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Retrospective evaluation of the results of immunodiagnostics for tuberculosis in children

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Abstract

Introduction. For early immunodiagnostics of tuberculosis (TB) in Russia, the Mantoux test (MT) has been used for decades; since 2013, the recombinant tuberculosis antigen (RTA) test has seen widespread use.

The objective of this retrospective analytic observational cohort study was to evaluate the results of immunodiagnostics for TB in children with newly diagnosed active TB.

Materials and methods. We studied data from Russian TB institutions on the results of MT and RTA assay in children with active and inactive TB first detected in 2013–2018, as well as children with active TB first detected in Moscow in 2017–2022.

Results and discussion. In 2013–2018, out of 12,902 examined children with active TB, 11,673 (90.5%) had positive results of both skin tests and 198 (1.5%) had negative results. A negative RTA assay result with positive MT was found in 861 (6.7%) patients, and a positive RTA assay result with negative MT in 170 (1.3%). The sensitivity of the RTA assay in detecting active TB was 91.3%, while the sensitivity of MT was 97.2% ($p < 0.01$). Similar data were obtained in the same regions in 14,127 children with inactive TB: the sensitivity of MT was higher than that of the RTA assay — 97.2% versus 95.2% ($p < 0.01$). In Moscow, due to the small number of observations in 2022, it was not possible to show statistical reliability of the difference between the sensitivity of MT and RTA assay in detecting active TB in 2017–2022 (95.8% and 92.1% respectively; $p > 0.5$). For the results obtained in 2017–2021, the difference was significant ($p < 0.05$).

Conclusion. The sensitivity of MT is higher than that of the RTA assay in screening children for TB. It is recommended to use the more sensitive MT test for screening children; screening with the RTA assay will increase the number of undetected and undiagnosed cases of active TB in children. Currently, MT cannot be excluded from the algorithm of early TB diagnosis in children.

Keywords: *tuberculosis in children, tuberculin diagnostics, Mantoux test, Diaskintest, recombinant tuberculosis allergen*

Ethics approval. The study was conducted with the voluntary informed consent of the legal representatives of underage patients to use the data for scientific purposes. The study protocol was approved by the Ethical Committee of the Central Research Institute of Epidemiology (protocol No. 136 of 25.05.2023).

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Оригинальное исследование
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Ретроспективная оценка результатов иммунодиагностики туберкулеза у детей

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Аннотация

Введение. Для ранней иммунодиагностики туберкулёза (ТБ) в России в течение десятилетий использовали пробу Манту (ПМ), с 2013 г. повсеместно массово применяется проба с антигеном туберкулёзным рекомбинантным (АТР).

Цель ретроспективного аналитического обсервационного когортного исследования — оценка результатов иммунодиагностики ТБ у детей с впервые выявленным активным ТБ.

Материалы и методы. Изучены данные противотуберкулезных учреждений России о результатах ПМ и проб с АТР у впервые выявленных в 2013–2018 гг. детей с активным и неактивным ТБ, а также детей с активным ТБ, впервые выявленных в Москве в 2017–2022 гг.

Результаты и обсуждение. В 2013–2018 гг. из 12 902 обследованных детей с активным ТБ у 11 673 (90,5%) результат обеих кожных проб был положительным, у 198 (1,5%) — отрицательным. Отрицательный результат пробы с АТР при положительной ПМ установлен у 861 (6,7%) больного, а положительный результат при отрицательной ПМ — у 170 (1,3%). Чувствительность пробы с АТР при выявлении активного ТБ составила 91,3%, а ПМ — 97,2% ($p < 0,01$). Аналогичные данные получены в тех же регионах у 14 127 детей с неактивным ТБ: чувствительность ПМ оказалась выше, чем пробы с АТР, — 97,2% против 95,2% ($p < 0,01$). В Москве вследствие малого числа наблюдений в 2022 г. статистическую достоверность разности показателей чувствительности ПМ и пробы с АТР при выявлении активного ТБ в 2017–2022 гг. (95,8% против 92,1%; $p > 0,5$) показать не удалось. По результатам за 2017–2021 гг. разница оказалась достоверной ($p < 0,05$).

Заключение. Чувствительность ПМ при скрининге детей на ТБ выше, чем пробы с АТР. Для скрининга детей рекомендуется использовать более чувствительный тест-ПМ, при скрининге с использованием пробы с АТР возрастет количество пропущенных и своевременно не диагностированных случаев активного ТБ у детей. В настоящее время ПМ не может быть исключена из алгоритма ранней диагностики ТБ у детей.

Ключевые слова: *туберкулез у детей, туберкулинодиагностика, проба Манту, Диаскинтест, аллерген туберкулезный рекомбинантный*

Этическое утверждение. Исследование проводилось при добровольном информированном согласии законных представителей несовершеннолетних пациентов на использование данных в научных целях. Протокол исследования одобрен Этическим комитетом ЦНИИ Эпидемиологии (протокол № 136 от 25.05.2023).

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

In order to control tuberculosis (TB) incidence, early diagnosis is an essential element. The importance of preventive screening for TB was particularly evident during the spread of COVID-19. It is estimated that during the 3 years of the pandemic, disruptions in active TB screening resulted in the late detection of 2011 TB patients (1.5% of the total number of TB patients first identified) [1].

Since infection with the TB pathogen usually occurs in childhood and adolescence and cases of infectious process manifestation in adults are associated with the activation of latent infection, the foundation of the early TB detection system is screening of the pediatric population. For more than a century, a clear system of TB detection in children using skin immunologic tests has been developed [2–4].

In recent decades, *in vitro* TB diagnostic methods based on quantitative determination of interferon-γ, which is released when effector T lymphocytes come into contact with specific ESAT-6 antigens, have emerged. However, due to high specificity, these tests have significant disadvantages: high cost, dependence on the supply of imported materials, the necessity for a specially equipped laboratory and for precautions during blood collection to preserve the viability of interferon-γ-producing lymphocytes, as well as intravenous manipulations, which especially limits the use of this test in children [5, 6]. Therefore, the algorithm for diagnosing the *Mycobacterium tuberculosis* infection has not changed fundamentally, and skin diagnostic tests are still used for screening [7].

For decades, screening of children for TB has been carried out using the Mantoux test (MT); since 2009, the test with recombinant tuberculosis antigen (RTA) was carried out in certain regions, and since 2013, it has seen widespread use [8, 9].

High sensitivity and specificity of the RTA assay when used in patients with clinical and radiologic signs of respiratory TB have been shown [10–12]. However, the RTA assay may be negative in people at early stages of *M. tuberculosis* infection, in TB patients

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with pronounced immunopathology disorders due to the severe course of the tuberculosis process, as well as in people with concomitant diseases accompanied by immunodeficiency state, which is especially relevant in the context of the spread of a new coronavirus infection [1, 13, 14].

A multitude of scientific papers have been devoted to the study and evaluation of the results of MT and the RTA assay [9, 11, 15]. The parameters of tuberculin diagnostics were established on a huge material (10.5 million children in Moscow for 7 years): intradermal MT with 2 TU (tuberculin units) of PPD-L (purified protein derivative modified by Linnikova). The sensitivity of the method was 94.7%, specificity — 41.7%. The probability of disease absence in case of a negative test was 99.9%. The probability of disease in a child with a positive test is 0.01% [16, 17], whereas negative reactions to RTA can be detected in persons with inactive TB infection [18, 19] and at early stages of infection with *M. tuberculosis* [19, 20].

When selecting tests for screening, sensitivity is the first factor taken into consideration. The sensitivity of a test is its ability to reliably detect the presence of a given disease in a patient. In other words, sensitive tests should not leave any patients unaccounted for, although it is almost inevitable that in certain cases the disease would be erroneously diagnosed for conditionally healthy individuals. Sensitive tests are recommended to be used in the early stages of diagnostic search to narrow its scope, when there are many possible variants and diagnostic tests will allow to exclude some of them. It should be noted that a negative result of a sensitive test is particularly informative in clinical practice [21].

Despite the differences in sensitivity and specificity of MT with 2 TU of PPD-L and RTA, which do not allow to consider these methods interchangeable, in the order of the Ministry of Health of Russia No. 951 of 29.12.2014[1], the replacement of MT with RTA for TB screening in children 8 years of age and older was approved. These recommendations contradicted the previously existing sanitary and epidemiological rules of SP 3.1.2.3114-13 "Tuberculosis Prevention"[2]. However, certain subjects of the Russian Federation started to conduct screening using the RTA assay [20]. Against this background, TB incidence increased in subgroup IIIA and in all subgroups of group VI of the dispensary registration group (DRG), which may be due to the cancellation of preventive treatment of children in these DRGs in case of a negative reaction to RTA [19, 20, 22].

Thus, the experience of the widespread use of the RTA assay accumulated over a decade must be objectively analyzed and evaluated, as there is still no consensus among specialists (phthisiatrists, pediatricians, epidemiologists) about the advisability of its use as an alternative to MT [7, 18–20, 22].

In this regard, a study was conducted to retrospectively evaluate the results of immunodiagnostics for TB in children with newly diagnosed active TB using MT and the RTA assay.

Materials and methods

A retrospective analytical observational cohort study was conducted. The materials for the study were the data received by Rospotrebnadzor from TB institutions in the federal subjects of Russia in accordance with the request No. 01/5300-15-27 of 18.05.2015 "On submission of information on TB screening of children" and Rospotrebnadzor letter No. 01/7238-15-27 of 06.06.2017 "On the results of the study of the comparative effectiveness of the Mantoux test (MT) and the test with recombinant tuberculosis allergen (RTA)". The data included information on the results of MT with 2 TU of PPD-L and the test with RTA in pediatric patients with newly diagnosed active and inactive TB in 2013-2018. The inactive form of the disease was considered to be TB in children registered in the III DRG (persons with clinically cured TB, with large and small residual changes)[3]. Furthermore, we analyzed the results of immunodiagnostics using MT and Diaskintest in child and adolescent patients (0–17 years old) with active TB in Moscow in 2018–2022 according to the data obtained from TB institutions of the city. The study was conducted with the voluntary informed consent of the legal representatives of underage patients to use the data for scientific purposes. The study protocol was approved by the Ethical Committee of the Central Research Institute of Epidemiology (protocol No. 136 of 25.05.2023).

Statistical processing of the results was carried out using parametric statistics methods with determination of the standard error of the relative value. Reliability of differences between the relative values compared was assessed using Student's t-criterion. The difference in results was considered statistically significant at $p < 0.05$.

[1] Order of the Ministry of Health of the Russian Federation of December 29, 2014, No. 951 "On Approval of Methodological Recommendations to Improve Diagnosis and Treatment of Respiratory Tuberculosis".

[2] Resolution of the Chief State Sanitary Doctor of the Russian Federation from 22.10.2013 № 60 (ed. from 14.09.2020) "On approval of sanitary and epidemiological rules SP 3.1.2.2.3114-13 "Tuberculosis Prevention" (together with "SP 3.1.2.2.3114-13...")".

[3] Order of the Ministry of Health of the Russian Federation of 21.03.2003 No. 109 "On improvement of anti-tuberculosis measures in the Russian Federation"; Order of the Ministry of Health of the Russian Federation of 13.03. 2019 No. 127n "On Approval of the procedure for dispensary monitoring of tuberculosis patients, persons who are or have been in contact with the source of tuberculosis, as well as persons suspected of tuberculosis and cured of tuberculosis and invalidation of paragraphs 16-17 of the Procedure for the provision of medical care to tuberculosis patients, approved by Order of the Ministry of Health of the Russian Federation of November 15, 2012 No. 932n".

Table 1. Results of MT and RTA assay in newly diagnosed active pediatric TB patients in 2013–2018

Year	Total children with newly diagnosed active tuberculosis	Of these with the results of the Mantoux test with 2 TE (MT) and the test with RTA							
		MT+ RTA–		MT+ RTA+		MT– RTA–		MT– RTA+	
		n	%	*n*	%	*n*	%	*n*	%
2013	4128	290	7,03	3750	90,84	46	1,11	42	1,02
2014	3850	261	6,78	3487	90,57	46	1,20	56	1,45
2015	1582	54	3,4	1485	93,5	32	2	11	0,7
2016	2435	232	9,3	2087	83,3	57	2,28	59	2,36
2017	522	12	2	502	82,6	7	1,2	1	0,2
2018	385	12	2,5	362	75,7	10	2,1	1	0,2
Total	12 902	861	6,7	11 673	90,5	198	1,5	170	1,3

Note. Here and in the Tables 2 and 3: "+" — positive result; "–" — negative result.

Results

According to data from TB institutions, 12,902 children were diagnosed with active TB for the first time in 2013–2018[4].

The absolute majority of patients (n = 11,673; 90.5%) were positive for both skin tests (**Table 1**). In 198 (1.5%) children with active TB, both samples were negative. A negative result of the RTA assay with positive MT was found in 861 (6.7%) patients, and a positive result with negative MT in 170 (1.3%). Consequently, the sensitivity of RTA assay in detecting active TB was 91.3% and the sensitivity of MT was 97.2% ($p < 0.01$). For 2013–2018, in 1059 children with newly diagnosed active TB, the RTA assay showed a negative result. Consequently, abandoning MT and switching to RTA screening will increase the number of undetected and undiagnosed cases of active TB in children.

Similar data were obtained when analyzing the results of skin tests in children with newly diagnosed inactive TB in the same regions of Russia in 2014–2018 (**Table 2**). The absolute majority of patients (n = 12,953; 91.7%) had positive results of both skin tests, 101 (0.7%) children had negative results. A negative result of the test with RTA in case of positive MT was detected in 775 (5.5%) patients, a positive result of the test with RTA in case of negative MT — in 495 (3.5%). Thus, in the detection of inactive TB, the sensitivity of MT was higher than that of the RTA assay and amounted to 97.2%, while the sensitivity of the RTA assay was 95.2% ($p < 0.01$). During 2014-2018, in 876 children with newly diagnosed inactive TB, the RTA assay was negative. Consequently, abandoning MT and switching to screening using the RTA assay will increase the number of undetected and undiagnosed cases of inactive TB in children in a timely manner.

Due to the cancellation of using the MT method on children over 7 years of age in 2018[5], it became impossible to continue the study nationwide. However, thanks to the data obtained from TB institutions in the capital, we were able to retrospectively evaluate the results of immunodiagnostics using MT and RTA assay in children and adolescents (0–17 years of age) with active TB in Moscow in 2017–2022.

A total of 515 cases of active TB in children were reported over 6 years, and 447 cases were reported in the epidemiologic investigation. Both skin tests were performed only in 240 people, which made comparative analysis difficult. Of the 240 children with active TB, 217 (90.4%) had a positive result of MT and RTA, while 6 (2.5%) were negative (**Table 3**). A positive result of tuberculin diagnostics with a negative test with RTA was obtained in 13 (5.4%) children. The test with RTA was negative in children diagnosed with focal, infiltrative pulmonary and intrathoracic lymph nodes TB. A positive result of the RTA assay with negative MT was recorded only in 4 (1.7%) children. Despite the fact that the sensitivity of MT in detecting active TB was higher than that of the RTA assay (95.8% and 92.1% respectively), statistical reliability of the difference between these indicators could not be demonstrated due to the small number of observations in 2022 (only 17 cases with the results of both tests). If we analyze the data for 2017–2021, the difference in the sensitivity of MT and RTA assay is significant ($p < 0.05$).

Discussion

The results of this analysis confirmed previously published data that the RTA assay can give false-negative results at the early stages of infection with *M. tuberculosis* and at the initial stage of TB process development, which, unlike MT, does not allow for the full

[4] Data were obtained from 57-81 subjects of the Russian Federation in different years.

[5] See: Screening examination of children and adolescents to detect tuberculosis infection: methodological guide. M.; 2018. p. 48

Table 2. Results of MT and RTA assay in newly diagnosed inactive pediatric TB patients in 2014–2018

Year	Total children with newly diagnosed inactive tuberculosis	Of these with the results of the Mantoux test with 2TE (MT) and the test with RTA							
		MT+ RTA–		MT+ RTA+		MT– RTA–		MT– RTA+	
		n	%	*n*	%	*n*	%	*n*	%
2014	2421	188	7,77	2170	89,63	22	0,91	41	1,69
2015	3002	157	5,23	2759	91,91	26	0,87	60	2
2016	2819	139	4,5	2862	92,8	17	0,6	66	2,1
2017	3090	175	5,7	2 654	85,9	16	0,5	218	7,1
2018	2795	116	4,2	2 508	89,7	20	0,7	110	3,9
Total	14 127	775	5,5	12 953	91,7	101	0,7	495	3,5

Table 3. Results of MT and RTA assay in newly diagnosed active TB patients in Moscow in 2017–2022

Year	Total children with newly diagnosed active tuberculosis	Of these with the results of the Mantoux test with 2TE (MT) and the test with RTA							
		MT+ RTA–		MT+ RTA+		MT– RTA–		MT– RTA+	
		n	%	*n*	%	*n*	%	*n*	%
2017	68	5	7,4	60	88,2	1	1,5	2	2,9
2018	48	3	6,3	43	89,6	1	2,1	1	2,1
2019	47	2	4,3	45	95,7	0	0	0	0
2020	22	1	4,5	20	90,9	1	4,5	0	0
2021	38	2	5,3	35	92,1	1	2,6	0	0
2022	17	0	0	14	82,4	2	11,8	1	5,9
Всего | Total	240	13	5,4	217	90,4	6	2,5	4	1,7

formation of risk groups, detection of the disease at the early stages of its development and increases the probability of not detecting the disease [22, 23].

Even at the stage of RTA drug approbation, its researchers [24] observed only 84.2% (95% CI 79.7–88.8) of positive results of this test in patients with active TB, and 94.5% (95% CI 83.0–97.9) in children and adolescents (n = 200) with active respiratory TB after the first phase of chemotherapy. Moreover, the response to MT was positive in all 200 children in this subgroup. It should be noted that the authors concluded on the basis of these quantitative data that the sensitivity of MT and the RTA assay were the same, despite the statistically significant difference in sensitivity ($p < 0.05$) [24].

A number of researchers have observed a negative reaction to the RTA assay in 13–20% of children with TB, including those with secondary forms of TB and disseminated processes, including cases with bacterial excretion [9, 15, 20, 25, 26].

Similar data were obtained by Y.A. Yarova et al. [19], who noted that TB in children with negative results of the RTA assay persisted in complicated forms of the primary period in 45.5 ± 15.0% of cases, uncomplicated forms — in 27.3 ± 13.4% of cases, generalized lesions — in 27.3 ± 13.4% of cases.

According to other data, among children with TB with negative reactions to RTA administration, patients with active forms of TB accounted for 20.4%. M.E. Lozovskaya et al. emphasized that mass tuberculin diagnostics is the leading method of detecting patients with negative results of the RTA assay, thanks to which TB was diagnosed in 70.4 ± 8.8% of cases, in children with residual post-tuberculosis changes — in 93.8 ± 4.7% of cases [23].

According to a large-scale retrospective observational study in 65 regions of the Russian Federation [27], the rate of positive reactions to RTA administration in children with active TB in the first DRG was more than 90% (92.1% in 2010, 90.1% in 2011, and 92.8% in 2012), which is almost identical to the results of the present study.

A meta-analysis of published results of the RTA assay over 10 years also showed that the proportion of positive reactions of the RTA assay in children with TB up to 14 years of age was lower (93.5%) compared to MT, which showed positive results in 97.9% of cas-

es (p = 0.688) [28]. At the same time, in most studies of the RTA assay and according to clinical guidelines [29], children with positive results were subjected to computed tomography (CT), so the sensitivity of the RTA assay was equal to that of CT, while children with suspected TB based on MT results were not referred to CT until they were positive for RTA [24, 30–32]. Furthermore, according to the instructions for Diaskintest, not only positive but also questionable and doubtful reactions to the RTA assay are subject to TB screening[6]. However, despite all the regulatory measures initially taken to increase the sensitivity of the RTA test for TB detection, the results of its use in practice have shown that its sensitivity is inferior to that of MT.

According to our preliminary estimates, in Russia as a whole, the number of undetected cases of active TB in children would be about 300 per year if the country switched to screening with only the RTA assay [33]. Therefore, in the algorithm of TB detection and diagnosis, the RTA assay and MT cannot be interchangeable and complement each other. MT is able to determine the presence of infection with *M. tuberculosis* and include the patient in the TB risk group, has a wide range of diagnostic capabilities in dynamics. The RTA assay has diagnostic value and demand in TB risk groups (contact, change of sensitivity to MT, social prerequisites, diseases with similar clinical and radiologic picture) [22].

Conclusion

1. In 6.2–7.9% of children with newly diagnosed active TB, the RTA assay was negative, while a negative MT result was detected in only 2.8–4.2% of them, i.e. the sensitivity of MT in screening children for TB is higher than that of the RTA assay. Between 2013 and 2018, in 1059 children with newly diagnosed active TB, the RTA assay was negative. Consequently, abandoning MT and switching to RTA screening will increase the number of undetected and undiagnosed cases of active TB in children.

2. A negative RTA assay result with a positive MT result cannot be a guarantee that a child does not have active TB, including bacteriuria, and requires additional testing.

3. For TB screening of children, MT should be used as a more sensitive test. As of now, MT cannot be excluded from the algorithm of early TB diagnosis in children and adolescents.

[6] Diaskintest. URL: http://www.diaskintest.ru

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