“Dunărea de Jos” University of Galați
Doctoral School of Biomedical Sciences
Doctoral field: Medicine

Abstract

DOCTORAL THESIS

Depressive disorders in children with tuberculosis

PhD Student,
Cristea (Mihailov) Oana-Mariana

President Professor Aurel Nechita, PhD
“Dunărea de Jos” University of Galați

PhD Coordinator Professor Anamaria Ciubară, PhD
“Dunărea de Jos” University of Galați

Official referees Professor Nicu Gavriluță, PhD
“Alexandru Ioan Cuza” University of Iași
Professor Vasile Valeriu Lupu, PhD
“Grigore T. Popa” University of Medicine and Pharmacy of Iași
Professor Lucreția Anghel, PhD
“Dunărea de Jos” University of Galați

Series M: Medicine No. 4

Galați, 2024

The series of doctoral theses publicly defended in UDJG since October 1, 2013 are:

Fundamental field **ENGINEERING SCIENCES**

Series I 1**: Biotechnologies**
Series I 2**: Computers and Information Technology**
Series I 3**: Electrical engineering**
Series I 4**: Industrial engineering**
Series I 5**: Materials Engineering**
Series I 6**: Mechanical Engineering**
Series I 7**: Food Engineering**
Series I 8: **Systems Engineering**
Series I 9**: Agricultural engineering and management and rural development**

Fundamental Field **SOCIAL SCIENCES**

Series E 1**: Economies**
Series E 2**: Management**
Series E 3: **Marketing**
Series SSEF: **The Science of Sport and Physical Education**
SJ Series: **Law**

Fundamental field **HUMANITIES AND ARTS**

U 1 Series**: Philology- English**
U 2 Series**: Philology- Romanian**
U 3 Series**: History**
U 4 Series**: Philology - French**

Fundamental field **of MATHEMATICS AND NATURAL SCIENCES**

Series C**: Chemistry**

Fundamental field **BIOLOGICAL AND BIOMEDICAL SCIENCES**

Series M**: Medicine**

Table of Contents

Tuberculosis (TB) is an infectious-contagious disease caused by the bacteria in the Mycobacterium tuberculosis (MTB) family. Generally, MTB infections are localized in the lungs, but they can also affect other parts of the body [1]. In addition, these bacteria can cause asymptomatic infections, known as latent tuberculosis. According to the literature, approximately 10% of latent infections progress to active disease which, if left untreated, has a mortality rate of about 50% [1]. The typical symptoms present in active TB infections are represented by the following: chronic cough, associated or not with muco-sanguinolent expectoration, fever, night sweats and weight loss. MTB infections localized at the level of other organs can cause a wide range of symptoms [1, 2].

Tuberculosis is airborne transmitted from one infected person to another. In the case of active pulmonary tuberculosis, airborne transmission occurs when the infected person coughs, sneezes, spits or speaks [3]. In contrast, people who have latent MTB infection do not spread the disease. The incidence of active infection is higher in immunocompromised, seropositive, and smoking individuals. Active tuberculosis is diagnosed following clinical and paraclinical assessments suggestive for it, such as: imaging investigations either by means of radiographies or computer tomography, examination of body fluids (sputum) by microscope and on culture [3]. Instead, latent tuberculosis is diagnosed based on tuberculin intradermal reaction (IDR to 5UPPD) or blood tests [4, 5].

Tuberculosis prevention involves screening the population that is at increased risk of developing tuberculosis, thus favoring its early detection and, therefore, its proper treatment, as well as vaccination with bacillus Calmette-Guérin (BCG) vaccine [4, 5].

Despite the availability of vaccination and chemoprophylaxis for almost 90 and 60 years respectively, tuberculosis remains the leading cause of death worldwide due to an infectious agent, surpassing human immunodeficiency virus / acquired immunodeficiency syndrome (HIV/AIDS) for the first time [4, 5]. The World Health Organization estimates that approximately 10.4 million new cases and 1.8 million deaths from tuberculosis (TB) are annually registered. A third of these new cases, about three million, are not registered within the health system and therefore many of them do not receive proper treatment.

TB treatment requires multiple drugs administered over several months. These long therapeutic treatments pose a challenge for both patients and the healthcare system, especially in low- and middle-income countries, where the burden of the disease often far exceeds local resources. In addition, in some areas, the incidence of drug-resistant tuberculosis, which requires longer treatment regimens and with drugs which are more expensive and difficult to tolerate, is increasing.

The Sustainable Development Goals (SDGs) aim to end the TB epidemic but, unfortunately, the decrease in incidence has been disappointing. Despite advances in TB treatment, there are currently major gaps when it comes to its effectiveness. In addition, at present, multi-resistant TB infection rates are showing an alarming increase globally. It is defined by its resistance to the two major drugs associated with standard treatment against tuberculosis, isoniazid and rifampicin [4, 5].

According to the literature, it is estimated that in 2018 about a quarter of the world's population has latent TB infection. Also, about 1% of the population registers new infections with MTB annually [6].

In 2018, most TB cases were recorded in the following regions: Southeast Asia (44%), Africa (24%) and the Western Pacific (18%). More than 50% of cases were recorded in eight countries: India (27%), China (9%), Indonesia (8%), Philippines (6%), Pakistan (6%), Nigeria (4%) and Bangladesh (4%). The number of new cases each year decreases by about 2% per year [7, 6].

In addition, it is estimated that 10 million people developed active tuberculosis in 2020, resulting in 1.5 million deaths, making them the second leading cause of death from an infectious disease, after COVID-19 [6].

The WHO Global Tuberculosis Report 2021 showed how "incidence has decreased due to pandemic-related service disruptions" [8]. According to WHO estimates, 10 million people developed tuberculosis in 2020, but only 5.8 million cases were diagnosed and reported – an 18% decrease compared to 2019, mainly affecting Asian countries [9].

The January 2022 New England Journal of Medicine article reported that although COVID-19 has had devastating effects on every aspect of global health, TB services have been disproportionately affected, with TB mortality rising worldwide for the first time in over 10 years. [9]

Romania reported the highest incidence rates among children under 15 years old: among children aged 0 to 4 years, the incidence rate was 14.1 cases per 100,000, and among those aged 5 to 14 years, the incidence rate was 26.7 cases per 100,000 children.

The period between 10 and 24 years represents a critical period in biological development, but also in the transitions that take place at the social level [10]. During this period, individuals acquire and develop the physical, emotional, cognitive, economic, and social resources that serve as the foundation for their lifelong well-being. Tuberculosis and its treatment can have a negative impact on this period and therefore, it can cause a derailment from the growth and transitions taking place at this stage [11].

The long-term treatment, of at least 6 months for treatment-susceptible tuberculosis or 18-24 months for multidrug-resistant tuberculosis (MDR-TB), the adverse drug reactions, the stigma and the financial burden of tuberculosis contribute to patient's non-adherence to treatment and to unsuccessful treatment results [12].

School disruption, the physical, psychological, and cognitive effects of illness and treatment, and household poverty can have an impact on a child's development, his/her educational level, and lifelong economic and work prospects. In the worst case, a TB diagnosis can lead a family into a cycle of poverty, which can be perpetuated through generations [13].

The entire study underlying this work was conducted following a phased model.

The first phase involved the selection of patients aged 7-18 years with a diagnosis of tuberculosis. All information on the subjects was obtained from the archives of the Pulmonology Hospital in Galati.

The next stage involved the analysis of the group of patients, with their final selection, resulting a group of 190 subjects and the follow-up of all socio-demographic, diagnostic (clinical and paraclinical), but also therapeutic characteristics to define the elements that can have an influence on their evolution.

The third phase involved the consecutive grouping of respondents into study subgroups, based on specific characteristics, comparative statistical analysis and clinical, paraclinical and therapeutic characteristics.

The last phase represents in fact the final goal of this work, namely the elaboration of an algorithm for diagnosis, treatment, follow-up, and prevention for depressive disorders in pediatric patients, depending on their age, symptoms, and TB characteristics.

Three studies had been performed in this paper: the study of clinical-paraclinical epidemiological and treatment peculiarities, the study **on the incidence of depressive disorders in pediatric patients with TB and the study of risk factors / potential influence of depressive disorders in the pediatric patient with TB.**

The study of clinical-paraclinical epidemiological and treatment peculiarities in the patients enrolled in the study group evaluates the epidemiological peculiarities present in the group, both clinically and paraclinically. Therefore, the rate of using the clinical and paraclinical investigation methods, the results provided by them, the personal pathological history, the reasons for presentation, the vaccination status, the stage of the disease at the time of registration will be statistically evaluated. Also, the distribution of the research group had been assessed according to its socio-demographic peculiarities, such as:

- ✧ Distribution by sexes of the research group
- ✧ Distribution by origin environment
- ✧ Distribution by age groups
- ✧ Distribution by weight of the group.

For an easier understanding of the conclusions offered by this chapter, we will review the most important ones, as follows:

- ✧ From the point of view of the origin environment, it will be noted that the majority (70.53%, n=134) of the subjects included in this study group came from rural areas, while only 29.47% (n=56) came from urban areas.
- ✧ According to the distribution by sexes of the study group, it will be concluded that most of the subjects included in this study group were male (54.21%, n=103), while the remaining 45.79% (n=87) were female, which suggests a quasi-equal distribution vis-à-vis their sex.

- Most subjects (49.47%, n=94) included in this study group were aged between 15 and 18 years, 29.47% (n=56) were aged between 11 and 14 years, and 21.05% (n=40) were aged between 7 and 10 years.
- Another socio-demographic characteristic of interest for the research was the weight of the subjects. With regard to this parameter, the following were concluded: the average weight was 47.57 to which a standard deviation of 17.174 is associated; the distribution of the group by weight is almost Gaussian, with a skewness asymmetry index of 0.608, signifying a slight positive asymmetry, and a Kurtosis vaulting index of 0.744; within the histogram, the curve is subtly leptokurtic.
- Performing the Pearson correlation at two ends also demonstrated statistically the existence of a dependence between the variable defined as the age of the subjects and their weight (with a correlation of .72, indicating a large effect size ($p < .001$, 95.00% CI = [.65, .79]).
- Most subjects must travel less than 50 km to access medical services.
- Most subjects had no personal pathological history, i.e., 73.2% (n=139).
- Also, its purpose was to identify the patients who came to the health facility following an epidemiological context, totaling 95.79% (n=182).
- One of the objectives of this research paper was to identify the main accusations that led to the presentation of the subjects in the health facilities. Therefore, it can be observed that the main reason for presentation was a TB contact (95.79%, n=182).
- From the point of view of paraclinical information associated with the group in question, it is noted that 18.42% (n=35) of the subjects had inflammatory syndrome, while most subjects did not have anemia syndrome (91.05%, n=173). BK sputum examinations performed to identify BK were performed in 41.05% (n=78) of cases; most subjects did not undergo ADA titration (97.89%, n=186). Biochemical evaluation of pleural puncture fluid revealed the presence of lymphocytes in 65% and 55% in 1.58% (n=3) of cases. Also, the puncture fluid was examined for the presence of BK, thus, 1.58% (n=3) of the subjects showed a negative BAAR result. Within the group, the intradermal reaction was used in 85.8% (n=163) of cases, in which case the following are highlighted: the mean IDR value is 11.14 with a standard deviation of 5.553, the distribution curve shows a shift to the right,

compared to the normal, Gaussian distribution; the distribution within the group is platykurtic, and cases are rarer at the base of the histogram curve.

- The mean value of the presentations is 4.77 with a standard deviation of 2.651; the distribution within the group is leptokurtic and the cases are rarer at the base of the histogram curve.
- From an imaging point of view, radiological examinations of chest X-ray- and chest CT-type were used. The vast majority (93.68%, n=178) of subjects included in this study group performed at least one chest X-ray, while the use rate of computed tomography was approximately inversely proportional to the use rate of chest X-ray. Specifically, 94.21% (n=179) did not perform CT.
- Few subjects underwent pleural puncture (2.63%, n=5). An analysis of Pearson correlation between the number of chest CT investigations and the number of presentations was performed. Cohen's standard was used to evaluate the strength of the relationship, where coefficients between .10 and .29 represent a small extent of the effect, the coefficients between .30 and .49 represent a moderate extent of the effect, and the coefficients above .50 indicate a considerable extent of the effect. The correlation result was examined based on an alpha value of .05. A significant positive correlation was observed between the number of chest CT investigations and the number of presentations, with a correlation of .187, indicating a small extent of the effect ($p = .010$, 95.00% CI = [.04, .31]). This suggests that as the number of chest CT investigations increases, the number of presentations tends to increase.
- The most frequent pathological variation of TB infection is Primary occult TB, most subjects presenting this type of infection (81.58%, n=155), followed by secondary tuberculosis, in a percentage of 11.05% (n=21); primary tuberculosis associated with adenopathy was found in 5.26% (n=10) of cases, while only 2.11 (n=4) had TB pleurisy.
- Most subjects were included in this study group at disease onset (98.95%, n=199).
- In terms of pharmacological treatment, hydrazide treatment was predominantly chosen (81.58%, n=155). The next most used treatment was DOT cat 1, used in a proportion of 16.84% (n=32) in the group. 1.58% (n=3) were treated in the

continuation phase of DOT. Of the 190 subjects, most showed good compliance to the treatment, 88.42% (n=168) of them did not abandon the treatment.

- ✧ It is observed that more than half of subjects (83%, n=157) had complete reassessment (all 3 appointments), while 11% (n=22) had incomplete reassessment (T0 and T1), 6% (n=6) had only T0 evaluation without reassessment.

All the aforementioned data are general information on the distribution of patients in the research group. An extremely important study element that outlined the research peculiarity of this chapter was represented by the identification of statistical peculiarities of correlation between epidemiological, treatment and socio-demographic variables.

As first intent, the particularities of the treatment used and of the epidemiological and socio-demographic variables were analyzed, mainly by performing Chi-square independence tests.

The hypothesis of an interdependence between the age of the subjects and the chosen treatment was evaluated, but the result suggested their independence.

The Chi-square test was used to demonstrate whether a dependency relationship exists between the TB Type and Environment variables, but the Chi-square test results were not significant based on an alpha value of .05, $\chi 2(21) = 1.620$, $p = .660$, suggesting that the variable defined as Type of TB and Environment shows no statistically significant correlations.

The same type of Chi-square test was also used to assess the degree of dependence between the type of TB and the sex of the subjects, but the results were not statistically significant ($p = .173$). Instead, it is important to mention that statistical significance ($p < 0.001$) was determined between the type of TB detected in subjects and their PPH.

The causal relationship between the type of treatment chosen and the type of TB disease identified was then investigated; the Chi-square test results were significant, based on an alpha value of 0.05, $\chi 2(63) = 202,700$, $p < 0.001$, suggesting that the Treatment variable and the TB type are related.

It was subsequently observed that treatment abandonment occurred only with hydrazide treatment, Chi-square test results were not significant based on an alpha

value of .05, $\chi2(3) = 5.618$, $p = .060$; suggesting that the two variables could be independent of each other.

In order to corroborate all the information presented above, research focusing on the type of TB found in the group and the used investigations was initiated. The data obtained were centralized as follows:

- Statistically significant dependencies were found between TB type and the existence of the inflammatory syndrome ($p = .000$) but also of the anemic syndrome ($p = .000$)
- Chi-square test results were significant, based on an alpha value of .05, $\chi2(42) = 45.193$, $p = .000$, suggesting that TB Type and BK Sputum are related.
- Chi-square test results were significant, based on an alpha value of .05, $\chi2(21) = 39.046$, $p < .001$, suggesting that TB Type and the Changes in blood count lines are related.
- Chi-square test results were significant, based on an alpha value of 0.05, $\chi2(20) = 47.059$, $p < 0.001$, suggesting that TB Type and ADA are related.
- Chi-square test results were significant, based on an alpha value of .05, $\chi2(21) = 12.699$, $p = .005$, suggesting that TB type and IDR are statistically related.
- Chi-square test results were significant, based on an alpha value of .05, $\chi2(42) = 33.424$, $p = .000$, suggesting that TB type and SLT common flora are related.
- There were no statistically significant differences suggesting dependence between the type of TB of the subjects and the collection/results of nasal and pharyngeal exudates. The p value <.001 defines the existence of statistically significant differences between the type of TB affectation and the performance of pleural puncture.
- Instead, from the point of view of performing radiological investigations, the existence of statistically significant differentiation relationships between performing the chest CT and the type of TB pathology was confirmed according to the Chi-square test (based on an alpha value of 0.05, $\chi2(21) = 58.854$, $p < 0.001$), but not with performance of chest radiographies ($p = 0.352$).

The second study conducted is **on the incidence of depressive disorders in pediatric TB patients.**

Major depressive disorder is a leading cause of chronic disability (and of mortality, worldwide [205, 206]. Many of the consequences on health associated with depression are due to the fact that this disorder predisposes and exacerbates other chronic medical conditions, including diseases related to the vegetative symptoms of depression, such as obesity and diabetes [207, 208]. Importantly, the vegetative symptoms to which these conditions are most closely related, namely appetite and weight modification, are not shared by all patients with depression. Patients with major depressive disorder exhibit marked appetite heterogeneity, with approximately 48% of depressed adult patients experiencing depression-related decreases in appetite, while approximately 35% exhibiting depression-related increases in appetite [209].

The clinical literature also suggests that irritability could be a significant subtyping variable in major depressive disorders, and their likelihood is higher in women and young people. They are also associated with more severe depression, lower functional status and quality of life and have a history of at least one suicide attempt. These differences could be of considerable importance, as irritability with anger attacks might be present in more than one-third of patients with major depressive disorder [210, 211, 212].

One of the most common residual symptoms of a partially resolved depression is fatigue. Broadly defined, fatigue symptoms can affect the physical, cognitive, and emotional function, the school and work performance, disrupt social and family relationships, and increase healthcare use. In addition, some of the medications used to treat major depressive disorders can induce fatigue as a side effect.

Several studies have demonstrated underlying personality characteristics that are associated with patients with affective disorder in general and patients with major depressive disorder specifically. These studies described personality characteristics associated with major depressive disorder, including high levels of neuroticism, decreased extroversion (i.e., increased introversion), increased avoidance of evil, increased fatiguability, histrionic traits, hostility, tendency to worry, strain, shyness, fear, a rigidity or perspective related to habits, greater intolerance to ambiguity, a tendency to be moved by feelings, being prone to guilt, perfectionist, low sociability,

lacking self-confidence, having a pessimistic perspective, low emotional stability and low objectivity [213, 214, 215]

The summary tables were structured based on the information which includes the characteristics of 190 patients aged 7–18 years and a certain diagnosis of TB, investigated, treated, and monitored at the Pulmonology Hospital in Galati and TB Dispensaries in Galati, Tecuci and Tg Bujor.

The totality of the information obtained from summarizing the subjects' observation sheets served as variables within the final summary table. Thus, sampling lists were made by excluding cases that did not comply with the inclusion criteria and, subsequently, subdividing the main group according to age categories, main diagnosis, presence of heart disease and personal pathological history, as well as clinical data on the status of vital functions and therapeutic attitude. The data thus obtained was entered into a summary table, more precisely Excel table, from the Microsoft Office 365 package, version 2019. Within this table, the data has been filtered according to different criteria. Subsequently, the statistical analysis performed on these data was performed using SPSS software version 24, with which causal relationships and existing correlations between variables that will be described later in this paper were studied.

The statistical study conducted within this doctoral paper addressed aspects of both descriptive and analytical statistics. Descriptive statistics were used to classify and synthesize the data obtained. Through it, existing information is concentrated, and statistical indicators specific to it express the characteristics and trends of the studied parameters.

Descriptive statistical indicators were calculated and analyzed for all variables where this calculation approach was considered useful. The indicators used to develop this type of statistical analysis are the following: amplitude, dispersion, standard deviation, mean square deviation and dispersion, Kurtosis index, mean, median, minimum, and maximum value.

The graphic representation in this paper was made with the help of pie graphs, histograms, scatterplots and QQ plots.

Chi-square dependency tests, Pearson correlations, and ANOVA tests were used to evaluate the statistical relationship between the different variables recorded within the group.

This subchapter evaluates the incidence of depressive disorders in pediatric TB patients. The conclusions drawn in this chapter treat distinctly and in stages the steps taken by the attending physician to establish the suspicion of depressive disorder in this group of subjects. Initially, the most essential element of statistical analysis was defined by assessing the incidence of anamnesis applicability, as well as by determining the patient reevaluation spectrum. Thus, it was observed that an overwhelming percentage of patients (99.5%) benefited from detailed anamnesis when coming to the Galati Pulmonology Hospital, but also to the assigned dispensaries.

In the statistical analysis of this chapter, it was assumed that pediatric depression should be assessed in the context of precipitating factors, stressors, and academic, social and family functioning. These factors will guide appropriate intervention, including a treatment plan that targets circumstances that maintain depression and put the teen at risk for future episodes. It will be noted that most subjects (n = 157) benefited from complete reassessment, meaning the initial detailed anamnesis, followed by two reassessments (at T1, respectively at the time of performing the CDI).

It will be observed that 90% of the subjects are classified as a patient with the potential for desolation of depressive disorders (of varying degrees and severities) from the moment of diagnosis (at the time of T0) until the completion of therapy. At T1, however, this time, there is no longer a 100% predominance of affirmative answers to the ten questions. The rate of suspicion of depressive disorder occurrence in patients at T1 decreased by approximately 15.8% compared to the value obtained at T0.

To assess the incidence of depressive disorders within the group, parameters considered significant in the development of psychiatric pathologies, both individually and in their relationships, were evaluated. Thus, the incidence of depressive disorders was delineated comparatively, at T0 and T1, respectively.

Detection T0	Detection T1 (in evolution)	Evolutive conclusions
Most subjects presented the alteration of the general state or negative disposition (78.95%, n=150)	92.78% (n=167) of subjects experienced altered general mood or negative mood	An increase in the prevalence of this manifestation can be observed between the two times of the assessment
Most subjects reported problems in their personal and/or family lives (91.58%%, n=174)	35% (n=63) of subjects reported these problems	It is observed a decrease in the prevalence of problems in personal and/or family life
48.95% (n=93) of subjects claim to feel inefficient	52.78% (n=95) of subjects show this manifestation	A quasi-equal distribution is observed, with a discrete decrease in the parameter at T1
73.16% (n=139) show low self-esteem	68.89% (n=124) had low self-esteem at the moment T1	Approximately 6% reduction in symptoms
most subjects experienced irritability at the moment T0 of the examination (84.21%, n=160)	45% (n=81) experienced irritability	An extremely significant decrease in the incidence rate of irritability (decrease by approximately 50%)
at the moment T0 of the assessment, most subjects presented fatigue (57.89%, n=110)	59.44% (n=107) presented this manifestation	There is a decrease in the prevalence of fatigue within the group
most subjects experienced insomnia at the moment T0 (57.37%, n=109)	42.22% (n=76) experienced insomnia upon reevaluation	Decrease in the prevalence of insomnia by about 20 percent
They experienced decreased appetite (70.53%, n=134)	57.22% (n=103) of subjects experienced a decrease in appetite	Reduction of symptoms by approximately 20%
most subjects (70%, n=133) were free of addictions or substance use at the moment T0	0.56% (n=1) of subjects experienced addictions or substance use	A significant decrease in prevalence is observed
at the moment T0, most subjects experienced introversion (70.53%, n=134)	76.67% (n=138) have shown introversion or signs indicating this trait	There is a slight increase in prevalence (about 6%)
In 90.00% (n=171) of subjects, suspicion of depressive disorders was identified	suspicion of depressive disorders was identified in 74.21% (n=141) of subjects; in 5.26% (n=10) of subjects, T1 reassessment was not performed	Reducing the suspicion of depressive disorders by approximately 15%

Next, the statistical analysis will be centered on presenting statistically significant conclusions, the evolution of subjects in terms of depression incidence, comparatively, between the two examination times (T0 and T1, respectively). For a more concise presentation of the data, we will outline a table similar to the previous one, identifying the *sig* indices, as well as the conclusions dependent on each parameter analyzed in these questionnaires.

Name of the analyzed item	Value of *sig* index (Chi-square test)	Statistical conclusion
General condition is affected	p = .256	No correlation significant from statistical point of view exists; no statistically significant differences exist between the two groups
Problems in personal life	p = .203	No correlation significant from statistical point of view exists; no statistically significant differences exist between the two groups
Inefficiency	p = .475	No correlation significant from statistical point of view exists; no statistically significant differences exist between the two groups
Low self-esteem	p = .085	No correlation significant from statistical point of view exists; no statistically significant differences exist between the two groups
Irritability	p = .229	No correlation significant from statistical point of view exists; no statistically significant differences exist between the two groups
Fatiguability	p = .846	No correlation significant from statistical point of view exists; no statistically significant differences exist between the two groups
Insomnia	p = .845	No correlation significant from statistical point of view exists; no statistically significant differences exist between the two groups
Decrease in appetite	p =0.034	Statistically significant differences exist between the two groups
Additions / substance use	p = .500	No correlation significant from statistical point of view exists; no statistically significant differences exist between the two groups
Introversion	p = .655	No correlation significant from statistical point of view exists; no statistically significant differences exist between the two groups

As a conclusion of this statistical analysis, an analysis of the Pearson correlation was performed between the total number of items present following the execution of T0 questionnaire and T1, respectively. Cohen's standard was used to evaluate the strength of the relationship, where coefficients between .10 and .29 represent a small extent of the effect, coefficients between .30 and .49 represent a moderate extent of the effect, and coefficients above .50 indicate a considerable extent of the effect [186]. The correlation result was examined based on an alpha value of .05. A significant positive correlation was observed between T0 - *Number of items present* and T1 - *Number of times present*, with a correlation of .249, indicating a moderate extent of the effect (p = .001, 95.00% CI = [.37, .59]). This suggests that as T0 *Number of items present* increases, T1 *Number of present times* tends to increase.

Number of items which received an affirmative answer (ANOVA tests)	Data analyzed	T0	T1
Origin environment	Value of p index	p=.391	p=.006
	Conclusion	There were no significant differences depending on the levels found in the analyzed variable	There were significant differences depending on the levels found in the analyzed variable
PPH	Value of p index	p=.526	p=.000
	Conclusion	There were no significant differences depending on the levels found in the analyzed variable	There were significant differences depending on the levels found in the analyzed variable
Sex	Value of p index	p=.568	p=.738
	Conclusion	There were no significant differences depending on the levels found in the analyzed variable	There were no significant differences depending on the levels found in the analyzed variable
Age groups	Value of p index	p=.061	p=.658
	Conclusion	There were no significant differences depending on the levels found in the analyzed variable	There were no significant differences depending on the levels found in the analyzed variable
Distance towards medical services	Value of p index	p = .406	p=.061
	Conclusion	There were no significant differences depending on the levels found in the analyzed variable	There were no significant differences depending on the levels found in the analyzed variable
Abandonment of therapy	Value of p index	p=.002	p=.856
	Conclusion	There were significant differences depending on the levels found in the analyzed variable	There were no significant differences depending on the levels found in the analyzed variable
Type of TB pathology	Value of p index	p=.003	p=.748
	Conclusion	There were significant differences depending on the levels found in the analyzed variable	There were no significant differences depending on the levels found in the analyzed variable
Treatment	Value of p index	p=.024	p=.588
	Conclusion	There were significant differences depending on the levels found in the analyzed variable	There were no significant differences depending on the levels found in the analyzed variable

From the point of view of evaluating the decision to conduct the CDI questionnaire, by reference to the conclusions obtained after calculating the number of affirmative items in T0, respectively T1, the following conclusions are identified:

- ✧ CDI was applied to 83.15% of the total study group, n = 158 subjects, of which, most patients (n = 140) showed suspicion of further development of depressive disorders.

- The value of the *sig* index obtained from the Chi-square test in relation to the conclusions obtained at T0 (*sig* = .155) demonstrates that there are no statistically significant differences between those suspected of developing depressive disorders at T0, respectively those performing the CDI.
- At the same time, performing the Chi-square test reveals a *sig* index lower than the reference value (*sig* = .000*), which is why it can be concluded that the decision of the attending physician to perform the CDI was dependent (from a statistical point of view) on the conclusion of the T1 reevaluation.
- The decision to perform the CDI correlates with 8 of the T0 items, so we can say that if we have over the value allowed for the 7 items, there will be an increased risk of developing depressive disorders, so it is necessary to perform the CDI.
- The decision to perform the CDI correlates with 4 of the T1 items, so from our point of view, we cannot predict the performance of CDI ONLY by the T1 result, as the phased testing must be performed (T0 then T1).

In **studying the risk factors / potential influence of depressive disorders in the pediatric TB patient, we used the CDI**, a valuable tool in a multitude of environments among which the most common are schools, clinics, ambulatories, psychiatric hospitals, child protection services and private practice offices. Specialized studies confirm that this questionnaire can be used for many purposes, among which we mention the clinical research, but also its use as screening, part of a comprehensive evaluation.

It is important to remember that performing this test is subject to fundamental ethical requirements regarding informed consent and post-test feedback. In the case of the present clinical research, we performed this type of testing in the presence of legal guardians, being a pediatric population. The assessor applied the test, after explaining in advance the reason for the test, respectively providing general information about the implications of this test. Subsequently, the results obtained were presented to the patients, respectively to their legal guardians and answers were provided to the questions received from them, as well as subsequent management indications were offered.

Children's Depression Inventory (CDI) [182] is constantly quoted in literature as one of the most valued tools to identify depressive symptoms in children and adolescents [240, 241, 242].

The literature confirms that over three-quarters of the studies using self-reporting measures have used CDI. However, although CDI is a good indicator of self-reported distress in children and has been reported as a good screening measure for depression [243, 242], some studies have demonstrated that it does not have adequate sensitivity and specificity as a depression screening measure [244, 245, 246, 247].

Specialized studies, corroborated with the results obtained from conducting clinical trials / research in the field, confirm that a key problem in assessing the predictive validity of an instrument (for a particular disorder) is defined by establishing the limit point. For CDI, Kovacs [182] suggests using a cut-off point of 12 or 13 for homogeneous (e.g., clinical) samples. A cut-off point below this value is supported by several studies quoted by Kovacs [248, 249, 250].

However, it is important to remember that in a study consisting of a total group of 621 Chinese adolescents, Chan [240] found that a cut-off point of 20 was a better option to identify depressive symptoms in his sample. Donnelly [251], Helsel and Matson [252] present another option by selecting depressed subjects based on a standard deviation higher than the average CDI.

In this study, the present clinical research focused on detecting indicators that possess statistical significance, aiming to expose the risk factors, or those with potential influence on the subsequent occurrence of depressive disorders in the pediatric patient diagnosed with pulmonary tuberculosis.

We will expose the statistically significant correlations, by concomitant reference to a series of individual characteristics of the subjects enrolled in the study group as follows:

- ✧ socio-demographic peculiarities.
- ✧ scalar variables, such as subject's weight at its registration, their height, as well as their body mass indices.
- ✧ peculiarities of detecting tuberculosis infection, among which we mention the existence of a TB contact in history, or even herederocolateral history of lung diseases.

- reference to the conclusions obtained from applying the questionnaires mentioned above, both at the time of patient takeover (T0) and at the subsequent reassessment at three months (T1).

This last statistical analysis study aims at issuing hypotheses / conclusions on the risk factors or on the factors having a potential of influence on the incidence of depressive disorders in pediatric patients diagnosed with TB.

The Children's Depression Inventory (CDI) [182] is consistently quoted in the literature as one of the most highly regarded tools to identify depressive symptoms in children and adolescents [240, 241, 242]. We will remind you from the beginning that specialized studies confirm that this questionnaire can be used for many purposes, such as clinical research, but it is also noted its use as screening, part of a comprehensive evaluation:

- From the point of view of the indicator called "negative disposition scale", it will be noted that at the level of the group a MV of 4.18 points is obtained, with an associated standard deviation of 2.50.
- Interpersonal problems are characterized by an average score of 2.16 points with SD equal to 1.72 points.
- An approximately equal value is detected in the case of the variable that analyzes the degree of inefficiency of the subjects (MV 3.01 points, with an SD of 1.97 points).
- Low self-esteem is defined by values of descriptive parameters such as MV of 5.37 and SD of 3.20.
- Low self-esteem is a scalar variable defined as MV of 2.77, SD 1.36.

The total value of points obtained from performing CDI is characterized in terms of central trend by a MV equal to 17.54 points, with a median of 18 points. The dispersion is defined by an SD of 8.70 points, with a wide distribution of values between a minimum of 0 points and a maximum value of 44 points. The distribution represented by the histogram is once again homogeneous, with the appearance of a normal Gaussian curve, with a wide implantation base, with a quasi-symmetric distribution of values, on both sides of the median. The maximum incidental peaks, on either side of the median, are around 22 points and 11 points, respectively.

It should be noted that out of the 158 patients who performed the CDI, 146 subjects showed (following the calculation of the final score) important clinical significance for the spectrum of these psychiatric disorders.

The results obtained from performing bivariate correlations with Pearson indicator between two variables of interest for statistical analysis in this subchapter (we mention here the one called "decision to perform the CDI" – coded under the indicators yes / no; respectively the "CDI clinical significance"; but also the conclusions resulting from the collection of data from the questionnaires applicable to T0 and T1 respectively:

- It is noted the existence of extremely statistically significant correlations between the decisions to perform the CDI, respectively the age groups of subjects (*sig* = .000*), the conclusions resulting from the questionnaires applied during the reevaluation (*sig* = .000*), but also with the clinical significance of depressive-type disorders, detected when interpreting the CDI results.
- Extremely significant correlations from a statistical point of view between the variable defined as "CDI clinical significance", respectively: the age groups of patients (*sig* = .001*), the conclusions obtained at T1 (*sig* = .000*), respectively the decision to perform the CDI (*sig* = 0.000*).

Regarding the decision to conduct the CDI, the following will be noted:

- It was performed mainly for subjects coming from rural areas (n – 110), with a percentage difference of 39.24% compared to the subgroup of patients coming from urban areas.
- CDI was mainly performed on patients who lived less than 10 km away from the follow-up health facility, but this does not have any statistical significance.
- Quasi-symmetric distribution of decisions to perform CDI depending on the sex of patients (with discrete predominance among male subjects, n = 84).
- The existence of a distribution characterized by an upward slope, depending on the ages of the subjects, with the consecutive predominance of CDI performed in those aged 15-18 years (n = 67), will be observed.

The clinical significance of CDI and the interpretation of the results obtained by the patients shows statistically, but also qualitatively significant distributions, with a series of parameters analyzed as follows:

- 36.98% percentage difference indicating the association of CDI values corresponding to clinically significant affective disorders scores, with rural origin.
- Predominance (n = 45) of clinical significance in subjects residing within 10 km of the health facility.
- Most male pediatric patients have clinically significant CDI scores (n=80).
- The distributions of clinical significance of CDI tests maintain the same upward distribution relative to patients' age groups as in the decisions to conduct the Children's Depression Inventory (mentioned above).

Thus, the profile of the pediatric patient diagnosed with TB can be drawn, profile presenting the highest occurrence rate of depressive disorder suspicion, subsequently confirmed by analyzing the significance of the CDI questionnaire. It is defined as follows: during the mentioned period of study, the majority stands out in the case of male patients, coming from rural areas (residing less than 50 km from the attending physician – information below the limitation given by the special pandemic situation existing at that time), respectively aged between 15-18 years.

All these data strengthen the previous conclusions, proving through the descriptive statistical analysis that from the point of view of incidental values, we can allow the exposure of defining working hypotheses for the analyzed group, namely:

- at the level of the group of 190 subjects initially included in the study, it is extremely important to know the socio-demographic characteristics, but also their age expressed in completed years (as all these factors represent in facto the parameters of interest for the present clinical research).
- after their classification in risk groups defined by the abovementioned individual parameters, scalar variables such as weight expressed in kg and the IDR diameter expressed in mm can be checked.
- T0 and T1 will be performed in all patients.
- The points obtained will be added up and then the CDI will be performed.

General conclusions

Following the corroboration of the distribution according to the background and sex of the subjects, it was observed that in rural areas there were mostly male subjects

(40.10%, n=77), while only 30.73% (n=59) were female. In contrast, in urban areas a symmetrical distribution between the two sexes can be observed, with 14.74% (n=28) being male and 14.74% (n=28) being female.

Following the corroboration of age groups with the origin environment, it was observed that in rural areas, most subjects were aged between 15 and 18 years (36.32%, n=69), 18.95% (n=36) between 11 and 14 years, and 15.26% (n=29) were aged between 7 and 10 years. On the other hand, the distribution in the urban area of subjects according to age group showed a quasi-symmetry between the age groups 15-18 and 11-14 years, representing 13.16% (n=25) and 10.53% (n=20) of the studied group, respectively. The subjects aged between 7 and 10 years from urban areas represented the lowest percentage of the study group (5.79%, n=11).

There are correlations between all items from T0 and all those from T1, as well as between the variables defined as Conclusions T0/T1 and the decision to perform the CDI.

The fact that at the time T0, there was 100% predominance of affirmative replies has led to several subsequent implications, among which we recall the following:

- ✧ It is hypothesized that it is not the mere exposure of the pulmonary TB diagnosis to the pediatric patient that determines (by being directly and solely responsible) the depressive disorder.
- ✧ It will often be observed that isolation / self-isolation of the subject (prior to issuing the diagnosis of certainty), the existence of associated disorders (inefficiency, insomnia, decreased appetite), detection of family dynamics disorders, these corroborated factors aggravate the psychological status of the patient.
- ✧ The fact that approximately 90% of young people (older children, pre-adolescents, but especially adolescents) are at risk of developing depressive disorders, often due to the individual/environmental peculiarities they face daily.

In the case of the questionnaire performed at T1, a new distribution is noted, which allows working hypotheses to be issued again, as follows:

- ✧ It can be suspected that, at T1, more precisely, 3 months after the initial evaluation, some of the patients enrolled in the study group showed improvements (at least from a subjective point of view) of the depressive-type disorders.

- ✧ The decrease in the incidence of affirmative answers may also be due to an extremely simple fact: as mentioned in the literature, the mere knowledge of a diagnosis of certainty, determines the subject to acquire the necessary materials for initiating healing, with consequent relief of symptoms.

From the point of view of suspicions on occurrence of affective disorders at the initial evaluation, respectively at the T1 reevaluation, the following will be highlighted:

- ✧ The average age in years is 14 years, in both cases.
- ✧ The patients recorded an average number of 5 presentations to the treating physician for evaluation / reevaluation until these suspicions were established.
- ✧ The average weight of the subjects expressed in kg, was 48 kg (for those suspected since T0 was performed) and 59 kg (for those for which T1 was also performed).
- ✧ The mean value of IDR expressed in mm was 11 mm for both categories of patients.
- ✧ For both groups of subjects, an average number of 2 cardiopulmonary radiographies were performed, until this suspicion was established.
- ✧ Oxygen saturations, established in atmospheric air, maintained an average value of 98%.
- ✧ The mean number of items that were identified as affirmative answers for T0 and T1 questionnaires is 6 items.
- ✧ The total (mean) CDI score for patients who may be at risk of further depressive disorder was 18 points, distributed as follows:
    - Negative disposition scale: 4-point MV for both situations.
    - Interpersonal problems with a 2-point MV.
    - Inefficiency as an indicator recorded a Mean Value of 3 points.
    - Anhedonia was defined by an average value of 5 points for the subgroup of those who performed T0 and 6 points for those in the T1 category.
    - Low self-esteem was defined as having a mean value of 3 points for both situations discussed above.

The value of the *sig* index obtained after performing the Chi-square test (T0 conclusion – decision to perform CDI) (*sig* = .155) demonstrates that there are no statistically significant differences between those suspected of developing depressive disorders at T0, respectively that of performing the CDI. Thus, it can be issued the null hypothesis at this time that the detection of suspecting a further development of

depressive disorder, at the time of registering the patient, is not a situation that necessarily indicates the need to perform / apply the CDI. As mentioned earlier, the existence of an incidence of affirmative responses greater than 50% to T0 may be partly due to the association of real problems existing in the patient's personal life, an atypical terrain, a (heredocolateral or pathological personal) history of psychiatric / psychological diseases, or simply due to the uncertainty of diagnosis.

At the same time, when the statistical analysis is made, from a descriptive point of view, by reference to the incidents of suspicion of depressive disorders, at the time of repeating the questionnaire, it will be noticed that this time the decision to perform the licensed depression questionnaire was taken for a total number of 158 patients. Of these, only 121 (76.58%) submitted more than half of the answers coded as "yes" when applying the individual questionnaire. This time, however, performing the Chi-square test reveals a *sig* index lower than the reference value (*sig* = .000*), which is why it can be concluded that the decision of the attending physician to perform the CDI was dependent (statistically) on the conclusion of the T1 reevaluation.

Thus, regarding the decision to perform CDI (in the 158 subjects, with the consecutive exclusion of 32 patients), the following details will be observed, which strengthen the management algorithm of the attending physician:

- It was performed predominantly for subjects coming from rural areas (n – 110), with a percentage difference of 39.24% compared to the subgroup of patients coming from urban areas. This is justifiable in part, if we start from the premise that patients coming from rural areas do not have such easy access to medical services (which is why their poor follow-up can "lose sight" of a series of clinical signs indicating the appearance of depressive disorders. It is also known that rural areas, due to the small community of people, can contribute to the desire for social isolation, due to the stigma associated with a diagnosis of this type. Over time, this social isolation, coupled with the loss of activities typical of the rural area (working in the fields, caring for animals, etc.) will accentuate the spectrum of affective disorders.
- CDI was mostly performed on patients who lived less than 10 km away from the monitoring health facility. Although there is no statistical significance regarding the interaction of these two variables, taking into consideration that the duration of the

study included the SARS CoV-2 pandemic (respectively the state of emergency), a working hypothesis that this made it difficult to monitor the subjects can be issued.

- ✧ Quasi-symmetric distribution of the decisions to perform CDI depending on the sex of patients (with discrete predominance among male subjects, n = 84).
- ✧ Previously, we have demonstrated that patients' age groups are a variable determining a significance extremely strong from statistical point of view (at two ends) with the decision to perform CDI. Thus, it will be observed the existence of a distribution characterized by an upward slope, depending on the ages of the subjects, with the consecutive predominance of CDI performed in those aged 15-18 years (n = 67).
- ✧ It correlates with 8 of the T0 items, so we can say that if we have over the permissible value for the 7 items, there will be an increased risk of developing depressive disorders, so it is necessary to perform CDI.
- ✧ It correlates with 4 of the T1 items, so from our point of view we cannot predict the performance of CDI ONLY by the T1 result, the phased testing must be performed (T0, then T1).

The clinical significance of CDI, the interpretation of the results obtained by patients shows statistically significant distributions, but also qualitatively with a series of parameters analyzed as follows:

- ✧ 36.98% percentage difference indicating the association of CDI values corresponding to scores with a clinical significance of affective disorders, with rural origin environment.
- ✧ Predominance (n = 45) of clinical significance in subjects residing less than 10 km from the health facility.
- ✧ Most male pediatric patients have clinically significant CDI scores (n=80).
- ✧ The distributions of clinical significance of CDI tests maintain the same upward distribution relative to patients' age groups, as in the decisions to conduct the Children's Depression Inventory (mentioned above).
- ✧ Based on the underlying summary tables, we performed a prediction score of depressive disorders of the pediatric patient diagnosed with a form of tuberculosis. The score obtained is a reference point for the research in question. It is the basis

of management therapy for TB patients who are at risk of developing depressive disorders.

✧ It is important to mention that this score represents a preliminary variant, which will be defined in a final form, as well as the future research perspective, with the expansion of the study group.

Summary table with the distribution of patients in the study group, dependent upon the responses obtained at T0 and T1

		T1 = general condition affected / negative disposition		T1 = problems in personal life / family life		T1 = inefficiency (as the patient considers it = work, studying, etc.)		T1 = low self-esteem		T1 = irritability		T1 = fatigability		T1 = insomnia		T1 = decrease in appetite		T1 = addictions / consumption of substances (alcohol, tabaco, drugs)		T1 = introversion (if the patient is one which is introverted, or if it presents the capacity to initiate / be involved in dialogues, looking square in the eye)		Conclusion T1		
		No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	There is no suspicion of depressive disorder occurrence	The suspicion of depressive disorder occurrence is identified	T1 was not performed
T0=general condition affected / negative disposition	No	4	30	30	4	24	10	9	25	20	14	15	19	29	5	11	23	34	0	12	22	13	21	6
	Yes	9	137	87	59	61	85	47	99	79	67	58	88	75	71	66	80	145	1	30	116	26	120	4
T0 = problems in personal life / family life	No	1	14	12	3	7	8	4	11	10	5	5	10	12	3	13	2	15	0	11	4	5	10	1
	Yes	12	153	105	60	78	87	52	113	89	76	68	97	92	73	64	101	164	1	31	134	34	131	9
T0 = inefficiency (as the patient considers it = work, studying, etc.)	No	5	89	80	14	42	52	28	66	56	38	33	61	48	46	39	55	93	1	19	75	20	74	3
	Yes	8	78	37	49	43	43	28	58	43	43	40	46	56	30	38	48	86	0	23	63	19	67	7
T0 = low self-esteem	No	2	47	32	17	38	11	20	29	27	22	17	32	24	25	23	26	48	1	14	35	16	33	2
	Yes	11	120	85	46	47	84	36	95	72	59	56	75	80	51	54	77	131	0	28	103	23	108	8
T0 irritability	No	2	27	16	13	16	13	17	12	13	16	9	20	13	16	15	14	29	0	10	19	7	22	1
	Yes	11	140	101	50	69	82	39	112	86	65	64	87	91	60	62	89	150	1	32	119	32	119	9
T0 = fatigability	No	5	73	55	23	32	46	23	55	57	21	31	47	44	34	35	43	78	0	13	65	17	61	2
	Yes	8	94	62	40	53	49	33	69	42	60	42	60	60	42	42	60	101	1	29	73	22	80	8

		T1 = general condition affected / negative disposition		T1 = problems in personal life / family life		T1 = inefficiency (as the patient considers it = work, studying, etc.)		T1 = low self-esteem		T1 = irritability		T1 = fatigability		T1 = insomnia		T1 = decrease in appetite		T1 = addictions / consumption of substances (alcohol, tabaco, drugs)		T1 = introversion (if the patient is one which is introverted, or if it presents the capacity to initiate / be involved in dialogues, looking square in the eye)		Conclusion T1		
		No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	There is no suspicion of depressive disorder occurrence	The suspicion of depressive disorder occurrence is identified	T1 was not performed
T0 = insomnia	No	5	74	56	23	33	46	23	56	58	21	32	47	45	34	35	44	79	0	13	66	18	61	2
	Yes	8	93	61	40	52	49	33	68	41	60	41	60	59	42	42	59	100	1	29	72	21	80	8
T0 decrease in appetite	No	3	52	32	23	22	33	13	42	31	24	23	32	41	14	30	25	55	0	14	41	14	41	1
	Yes	10	115	85	40	63	62	43	82	68	57	50	75	63	62	47	78	124	1	28	97	25	100	9
T0 addictions / consumption of substances (alcohol, tabaco, drugs	No	3	53	33	23	23	33	13	43	32	24	24	32	42	14	30	26	56	0	14	42	15	41	1
	Yes	10	114	84	40	62	62	43	81	67	57	49	75	62	62	47	77	123	1	28	96	24	100	9
T0 = introversion (if the patient is one which is introverted, or if it presents the capacity to initiate / be involved in dialogues, looking square in the eye)	No	3	52	32	23	22	33	13	42	31	24	23	32	41	14	30	25	55	0	14	41	14	41	1
	Yes	10	115	85	40	63	62	43	82	68	57	50	75	63	62	47	78	124	1	28	97	25	100	9
Conclusion T0	There is no suspicion of depressive disorder occurrence	1	17	15	3	10	8	7	11	11	7	6	12	14	4	12	6	18	0	10	8	6	12	1

		T1 = general condition affected / negative disposition		T1 = problems in personal life / family life		T1 = inefficiency (as the patient considers it = work, studying, etc.)		T1 = low self-esteem		T1 = irritability		T1 = fatigability		T1 = insomnia		T1 = decrease in appetite		T1 = addictions / consumption of substances (alcohol, tabaco, drugs)		T1 = introversion (if the patient is one which is introverted, or if it presents the capacity to initiate / be involved in dialogues, looking square in the eye)		Conclusion T1		
		No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	There is no suspicion of depressive disorder occurrence	The suspicion of depressive disorder occurrence is identified	T1 was not performed
	There is no suspicion of depressive disorder occurrence	12	150	102	60	75	87	49	113	88	74	67	95	90	72	65	97	161	1	32	130	33	129	9

Source: author's contribution

Summary table of the results obtained when performing CDI

				Decision on performing the CDI		Clinical significance of CDI		
				It was not performed.	It was performed.	Without values significant from clinical point of view	The values obtained have a clinical significance	CDI was not performed
Conclusion T0	There is no suspicion of depressive disorder occurrence			1	18	3	15	1
	Suspicion of the depressive disorder occurrence is identified			31	140	9	131	31
Conclusion T1	There is no suspicion of depressive disorder occurrence			2	37	8	29	2
	Suspicion of depressive disorder occurrence is identified			20	121	4	117	20
	T1 not performed			10	0	0	0	10
Conclusion T0	There is no suspicion of depressive disorder occurrence	Conclusion T1	There is no suspicion of depressive disorder occurrence	0	6	1	5	0

				Decision on performing the CDI		Clinical significance of CDI		
				It was not performed.	It was performed.	Without values significant from clinical point of view	The values obtained have a clinical significance	CDI was not performed
			The suspicion of depressive disorders occurrence is identified.	0	12	2	10	0
			T1 not performed.	1	0	0	0	1
	Suspicion of depressive disorder occurrence is identified	Conclusion T1	There is no suspicion of depressive disorder occurrence	2	31	7	24	2
			Suspicion of the depressive disorder occurrence is identified	20	109	2	107	20
			T1 not performed	9	0	0	0	9

Source: author's contribution

Total value = 9 points, theoretically established threshold value = 4 or 5

At T0:

- ✧ under 25% positive results = 0 points
- ✧ 25-50% positive results = 1 point
- ✧ 50-75% positive results = 2 points
- ✧ above 75% positive results = 3 points

At T1:

- ✧ under 25% positive results = 0 points
- ✧ 25-50% positive results = 1 point
- ✧ 50-75% positive results = 2 points
- ✧ above 75% positive results = 3 points

CDI: 5 items in total

- ✧ if we have under 2 items modified = 1 point

- 2-3 items modified = 2 points
- 4-5 items modified = 3 points.

Final score: the reporting to the nine points in total

- If the value is under 4 points = minor risk of occurrence of affective disorders
- If the value is between 4 and 6 points = average risk of occurrence of affective disorders
- If the value is over 6 points = severe risk of occurrence of affective disorders.

Thus, the profile of the pediatric patient diagnosed with TB can be drawn, patient with the highest rate of occurrence of depressive disorder suspicion, subsequently confirmed by analyzing the significance of the CDI questionnaire. It is defined as follows: during the mentioned period of study, it is observed in the case of male patients coming from rural areas (residing less than 50 km from the attending physician – information below the limitation given by the special pandemic situation existing at that time), respectively aged between 15-18 years.

All these data strengthen the previous conclusions, proving through the descriptive statistical analysis that from the point of view of incidence values, we can allow the presentation of working hypotheses defining for the analyzed group, namely:

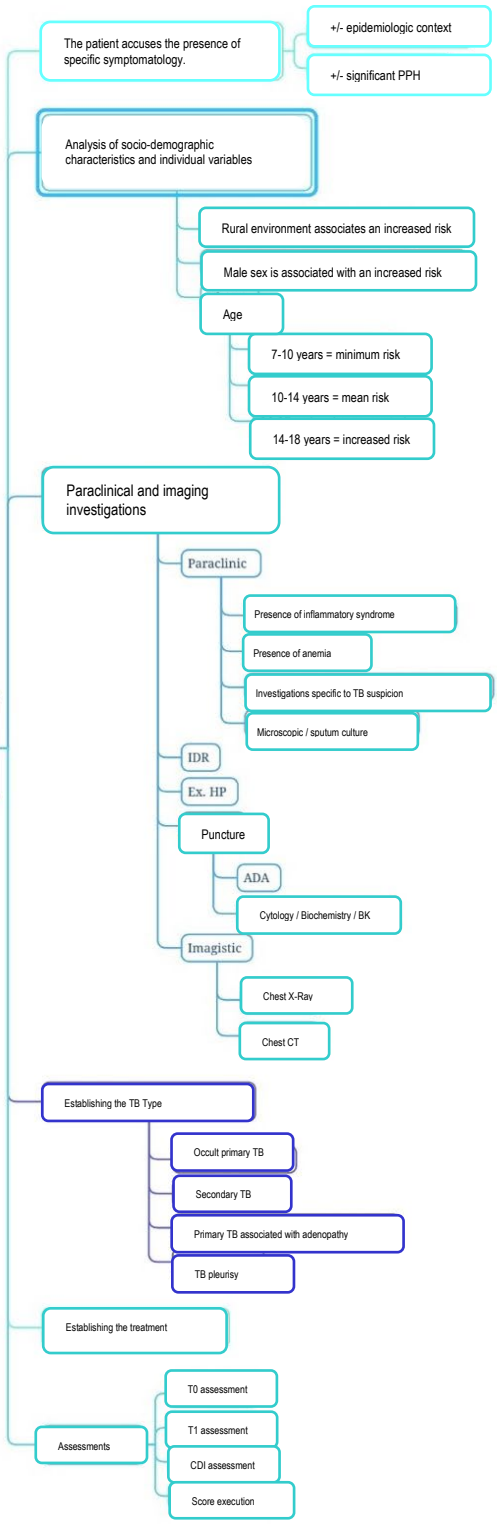
- At the level of the group of 190 subjects initially included in the study, it is extremely important to know the socio-demographic characteristics, but also their age expressed in completed years (as all these factors are in facto parameters of interest for the present clinical research).
- After their classification in risk groups defined by the abovementioned individual parameters, scalar variables such as weight expressed in kg and the IDR diameter expressed in mm, can be checked.
- T0 and T1 will be performed on all patients.
- The points obtained will be added up and then the CDI will be performed.
- If the final score value has the values:

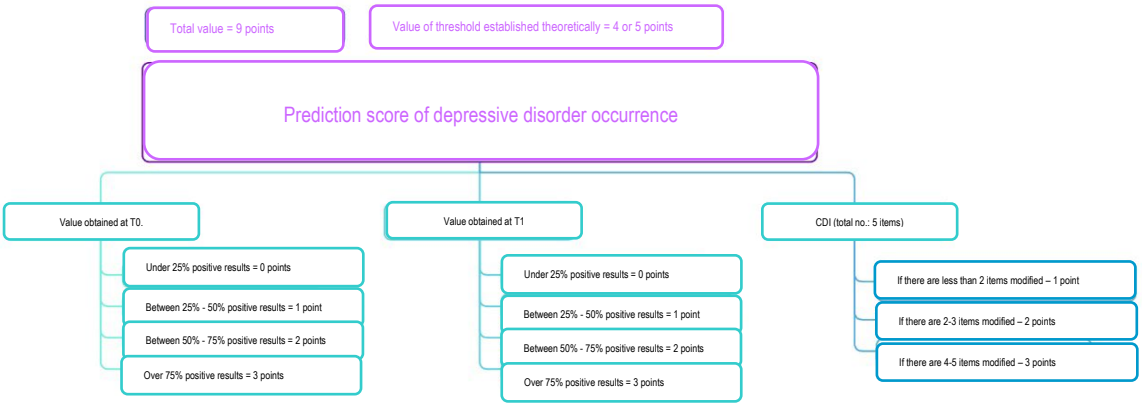
a. **under 4 points** = minor risk of affective disorder occurrence ➔ a conservative attitude, with expectation from the point of view of psychiatric approach, will be chosen.
b. **between 4 and 6 points** = average risk of affective disorder occurrence:
    i. it can be opted for involving a psychotherapy service for specialized opinion.
    ii. CDI will be repeated after 1 month, and afterwards, after 3 months:
        - If the score at 1 month is lower than the initial one obtained, it will be opted for an expectant attitude, with psychotherapy services of about 6 months and reevaluation after 1 year.
        - If the risk remains in both tests, he/she will be redirected to the psychiatric service.
c. **above 6 points** = severe risk of developing affective disorders, the patient will be redirected to the psychiatric service.

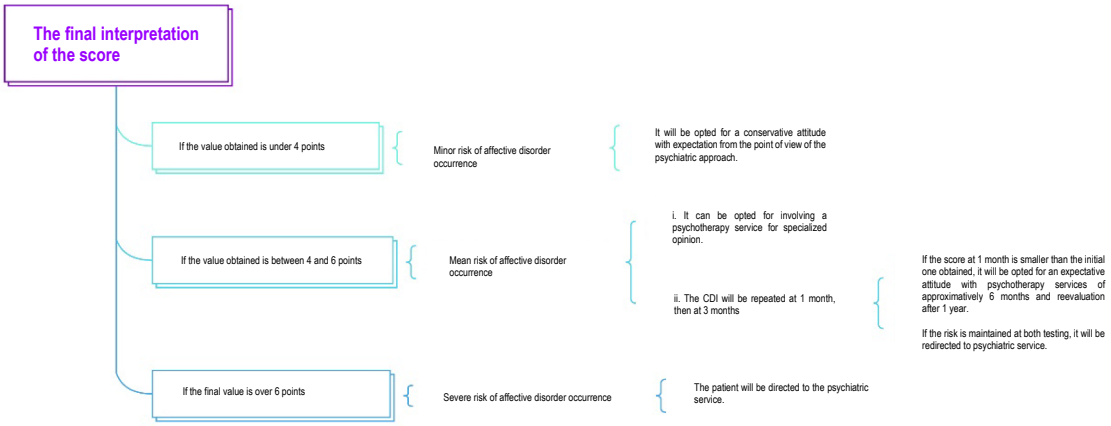
✧ With all this information at hand, preliminary hypotheses can be made as soon as the subjects are registered. Although, of course, it is important to note that one of the current limitations of research is defined by the size of the analyzed group.

Personal contributions – presenting a pediatric patient management algorithm.

THE PEDIATRIC PATIENT GOES TO "SF. SPIRIDON" PULMONOLOGY HOSPITAL IN GALATI / TB CLINIC IN GALATI / TECUCI / TG. BUJOR




Total value = 9 points
Value of threshold established theoretically = 4 or 5 points
Prediction score of depressive disorder occurrence
Value obtained at T0.
Under 25% positive results = 0 points
Between 25% - 50% positive results = 1 point
Between 50% - 75% positive results = 2 points
Over 75% positive results = 3 points
Value obtained at T1
Under 25% positive results = 0 points
Between 25% - 50% positive results = 1 point
Between 50% - 75% positive results = 2 points
Over 75% positive results = 3 points
CDI (total no.: 5 items)
If there are less than 2 items modified – 1 point
If there are 2-3 items modified – 2 points
If there are 4-5 items modified – 3 points


The final interpretation of the score
If the value obtained is under 4 points
Minor risk of affective disorder occurrence
It will be opted for a conservative attitude with expectation from the point of view of the psychiatric approach.
If the value obtained is between 4 and 6 points
Mean risk of affective disorder occurrence
i. It can be opted for involving a psychotherapy service for specialized opinion.
ii. The CDI will be repeated at 1 month, then at 3 months
If the score at 1 month is smaller than the initial one obtained, it will be opted for an expectative attitude with psychotherapy services of approximatively 6 months and reevaluation after 1 year.
If the risk is maintained at both testing, it will be redirected to psychiatric service.
If the final value is over 6 points
Severe risk of affective disorder occurrence
The patient will be directed to the psychiatric service.

Bibliography

1. Ferri FF, 2010. Ferri's differential diagnosis: a practical guide to the differential diagnosis of symptoms, signs, and clinical disorders, 2nd ed. Philadelphia, PA: Elsevier/Mosby. p. Chapter T.
2. Adkinson NF, Bennett JE, Douglas RG, Mandell GL, 2010. Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 7th ed. Philadelphia, PA: Churchill Livingstone/Elsevier. p. Chapter 250
3. Konstantinos A, 2010, "Testing for tuberculosis". Australian Prescriber. 33 (1), pp: 12–18.
4. Harris RE, 2013, Epidemiology of chronic disease: global perspectives. Burlington, MA: Jones & Bartlett Learning. p. 682
5. Hawn TR, Day TA, Scriba TJ, Hatherill M, Hanekom WA, Evans TG, et al., 2014. "Tuberculosis vaccines and prevention of infection". Microbiology and Molecular Biology Reviews. 78 (4), pp: 650–71
6. WHO, 2020, https://www.who.int/news-room/fact-sheets/detail/tuberculosis
7. WHO, 2013, https://www.who.int/teams/global-tuberculosis-programme/tb-reports
8. World Health Organization. Global Tuberculosis Report; WHO: Geneva, Switzerland, 2021.
9. Pai, M.; Kasaeva, T.; Swaminathan, 2022, S. COVID-19's Devastating Effect on Tuberculosis Care—A Path to Recovery. N. Engl. J. Med. 2022, 386, 1490–1493
10. Susan M Sawyer, Peter S Azzopardi, Dakshitha Wickremarathne, George C Patton, The age of adolescence, The Lancet Child & Adolescent Health, Volume 2, Issue 3, 2018, Pages 223-228, ISSN 2352-4642
11. Ross D.A., Hinton R., Melles-Brewer M., Engel D., Zeck W., Fagan L., Herat J., Phaladi G., Imbago-Jácome D., Anyona P., et al., 2020, Adolescent Well-Being: A Definition and Conceptual Framework. J. Adolesc. Health. 67:472–476.
12. Baral S, Karki D, Newell J, 2007, Causes of stigma and discrimination associated with tuberculosis in Nepal: a qualitative study. BMC Public Health 7: 211
13. Vanleeuw, L., Zembe-Mkabile, W., & Atkins, S., 2022. "I'm suffering for food": Food insecurity and access to social protection for TB patients and their households in Cape Town, South Africa. Plos one, 17(4), e0266356.
14. Lawn SD, Zumla AI, 2011. "Tuberculosis". Lancet. 378 (9785) pp: 57–72
15. Rothschild BM, Martin LD, Lev G, Bercovier H, Bar-Gal GK, Greenblatt C, et al. 2001. "Mycobacterium tuberculosis complex DNA from an extinct bison dated 17,000 years before the present". Clinical Infectious Diseases. 33 (3) pp: 305–11.
16. Pearce-Duvet JM, 2006. "The origin of human pathogens: evaluating the role of agriculture and domestic animals in the evolution of human disease". Biological Reviews of the Cambridge Philosophical Society. 81 (3) pp: 369–82.

17. Comas I, Gagneux S, 2009. Manchester M (ed.). "The past and future of tuberculosis research". PLOS Pathogens. 5 (10) p: e1000600.
18. Zink AR, Sola C, Reischl U, Grabner W, Rastogi N, Wolf H, et al., 2003, "Characterization of Mycobacterium tuberculosis complex DNAs from Egyptian mummies by spoligotyping". Journal of Clinical Microbiology. 41 (1 pp): 359–67.
19. Konomi N, Lebwohl E, Mowbray K, Tattersall I, Zhang D, 2002. "Detection of mycobacterial DNA in Andean mummies". Journal of Clinical Microbiology. 40 (12) pp: 4738–40.
20. Sledzik PS, Bellantoni N, 1994. "Brief communication: bioarcheological and biocultural evidence for the New England vampire folk belief" (PDF). American Journal of Physical Anthropology. 94 (2) pp: 269–74.
21. Marten B, 1720. A New Theory of Consumptions—More Especially a Phthisis or Consumption of the Lungs. London, England: T. Knaplock. P. 51
22. Trail RR, 1970. "Richard Morton (1637-1698)". Medical History. 14 (2) pp: 166–74.
23. Schönlein JL, 1832. Allgemeine und specielle Pathologie und Therapie [General and Special Pathology and Therapy] (in German). vol. 3. Würzburg, (Germany): C. Etlinger. p. 103.
24. Jay SJ, Kırbıyık U, Woods JR, Steele GA, Hoyt GR, Schwengber RB, Gupta P, 2018. "Modern theory of tuberculosis: culturomic analysis of its historical origin in Europe and North America". The International Journal of Tuberculosis and Lung Disease. 22 (11) pp: 1249–1257.
25. McCarthy OR, 2001. "The key to the sanatoria". Journal of the Royal Society of Medicine. 94 (8) pp: 413–417
26. Villemin JA, 1865. "Cause et nature de la tuberculose" [Cause and nature of tuberculosis]. Bulletin de l'Académie Impériale de Médecine (in French). 31 pp: 211–216
27. Burdon-Sanderson, John Scott.,1870, "Introductory Report on the Intimate Pathology of Contagion." Appendix to: Twelfth Report to the Lords of Her Majesty's Most Honourable Privy Council of the Medical Officer of the Privy Council [for the year 1869], Parliamentary Papers (1870), vol. 38, pp:229-256.
28. Koch, Robert, 1882. "Die Ätiologie der Tuberkulose" [The Etiology of Tuberculosis]. Berliner Klinische Wochenschrift. 19 pp: 221–30
29. Waddington K, 2004. "To stamp out 'so terrible a malady': bovine tuberculosis and tuberculin testing in Britain, 1890–1939". Medical History. 48 (1) pp: 29–48
30. Bonah C, 2005. "The 'experimental stable' of the BCG vaccine: safety, efficacy, proof, and standards, 1921–1933". Studies in History and Philosophy of Biological and Biomedical Sciences. 36 (4) pp: 696–721.
31. Comstock GW, 1994. "The International Tuberculosis Campaign: a pioneering venture in mass vaccination and research". Clinical Infectious Diseases. 19(3) pp: 528–40.
32. Bloom BR, 1994. Tuberculosis: pathogenesis, protection, and control. Washington, DC: ASM Press
33. Zürcher, Kathrin; Zwahlen, Marcel; Ballif, Marie; Rieder, Hans L.; Egger, Matthias; Fenner, Lukas, 2016. "Influenza Pandemics and Tuberculosis Mortality in 1889 and 1918: Analysis of Historical Data from Switzerland". PLOS ONE. 11 (10) pp: e0162575

34. Persson S, 2010. Smallpox, Syphilis and Salvation: Medical Breakthroughs That Changed the World. ReadHowYouWant.com. p. 141.
35. Shields T, 2009. General thoracic surgery (7th ed.). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 792. ISBN 978-0-7817-7982-1. Archived from the original on 6 September 2015
36. Lalloo UG, Naidoo R, Ambaram A, 2006. "Recent advances in the medical and surgical treatment of multi-drug resistant tuberculosis". Current Opinion in Pulmonary Medicine. 12 (3) pp: 179–85
37. Frieden, T. R., Sterling, T. R., Munsiff, S. S., Watt, C. J. & Dye, C. 2003. Tuberculosis. Lancet, 362, pp: 887–899
38. World Health Organization (2004). TB/HIV. A Clinical Manual, 2nd Edn. Document WHO/HTM/ TB/2004.329. Geneva: WHO.
39. Pedro-Botet, J., Gutierrez, J., Miralles, R., Coll, J. & Rubies-Prat, J. 1992. Pulmonary tuberculosis in HIV-infected patients with normal chest radiographs. AIDS, 6, pp:91–93
40. Hargreaves, N. J., Kadzakumanja, O., Phiri, S., Nyangulu, D. S., Salaniponi, F. M. L., Harries, A. D. & Squire, S. B.,2001. What causes smearnegative pulmonary tuberculosis in Malawi, an area of high HIV seroprevalence? International Journal of Tuberculosis and Lung Disease, 5, pp;113–122.
41. Bass JB Jr, Farer LS, Hopewell PC, et al., 1994. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. Am J Respir Crit Care Med, 149(5) pp:1359-1374.
42. Blumberg HM, Burman WJ, Chaisson RE, et al., 2003. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med . 167(4) pp:603-662
43. CDC, 1992, Control of tuberculosis in the United States. American Thoracic Society. Am Rev Respir Dis. 146(6) pp:1623-1633.
44. CDC., 2000, Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Morb Mortal Wkly Rep.. 49(RR-6) pp:1-51.
45. Taylor Z, Nolan CM, Blumberg HM, et al., 2005. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. MMWR Recomm Rep. 54(RR-12) pp:1-81
46. OMS, 2014. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in ChildrenGuidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. 2nd ed. World Health Organization.
47. Jacob JT, Mehta AK, Leonard MK, 2009. "Acute forms of tuberculosis in adults". The American Journal of Medicine. 122 (1) pp: 12–17.
48. Mazza-Stalder J, Nicod L, Janssens JP, 2012. "La tuberculose extrapulmonaire ". Revue des Maladies Respiratoires. 29 (4): pp:566–578.
49. Ketata W, Rekik WK, Ayadi H, Kammoun S, 2015, "Les tuberculoses extrapulmonaires". Revue de Pneumologie Clinique. 71 (2–3) pp: 83–92.

50. Southwick F, 2007. "Chapter 4: Pulmonary Infections". Infectious Diseases: A Clinical Short Course, 2nd ed. McGraw-Hill Medical Publishing Division. pp. 104, 313–314
51. Jindal SK, 2011. Textbook of Pulmonary and Critical Care Medicine. New Delhi: Jaypee Brothers Medical Publishers. p. 525.
52. Niederweis M, Danilchanka O, Huff J, Hoffmann C, Engelhardt H, 2010. "Mycobacterial outer membranes: in search of proteins". Trends in Microbiology. 18 (3) pp: 109–116
53. Madison BM, 2001. "Application of stains in clinical microbiology". Biotechnic & Histochemistry. 76 (3) pp: 119–125.
54. Parish T, Stoker NG, 1999. "Mycobacteria: bugs and bugbears (two steps forward and one step back)". Molecular Biotechnology. 13 (3) pp: 191–200.
55. Kommareddi S, Abramowsky CR, Swinehart GL, Hrabak L, 1984. "Nontuberculous mycobacterial infections: comparison of the fluorescent auramine-O and Ziehl-Neelsen techniques in tissue diagnosis". Human Pathology. 15 (11) pp: 1085–1089.
56. van Lettow M, Whalen C, 2008. Semba RD, Bloem MW (eds.). Nutrition and health in developing countries (2nd ed.). Totowa, N.J.: Humana Press. p. 291.
57. Thoen C, Lobue P, de Kantor I, 2006. "The importance of Mycobacterium bovis as a zoonosis". Veterinary Microbiology. 112 (2–4) pp: 339–45
58. Niemann S, Rüsch-Gerdes S, Joloba ML, Whalen CC, Guwatudde D, Ellner JJ, et al., 2002. "Mycobacterium africanum subtype II is associated with two distinct genotypes and is a major cause of human tuberculosis in Kampala, Uganda". Journal of Clinical Microbiology. 40 (9) pp: 3398–405.
59. Acton QA, 2011. Mycobacterium Infections: New Insights for the Healthcare Professional. ScholarlyEditions. p. 1968.
60. Pfyffer GE, Auckenthaler R, van Embden JD, van Soolingen D, 1998. "Mycobacterium canettii, the smooth variant of M. tuberculosis, isolated from a Swiss patient exposed in Africa". Emerging Infectious Diseases. 4 (4) pp: 631–634.
61. Panteix G, Gutierrez MC, Boschiroli ML, Rouviere M, Plaidy A, Pressac D, et al., 2010. "Pulmonary tuberculosis due to Mycobacterium microti: a study of six recent cases in France". Journal of Medical Microbiology. 59 (Pt 8) PP: 984–989
62. American Thoracic Society, 1997. "Diagnosis and treatment of disease caused by nontuberculous mycobacteria. This official statement of the American Thoracic Society was approved by the Board of Directors, March 1997. Medical Section of the American Lung Association". American Journal of Respiratory and Critical Care Medicine. 156 (2 Pt 2) pp: S1–25
63. Skolnik R, 2011. Global health 101 (2nd ed.). Burlington, MA: Jones & Bartlett Learning. p. 253
64. Mainous III AG, Pomeroy C, 2009. Management of antimicrobials in infectious diseases: impact of antibiotic resistance (2nd rev. ed.). Totowa, NJ: Humana Press. p. 74
65. Houben EN, Nguyen L, Pieters J, 2006. "Interaction of pathogenic mycobacteria with the host immune system". Current Opinion in Microbiology. 9 (1) pp: 76–85
66. Queval CJ, Brosch R, Simeone R, 2017. "Mycobacterium tuberculosis". Frontiers in Microbiology. 8 p: 2284

67. Khan, 2011. Essence of Paediatrics. Elsevier India. p. 401
68. Herrmann JL, Lagrange PH, 2005. "Dendritic cells and Mycobacterium tuberculosis: which is the Trojan horse?". Pathologie-Biologie. 53 (1) pp: 35–40.
69. Agarwal R, Malhotra P, Awasthi A, Kakkar N, Gupta D, 2005. "Tuberculous dilated cardiomyopathy: an under-recognized entity?". BMC Infectious Diseases. 5 (1) p: 29.
70. Grosset J, 2003. "Mycobacterium tuberculosis in the extracellular compartment: an underestimated adversary". Antimicrobial Agents and Chemotherapy. 47(3) pp: 833–836.
71. Bozzano F, Marras F, De Maria A, 2014. "Immunology of tuberculosis". Mediterranean Journal of Hematology and Infectious Diseases. 6 (1) p: e2014027
72. Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson; & Mitchell, Richard N., 2007. Robbins Basic Pathology (8th ed.). Saunders Elsevier. pp. 516-522
73. Burke and Parnell, 1948, Minimal Pulmonary Tuberculosis. Canadian Medical Association Journal. 59 p:348
74. Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, et al., 2006. "Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review". The Lancet. Infectious Diseases. 6 (9) pp: 570–581
75. Brown M, Varia H, Bassett P, Davidson RN, Wall R, Pasvol G. 2007. "Prospective study of sputum induction, gastric washing, and bronchoalveolar lavage for the diagnosis of pulmonary tuberculosis in patients who are unable to expectorate". Clinical Infectious Diseases. 44 (11) pp: 1415–1420
76. Drobniewski FA, Caws M, Gibson A, Young D, 2003. "Modern laboratory diagnosis of tuberculosis". The Lancet. Infectious Diseases. 3 (3): 141–147
77. Moore DA, Evans CA, Gilman RH, Caviedes L, Coronel J, Vivar A, et al., 2006. "Microscopic-observation drug-susceptibility assay for the diagnosis of TB". The New England Journal of Medicine. 355 (15) pp: 1539–1550
78. Rossi SE, Franquet T, Volpacchio M, Giménez A, Aguilar G, 2005. "Tree-in-bud pattern at thin-section CT of the lungs: radiologic-pathologic overview". Radiographics. 25(3) pp: 789–801
79. Nakamura RM, Einck L, Velmonte MA, Kawajiri K, Ang CF, Delasllagas CE, Nacy CA 2001. "Detection of active tuberculosis by an MPB-64 transdermal patch: a field study". Scandinavian Journal of Infectious Diseases. 33 (6) pp: 405–407.
80. Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, et al., 2007. "A systematic review of rapid diagnostic tests for the detection of tuberculosis infection". Health Technology Assessment. 11 (3) pp: 1–196.
81. Guerra RL, Hooper NM, Baker JF, Alborz R, Armstrong DT, Maltas G, et al., 2007. "Use of the amplified mycobacterium tuberculosis direct test in a public health laboratory: test performance and impact on clinical care". Chest. 132 (3) pp: 946–951
82. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al., 2011. "Three months of rifapentine and isoniazid for latent tuberculosis infection". The New England Journal of Medicine. 365 (23) pp: 2155–2166
83. Ghid pentru managementul cazurilor de TB la copii, Bucuresti, 2017

84. Wang JY, Hsueh PR, Jan IS, Lee LN, Liaw YS, Yang PC, Luh KT, et al., 2006. "Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas". Thorax. 61 (10) pp: 903–908.
85. David HL, 1970. "Probability distribution of drug-resistant mutants in unselected populations of Mycobacterium tuberculosis". Applied Microbiology. 20 (5) pp: 810–814
86. Ghidul Național al PNPSCT, 2015
87. Ghidul OMS de Management al TBC la copii, ed. 2014
88. Iordăchescu F, Georgescu A, Miron I, Mărginean O, 2019, Tratat de pediatrie. Ed. ALL. 2019. Pag 1487-1489.
89. Hong Kong Chest Service Tuberculosis Research Centre, British Medical Research Council. 1989. "A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 5 years. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council". The American Review of Respiratory Disease. 139 (4 pp): 871–876
90. Jullien S, Ryan H, Modi M, Bhatia R, et al. (Cochrane Infectious Diseases Group), 2016. "Six months therapy for tuberculous meningitis". The Cochrane Database of Systematic Reviews. 9 P: CD012091
91. World Health Organization, 2010. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. World Health Organization (WHO)
92. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al., 2012. "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010". Lancet. 380(9859) pp: 2095–2128
93. Douglas AS, Strachan DP, Maxwell JD, 1996 "Seasonality of tuberculosis: the reverse of other respiratory diseases in the UK". Thorax. 51 (9) pp: 944–946
94. Martineau AR, Nhamoyebonde S, Oni T, Rangaka MX, Marais S, et al., 2011. "Reciprocal seasonal variation in vitamin D status and tuberculosis notifications in Cape Town, South Africa". Proc Natl Acad Sci U S A. 108 (47) pp: 19013–19017.
95. Korthals Altes H, Kremer K, Erkens C, Van Soolingen D, Wallinga J, 2012. "Tuberculosis seasonality in the Netherlands differs between natives and non-natives: a role for vitamin D deficiency?". Int J Tuberc Lung Dis. 16 (5) pp: 639–644
96. Kuddus MA, McBryde ES, Adegboye OA, 2019. "Delay effect and burden of weather-related tuberculosis cases in Rajshahi province, Bangladesh, 2007-2012". Scientific Reports. 9 (1) pp: 12720
97. Griffith DE, Kerr CM, 1996. "Tuberculosis: disease of the past, disease of the present". Journal of PeriAnesthesia Nursing. 11 (4) pp: 240–245.
98. FitzGerald JM, Wang L, Elwood RK, 2000. "Tuberculosis: 13. Control of the disease among aboriginal people in Canada". Canadian Medical Association Journal. 162(3) pp: 351–355
99. OMS, 2020. Global tuberculosis report 2020. [online] Who.int. Available at: <https://www.who.int/publications/i/item/9789240013131> [Accessed 11 December 2021].

100. OMS, 2021. Global Tuberculosis Report 2021. [online] Who.int. Available at: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2021> [Accessed 11 December 2021].
101. Kennard BD, Silva SG, Tonev S, et al, 2009. Remission and recovery in the Treatment for Adolescents with Depression Study (TADS): Acute and long-term outcomes. J Am Acad Child Adolesc Psychiatry 48(2) pp:186-195.
102. LeMoult J, Humphreys KL, Tracy A, et al, 2020. Meta-analysis: Exposure to early life stress and risk for depression in childhood and adolescence. J Am Acad Child Adolesc Psychiatry 59(7) pp 842-855
103. Dwyer JB, Bloch MH, 2019. Antidepressants for pediatric patients. Curr Psychiatr 8(9) pp:26-42F.
104. Allen CG, Kluger BM, Buard I, 2017 Safety of transcranial magnetic stimulation in children: A systematic review of the literature. Pediatr Neurol 68 pp:3-17
105. Donaldson AE, Gordon MS, Melvin GA, et al, 2014. Addressing the needs of adolescents with treatment resistant depressive disorders: A systematic review of rTMS. Brain Stimul 7(1) pp:7-12.
106. Kendall T, Morriss R, Mayo-Wilson E, et al, 2014. Assessment and management of bipolar disorder: Summary of updated NICE guidance.
107. Yatham LN, Kennedy SH, Parikh SV, et al, 2013. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: Update 2013. Bipolar Disord 15(1) pp:1-44.
108. Anamaria Ciubara, Roxana Chirita, Stefan Lucian Burlea, Ancuta Ignat, Smaranda Diaconescu, Ilinca Untu, Valeriu Vasile Lupu, 2015. Clinico-demographic patterns of depression and anxiety in children and adolescents
109. LeMoult, J., Humphreys, K. L., Tracy, A., Hoffmeister, J. A., Ip, E., & Gotlib, I. H., 2020, Meta-analysis: exposure to early life stress and risk for depression in childhood and adolescence. Journal of the American Academy of Child & Adolescent Psychiatry, 59(7), 842-855.
110. Mihailov, O., Rădulescu, I. D., Mihailov, R., & Ciubară, A., 2021, Depressive disorders and children with chronic illness. European Psychiatry, 64(S1), S219-S219. doi: 10.1192/j.eurpsy.2021.584
111. Burlea, A., Chiriţă, V., Săcuiu, I., & Chiriţă, R., 2010, Socioeconomic implications of underdiagnosing teenagers' depression. Revista Medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi, 114(2), 391-398.
112. Luca, L., Ciubara, A. B., Fulga, I., Burlea, S. L., Terpan, M., & Ciubara, A., 2020, Social Implications for Psychiatric Pathology of Depressive and Anxiety Disorders, Alcohol Addiction and Psychotic Disorders during the COVID-19 Pandemic in Romania. Analysis of two Relevant Psychiatry Hospitals. Revista de cercetare si interventie sociala, 69.
113. Mihailov, O., Matei, L., Ciubara, A. B., Dragostin, M., Mihailov, R., & Ciubara, A. (2021). The Evolution of Depressive Disorders in Children with History of Tuberculosis (Clinical Study in the Context of COVID-19 Pandemic in Romania). BRAIN. Broad Research in Artificial Intelligence and Neuroscience, 12(2), 222-236.

114. Bolos, A., Ciubara, A. M., & Chirita, R. (2012). Moral and ethical aspects of the relationship between depression and suicide. Revista Romana de Bioetica, 10(3).
115. Joshi R, Maharjan M, Mark D.Z., 2006. Tuberculosis Awareness Among TB Patients visiting in DOTS Clinic. Saarc J, Tuberc, Lung Dis, 3 pp:20-5
116. Adam J, Trenton BA, Glenn WC., 2001. Treatment of Co-morbid Tuberculosis and Depression. Prim Care Companion J Clin Psychiatry., 3(6) pp: 236–243
117. Kunik ME, Roundy K, Veazey C, Souchek J, Richardson P, Wray NP, Stanley MA, 2005.Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. Chest; 127 pp: 1205-11.
118. Paschalides C, Wearden AJ, Dunkerley R, Bundy C, Davies R, Dickens CM, 2004.The associations of anxiety, depression and personal illness representations with glycaemic control and health-related quality of life in patients with tuberculosis. J. Psychosom Res; 57 pp: 557-564.
119. Lin EH, Katon W, Rutter C, Simon GE, Ludman EJ, Von Korff M, Young B, Oliver M, Ciechanowski PC, Kinder L, Walker E, 2006. Effects of enhanced depression treatment on Diabetes self-care. Ann Fam Med, ;4 pp:46-53.
120. Hussain MO, Dearman SP, Chaudhry IB, Rizvi N, Waheed W., 2008. The relationship between anxiety, depression and illness perception in tuberculosis patients in Pakistan. Clin Pract Epidemil Mental Health, 4 pp: 179-187
121. Mason PH, Sweetland AC, Fox GJ, Halovic S, Nguyen TA, Marks GB., 2016. Tuberculosis and mental health in the Asia-Pacific. Australas Psychiatry.; 24 pp: 553- 555
122. Koyanagi A, Vancampfort D, Carvalho AF, et al., 2017. Depression comorbid with tuberculosis and its impact on health status: cross-sectional analysis of community-based data from 48 low- and middle-income countries. BMC Med.; 15 p: 209.
123. Dasa TT, Roba AA, Weldegebreal F, et al., 2019. Prevalence and associated factors of depression among tuberculosis patients in Eastern Ethiopia. BMC Psychiatry.; 19 p: 82.
124. Doherty AM, Kelly J, McDonald C, O'Dywer AM, Keane J, Cooney J., 2013. A review of the interplay between tuberculosis and mental health. Gen Hosp Psychiatry. 35 pp: 398- 406
125. Phillips AC, Carroll D, Der G, 2015. Negative life events and symptoms of depression and anxiety: stress causation and/or stress generation. Anxiety Stress Coping., 28 pp: 357- 371
126. Konsman JP, Parnet P, Dantzer R, 2002. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci. 25 pp: 154- 159
127. van West D, Maes M., 1999. Activation of the inflammatory response system: a new look at the etiopathogenesis of major depression. Neuro Endocrinol Lett.; 20 pp: 11- 17
128. Miller AH, Maletic V, Aguglia E, Pariante CM. 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry.; 65: 732- 741.
129. Bufalino C, Hepgul N, Aguglia E, Pariante CM., 2013. The role of immune genes in the association between depression and inflammation: a review of recent clinical studies. Brain Behav Immun., 31 pp: 31- 47.

130. Mayer-Barber KD, Andrade BB, Oland SD, et al., 2014. Host-directed therapy of tuberculosis based on interleukin-1 and type I interferon crosstalk. Nature.; 511 pp: 99- 103
131. Vladimer GI, Marty-Roix R, Ghosh S, Weng D, Lien E., 2013. Inflammasomes and host defenses against bacterial infections. Curr Opin Microbiol.; 16 pp: 23- 31
132. Martinon F, Burns K, Tschopp J., 2002. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell.; 10 pp: 417- 426.
133. Miao EA, Rajan JV, Aderem A., 2011. Caspase-1-induced pyroptotic cell death. Immunol Rev.; 243 pp: 206- 214
134. Dorhoi A, Nouailles G, Jörg S, et al., 2012. Activation of the NLRP3 inflammasome by Mycobacterium tuberculosis is uncoupled from susceptibility to active tuberculosis. Eur J Immunol.; 42 pp: 374- 384.
135. Wong KW., 2011. Critical role for NLRP3 in necrotic death triggered by Mycobacterium tuberculosis. Cell Microbiol.; 13 pp: 1371- 1384.
136. Lowe DM, Redford PS, Wilkinson RJ, O'Garra A, Martineau AR., 2012. Neutrophils in tuberculosis: friend or foe? Trends Immunol.; 33 pp: 14- 25
137. Mishra BB, Lovewell RR, Olive AJ, et al, 2017. Nitric oxide prevents pathogen-permissive granulocytic inflammation during tuberculosis. Nat Microbiol.; 2 p:17072.
138. Elkington PT, Friedland JS, 2006. Matrix metalloproteinases in destructive pulmonary pathology. Thorax.; 61 pp: 259- 266.
139. Miller AH., 2010. Depression and immunity: a role for T cells. Brain Behav Immun.; 24 pp: 1- 8
140. Kaufmann SH, Dorhoi A., 2013. Inflammation in tuberculosis: interactions, imbalances and interventions. Curr Opin Immunol.; 25 pp: 441- 449.
141. Bloom J, Al-Abed Y., 2014. MIF: mood improving/inhibiting factor? J Neuroinflammation.; 11 p: 11
142. Gomez LM, Sanchez E, Ruiz-Narvaez EA, López-Nevot MA, Anaya JM, Martín J., 2007. Macrophage migration inhibitory factor gene influences the risk of developing tuberculosis in northwestern Colombian population. Tissue Antigens.; 70 pp: 28- 33
143. Calandra T, Roger T, 2003. Macrophage migration inhibitory factor: a regulator of innate immunity. Nat Rev Immunol.; 3 pp: 791- 800
144. Fan H, Kao W, Yang YH, et al., 2014. Macrophage migration inhibitory factor inhibits the antiinflammatory effects of glucocorticoids via glucocorticoid-induced leucine zipper. Arthritis Rheumatol.; 66 pp: 2059- 2070
145. Conboy L, Varea E, Castro JE, et al., 2011. Macrophage migration inhibitory factor is critically involved in basal and fluoxetine-stimulated adult hippocampal cell proliferation and in anxiety, depression, and memory-related behaviors. Mol Psychiatry.; 16 pp: 533- 547
146. Das R, Koo MS, Kim BH, et al., 2013. Macrophage migration inhibitory factor (MIF) is a critical mediator of the innate immune response to Mycobacterium tuberculosis. Proc Natl Acad Sci USA.; 110 pp: E2997- E3006
147. Kaharuza FM, Bunnell R, Moss S, et al., 2006. Depression and CD4 cell count among persons with HIV infection in Uganda. AIDS Behav.; 10 pp: S105- S111.

148. Rothermundt M, Arolt V, Fenker J, Gutbrodt H, Peters M, Kirchner H., 2001. Different immune patterns in melancholic and non-melancholic major depression. Eur Arch Psychiatry Clin Neurosci.; 251 pp: 90- 97
149. Haapakoski R, Ebmeier KP, Alenius H, Kivimäki M., 2016. Innate and adaptive immunity in the development of depression: an update on current knowledge and technological advances. Prog Neuropsychopharmacol Biol Psychiatry.; 66 pp: 63- 72.
150. Zorrilla EP, Luborsky L, McKay JR, et al., 2001. The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav Immun.; 15 pp: 199- 226
151. Pavon L, Sandoval-Lopez G, Eugeniahernandez M, et al., 2006. Th2 cytokine response in major depressive disorder patients before treatment. J Neuroimmunol.; 172 pp: 156- 165
152. Herrera MT, Torres M, Nevels D, et al., 2009. Compartmentalized bronchoalveolar IFN-gamma and IL-12 response in human pulmonary tuberculosis. Tuberculosis.; 89 pp: 38- 47.
153. Peyron P, Vaubourgeix J, Poquet Y, et al., 2008. Foamy macrophages from tuberculous patients' granulomas constitute a nutrient-rich reservoir for M. tuberculosis persistence. PLoS Pathog.; 4 pp:e1000204.
154. Cotes K, Bakala N'goma J C, Dhouib R, et al., 2008. Lipolytic enzymes in Mycobacterium tuberculosis. Appl Microbiol Biotechnol.; 78 pp: 741- 749
155. Singh G, Singh G, Jadeja D, Kaur J., 2010. Lipid hydrolizing enzymes in virulence: Mycobacterium tuberculosis as a model system. Crit Rev Microbiol.; 36 pp: 259- 269.
156. Lee W, VanderVen BC, Fahey RJ, Russell DG., 2013. Intracellular Mycobacterium tuberculosis exploits host-derived fatty acids to limit metabolic stress. J Biol Chem.; 288 pp: 6788- 6800
157. Rameshwaram NR, Singh P, Ghosh S, Mukhopadhyay S., 2018. Lipid metabolism and intracellular bacterial virulence: key to next-generation therapeutics. Future Microbiol.; 13 pp: 1301- 1328
158. Oh J, Kim TS., 2017. Serum lipid levels in depression and suicidality: the Korea National Health and Nutrition Examination Survey (KNHANES) 2014. J Affect Disord.; 213: 51- 58
159. Gui SW, Liu YY, Zhong XG, et al., 2018, Plasma disturbance of phospholipid metabolism in major depressive disorder by integration of proteomics and metabolomics. Neuropsychiatr Dis Treat.; 14 pp: 1451- 1461.
160. Peng R, Dai W, Li Y., 2018. Low serum free thyroxine level is correlated with lipid profile in depressive patients with suicide attempts. Psychiatry Res.; 266 pp: 111- 115
161. Almeida PE, Silva AR, Maya-Monteiro CM, et al., 2009. Mycobacterium bovis bacillus Calmette-Guerin infection induces TLR2-dependent peroxisome proliferator-activated receptor gamma expression and activation: functions in inflammation, lipid metabolism, and pathogenesis. J Immunol.; 183 pp: 1337- 1345
162. Mahajan S, Dkhar HK, Chandra V, et al., 2012. Mycobacterium tuberculosis modulates macrophage lipid-sensing nuclear receptors PPARgamma and TR4 for survival. J Immunol.; 188 pp: 5593- 5603.
163. Janeway CA, Jr, Medzhitov R., 2002. Innate immune recognition. Annu Rev Immunol.; 20 pp: 197- 216.

164. Rosenberger K, Derkow K, Dembny P, Krüger C, Schott E, Lehnardt S., .2014 The impact of single and pairwise Toll-like receptor activation on neuroinflammation and neurodegeneration. J Neuroinflammation.; 11 p: 166.
165. Lang UE, Beglinger C, Schweinfurth N, Walter M, Borgwardt S., 2015. Nutritional aspects of depression. Cell Physiol Biochem.; 37 pp: 1029- 1043.
166. Fernandes MF, Mutch DM, Leri F., 2017. The relationship between fatty acids and different depression-related brain regions, and their potential role as biomarkers of response to antidepressants. Nutrients.; 9 p: E298
167. Marventano S, Kolacz P, Castellano S, et al., 2015. A review of recent evidence in human studies of n-3 and n-6 PUFA intake on cardiovascular disease, cancer, and depressive disorders: does the ratio really matter? Int J Food Sci Nutr.; 66 pp: 611- 622
168. Dietzold J, Gopalakrishnan A, Salgame P., 2015. Duality of lipid mediators in host response against Mycobacterium tuberculosis: good cop, bad cop. F1000Prime Rep.; 7 p: 29
169. Chen M, Divangahi M, Gan H, et al., 2008. Lipid mediators in innate immunity against tuberculosis: opposing roles of PGE2 and LXA4 in the induction of macrophage death. J Exp Med.; 205 pp: 2791- 2801
170. Divangahi M, Behar SM, Remold H., 2013. Dying to live: how the death modality of the infected macrophage affects immunity to tuberculosis. Adv Exp Med Biol. ; 783 pp: 103- 120
171. Lee JY, Jung YW, Jeong I, et al., 2015. Immune parameters differentiating active from latent tuberculosis infection in humans. Tuberculosis. ; 95 pp: 758- 763.
172. Del Castillo-Barrientos, H., Centeno-Luque, G., Untiveros-Tello, A., Simms, B., Lecca, L., Nelson, A. K., ... & Shin, S., 2014. Clinical presentation of children with pulmonary tuberculosis: 25 years of experience in Lima, Peru. The international journal of tuberculosis and lung disease, 18(9), 1066-1073.
173. Puryear, S., Seropola, G., Ho-Foster, A., Arscott-Mills, T., Mazhani, L., Firth, J., ... & Steenhoff, A. P., 2013, Yield of contact tracing from pediatric tuberculosis index cases in Gaborone, Botswana. The International journal of tuberculosis and lung disease, 17(8), 1049-1055.
174. Blount, R. J., Tran, B., Jarlsberg, L. G., Phan, H., Thanh Hoang, V., Nguyen, N. V., ... & Nahid, P., 2014, Childhood tuberculosis in northern Viet Nam: a review of 103 cases. PLoS One, 9(5), e97267.
175. Chisti, M. J., Salam, M. A., Shahid, A. S., Shahunja, K. M., Das, S. K., Faruque, A. S. G., ... & Ahmed, T., 2017, Diagnosis of Tuberculosis Following World Health Organization–Recommended Criteria in Severely Malnourished Children Presenting with Pneumonia. Global Pediatric Health, 4, 2333794X16686871.
176. Jaganath, D., & Mupere, E., 2012, Childhood tuberculosis and malnutrition. The Journal of infectious diseases, 206(12), 1809-1815.
177. DHS, M. (2011). Population Division Ministry of Health and Population Ramshah Path, Kathmandu Nepal.

178. Chisti, M. J., Graham, S. M., Duke, T., Ahmed, T., Ashraf, H., Faruque, A. S. G., ... & Salam, M. A. (2014). A prospective study of the prevalence of tuberculosis and bacteraemia in Bangladeshi children with severe malnutrition and pneumonia including an evaluation of Xpert MTB/RIF assay. PloS one, 9(4), e93776.
179. Meshram, H. S., Ali, S. M., & Shehab, T. (2017). Spectrum of co-morbidities in severe acute malnutrition with unexpected dyselectrolytemia in diarrhea. Tuberculosis, 39(13), 10-18231.
180. Centers for Disease Control and Prevention. (2019). Data and statistics on children's mental health, CDC.
181. Kovacs M., 2003, Children's Depression Inventory: Technical manual update. Toronto, ON: Multi-Health Systems, Inc.
182. Kovacs M., 1992, Children's Depression Inventory CDI Manual. New York: Multi-Health Systems. North Tonawanda, NY: Multi-Health Systems, Inc.
183. Cho, S. C., & Lee, Y. S., 1990, Development of the Korean form of the Kovacs' Children's Depression Inventory. J Korean Neuropsychiatr Assoc, 29(4), 943-956.
184. Yang, J. W., Kim, Y. J., Kim, H. S., Shin, K. M., & Shin, Y. M., 2012, Difference between children's self-reports on depression and parents' assessment of children's behaviors. Journal of the Korean Academy of Child and Adolescent Psychiatry, 23(2), 76-81.
185. McHugh, ML (2013). Testul chi-pătrat al independenței. Biochemia Medica, 23(2), 143-149. https://doi.org/10.11613/BM.2013.018
186. Cohen, J. (1988). Analiza statistică a puterii pentru științele comportamentului (ed. a II-a). Editura de Vest.
187. Conover, WJ și Iman, RL (1981). Clasați transformările ca o punte între statisticile parametrice și neparametrice. The American Statistician, 35(3), 124-129. https://doi.org/10.1080/00031305.1981.10479327
188. María José Mellado Peñaa, Begoña Santiago Garcíaa, Fernando Baquero-Artigaoa, David Moreno Péreza, Roi Piñeiro Péreza, Ana Méndez Echevarríaa, José Tomás Ramos Amadora, David Gómez-Pastrana Duránа, Antoni Noguera Julianа, Working Group on Tuberculosis and Other Mycobacterial Infections of the Spanish Society for Pediatric Infectious Diseases: Tuberculosis treatment for children: An update. 01 January 2018. Vol. 88. Issue 1.pages 52.e1-52.e12
189. Center for Disease Control and Prevention. TB in Children
190. Thee S, et al. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations. Antimicrobial Agents and Chemotherapy. 2011;55:5560–5567
191. McIlleron H, et al. Isoniazid plasma concentrations in a cohort of South African children with tuberculosis: implications for international pediatric dosing guidelines. Clinical Infectious Diseases. 2009;48(11):1547–1553
192. Donald PR. Antituberculosis drug-induced hepatotoxicity in children. Pediatric Reports. 2011;3(2):e16
193. WHO G. Global tuberculosis report 2020. Glob. Tuberc. Rep. 2020 Oct 21

194. Seddon JA, Jenkins HE, Liu L et al., 2015, Counting children with tuberculosis: why numbers matter. Int J Tuberc Lung Dis. 19: 9-16
195. Menzies HJ, Winston CA, Holtz TH, Cain KP, Mac Kenzie WR, 2010, Epidemiology of tuberculosis among US- and foreign-born children and adolescents in the United States, 1994–2007. Am J Public Health, 100: 91724-91729
196. World Health Organization, 'Global Tuberculosis Report 2015', WHO, Geneva, 2015
197. World Health Organization, 'Global Tuberculosis Report 2018', WHO, Geneva, 2018
198. Marais BJ, Gie RP, Schaaf HS, et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004;8(3):278–285
199. Srichand Batra, Afsheen Ayaz,Ali Murtaza,Shakil Ahmad,Rumina Hasan ,Ruth Pfau, Childhood Tuberculosis in Household Contacts of Newly Diagnosed TB Patients. July 31, 2012
200. Babamahmoodi F, Alikhani A, Yazdani Charati J, Ghovvati A, Ahangarkani F, Delavarian L, Babamahmoodi A. Clinical epidemiology and paraclinical findings in tuberculosis patients in north of Iran. Biomed Res Int. 2015; 2015:381572. doi: 10.1155/2015/381572. Epub 2015 Jan 28. PMID: 25695067; PMCID: PMC4324112.
201. Vallejo JG, Ong LT, Starke JR. Clinical features, diagnosis, and treatment of tuberculosis in infants. Pediatrics. 1994 Jul;94(1):1-7. PMID: 8008511.
202. Triasih, R.; Robertson, C.F.; Duke, T.; Graham, S.M. A prospective evaluation of the symptom-based screening approach to the management of children who are contacts of tuberculosis cases. Clin. Infect. Dis. 2015, 60, 12–18. [CrossRef]
203. Dr Peter J Dodd, Charalambos Sismanidis, James A Seddon. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. The Lancet Infectious Disease. Volume 16, Issue 10, October 2016, Pages 1193-1201
204. Spyridis, N. P., Spyridis, P. G., Gelesme, A., Sypsa, V., Valianatou, M., Metsou, F., ... & Tsolia, M. N., 2007, The effectiveness of a 9-month regimen of isoniazid alone versus 3-and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clinical Infectious Diseases, 45(6), 715-722.
205. Vos e T, Flaxman AD, Naghavi M, Lozano R, et al., 2012. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet., 380 pp:2163–2196
206. Mykletun A, Bjerkeset O, Overland S, Prince M, Dewey M, Stewart R., 2009. Levels of anxiety and depression as predictors of mortality: the HUNT study. Br J Psychiatry. ;195 pp:118–125.
207. Chien IC, Wu EL, Lin CH, Chou YJ, Chou P., 2012. Prevalence of diabetes in patients with major depressive disorder: a population-based study. Compr Psychiatry.; 53 pp:569–575.
208. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG., 2010. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry.; 67 pp:220–229

209. Maxwell MA, Cole DA., 2009. Weight change and appetite disturbance as symptoms of adolescent depression: toward an integrative biopsychosocial model. Clinical psychology review.; 29(3) pp:260–273.
210. Fava M, Alpert J, Nierenberg AA, Ghaemi N, O'Sullivan R, Tedlow J et al., 1996.Fluoxetine treatment of anger attacks: a replication study. Ann Clin Psychiatry; 8 pp: 7–10. ;
211. Fava M, Nierenberg AA, Quitkin FM, Zisook S, Pearlstein T, Stone A et al. 1997.A preliminary study on the efficacy of sertraline and imipramine on anger attacks in atypical depression and dysthymia. Psychopharmacol Bull; 33 pp: 101–103.;
212. Fava M, Rosenbaum JF, Pava JA, McCarthy MK, Steingard RJ, Bouffides E. 1993. Anger attacks in unipolar depression, Part 1: clinical correlates and response to fluoxetine treatment. Am J Psychiatry; 150 pp: 1158–1163.
213. Heerlein A, Richter P, Gonalez M, Santander J 1998: Personality patterns and outcome in depressive and bipolar disorders. Psychopathology, 31 pp:15–22.
214. Bagby RM, Cox BJ, Schuller DR, et al., 1992.: Diagnostic specificity of the dependent and self-critical personality dimensions in major depression. J Affect Disord, 26 pp:59–63.
215. Bagby RM, Joffee RT, Parker JD, et al. 1995: Major depression and the five-factor model of personality. J Pers Disord, 9 pp:224–234.
216. Zuckerbrot, R. A., Cheung, A. H., Jensen, P. S., Stein, R. E., Laraque, D., & Glad-PC Steering Group, 2007, Guidelines for Adolescent Depression in Primary Care (GLAD-PC): I. Identification, assessment, and initial management. Pediatrics, 120(5), e1299-e1312.
217. Birmaher, B., Brent, D., & AACAP Work Group on Quality Issues, 2007, Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. Journal of the American Academy of Child & Adolescent Psychiatry, 46(11), 1503-1526.
218. Crowe M, Ward N, Dunnachie B, Roberts M., 2006. Characteristics of adolescent depression. Int J Ment Health Nurs; 15 pp: 10–18.;
219. Ryan ND, Puig-Antich J, Ambrosini P, Rabinovich H, Robinson D, Nelson B et al., 1987. The clinical picture of major depression in children and adolescents. Arch Gen Psychiatry; 44 pp: 854–861
220. Nierenberg AA, Keefe BR, Leslie VC, et al., 1999. Residual symptoms in depressed patients who respond acutely to fluoxetine. J Clin Psychiatry.; 60 pp:221–225.
221. Fava M., 2003.Symptoms of fatigue and cognitive/executive dysfunction in major depressive disorder before and after antidepressant treatment. J Clin Psychiatry.; 64 (suppl 14), pp:30–34.
222. Demyttenaere K, Fruyt J, Stahl SM., 2004. The many faces of fatigue in major depressive disorder. Int J Neuropharmacol. ;8 pp:93–105.
223. Jindal RD., Thase ME. 2004. Treatment of insomnia associated with clinical depression. *Sleep Med Rev.;* 8 pp:19–30.
224. Agargun MY., Kara H., Solinaz M., 1997. Sleep disturbances and suicidal behavior in patients with major depression. *J Clin Psychiatry.* ;58 pp:249–251

225. DeCarlo, LT, 1997, Despre semnificația și utilizarea kurtozei. Metode psihologice, 2(3), 292-307. https://doi.org/10.1037/1082-989X.2.3.292
226. O'Connor, B. C., Lewandowski, R. E., Rodriguez, S., Tinoco, A., Gardner, W., Hoagwood, K., & Scholle, S. H., 2016, Usual care for adolescent depression from symptom identification through treatment initiation. JAMA pediatrics, 170(4), 373-380.
227. Hetrick, S. E., Cox, G. R., Witt, K. G., Bir, J. J., & Merry, S. N., 2016, Cognitive behavioural therapy (CBT), third-wave CBT and interpersonal therapy (IPT) based interventions for preventing depression in children and adolescents. Cochrane database of systematic reviews, (8).
228. Yohannes, K., Mokona, H., Abebe, L. et al. Prevalence of depressive symptoms and associated factors among patients with tuberculosis attending public health institutions in Gede'o zone, South Ethiopia. BMC Public Health 20, 1702 (2020). https://doi.org/10.1186/s12889-020-09794-z
229. Sweetland A.C., Kritski A., Oquendo M.A. Addressing the Tuberculosis-Depression Syndemic to End the Tuberculosis Epidemic. Int. J. Tuberc. Lung Dis. 2017; 21:852–861. doi: 10.5588/ijtld.16.0584
230. Ambaw F, Mayston R, Hanlon C, et al., 2015, Depression among patients with tuberculosis: determinants, course and impact on pathways to care and treatment outcomes in a primary care setting in southern Ethiopia—a study protocolBMJ Open 2015;5: e007653. doi: 10.1136/bmjopen-2015-007653
231. Ambaw F, Mayston R, Hanlon C, Alem A. Burden and presentation of depression among newly diagnosed individuals with TB in primary care settings in Ethiopia. BMC Psychiatry. 2017;17(1):57
232. Kam A., Ford-Jones L., Malloy P., Khan K., Kitai I. Active Tuberculosis among Adolescents in Toronto, Canada: Clinical Features and Delays in Diagnosis. Pediatr. Infect. Dis. J. 2007; 26:355–356. doi: 10.1097/01.inf.0000258700. 86040.b6
233. Avdeeva T., Otvagin I., Myakisheva T., Rashkevich E. Tuberculosis in Adolescents and Young Patients in High Prevalence Region. Eur. J. Microbiol. Immunol. 2012; 2:297–301. doi: 10.1556/EuJMI.2.2012.4.9
234. Xiao-bo Wang, Xue-lian Li, Qing Zhang, Juan Zhang, Hong-yan Chen, Wei-yuan Xu, Ying-hui Fu, Qiu-yue Wang, Jian Kang and Gang Hou, A Survey of Anxiety and Depressive Symptoms in Pulmonary Tuberculosis Patients with and Without Tracheobronchial Tuberculosis, Psychiatry, 19 July 2018
235. Shen R, Zong K, Liu J, Zhang L. Risk Factors for Depression in Tuberculosis Patients: A Meta-Analysis. Neuropsychiatr Dis Treat. 2022; 18:847-866 https://doi.org/10.2147/NDT.S347579
236. Ruiz-Grosso P, Cachay R, de la Flor A, Schwalb A, Ugarte-Gil C (2020) Association between tuberculosis and depression on negative outcomes of tuberculosis treatment: A systematic review and meta-analysis. PLoS ONE 15(1): e0227472. https://doi.org/10.1371/journal.pone.0227472
237. Das M., Mathur T., Ravi S., Meneguim A.C., Iyer A., Mansoor H., Kalon S., Hossain F.N., Acharya S., Ferlazzo G. Challenging Drug-Resistant TB Treatment Journey for Children, Adolescents and Their Caregivers: A Qualitative Study. PLoS ONE. 2021;16: e0248408. doi: 10.1371/journal.pone.0248408

238. Zvonareva O., Witte S., Kabanets N., Filinyuk O. Adolescents in a Tuberculosis Hospital: Qualitative Study of How Relationships with Doctors, Caregivers, and Peers Mediate Their Mental Wellbeing. PLoS ONE. 2021;16: e0257379. doi: 10.1371/journal.pone.0257379.
239. Karayeva E. Master's Thesis. Brown University School of Public Health; Providence, RI, USA: 2020. The Impact of Hospitalization on Ukrainian Adolescents Who Have Completed Tuberculosis Treatment in Kyiv City, Ukraine
240. Chan, D. W., 1997, Depressive symptoms and perceived competence among Chinese secondary school students in Hong Kong. Journal of Youth and Adolescence, 26(3), 303-319.
241. Fristad, M.A.; Emery, B.L.; Beck, S.J., 1997, Use and abuse of the children's Depression Inventory. Journal of consulting and clinical psychology USA, v. 65, n. 4, p. 699-702.
242. Nurcombe, B., Seifer, R., Scioli, A., Tramontana, M. G., Grapentine, W. L., & Beauchesne, H. C., 1989, Is major depressive disorder in adolescence a distinct diagnostic entity? Journal of the American Academy of Child & Adolescent Psychiatry, 28(3), 333-342.
243. Kovacs, M., 1983, The Children's Depression Inventory: A se~-rated depression scale for schoolaged youngsters. Unpublished manuscript, University of Pittsburgh, School of Medicine.
244. Fristad, M. A., Weller, R. A., Weller, E. B., Teare, M., & Preskorn, S. H., 1991, Comparison of the parent and child versions of the Children's Depression Inventory (CDI). Annals of Clinical Psychiatry, 3(4), 341-346.
245. Nelson III, W. M., Politano, P. M., Finch Jr, A. J., Wendel, N., & Mayhall, C., 1987, Children's Depression Inventory: Normative data and utility with emotionally disturbed children. Journal of the American Academy of Child & Adolescent Psychiatry, 26(1), 43-48.
246. Saylor, C. F., Finch, A. J., Spirito, A., & Bennett, B., 1984, The children's depression inventory: a systematic evaluation of psychometric properties. Journal of consulting and clinical psychology, 52(6), 955.
247. Weiss, B., Weisz, J. R., Politano, M., Carey, M., Nelson, W. M., & Finch, A. J., 1991, Developmental differences in the factor structure of the Children's Depression Inventory. Psychological Assessment: A Journal of Consulting and Clinical Psychology, 3(1), 38.
248. Garvin, V., Leber, D., & Kalter, N., 1991, Children of divorce: Predictors of change following preventive intervention. American Journal of Orthopsychiatry, 61(3), 438-447.
249. Kazdin, A. E., Colbus, D., & Rodgers, A., 1986, Assessment of depression and diagnosis of depressive disorder among psychiatrically disturbed children. Journal of Abnormal Child Psychology, 14(4), 499-515.
250. Lobovits, D. A., & Handal, P. J., 1985, Childhood depression: Prevalence using DSM-III criteria and validity of parent and child depression scales. Journal of pediatric psychology, 10(1), 45-54.
251. Donnelly, M. (1995). Depression among adolescents in Northern Ireland. Adolescence, 30, 339-350.
252. Helsel W.J. & Matson J.L., 1984, The assessment of depression in children: the internal structure of the child depression inventory. Behaviour Research and Therapy 22, 289–98.

253. Sund AM, Larsson B, Wichstrøm L. Psychosocial correlates of depressive symptoms among 12-14-year-old Norwegian adolescents. J Child Psychol Psychiatry Allied Discip. 2003;44: 588–597. 10.1111/1469-7610.00147
254. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. Lancet. 2012;379: 1056–1067. 10.1016/S0140-6736(11)60871-4
255. Katon WJ, Lin EHB, Von Korff M, Ciechanowski P, Ludman EJ, Young B, et al. Collaborative care for depression and chronic illnesses. N Engl J Med. 2010;363: 2611–2620. 10.1056/NEJMoa1003955
256. Bernaras E, Jaureguizar J, Soroa M, Ibabe I, Cuevas C. Child depression in the school context. Procedia—Soc Behav Sci. 2011;29: 198–207. 10.1016/j.sbspro.2011.11.225
257. Allgaier, A. K., Pietsch, K., Frühe, B., Sigl-Glöckner, J., & Schulte-Körne, G., 2012, Screening for depression in adolescents: validity of the patient health questionnaire in pediatric care. Depression and anxiety, 29(10), 906-913.
258. Reynolds WM, Mazza JJ., 1998, Reliability and Validity of the Reynolds Adolescent Depression Scale with Young Adolescents. J Sch Psychol.; 36: 295–312. 10.1016/S0022-4405(98)00010-7
259. Burleson Daviss, W., Birmaher, B., Melhem, N. A., Axelson, D. A., Michaels, S. M., & Brent, D. A., 2006, Criterion validity of the Mood and Feelings Questionnaire for depressive episodes in clinic and non-clinic subjects. Journal of Child Psychology and Psychiatry, 47(9), 927-934.
260. Scott WD, Clapp J, Mileviciute I, Mousseau A., 2016, Children's depression inventory: A unidimensional factor structure for American Indian and Alaskan native youth. Psychol Assess. 28: 81–91. 10.1037/pas0000145
261. Beck AT, Steer RA, Carbin MG., 1988, Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. Clin Psychol Rev. 8: 77–100. 10.1016/0272-7358(88)90050-5
262. WHO, 2019, https://iris.who.int/bitstream/handle/10665/324835/9789241565707-eng.pdf?sequence=9
263. Ahmed MM, Mazhar M, Zaidi A. Depression in tuberculosis patients and its relationship to socio demographic factors. J Rawalpindi Med Coll. 2016;20(4):296–9.
264. Ravi CS, Dinesh DS, Neeraj K, Manish KT, Pankaj K. Assessment of the frequency of depression and anxiety among tuberculosis patients at a tertiary care health centre. A cross sectional study. Eur J Pharm Med Res. 2018;5(4):496–9.
265. Kumar K, Kumar A, Chandra P, Kansal HM. A study of prevalence of depression and anxiety in patients suffering from tuberculosis. J Fam Med Prim Care. 2016; 5:150–3.
266. Wang PS, Bohn RL, Knight E, Glynn RJ, Mogun H, Avorn J, 2002. Noncompliance with antihypertensive medications: the impact of depressive symptoms and psychosocial factors. J Gen Intern Med 17: 504–511.
267. Snow K.J., Cruz A.T., Seddon J.A., Ferrand R.A., Chiang S.S., Hughes J.A., Kampmann B., Graham S.M., Dodd P.J., Houben R.M., et al. Adolescent Tuberculosis. Lancet Child Adolesc. Health. 2020; 4:68–79. doi: 10.1016/S2352-4642(19)30337-2.

General bibliography

1. A van Riea, N Beyersa, R P Giea, M Kunnekeb, L Zietsmanb, P R Donalda. Childhood tuberculosis in an urban population in South Africa: burden and risk factor. Arch Dis Child 1999; 80:433–437
2. ATS/CDC Statement Committee on Latent Tuberculosis Infection, 2000. "Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society". MMWR Recomm Rep. 49 (RR–6) pp: 1–51
3. Bates, D., Mächler, M., Bolker, B. și Walker, S. (2014). Ajustarea modelelor liniare cu efecte mixte folosind lme4: arXiv preprint arXiv, Journal of Statistical Software. https://doi.org/10.18637/jss.v067.io1
4. Beck AT, Bredemeier K. A unified model of depression: Integrating clinical, cognitive, biological, and evolutionary perspectives. Clin Psychol Sci. 2016;4: 596–619. 10.1177/2167702616628523 [CrossRef] [Google Scholar]
5. Chaisson, RE, Martinson, NA, 2008. "Tuberculosis in Africa--combating an HIV-driven crisis". The New England Journal of Medicine. 358 (11) pp: 1089–92.
6. Costello EJ, Erkanli A, Angold A. Is there an epidemic of child or adolescent depression? J Child Psychol Psychiatry Allied Discip. 2006;47: 1263–1271. [PubMed] [Google Scholar]
7. Davies PD, 2003. "The world-wide increase in tuberculosis: how demographic changes, HIV infection and increasing numbers in poverty are increasing tuberculosis". Annals of Medicine. 35 (4) pp: 235–243
8. Davies PD, Yew WW, Ganguly D, Davidow AL, Reichman LB, Dheda K, Rook GA, 2006. "Smoking and tuberculosis: the epidemiological association and immunopathogenesis". Transactions of the Royal Society of Tropical Medicine and Hygiene. 100 (4) pp: 291–298
9. Davis L, 1995. "Vegetarian diet and tuberculosis in immigrant Asians". Thorax. 50 (8) pp: 915–916
10. Field, A. (2017). Descoperirea statisticilor folosind statisticile IBM SPSS: ediția nord-americană. Publicații Sage
11. Frank, E., Anderson, B., Reynold, C. F., Ritenour, A., and Kupfer, D. J. (1994). Life events and the research diagnostic criteria endogenous subtype. A confirmation of the distinction using the Bellford College methods. Arch. Gen. Psychiatry 51, 519–524. doi: 10.1001/archpsyc.1994.03950070011005
12. Harries, A. D., et al, 2010. "Defining the Research Agenda to Reduce the Joint Burden of Disease from Diabetes Mellitus and Tuberculosis " Tropical medicine & international health:
13. Intellectus Statistics [Software de calculator online]. (2021). Statistica Intellectus. https://analyze.intellectusstatistics.com/
14. Larouzé B, Sánchez A, Diuana V, 2008. "Tuberculosis behind bars in developing countries: a hidden shame to public health". Trans. R. Soc. Trop. Med. Hyg. 102 (9) pp: 841–842
15. Lee JH, 1948. "Tuberculosis and Silicosis". Can Med Assoc J. 58 (4) pp: 349–353.
16. Leung CC, 2007. "Lower risk of tuberculosis in obesity". Arch. Intern. Med. 167(12) pp: 1297–304

17. Levene, H. (1960). Contribuții la probabilitate și statistică. Eseuri în onoarea lui Harold Hotelling, I. Olkin et al. eds., Stanford University Press, 278-292.
18. Lönnroth K, Raviglione M, 2008. "Global epidemiology of tuberculosis: prospects for control". Seminars in Respiratory and Critical Care Medicine. 29 (5) pp: 481–491.
19. Marais B.J., Gie R.P., Schaaf H.S., Hesseling A.C., Obihara C.C., Starke J.J., Enarson D.A., Donald P.R., Beyers N. The Natural History of Childhood Intra-Thoracic Tuberculosis: A Critical Review of Literature from the Pre-Chemotherapy Era. Int. J. Tuberc. Lung Dis. 2004; 8:392–402. [PubMed] [Google Scholar]
20. Millard, SP și Neerchal, NK (2000). Statistici de mediu cu S-Plus. CRC Press.https://doi.org/10.1201/9781420037173
21. Mishra, Gyanshankar; Munje, Radha; Dawkore, Madhav. "Diabetes and Tuberculosis – Tackling Double Trouble" (PDF). Indian Journal of Basic and Applied Medical Research. 8 (1): 256–260
22. Möller, M; Hoal, EG, 2010. "Current findings, challenges and novel approaches in human genetic susceptibility to tuberculosis". Tuberculosis (Edinburgh, Scotland). 90 (2) pp: 71–83
23. Mutlu G, Mutlu E, Bellmeyer A, Rubinstein I, 2006. "Pulmonary adverse events of anti-tumor necrosis factor-alpha antibody therapy". Am J Med. 119 (8) pp: 639–646?
24. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al., 2016. "Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis". Clinical Infectious Diseases. 63 (7) pp: e147–e195
25. Nijland HMJ, et al. 2006. "Exposure to rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes". Clin Infect Dis. 43 (7) pp: 848–854.
26. Niobe-Eyangoh SN, Kuaban C, Sorlin P, Cunin P, Thonnon J, Sola C, et al., 2003. "Genetic biodiversity of Mycobacterium tuberculosis complex strains from patients with pulmonary tuberculosis in Cameroon". Journal of Clinical Microbiology. 41 (6) pp: 2547–53
27. Nnoaham KE, Clarke A, 2008. "Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis". Int J Epidemiol. 37 (1) pp: 113–119.
28. Oana Mihailov, Loredana Matei, Alexandru Bogdan Ciubara, Miruna Dragostin, Raul Mihailov, Anamaria Ciubara, 2021. The Evolution of Depressive Disorders in Children with History of Tuberculosis (Clinical Study in the Context of COVID-19 Pandemic in Romania)
29. Osborne, J., & Waters, E. (2002). Patru ipoteze ale regresiei multiple pe care cercetătorii ar trebui să le testeze întotdeauna. Evaluare practică, cercetare și evaluare, 8(2), 1-9.
30. Pituch, KA și Stevens, JP (2015). Statistică multivariată aplicată pentru științe sociale (ed. a VI-a). Routledge Academic. https://doi.org/10.4324/9781315814919
31. Restrepo, BI, 2007. "Convergence of the tuberculosis and diabetes epidemics: renewal of old acquaintances". Clin Infect Dis. 45 (4) pp: 436–438.
32. Richter, C., Ndosi, B., Mwammy, A. S. & Mbwambo, R. K.,1991. Extrapulmonary tuberculosis — a simple diagnosis? Tropical and Geographical Medicine, 43, pp;375–378.
33. Schaible UE, Kaufmann SH, 2007. "Malnutrition and Infection: Complex Mechanisms and Global Impacts". PLOS Medicine. 4 (5) pp: e115.

34. Segall L, Covic A, 2010. "Diagnosis of tuberculosis in dialysis patients: current strategy". Clin J Am Soc Nephrol. 5 (6) pp: 1114–1122
35. Strachan DP, Powell KJ, Thaker A, Millard FJ, Maxwell JD, 1995. "Vegetarian diet as a risk factor for tuberculosis in immigrant south London Asians". Thorax. 50 (2) pp: 175–180
36. Ustianowski A, Shaffer R, Collin S, Wilkinson RJ, Davidson RN, 2005. "Prevalence and associations of vitamin D deficiency in foreign-born persons with tuberculosis in London". J Infect. 50 (5) pp: 432–437.
37. WHO global estimates on depression and other common mental disorders. 2017 https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf?sequence=1. Accessed 28 Feb 2019.
38. WHO,2011https://web.archive.org/web/20110808115404/http://www.who.int/tb/hiv/faq/en/
39. World Health Organization (2004b). Interim Policy on Collaborative TB/HIV Activities. Stop TB
40. Department and Department of HIV/AIDS. Document WHO/ HTM/TB/2004.330. Geneva: WHO.
41. World Health Organization. Roadmap towards ending TB in children and adolescents, second edition. Geneva; 2018.