

## Study on Therapeutic Dropout Rates of a Pediatric Population in South-Eastern Central Europe, Dependent on Individual Particularities

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**Abstract:** *Specialized studies conducted in the last decade have shown that the therapeutic success of specific treatment with tuberculostatic drugs, along with the decrease in the risk of relapse are elements that can only be achieved by increasing patients' adherence to treatment. This is of paramount importance, especially for pediatric populations, as they are subject to a higher rate of therapeutic dropout, dependent on a number of individual particularities (from socio-demographic characteristics, to the incidence of depressive disorders, to pathological personal history, etc.). When we talk about patient behavior, we refer to how he/she complies with the specialist's recommendation regarding medication administration; following a diet; lifestyle changes.*

**Keywords:** *Tuberculosis, children, therapeutic dropout, depressive disorders, CDI scores.*

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## 1. Purpose and objectives

The present paper represents a study centered on a group consisting of a total number of 192 pediatric patients, aged between 7-18 years, whose information was obtained by analyzing the medical records existing in the archives of the Pneumophthisiology Hospital, Galati.

The purpose of this research is to highlight the impact of a series of individual peculiarities in the case of pediatric patients (diagnosed with tuberculosis [TB]), regarding the drug treatment's dropout rate.

For an easier understanding of this paper's structure, we decided to expose the objectives in stages, depending on their importance, as follows:

- Main objective: determination (with statistical support) of the therapeutic dropout rate of TB-diagnosed pediatric patients, dependent on the particular characteristics of this population (socio-demographic characteristics, history, clinical-paraclinical and imaging assessments)
- Secondary objectives:
  - Identifying the peculiarities of the socio-demographic distribution at group level;
  - Analyzing the impact of patients' age on their evolution, as well as in determining the prognosis on the risk of therapeutic dropout;
  - Assessing the CDI scores obtained by patients, as well as the corroboration of all individual particularities in order to determine the risk of therapeutic dropout;
  - Determining the need for constant, phased reassessments throughout the entire healing process to decrease the risk of therapeutic dropout;
  - The need to involve an interdisciplinary team (pediatrician, pulmonologist, psychologist / psychiatrist) to analyze all the particular characteristics of patients.

### ***1.2 Material and methods***

As mentioned earlier, a total of 192 pediatric patients aged 7-18 years were included in the present clinical research. The subjects were monitored retrospectively, from the moment of admission (in the context of TB diagnosis and initiation of treatment) to the moment they were discharged (upon request, or if their clinical and laboratory situation allowed it).

The clinical research presented in this report was conducted after obtaining the approval of the Ethics Commission of Pneumophthisiology Hospital, Galati. At the same time, in order to include the patients in the present clinical trial, an informed consent was completed in advance (by the parents or, in the case, by the legal guardians of the patients).

Thus, the purpose of this paper is to draw an algorithm for establishing a system of risk groups that will emit “alarm signals” on the negative developments of the subjects, from the point of view of increasing the incidence of therapeutic dropout rates, with the detection of all the characteristics that determined this.

The individual characteristics of the patients were subsequently analyzed based on inclusion and exclusion criteria, as well as on sampling lists, all of which were elements that formed the basis for centralizing information from the final structure of the doctoral thesis database.

Inclusion criteria:

- Ages between 7-18 years
- Patients whose legal guardians have agreed to sign the written agreement to be included in this study group
- Pediatric patients presented with a definite diagnosis of TB, documented by existing clinical-biological assessments

Exclusion criteria:

- Ages outside the previously defined range
- Pediatric patients presenting for other respiratory symptoms
- Patients who associate chronic diseases, faulty organisms that can influence the result of analyzes, from a statistical point of view
- Patients whose legal guardians refused to sign the agreement

Thus, as a preliminary conclusion, we can accept that, from the point of view of the characteristics of the present study, it is analytical, descriptive and retrospective.

Based on the information obtained, along with their corroboration with data from the specialized literature and statistical data obtained by extrapolating the statistical analysis underlying the doctoral thesis, we will develop a management and prognosis system of the TB-diagnosed pediatric patient.

The recorded data were included in sampling lists, on which summary tables were subsequently made. These were analyzed using SPSS V.26 software. (IBM Statistical Package for the Social Sciences, Chicago, Illinois).

The statistical study addressed two aspects: descriptive statistics and analytical statistics. The descriptive statistics presents the classification and

synthesis of observational data. It concentrates the existing information with the help of certain statistical indicators expressing characteristics and trends of the studied parameter. Within the descriptive statistics, the values of localization (mean, median, modal value) and scattering (dispersion, standard deviation, amplitude) indicators were calculated and we determined, as appropriate, the range of variation with 95% confidence (for the study of proportions).

In the statistical analysis, we applied regression pattern tests, mean comparison, Chi square test ( $\chi^2$ ) to compare proportions and we tested the sensitivities of the diagnostic methods. Thus, some associations, relationships and interdependencies between variables could be highlighted.

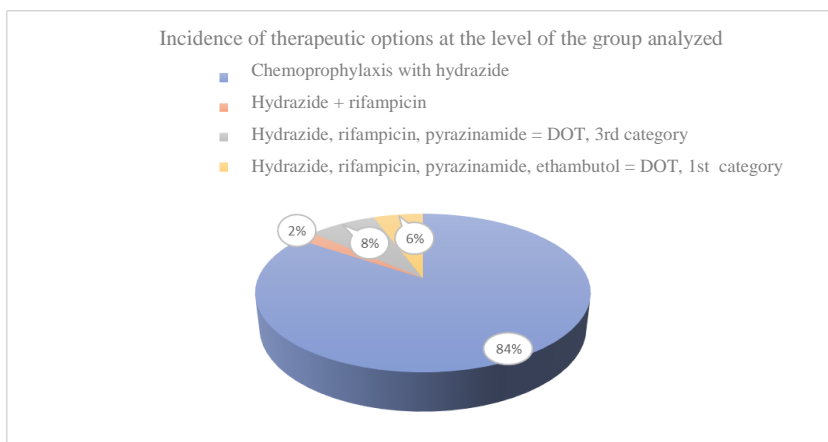
### ***1.3 Results***

From the gender distribution of the group, it can be seen that most of the subjects included in this study group were male (54.7%, n=105), while only 45.3% (n=87) were female. At the same time, there is a predominance of subjects coming from rural areas (n = 136, meaning a percentage of 70.8%), compared to 29.2% coming from urban areas.

Following to corroborating the distribution according to the origin environment and the gender of the subjects, it was observed that in rural areas, the number of male subjects was the majority (36.45%, n=70), while only 30.72% (n=59) were female. In contrast, in urban areas, an identical distribution between the two genders can be observed, with 14.58% (n=28) being male and 14.58% (n=28) being female.

The analysis of the scalar variable determined by the age of the subjects defines a mean value of 13.61 years, with an associated SD of  $\pm 3.30$  years, from a minimum value of 7 years, to a maximum extreme of 18 years. Subsequently, the analyzed group was broken down by age groups, as follows: between 7-10 years, 11-14 years, respectively 15-18 years.

As it can be seen in ANNEX 1, the occult primary type TB forms predominate at the level of the analyzed group. As previously mentioned, the distribution of therapeutic options will be analyzed in this paper, by direct reference to a series of individual, socio-demographic, but also clinical-biological, respectively imaging parameters. The figure below shows the incidence of therapeutic options as represented at group level; with a therapeutic dropout rate in 22 subjects (representing 11.5%).



**Figure 1.** Incidence of therapeutic options at the group level  
*Authors own conception*

The table below provides a centralized picture of the distribution of the number of pediatric patients who associated a therapeutic dropout, depending on the type of treatment chosen. It can be observed how all the cases of subjects who associated therapeutic dropout are found among those who benefited from chemoprophylaxis with hydrazide. According to the chi square test, a sig indicator value of 0.203 will be obtained, which refutes the existence of statistically significant differences between the two groups represented by the therapeutic dropout.

		Dropout of the treatment						Sig. Chi-square test
		NO			YES			
		Count	Column Valid N %	Row Valid N %	Count	Column Valid N %	Row Valid N %	
Treatment	Chemoprophylaxis with hydrazide	140	82.4%	86.4%	22	100.0%	13.6%	0.203
	Hydrazide+ rifampicin	4	2.4%	100.0%	0	0.0%	0.0%	
	Hydrazide, rifampicin, pyrazinamide = DOT, 3 <sup>rd</sup> category	15	8.8%	100.0%	0	0.0%	0.0%	
	Hydrazide, rifampicin, pyrazinamide, ethambutol= DOT, 1 <sup>st</sup> category	11	6.5%	100.0%	0	0.0%	0.0%	

**Table 1.** Incidence of therapeutic dropout dependent on the type of treatment chosen  
*Authors own conception*

In the following underlying images, patient distributions can be analyzed by concomitant reference to therapeutic dropout, respectively a series of individual parameters. The following conclusions can be drawn:

- The predominance of the risk of therapeutic dropout in patients with average ages of 15 years is noted, which allows us

to hypothesize initially that adolescents are prone to this risk, partly through the impact of the association with a diagnosis of this type, but also through the responsibility to rigorously follow a certain therapeutic scheme, for a longer period of time

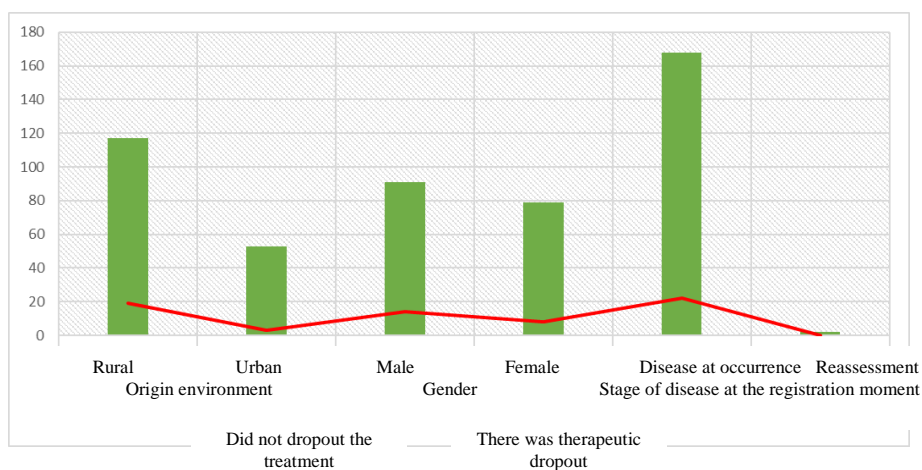
- At the same time, the subjects who dropped out from therapy are noted to have a higher weight, compared to those who decided to follow the therapeutic scheme (with a percentage difference of 5.2%)
- Predominantly, therapeutic dropout is detected in those coming from rural areas (with a percentage difference of 72.72% compared to those living in urban areas). This may be due to poor access to medical information, to healthcare units, but also to the difficulty with which these patients manage to get in touch with their coordinating doctors.
- The dropout rates are higher among male subjects ( $n = 14$ ).
- It can be noted that the dropout from therapy is associated with a low number of patient presentations to reassessments (this can be considered a negative predictor of the pediatric patients' evolution, case where the decrease in the incidence of reassessments, or even the absence of subjects from these reassessments may indicate subsequent therapeutic dropout).
- All 22 patients who reported the dropout from therapy are noted to be part of the category of patients who were included in the study at the time of the TB pathology diagnosis.
- There are no statistically significant differences between all these population groups (chi squared tests with sig greater than the reference value).

		Dropout of treatment					Sig. chi-square test	
		NO			YES			
		Mean	Row Valid N %	Count	Mean	Row Valid N %		Count
Age expressed in full years		13	88.5%		15	11.5%		
Actual weight in kg		46	88.5%		56	11.5%		
Origin Environment	rural		86.0%	117		14.0%	19	0.089
	urban		94.6%	53		5.4%	3	
Gender	Male		86.7%	91		13.3%	14	0.37
	Female		90.8%	79		9.2%	8	
Number of visits		5	88.5%		3	11.5%		
Stage of disease at the moment of registration	Disease at occurrence		88.4%	168		11.6%	22	0.609
	Reassessment		100.0%	2		0.0%	0	

*Authors own conception*

**Table 2.** Distribution of patients related to therapeutic dropout and individual parameters

*Authors own conception*



**Figure 2.** Distribution of patients related to therapeutic dropout

*Authors own conception*

Each of the 22 subjects who found themselves dropping out the therapy necessary for the diagnosed pathology benefited from questionnaires for detecting the occurrence of affective disorders, at the time of

registration. At the same time, they associated the existence of CDI questionnaires with important clinical significance.

Performing CDI questionnaires confirms that, at the level of the analyzed group, a series of null hypotheses can be exposed, regarding the prediction variations of the occurrence of affective disorders among the analyzed subjects, by correlation with therapeutic dropout rates. In the following, we will present the incidence of therapeutic dropout among patients, by reference to the results obtained at the time of applying the questionnaire in T0 (at the time of registration).

It will be observed that 100% of patients who have impaired general condition, associated or not with negative disposition at T0, subsequently dropped out the treatment. The problems in family dynamics determined 14 of the 22 subjects to abandon the therapeutic regimen. Low self-esteem, a parameter of interest in terms of affective degradation, is responsible for 95.94% of therapeutic dropouts.

In addition, as can be concluded from the statistical analysis set out in the underlying table, two null assumptions (based on performing statistical significance chi-square tests) will be admitted as follows:

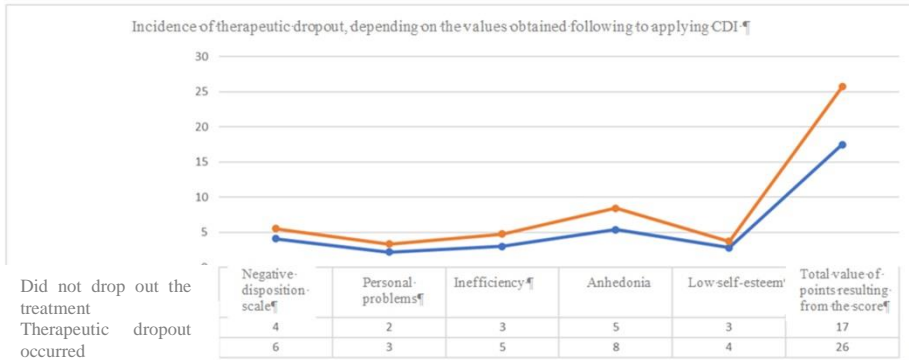
- The presence of nervous system alterations at the time of diagnosis (such as irritability) determines statistically significant differences in relation to the incidence of therapy dropout (corresponding to a sig = 0.005)
- The existence of phenomena such as introversion (the patient is not detected with the ability to initiate / conduct dialogues, he/she does not maintain visual contact with the attending physician, etc.) at the time of registration, although it determines the existence of an approximately equal distribution of the therapeutic dropout (it associates a dropout rate of 54.55%), it associates a value of the sig index of 0.000 \*.



Patients who presented the following modifications at the moment T0 of applying the questionnaire	Dropout of treatment		Value of sig. index according to chi- square test
	NO	YES	
T0 = general affected state / negative disposition	154	22	0.133
T0 = problems in personal life / family life	76	14	0.094
T0 = inefficient (as the patient considers it = work, study, etc.)	125	17	0.707
t0 = low self-esteem	139	21	0.105
T0 = irritability	85	18	0.005
T= fatiguability	94	13	0.736
T0 = insomnia	114	18	0.16
T0 = decrease in appetite	149	21	0.279
T0 = vices / consumption of substances (alcohol, tabaco, drugs)	12	1	0.69
T0 = Introversi0n (if the patient is introvert, or if he/she has the capacity to have a dialogue; looking in the eyes of the dialogue partner)	153	12	0.000

**Table 3.** Distribution of patients dependent on CDI values applied at T0 time

Finally, the underlying image shows the centralization of the values obtained from the final application of CDI questionnaires. It thus serves as a preliminary conclusion, which only strengthens the initial hypothesis underlying the materialization of this research, namely: that the risk of developing affective disorders in pediatric patients diagnosed with pulmonary TB is associated (additionally) with an increased risk of therapeutic dropout. A significant percentage difference can be observed in terms of mean values of the final score, existing after application of CDI, the mean values being increased (obtaining a score of 26) if patients subsequently dropped out the specific TB therapy, compared to mean values of 17 of the CDI score.



**Figure 3.** Distribution of patients depending on CDI values  
*Authors own conception*

### 1.4 Discussions

Following numerous studies, in 2017 it was observed that over 67 million healthy children have latent infection, who are at risk of developing the disease in the future (Kunik et al., 2005) and approximately 300,000 children under 5 years of age have initiated preventive measures not to develop TB (Bass et al., 1994). Globally, it is responsible for more than three million deaths each year and one of the leading causes of mortality worldwide (Lupu et al., 2017; Joshi et al., 2006)

TB is particularly common among individuals with mood disorders, for example, anxiety and depression (Schenker et al., 2022). Because of the TB frequent comorbidity and mood disorders, it is important that in primary care treating TB patients, special attention is paid to clinical manifestations of depression. Due to the highly infectious nature of this pathology, psychiatrists should be aware of the diagnostic and treatment considerations of this disease (Adam et al., 2001; Burlea et al., 2010). Mental pathologies are also an important global health problem, with depression affecting nearly 322 million people worldwide (Mason et al., 2016). Both TB and depression share common risk factors, which explains the high prevalence of their comorbidity, reported to range between 10-52% (Koyanagi et al., 2017).

From studies that have traced the natural history of TB, we learn that age plays an important role in determining which children will develop to the disease. Thus, we see that the highest risk (50%) is presented by infected infants, aged less than 12 months, followed by those aged between 1 and 2 years who have a risk of 20-30%. With age, the risk of developing

the disease decreases, so children aged 3-5 years will have a 5% risk, and those aged 5-10 years will have a 2% risk. According to a study conducted on the contacts of those with TB with children, it was observed that out of 6613 children who had contact with people with TB, 40.25% were male and 59.7% were female. (Lawn & Zumla, 2011.) TB is a chronic disease, and research has indicated that psychiatric disorders, especially depression, as well as patient perceptions of the disease, predict poor control of therapy administration (Paschalides et al., 2004). The efficacy of psychological treatments to improve treatment compliance has also been demonstrated (Lin et al., 2006). Isoniazid monotherapy is recommended for latent TB for a period of 9 months, but due to the oscillation of the treatment compliance level, the physicians have also adopted therapies for shorter durations, such as combination therapy with isoniazid and rifampicin, for a period of 3-4 months. (Mazza-Stalder et al., 2012)

According to a study conducted between 1988 and 2014, approximately 850,000 children developed TB in 2014. Of these, 58,000 had isoniazid-monootherapy resistant TB, 25,000 had MDR TB and 1,200 XDR TB. The burden of treatment-resistant TB was also analyzed in the same study, demonstrated by an increased number of cases in Africa, Southeast Asia, the Western Pacific region and the WHO region of the Eastern Mediterranean (Panteix et al., 2010)

The results of the study carried out between 1995 and 2005 highlighted the level of treatment compliance on the part of pediatric patients, which was generally good. The patients who received isoniazid monotherapy had lower levels of treatment compliance than those who received combination therapy (isoniazid and rifampicin) of short duration. Also in the same study, it was highlighted that after therapy, after X-rays, 24% had a possible active disease, these being patients who followed isoniazid monotherapy. (Davies et al., 2006.)

### ***1.5 Conclusions***

Following the statistical analysis performed in the present clinical research, the following conclusions will be drawn:

- Overall, primary occult TB predominates in the group, therapeutic dropout rates being 11.5% of the total group (n = 22). All 22 patients who reported dropout of therapy are noted to be part of the category of patients who were included in the study at the time of TB pathology diagnosis.
- The existing group is defined by the existence of a quasi-symmetrical distribution depending on the gender of the

patients (the therapeutic dropout rate being higher among male subjects), but it associates the predominance of cases of patients coming from rural areas. Predominantly, therapeutic dropout is detected in those coming from rural areas (with a percentage difference of 72.72% compared to those living in urban areas) and the mean age of subjects is 13.61 years with an associated SD of 3.30 years, the incidence of therapeutic dropout being in those with an average age of 15 years.

- There are no statistically significant differences between the therapeutic dropout rate and the type of therapy chosen ( $\text{sig} = 0.203$ ) and the therapy dropout is associated with a low number of patient visits to reassessments (this can be considered a negative predictor of the evolution of pediatric patients, in which case the decrease in the incidence of reassessments, or even the absence of subjects from these reassessments may indicate subsequent therapeutic dropout).
- Each of the 22 subjects who found themselves dropping out the therapy necessary for the diagnosed pathology benefited from questionnaires for detecting the occurrence of affective disorders, at the time of registration. At the same time, they associated the existence of CDI questionnaires with important clinical significance.
- The presence of alterations of the nervous system at the time of diagnosis (such as irritability) determines statistically significant differences in relation to the incidence of therapy dropout (corresponding to a  $\text{sig} = 0.005$ ) and the existence of phenomena such as introversion (the patient is not detected with the ability to initiate / conduct dialogues, he/she does not maintain visual contact with the attending physician, etc.) at the time of registration, although it determines the existence of an approximately equal distribution of the therapeutic dropout (it associates a dropout rate of 54.55%), it associates a sig index value of 0.000\*

### **Conflict of interest disclosure**

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

### **Compliance with ethical standards**

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Hospital of Pneumophthisiology “Sfantul Spiridon” Galați, Romania for studies involving humans, this study being part of the doctoral study of Dr. Oana Mariana Mihailov.

### **Acknowledgments**

All authors have contributed equally to this paper.

ANNEX 1

		TB Type			
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Occult primary TB	159	82.8	82.8	82.8
	Nodular infiltrative pulmonary TB	2	1.0	1.0	83.9
	Secondary nodular and cavitary infiltrative TB	4	2.1	2.1	85.9
	Secondary TB	2	1.0	1.0	87.0
	Hilar adenopathy	3	1.6	1.6	88.5
	Primary TB	1	.5	.5	89.1
	Primary TB	1	.5	.5	89.6
	Nodular infiltrative pulmonary TB and paratracheal adenopathy	1	.5	.5	90.1
	Secondary caseous-cavitary pulmonary TB + BK+	1	.5	.5	90.6
	Secondary infiltrative caseous and nodular infiltrative pulmonary TB	3	1.6	1.6	92.2
	Ulcerated infiltrative secondary TB	2	1.0	1.0	93.2
	Pleurisy	2	1.0	1.0	94.3
	Pleural TB	2	1.0	1.0	95.3
	Parahilar nodular infiltrative secondary pulmonary TB	1	.5	.5	95.8
	Cavitary caseous secondary TB	1	.5	.5	96.4
	Fibro-caseous-cavitary pulmonary TB	1	.5	.5	96.9
	Latent primary TB	1	.5	.5	97.4
	Intrathoracic lymph nodes TB	1	.5	.5	97.9
	Secondary pulmonary TB, BK+ and pleurisy	1	.5	.5	98.4
	Secondary pulmonary TB and BK+	1	.5	.5	99.0
	NEPLP	1	.5	.5	99.5
	Primary TB and hilar adenopathy	1	.5	.5	100.0
	Total		192	100.0	100.0

## References

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- Adam, J., Trenton, B.A., Glenn, W.C. (2001). Treatment of co-morbid Tuberculosis and depression. *Prim Care Companion J Clin Psychiatry.*, 3(6) pp: 236–243
- Bass Jr, J. B., Farer, L. S., Hopewell, P. C., O'Brien, R., Jacobs, R. F., Ruben, F., ... & Thornton, G. (1994). Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. *American journal of respiratory and critical care medicine*, 149(5), 1359-1374.  
<https://doi.org/10.1164/ajrccm.149.5.8173779>
- Burlea, G., Burlea, A. M., Milici, R.C. (2010). Prevention and intervention in speech and language therapy for the success of lexicographical acquisitions. *Revista de Cercetare și Intervenție Socială*, 30, 86
- Davies, P. D., Yew, W. W., Ganguly, D., Davidow, A. L., Reichman, L. B., Dheda, K., Rook, G. A. (2006). Smoking and tuberculosis: the epidemiological association and immunopathogenesis. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 100 (4) pp: 291–298.  
<https://doi.org/10.1016/j.trstmh.2005.06.034>
- Joshi, R., Maharjan, M., Mark, D.Z. (2006). Tuberculosis awareness among TB patients visiting in DOTS clinic Saarc J. *Tuber, Lung Dis*, 3 pp:20-5
- Koyanagi, A., Vancampfort, D., Carvalho, A. F., DeVlyder, J. E., Haro, J. M., Pizzol, D., ... & Stubbs, B. (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 medicine*, 15(1), 1-10. <https://doi.org/10.1186/s12916-017-0975-5>
- Kunik, M.E., Roundy, K., Veazey, C., Soucek, J., Richardson, P., Wray, N.P., Stanley, M.A. (2005). Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. *Chest*, 127 pp: 1205-11.
- Lawn, S. D. & Zumla, A. I. (2011). *Tuberculosis*". *Lancet*. 378 (9785) pp: 57–72 DOI:[10.1016/S0140-6736\(10\)62173-3](https://doi.org/10.1016/S0140-6736(10)62173-3)
- Lin, E.H., Katon, W., Rutter, C., Simon, G.E., Ludman, E.J., Von Korff, M., Young, B., Oliver, M., Ciechanowski, P. C., Kinder, L., Walker, E. (2006). Effects of enhanced depression treatment on Diabetes self-care. *Ann Fam Med*, 4 pp:46-53. DOI: <https://doi.org/10.1370/afm.423>
- Lupu, V. V., Ignat, A., Stoleriu, G., Ciubara, A. B., Ciubara, A., Lupu, V., Burlea, M., Stratciuc, S. (2017). Vaccination of children in Romania between civic obligation and personal choice. *Revista de Cercetare și Intervenție Socială*, 56, 123-132
- Mason, P. H., Sweetland, A. C., Fox, G. J., Halovic, S., Nguyen, T. A., & Marks, G. B. (2016). Tuberculosis and mental health in the Asia-Pacific. *Australasian Psychiatry*, 24(6), 553-555. <https://doi.org/10.1177/1039856216649770>

- Mazza-Stalder, J., Nicod, L., Janssens, J. P. (2012). La tuberculose extrapulmonaire. *Revue des maladies respiratoires*, 29 (4): pp:566–578. <https://doi.org/10.1016/j.rmr.2011.05.021>
- Panteix, G., Gutierrez, M. C., Boschirolì, M. L., Rouviere, M., Plaidy, A., Pressac, D., ... & Godreuil, S. (2010). Pulmonary tuberculosis due to *Mycobacterium microti*: a study of six recent cases in France. *Journal of medical microbiology*, 59(8), 984-989. <https://doi.org/10.1099/jmm.0.019372-0>
- Paschalides, C., Wearden, A. J., Dunkerley, R., Bundy, C., Davies, R., & Dickens, C. M. (2004). The associations of anxiety, depression and personal illness representations with glycaemic control and health-related quality of life in patients with type 2 diabetes mellitus. *Journal of psychosomatic research*, 57(6), 557-564. <https://doi.org/10.1016/j.jpsychores.2004.03.006>
- Schenker, R. A., Ciurea, M. E., Stovicek, P. O., Ciubara, A. ., Schenker, M. ., & Marinescu, I. . (2022). Depression and anxiety - Risk factors in the evolution of breast cancer in women. *BRAIN. Broad Research in Artificial Intelligence and Neuroscience*, 13(1Sup1), 135-158. <https://doi.org/10.18662/brain/13.1Sup1/309>