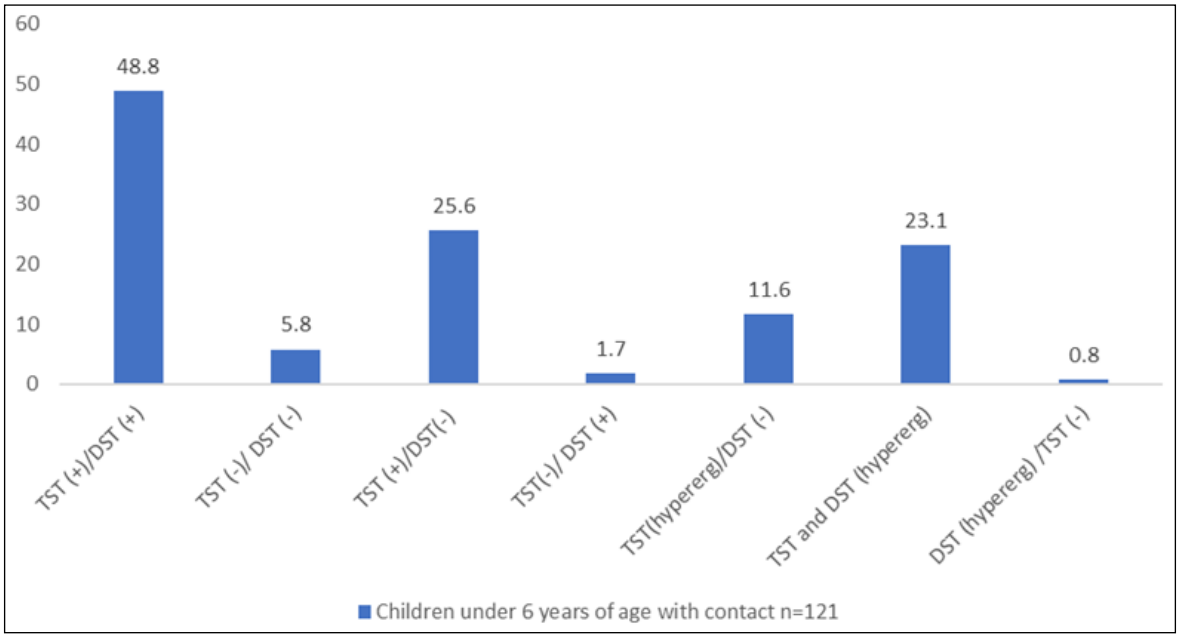

Figure 2.Results of Immunologic Samples Depending on the Presence of Contact with a TB Patient in Children under 6 Years of Age (N = 121)

(+): Positive result, (-): Negative result

When children from risk groups were placed under surveillance, the results of the ATR test were considered. As ATR lowers the quantity of false positives, it was an extra test for LTBI surveillance and preventive care. TST with ATR lowers the need to see a pulmonologist by 4 times ($p < 0.05$) compared to the TST with 2 TE of PPD-L. The dispensary registration rate was 90.7% for the referred children, but the TST resulted in 32.1% of cases. Among the participants of group III A and group III B, 48.1% ($p < 0.05$) and 42.6% ($p < 0.05$) respectively, were taken for follow-up, while the corresponding percentages for TST 2 TE PPD-L were 14.8% and 16.3% (Figure 3).

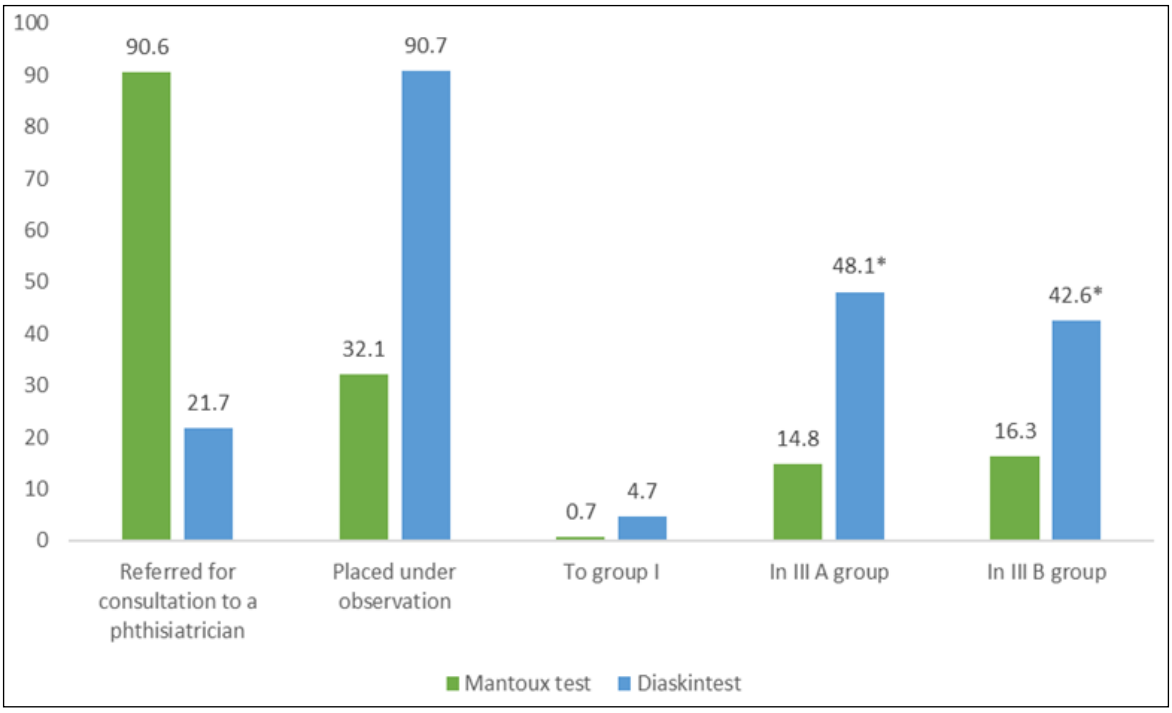

Figure 3.Results of Screening Children for TB Infection (N = 595)

*Statistically significant in relation to the TST, $p < 0.05$

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Efficacy of Screening for Tuberculosis Infection in School-age Children using the ATR and TST with 2 TE of PPD-L A comparison study was conducted to evaluate the efficacy of mass screening children in the Chui and Bishkek areas for TB using the ATR and TSTs with 2 TE of PPD-L. A total of 3581 children were analysed, including 1873 (52.3%) children of primary school age (7 to 10 years old) and 1708 (47.7%) of senior school age (11 to 14 years old).

The study's findings demonstrated that out of all children (n = 3581) aged 7 to 14 years, 2371 (66.2%) had a negative TST result, 1210 (33.8%) had a positive sample, and 558 (46.1%) had hyperergic reactions (among those who had positive reactions). In this age group, 83.9% of skin reactions to ATR were negative (n = 3003), whereas 16.1% of skin reactions were positive (n = 578), with hyperergic reactions observed in 62.1% of cases (n = 359). When comparing the TST PPD-L to the ATR test, the frequency of positive reactions was two times greater ($p < 0.05$), while the frequency of hyperergic reactions was 1.3 times lower.

The percentage of hyperergic tests (out of positive responses) was 32.3% (n = 282), and the percentage of positive TSTs with 2 TE of PPD-L was 46.7% (n = 874) among children aged 7 to 10 years. Children who were seven years old had the highest frequency of hyperergic responses (20.9%). When compared to identical reactions during the TST, the results of hyperergic reactions during the ATR test were substantially greater (59.8% vs 47.6%, respectively, $p < 0.001$). The highest incidence of hyperergic reactions (10.0%) was seen in children aged 10 years. The same statistical data were obtained when the results of the two immunologic tests in schoolchildren aged 11 to 14 years were analysed. The trends in the dynamics of indicators were similar in children aged 7 to 10 years, with the exception of a slight increase in the frequency of positive and hyperergic reactions. When using 2 units of PPD-L for stages of an intradermal TST in children aged 11–14 years, the frequency of positive reactions was found to be 49.9% (n = 851), and the rate of hyperergic reactions was 32.4% (n = 276). These rates were statistically significant ($p < 0.05$) when staging with ATR at 17.4% (n = 297) and 64.3% (n = 191), respectively.

Variants of the coincidence or mismatch combination between two immunologic tests were examined. The findings of these tests showed no differences in ratios between boys and girls; however, hyperergic TST with 2 TE of PPD-L was more frequently associated with negative results of ATR in females as compared to males (8.3% vs 5.9%). In females, 119 (6.5%) had hyperergic skin test sizes, 704 (38.7%) had negative results from both immunologic tests, and 237 (13.0%) had positive responses from both tests (Table 2).

It was found that the frequency of complete coincidence of positive samples was 40.5% (83 out of 205 children), the frequency of negative two samples was 41.5% (n = 85), and the frequency of hyperergic samples was 25.4% (n = 52) while examining the various variations of coincidence of two immunologic tests in children who had come in contact with a TB patient. The aforementioned variations in the frequency of perfect concordance of two immunologic tests were 11.2% (n = 360), 44.2% (n = 1427), and 5.0% (n = 161), respectively, in children who had no overt contact (n = 3227) with TB patients. Children who had contact had nearly four times higher levels of MTB infection than children who had no established contact, and those who had contact had five times higher levels of high immunologic reactivity (hyperergic reactions to allergens) than those who had no apparent contact ($p < 0.05$).

Children were grouped into treatment groups for monitoring based on the outcomes of the ATR test. Psychologists evaluated children who tested positive on the TST and ATR, and based on the results, surveillance groups were established (Figure 4).

Table 2.Frequency of Concordance of TST 2 TE PPD-L and ATR Results in Children Aged 7–14 Years Old

	TST (+)/ ATR (+) n (%)	TST (-)/ ATR (-) n (%)	TST (+)/ ATR (-) n (%)	TST (-)/ ATR (+) n (%)	TST (Hyper)/ ATR (-) n (%)	TST & ATR (Hyper) n (%)	TST (Hyper)/ TST (-) n (%)
Total (N = 3581)	445 (12.4)	1391 (38.8)	1173 (32.8)	127 (3.5)	256 (7.1)	214 (6.0)	72 (2.0)
Boys (n = 1760)	208 (11.8)	687 (39.0)	565 (32.1)	66 (3.75)	104 (5.9)	95 (5.4)	35 (2.0)
Girls (n = 1821)	237 (13.0)	704 (38.7)	608 (33.4)	61 (3.3)	152 (8.3)	119 (6.5)	37 (2.0)

(+): Positive result, (-): Negative result

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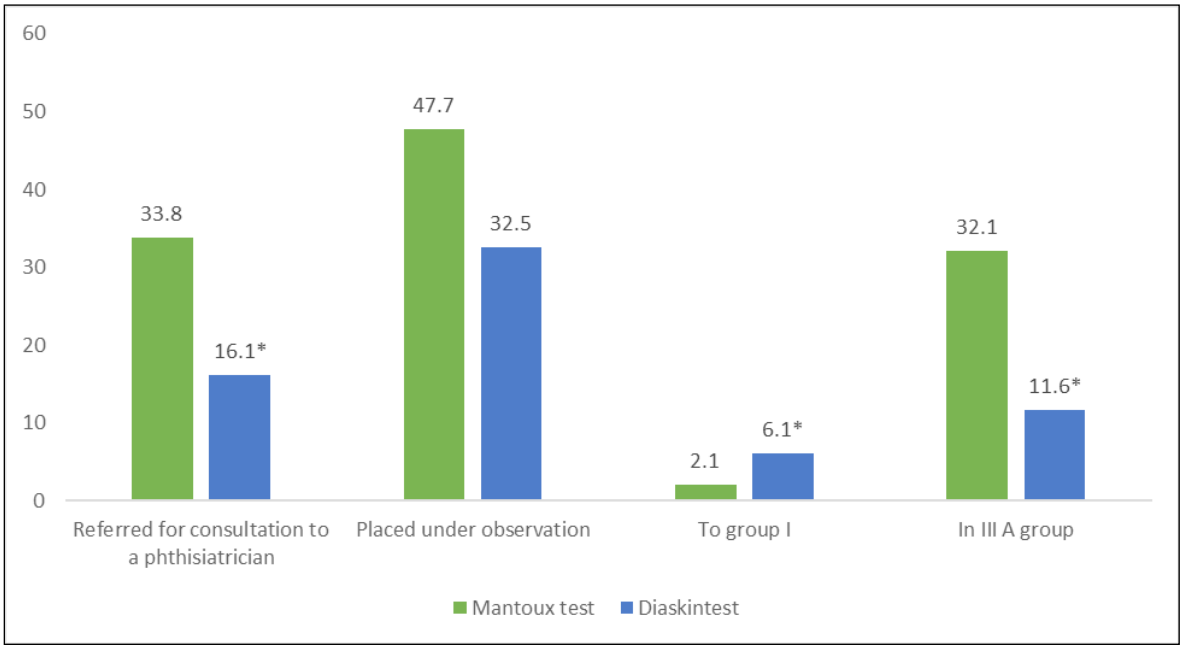

Figure 4.Results of Screening 7–14 Years Old Children for TB Infection (N = 3581)
*Statistically significant in relation to the TST, $p < 0.05$

Based on TST findings, III A surveillance included 389 (10.8%) infected children (infiltrate size bigger than 10 mm or more), of whom 26 (0.7%) were suspected of having active TB. A total of 576 (16.1%) children were monitored as per the result of TST.

ATR allowed for the exclusion of 248 (7.0%) children and the inclusion of 141 (3.9%) children in the III A observation group due to TB infection. School-age children who had positive ATR findings underwent further radiographic and clinical testing. Localised pulmonary TB was identified in 33 children (1.0%).

Among the participants, 576 (16.1%) completed the TST with 2 TE PPD-L, indicating that they qualified for preventive treatment. This is twice as many children as the ATR test results indicated to be eligible for therapy; yet, only 141 (3.9%) children met the ATR test data eligibility requirements ($p < 0.05$). The prevalence of LTBI in this group of children was 15.9%, according to a thorough assessment of children aged 7 to 14 years that took into consideration the immunologic ATR test's severity.

Accordingly, the study's findings suggested that in children who test positive for tuberculin, false-positive responses may be ruled out when using an ATR skin test. As a result, compared to the ATR, there were more positive responses (33.8% vs 16.1%) in children aged 7–14 years when using an intradermal TST with 2 TE of PPD-L.

Effectiveness of the ATR and TST with 2 TE PPD-L for Screening of TB in Adolescents

This study compared the effectiveness of ATR and TSTs using 2 TE PPD-L for the mass screening of TB in 15–17-year-olds in the Bishkek and Chui regions. The study group consisted of 365 girls (50.5%) and 358 boys (49.5%) with no significant difference in gender.

The study found that among 15–17-year-olds, the distribution of negative and positive reactions to the two allergens varied. The intensity and nature of the local reactions to the tests in this age group were diverse, with no clear trend. A positive TST 2 with the TE PPD-L test was observed in 151 cases (20.9%), while a positive ATR test was observed in 154 cases (21.3%). A negative TST 2 TE PPD-L test result was observed in 545 teens (75.4%), and 523 teens (72.3%) had negative reactions to ATR (Figure 5).

The proportions of doubtful reactions to tuberculin and ATR were 3.7% (n = 27) and 6.4% (n = 46), respectively ($p < 0.05$). Among adolescents with questionable reactions to tuberculin, 85.2% reacted negatively to ATR (23 of 27 adolescents) and 14.8% reacted questionably (4 of 27 adolescents). Hyperergic reactions were observed in 115 (15.9%) adolescents who underwent the ATR test compared to 51 (7.1%) adolescents who underwent TST with 2 TE PPD-L ($p < 0.05$). This indicates that teenagers with positive ATR results had stronger local reactions than those with positive TST results using 2 TE PPD-L.

When comparing the TST and ATR tests in adolescents, it was observed that 11 (11.0%) cases exhibited a positive reaction to both tests, whereas 35 (68.6%) and 419 (76.9%) cases displayed hyperergic and negative reactions, respectively. Table 3 reveals that 115 adolescents (15.9%) had hyperergic reactions to ATR, and only 51 adolescents (7.1%) experienced hyperergic reactions to TST with 2 TU PPD-L.

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Table 3.Frequency of Concordance of TST and ATR Results in Adolescents

TST Results	Indicators (%) of Agreed ATR Results				Total N (%)
	Negative n (%)	Doubtful n (%)	Positive n (%)	Hyperergic n (%)	
Negative n (%)	419 (76.9)	36 (6.6)	24 (4.4)	66 (12.1)	545 (75.4)
Doubtful n (%)	23 (85.2)	4 (14.8)	0 (0.0)	0 (0.0)	27 (3.7)
Positive n (%)	70 (70.0)	5 (5.0)	11 (11.0)	14 (14.0)	100 (13.8)
Hyperergic n (%)	11 (21.6)	1 (2.0)	4 (7.8)	35 (68.6)	51 (7.1)
Total N (%)	523 (72.3)	46 (6.4)	39 (5.4)	115 (15.9)	723 (100.0)

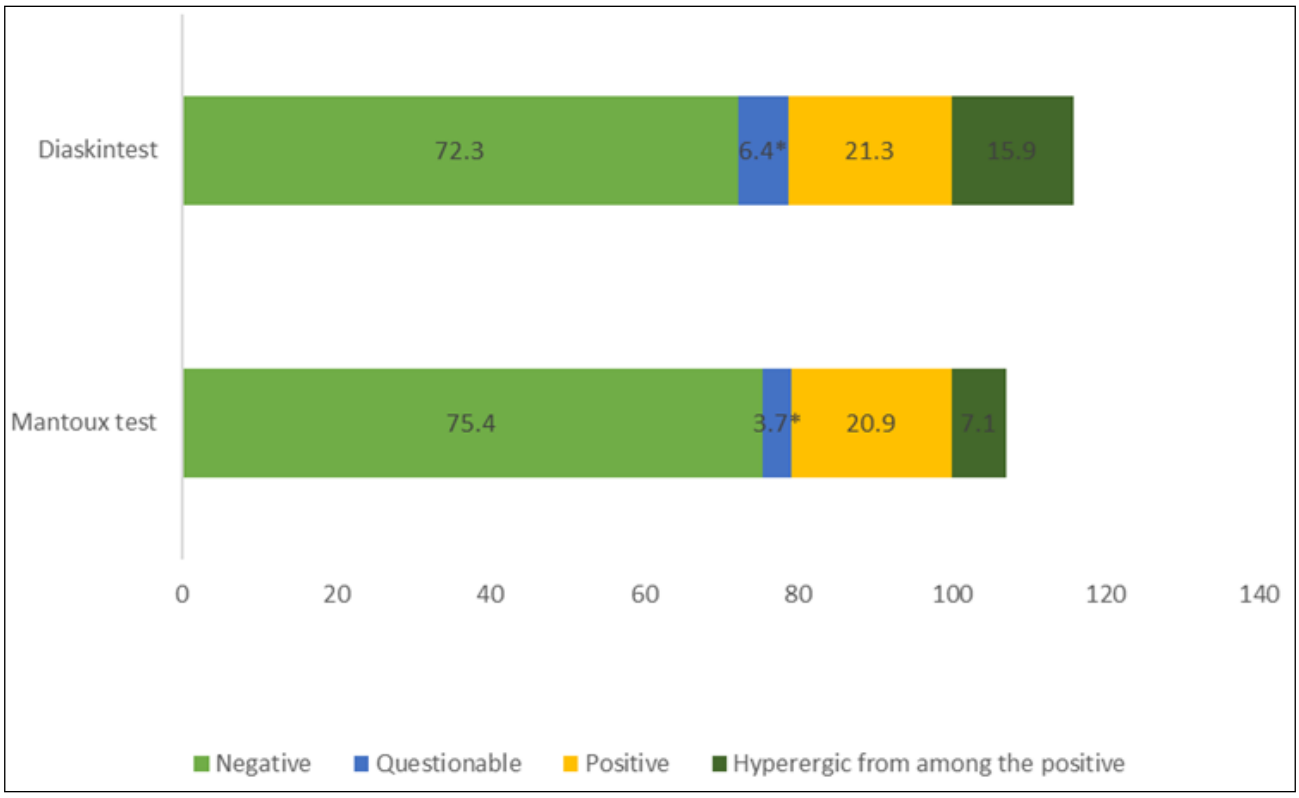

Figure 5.Results of Two Immunologic Samples in Adolescents (in %)

*Statistically significant in relation to the TST, $p < 0.05$

Utilising the TST for screening and examining adolescents allowed for the identification of more teens requiring a full physical examination, which sometimes included computed tomography to rule out localised forms of pulmonary TB. The ATR test results demonstrated better sensitivity and specificity due to a significant percentage of hyperergic responses, leading to fewer reasons for radiologic, clinical, and laboratory tests and preventive treatment.

Among adolescents who had been exposed to TB cases with bacteriological confirmation, all responded positively to both tuberculin and ATR. Seventy-five percent of the patients exhibited hyperergic sensitivity, indicating that the results of the two immune system tests were identical. After radiologic analysis of all contacts, two (0.3%) adolescents with active signs of a specific process were identified. Following a comprehensive evaluation with two different types of skin testing, it was found that 20.9% of patients had LTBI, 78.8% had eliminated infection, and 0.4% had specific radiographic abnormalities detected during the contact examination.

This study emphasises the importance of skin testing for detecting LTBI and determining infection in adolescents.

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Radiologic approach and contact examination play a crucial role in identifying TB among adolescents.

Discussion

A history of receiving the BCG vaccine does not lead to false-positive outcomes when undergoing IGRA testing, which can be obtained within 24 h of the test and only requires a single visit. However, the test is expensive, necessitates IV involvement (especially in young children), calls for laboratory equipment, and requires fast processing of the blood sample. Additionally, it may not be entirely accurate for patients with HIV infection.[12,13]

Currently, the recommended course of action for detecting TB is a two-step process. The first step involves administering a TST with 2 TU PPD-L, followed by IGRA testing.[10,14–16]

A test that can distinguish between post-vaccination allergies and other types of allergies is required. One such test is the Diaskintest, which utilises the ESAT6-CFP10 protein, an ATR, in skin testing.[17] In 2009, the Russian Ministry of Health authorised the Diaskintest for differentiating between infectious and post-vaccinal allergies. For every child who tested positive for the Diaskintest, further evaluation is necessary to rule out localised forms of TB and, if nothing is found, to start LTBI preventive medication. Individuals who test positive for the Diaskintest have a ten-fold increased risk of tuberculin positivity.[18] The ESAT-6 and CPF-10 proteins are not used independently for the skin test; rather, a single recombinant protein derived from Escherichia coli BL21 (DE3)/ pCFP-ESAT is employed.[12,14] The mode of action of ATR is based on the identification of cellular immunological responses to antigens unique to M. TB. When medication is administered intradermally to patients with LTBI or active TB, certain skin reactions are observed. The purpose of ATR was to offer a test that could be used for mass screening but was also more precise than TST.[19–21]

According to a comprehensive meta-analysis, the overall accuracy of ATR in HIV-positive individuals is 95.1% (95% CI of 95.06-95.1) and 92.4% (95% CI of 91.9-92.7).[22] ATR had a sensitivity of 100% in paediatric TB cases and 86.0% (95% CI. 80.0-92.0) in patients with active TB. ATR produced more positive samples (80.5%) than QuantiFERON (67.0%) and T-SPOT. TB (72.2%), but lower than that of the TST (91.2%). In individuals with HIV infection and tuberculosis, the percentage of positive ATR findings (59.3%) was similar to that of QuantiFERON (1.3%), which was lower than that of T-SPOT. TB (67.2%), but was much higher than that of TST (15.1%).[23,24]

Conclusions

Compared to traditional TST with 2 TE PPD-L, ATR was more effective in eradicating post-vaccinal allergies in children under six years of age. Specifically, it was eight times more effective in detecting LTBI diagnosis in this age group, with 78.3% of the children testing positive compared to 9.4% for the TST ($p < 0.05$). Additionally, true infections were detected 1.5 times less frequently with ATR than TST (17.9% vs. 29.6%, $p < 0.05$). A comparative analysis between the two immunological tests revealed that ATR was twice as effective in detecting positive results in the age group of 7–14 years (33.8% vs 16.1%, $p < 0.05$). However, no significant differences were found between the two tests for adolescents (21.3% and 20.9%, respectively). In contrast, a significant difference was observed in children under six years of age (21.6% and 90.6%, respectively), suggesting a true infection rather than a vaccination allergy. A pre-survey of individuals who tested positive in the ATR test in the general population revealed that 15.9% of school-aged children (7–14 years) and 20.9% of teenagers (15–17 years) had LTBI ($p < 0.001$). Among preschool-aged children, 21.6% had LTBI, and the number of infections resulting from contact with TB patients was significantly higher (48.8%).

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