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QuantiFERON TB and TB Plus tests in Slovenia between 2008 and 2019

Testa QuantiFERON TB in TB Plus v Sloveniji v obdobju 2008–2019

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Abstract

Background: The QuantiFERON TB (QFT TB) test is primarily intended to detect latent (LTBI) tuberculosis (TB) infections. This work is based on a retrospective analysis of QFT TB test results in Slovenia between 2008 and 2019. It also draws attention to the influence of pre-analytical factors on a test result, on reasons that lead to indeterminate results, and on the sensitivity of the test in patients with active tuberculosis (TB).

Methods: Between 2008 and 2019, we performed the QFT TB test in Laboratory for Mycobacteria of the University Clinic Golnik on 29,352 blood samples of patients from various health care institutions in Slovenia. A retrospective analysis was performed on QFT TB test results.

Results: The proportion of positive QFT TB test results is gradually decreasing. In 2008, the proportion was 20.8% and in 2019, it declined to 10.7%, meaning that it has decreased by 48.6% in the last 12 years. The biggest problem are indeterminate results (on average 4.3% per year), as they are unpredictive to a physician. The sensitivity of the QFT TB test in patients with active TB is 82.9%, which is comparable to the data from abroad.

Conclusion: The QFT TB test is highly sensitive to pre-analytical factors and the clinical condition of subjects therefore it is crucial that we follow instructions regarding blood taking and dispatching. The proportion of positive QFT TB test results has been rapidly declining over the years, which is a consequence of efforts to limit the spread of active TB in our country.

Izvleček

Izhodišča: Test QuantiFERON TB (QFT TB) je prvenstveno namenjen za odkrivanje latentne (LTBI) okužbe z bacili tuberkuloze (TB). Članek obsega retrospektivno analizo rezultatov testa QFT TB v Sloveniji med letoma 2008 in 2019, opozarja na vplive predanalitskih dejavnikov na rezultate testa ter govori o razlogih za nastanek nejasnih rezultatov in o občutljivosti testa pri bolnikih z aktivno obliko TB.

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Key words: tuberculosis; latent tuberculosis; QuantiFERON TB test; preanalytical factors; indeterminate result

Ključne besede: tuberkuloza; latentna tuberkuloza; test QuantiFERON TB; predanalitski dejavniki; nejasen rezultat

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Metode: V obdobju 2008–2019 smo v Laboratoriju za mikobakterije Klinike Golnik s testom QFT TB testirali 29.352 vzorcev krvi bolnikov iz različnih zdravstvenih ustanov v Sloveniji. Na rezultatih testa QFT TB smo izvedli retrospektivno analizo.

Rezultati: Delež pozitivnih rezultatov testa QFT TB se z leti postopno znižuje. V letu 2008 je znašal 20,8 %, v letu 2019 pa 10,7 %, kar pomeni, da je v zadnjih dvanajstih letih upadel za 48,6 %. Največjo težavo predstavljajo nejasni rezultati (letno povprečno 4,3 %), saj so za zdravnika nepovedni. Občutljivost testa QFT TB pri bolnikih z aktivno obliko TB je 82,9 %, kar je primerljivo s podatki iz tujine.

Zaključek: Pomembno je, da pri odvzemu in pošiljanju krvi dosledno sledimo navodilom, saj je test QFT TB zelo občutljiv na predanalitske dejavnike in klinično stanje preiskovancev. Delež pozitivnih rezultatov testa QFT TB z leti pospešeno upada, kar je povezano z napori za omejitev širjenja TB in upadom primerov aktivne TB v naši državi.

1 Introduction

Tuberculosis (TB) is a disease caused by bacilli of the *Mycobacterium tuberculosis complex*. Globally, the incidence of active TB decreases by about 2% annually. Nevertheless, about 10 million people worldwide still fall ill each year (1-3). Between 2015 and 2019, the incidence of active TB in the world decreased by a total of 9%. This is less than half of the set goal, which is a 20% decrease in the incidence of the disease by 2020, pursued by the World Health Organization in the framework of the End TB Strategy. In 2019, 87% of new TB cases were from 30 high TB burden countries. Two-thirds of these were contributed by eight countries, including India, Indonesia, China and South Africa. The incidence of TB in EU countries is low, but has been declining more slowly in recent years (2). This is greatly influenced by risk groups, especially refugees coming from countries with a worsening epidemiological picture (2,3). 5-15% of people infected with TB bacilli will develop active disease, while the rest have a latent TB infection (LTBI) (1,3). Timely detection and preventive treatment of LTBI with antimicrobial agents prevent the progression from latent to active TB, which is especially important in patients with weakened immune systems (4,5).

The tuberculin skin test (TST), which is based on the detection of a delayed hypersensitivity reaction to tuberculin antigens, has been used for decades to detect LTBI. Disadvantages of the TST are the inability to differentiate between active and latent TB, non-specificity (response to other mycobacterial infections), and the possibility of a false-positive result in people vaccinated with BCG (6). Over the last 15 years, the TST has largely been replaced by the IGRA (interferon-γ release assay) tests, which include the QFT TB test (7).

The QFT TB test measures the concentration of interferon-γ (IFN-γ) released from a patient's lymphocytes, which occurs as an immune response to a mixture of specific antigens of bacilli from the *M. tuberculosis complex*: ESAT-6 (early secretory antigenic target), CFP-10 (culture filtrate protein) and TB 7.7 (3,5,8). To identify LTBI, the QFT TB test is more specific than TST, as most non-tuberculous mycobacteria do not produce these specific antigens, which are also not present in the BCG vaccine (5,8). Two of the major shortcomings of the QFT TB test are the inability to differentiate between TB and LTBI and the poor sensitivity of the test in patients with microbiologically proven active TB (65–100%) (9). The sensitivity of the test to many pre-analytical factors and the clinical condition of the subjects is also a problem (7-10).

LTBI testing is recommended especially for: i) people coming from countries with a higher incidence of TB; ii) people who have been in contact with a person with active TB; iii) workers from an environment at high risk of infection (long-term care facilities, homeless shelters, asylum homes); iv) workers caring for patients at higher risk of developing TB; v) patients at higher risk of developing TB, including HIV patients, patients with weakened immune systems, patients, who are receiving immunosuppressive drugs, the elderly, and those who have not been properly treated for active TB in the past. The test can also be used as an aid in the diagnosis of active TB as a supplement to classical methods, especially for the detection of TB in children (11).

In the Laboratory for Mycobacteria of the University Clinic of Pulmonary and Allergic Diseases (UCPAD) Golnik we started testing the QFT TB test in 2004. Firstly, a version of the test with two test tubes was used, zero (Nil) tube without added peptide antigens and antigenic or TB tube. This version was replaced by the next generation of the QFT TB Gold test, which, in addition to the antigen tube, also contained a mitogen (Mit) test tube with phytohaemagglutinin (PHA) to check the subject's immune response. The latest generation of the QFT TB Gold Plus test is an upgrade of the older version and

contains two antigen tubes – TB1 and TB2. Both antigen tubes contain peptide antigens associated with the *M. tuberculosis* complex (12). The first TB1 antigen tube contains the ESAT-6 and CFP-10 peptides, which trigger an immune response of CD4+ T-lymphocytes in the body. The second TB2 antigen tube contains additional lipids that stimulate the immune response of both CD4+ and CD8+ T-lymphocytes. Both cell types are involved in the body's defences during TB infection through the release of IFN-γ (12,13).

The purpose of this article is a retrospective analysis of the QFT TB test results between 2008 and 2019 and a comparison of the results with the incidence of active TB in Slovenia. At the same time, we would like to draw attention to factors that may lead to incorrect or indeterminate QFT TB test results.

2 Methods

We performed a retrospective analysis of the QFT TB test results between 2008 and 2019. The test was performed on blood samples received by the Laboratory for Mycobacteria of the UCPAD Golnik. The total number of samples received during this time was 29,352.

The research was conducted in accordance with the principles of the Helsinki Declaration, the Oviedo Convention on Human Rights and Biomedicine and the Slovene Code of Medical Deontology. The research was approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 0120-94/2021/3, dated 25 March 2021).

2.1 Sample adequacy control and QFT TB test performance

The QFT TB test was performed according to the manufacturer's instructions (Qiagen, Hilden, Germany). We received three (between 2008 and 2015) or four (from 2015 onwards) test tubes for the QFT TB test with the blood of the subjects, both from the UCPAD Golnik and from various external clients from all over Slovenia.

Upon receiving the samples, we first checked their adequacy and rejected the inadequate ones. Examples of inadequate samples are incorrectly labelled samples, blood collected in inappropriate test tubes, samples with an incorrect amount of blood collected, samples where more than 16 hours passed since collection, and samples that were stored in the refrigerator while waiting to be transported. All factors that may affect the result of the QFT TB test are listed in Table 1.

After checking their adequacy, the tubes were mixed eight times around the longer axis and then incubated at 37°C for 16–24 hours. After incubation, the tubes were centrifuged for 15 min at 2727 rpm). This was followed by the measurement of IFN-γ release using the ELISA method (13).

2.2 Interpretation of results

After a preliminary incubation, the IFN-γ release level from three (QFT TB-Gold) or four (QFT TB-Gold Plus) tubes, Nil, TB1, TB2, and Mit, was measured in the blood sample of each subject. The Nil result, which

Table 1: Pre-analytical factors and possible effects on the QuantiFERON-TB (QFT) test result.

Pre-analytical factor	Possible consequence	Source
Insufficiently disinfected blood collection site	false positive result	10,14
Blood collected in cold tubes	false positive result indeterminate result	5
Volume of blood collected (opt. 0.8–1.2 mL) * < 0.8 mL	inability to perform the test	
* > 1.2 mL	false positive result indeterminate result	9,10
Uneven mixing of test tubes	false negative result false positive result	9,10
Transportation of the sample to the laboratory (> 6 hours)	indeterminate result false negative result	9,10,15
Transportation of samples at too low a temperature	indeterminate result false negative result	5,10,16

Table 2: Interpretation of QuantiFERON-TB Gold and QuantiFERON-TB Gold Plus test results. Taken from (13).

QFT TB test results	Released IFN-γ values (IU / mL)
Negative	
TB1 – Nil / TB2 – Nil	< 0.35
Mit – Nil	> 0.50
Positive	
TB1 – Nil / TB2 – Nil	> 0.35
Mit – Nil	> 0.50
Indeterminate	
Nil	> 10
Mit – Nil	< 0.50

Legend: Nil – the IFN-γ value in the Nil tube; TB1 – Nil and TB2 – Nil – the IFN-γ value in antigen tubes minus the Nil value; Mit – Nil – the IFN-γ value in the mitogen tube minus the Nil value; QFT TB – QuantiFERON TB.

serves as a background measurement, was subtracted from the rest. This was followed by the interpretation of the results according to the amount of released IFN-γ in TB1 – Nil, TB2 – Nil, and Mit – Nil tubes. Possible test results are negative, positive and indeterminate (Table 2).

Based on our own observations, we added a negative result with an asterisk (neg*), which represents the limit values (0.25–0.35 IU/mL) and for which we recommend the test be repeated. In our study, these results are considered negative.

2.3 Retrospective analysis of the routine QFT TB test results and the QFT TB test results in patients with active TB

The analysis included all blood samples received in the laboratory from both the UCPAD Golnik and from external clients between 2008 and 2019. The results were anonymized, the proportions of positive, negative, indeterminate, and rejected QFT TB test results (equation 1) were calculated, and compared by years.

Equation 1:

$$X_{outcome,\ year} = n_{outcome,\ year} / N_{year}$$

$X_{outcome,\ year}$ – the relative share of a specific test result in a specific year;

$n_{outcome,\ year}$ – the number of outcomes of a specific test result in a specific year;

N_{year} – the number of all blood samples received in a specific year.

The decrease in the proportion of positive QFT TB test results (p) was calculated by equation 2.

Equation 2:

$$p = X_{QFT\ positive,\ 2019} - X_{QFT\ positive,\ 2008} / X_{QFT\ positive,\ 2008}$$

We also analyzed the results of the QFT TB test in patients with active TB. Data on patients with active TB were obtained from the UCPAD Golnik TB Registry and the number of patients who underwent the QFT TB test was checked. If several blood samples were taken from an individual patient for the QFT TB test, the result of the test performed closest to the date of obtaining the clinical sample from which the active TB was confirmed was taken into account, but no later than three months before or after confirmation.

For patients with confirmed active TB and a negative or indeterminate result of the QFT TB test, data on the patient's clinical picture, associated diseases and treatment were also obtained from the Golnik TB Registry.

3 Results

3.1 Sample adequacy control and analysis of QFT TB routine test results

In the 12-year period, the Laboratory for Mycobacteria of the UCPAD Golnik received 29,352 blood samples for the QFT TB test, mostly from external clients from health institutions in Slovenia (Figure 1). Among those received, samples from pulmonology, dermatovenereology, rheumatology, and gastroenterology departments and outpatient clinics predominated.

Samples for which the influence of pre-analytical factors was detected and samples with incomplete data on the accompanying referral (e.g. missing date and the collection time) were rejected. The proportion of rejected samples remains fairly constistent over the years, ranging from a minimum of 0.8% to a maximum of 1.9% per year.

The share of positive results was the highest in 2008 with 20.8% and the lowest in 2019 with 10.7%, which indicates a drop in LTBI infections by 10.1 percentage point or 48.6% (Figure 2). The trend of the negative QFT TB test results is expected to be reversed from the positive ones. The highest share of negative results was recorded in 2019 at 83.8% and the lowest in 2008, when it was 66.8% (Figure 2).

The biggest problem in detecting LTBI is the indeterminate results of the QFT TB test, in which the amount of IFN-γ released in the Mitogen tube (positive control) does not exceed 0.5 IU/mL or the amount of IFN-γ released in

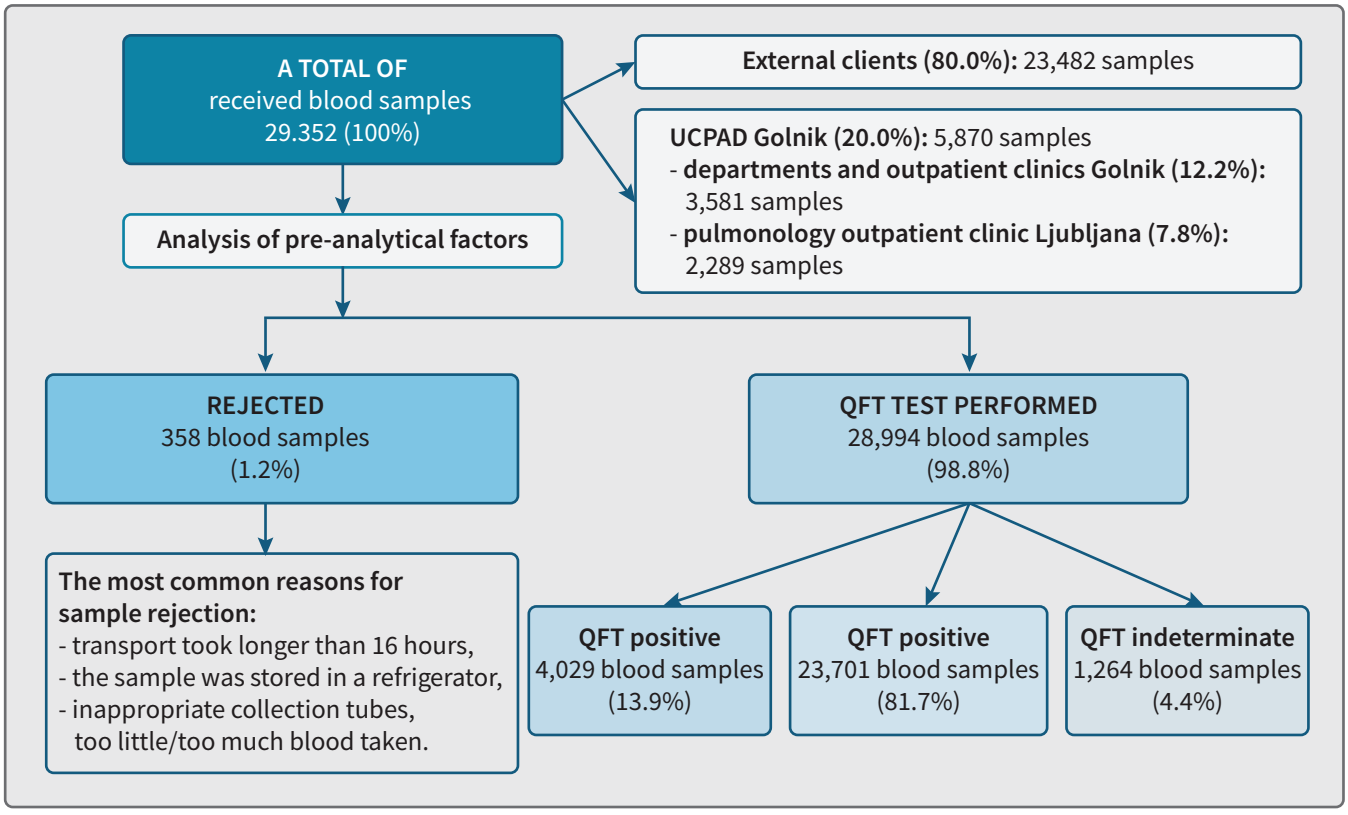

Figure 1: Schematic presentation of received and rejected blood samples for the QFT TB test and the results of tests performed between 2018 and 2019.
Legend: QFT – QuantiFERON.

the Nil tube (negative control) exceeds 10 IU/mL. The share of indeterminate results has fluctuated over the last 12 years, with an average of 4.3% over the period between 2008 and 2019. The highest was in 2008 with 11.2% (93 samples) and the lowest in 2011 with 2.4% (54 samples) (Figure 2).

3.2 Analysis of QuantiFERON-TB (QFT) test results in patients with active tuberculosis (TB)

Out of 499 cases of active TB in Slovenia between 2015 and 2020, the QFT TB test was ordered in 152 patients

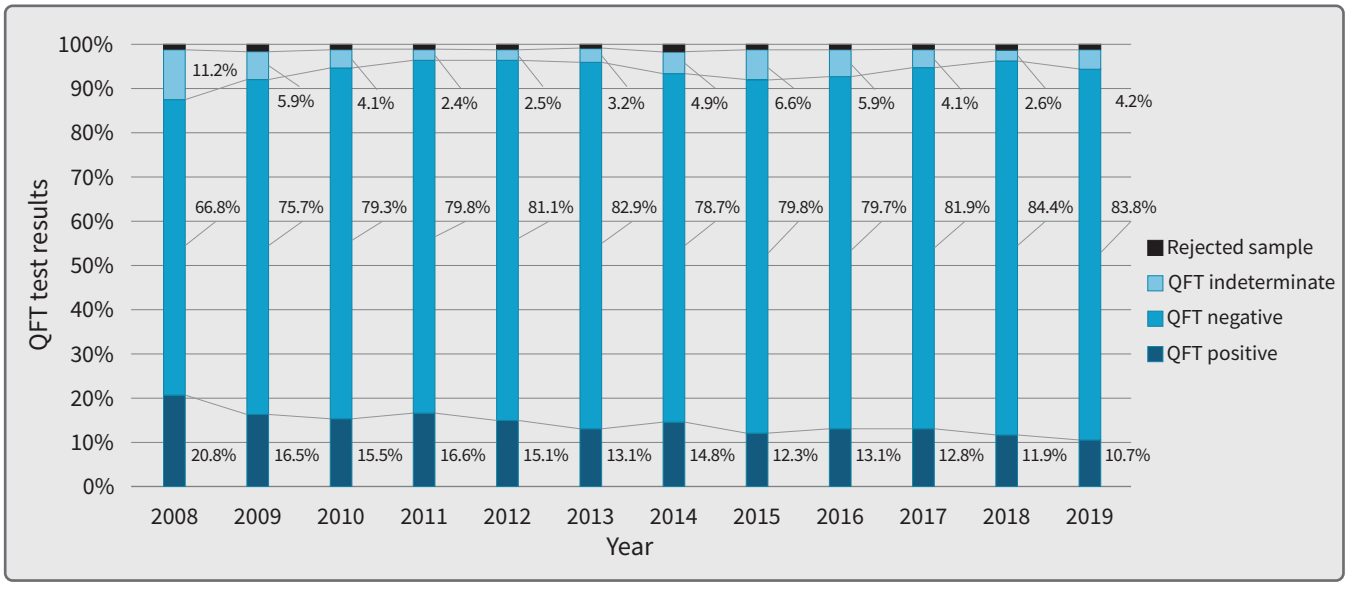

Figure 2: A chart of QuantiFERON-TB (QFT) test results between 2008 and 2019.

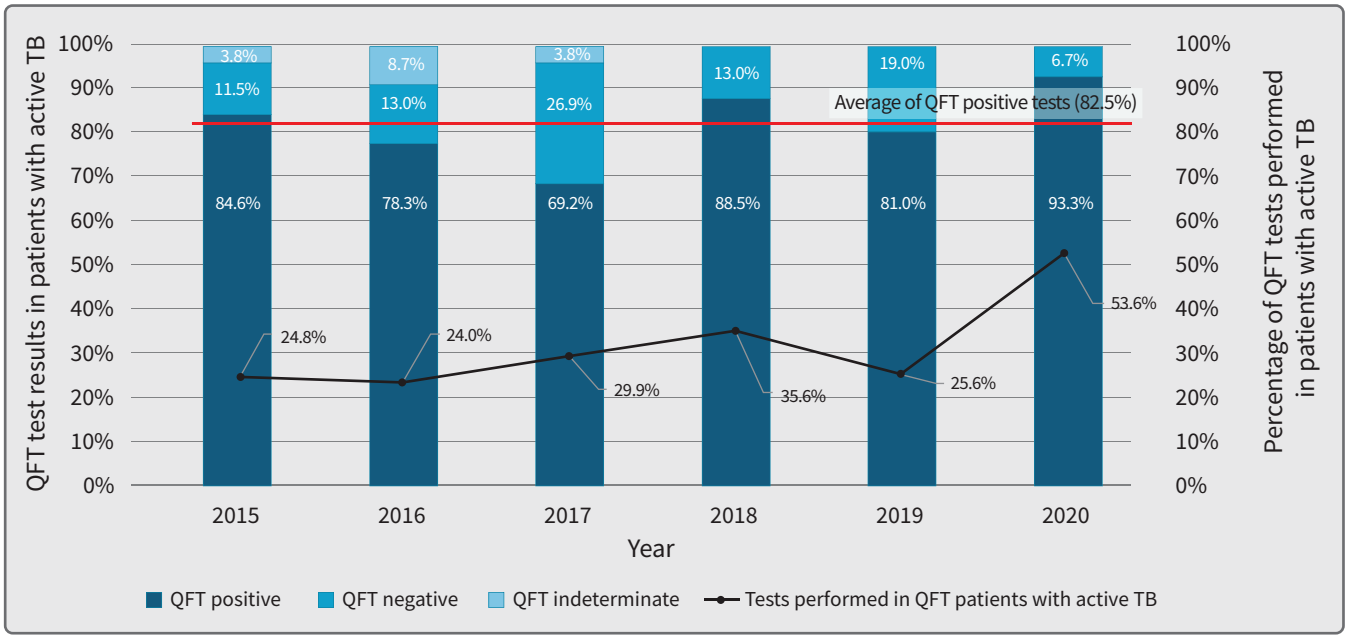

Figure 3: A chart of QuantiFERON-TB (QFT) test results in patients with microbiologically confirmed active tuberculosis (TB).

(30.5%). The fewest were performed in 2016 (24.0%) and the most in 2020 (53.6%) (Figure 3).

In 126 patients (82.9%) with proven active TB, the QFT TB test was positive. Of these, the share of positive results of the QFT TB test was the lowest in 2017 with 69.2% (18 samples) and the highest in 2020 with 93.3% (28 samples) (Figure 3).

In 26 patients with confirmed active TB (17.1%), the result of the QFT TB test was negative or indeterminate. Of these, 15 patients had pulmonary TB (57.7%), five patients had pulmonary and extrapulmonary TB (19.2%), five patients only had extrapulmonary TB (19.2%), and one patient had miliary TB (3.9%). Of the extrapulmonary TB, as many as four patients had lymph node TB, two had tuberculous pericarditis, two had bone TB (spinal TB), and one had cutaneous TB and pleural TB.

The results were also compared with associated diseases and treatments. Ten of the 26 patients with active TB (38.5%) received corticosteroids, biologics or other immunosuppressive drugs. Five patients (19.2%) also had other associated diseases or conditions such as diabetes, chronic kidney disease, and alcoholism. In six patients with active TB (23.1%), no diseases or treatments were observed, which are often associated with false-negative or indeterminate QFT TB test results.

3.3 Decline in active and latent TB in Slovenia

We also analyzed the results of routine QFT TB tests compared to the incidence of active TB in Slovenia. The incidence of TB in Slovenia has been declining over the years (11) (Figure 4). It decreased by 55% between 2008 and 2019 (9), with no definitive data for 2020. The declining trend in the incidence of active TB is also followed by a decline in the share of positive results of the QFT TB test, which decreased by 48.6% in 12 years.

4 Discussion

The purpose of our study was a retrospective analysis of the results of the QFT TB test over a 12-year period and a comparison of the results with the incidence of active TB in Slovenia. We found that the incidence of TB in Slovenia has decreased by 55% in the last 12 years (11). With our research, we have shown that the declining trend in the incidence of active TB is followed by a decline in LTBI. This is to be expected, as fewer cases of active TB mean less risky contact and transmission of infection.

Of the active TB cases treated between 2015 and 2020, the QFT TB test was performed in only 30.5%, which is a relatively small percentage. For the diagnosis of pulmonary TB in adults, microscopic examination, cultivation, and molecular biological tests (polymerase chain reaction or RT PCR) are primarily used. Cultivation is also the only way to differentiate between active TB and LTBI. The result of the QFT TB test is positive in most patients with active TB (average 82.5%), which is comparable to other studies that report a 65 to 100% sensitivity of the QFT TB test (9). This should not mislead us and make

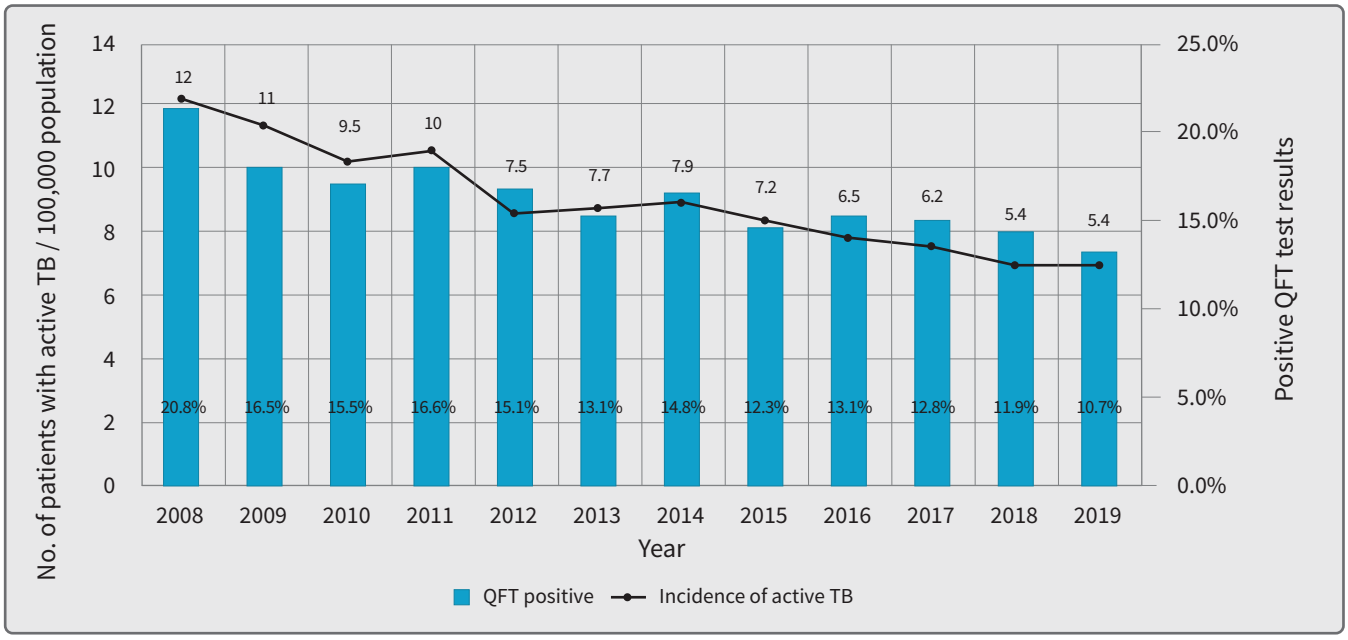

Figure 4: A chart of the decline in the incidence of active tuberculosis (TB) and the share of positive QuantiFERON-TB (QFT) test results in Slovenia between 2008 and 2019. The incidence of active TB taken from (11 and the Golnik TB Register).

us stop considering a possible diagnosis of TB if the QFT TB test is negative (9,12). The QFT TB test is often negative in severe forms of TB, such as tuberculous meningitis, miliary TB, pericarditis, and bone TB (17).

The QFT TB test is very sensitive to pre-analytical factors and the immune status or clinical picture of the subject (18). Early detection of LTBI is especially important in patients at risk for TB progressing from latent to active. This early detection is often complicated by the indeterminate results of the QFT TB test, typical in these very groups of patients (3,8,15).

Indeterminate results are those with too low a response in a Mitogen tube (<0.5 IU / mL) of which the interior is coated with phytohaemagglutinin (PHA), which triggers a general immune response (5,7). The response to PHA, with strict consideration of analytical procedures, depends primarily on the functional integrity of lymphocytes and the ability to release IFN-γ, which may change due to various clinical conditions and procedures. The incidence of indeterminate results is higher in people with health issues than in healthy people, and depends on the therapy the patient is receiving (anti-TNF-α biologics, antiretroviral therapy, steroids, and nonsteroidal anti-inflammatory drugs), age, immunological parameters, and medical condition (5,8,15,18,19).

This explains a significant part of the indeterminate results of the QFT TB test, as in recent years, in addition to samples from pulmonary, many samples from gastroenterology, rheumatology, dermatology, and infection departments and outpatient clinics have been accepted in the laboratory for the purpose of examination prior to introducing biologics or organ transplantation (19). Often, however, indeterminate, false-positive, and false-negative QFT TB test results may also be due to pre-analytical factors (Table 1).

If we observe the share of indeterminate results by years, it was by far the highest in 2008. At that time the QFT TB-Gold test was introduced, which now contained a Mitogen test tube to check the immune response of the subject and which also acted as the indicator of transport temperature adequacy. This is especially important, because in our laboratory, in addition to samples from UCPAD Golnik, we also accept blood samples from various medical institutions from more distant Slovenian cities, which makes it more difficult to ensure their proper collection and transport (20). In the following years, the proportion of indeterminate results decreased significantly through continuous monitoring, correct sample collection and transport instructions, inspection of test tubes on admission to the laboratory, and notifying and training of nurses and couriers (20). Compared to research from abroad, which in routine testing shows shares of indeterminate results to be between 5 and 40%, this share being on average 6% in testing health professionals, we are in an enviable position with an average of 4.3% (15,18,21).

5 Conclusion

With our retrospective analysis of the QFT TB test results, we confirmed that the share of positive QFT TB test results in Slovenia is declining together with the decline of the incidence of active TB. This is a good incentive for further managing TB infections. When performing the QFT TB test, we still encounter a significant share of indeterminate results due to the variety of therapies before taking blood samples for the QFT TB test (e.g. immunosuppressants), the clinical picture of the patient as well as pre-analytical factors. If the first two cannot be influenced, we are convinced that by following blood collection and transport instructions, the impact of pre-analytical factors can further be reduced and thus the diagnosis of LTBI can be improved.

The sensitivity of the QFT TB test in detecting active TB is around 80%. This should be considered when using the QFT TB test to diagnose active TB (especially in the case of extrapulmonary and paediatric TB diagnosis). In the most severe forms of TB (meningitis, miliary, extrapulmonary TB), the QFT TB test is often false negative.

Conflict of interest

None declared.

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