

The Importance of Involving a Multidisciplinary Team in the Management of a Patient Diagnosed With TB, Associating Erythema Nodosum

Oana Mariana MIHAILOV¹

Raul MIHAILOV*²

Ciprian DINU³

Alexandru Bogdan CIUBARA⁴

¹ Clinical Hospital of Psychiatry “Elisabeta Doamna”, 290 Traian Street, 800179, Galați, Romania, raul.mihailov@ugal.ro

² “Dunărea de Jos” University of Galați, Galați, România, raul.mihailov@ugal.ro

³ “Dunărea de Jos” University of Galați, Galați, România, raul.mihailov@ugal.ro

⁴ “Dunărea de Jos” University of Galați, Galați, România, Bogdan.ciubara@ugal.ro

Abstract: *Tuberculosis (TB) is an important and topical problem at global level, so it remains a challenge for public health policies. According to the World Health Organization (WHO), in 2018, about 10 million new TB cases worldwide were estimated. Of these, 11% are children under the age of 15. In addition to these alarming data, TB is responsible for 130,000 deaths per year in children and it is estimated that there are approximately 1 million TB-cases in the global population of children, being one of the top 10 causes of death in children worldwide. According to the WHO, there are economic, social, cultural, ethnic/racial, psychological and behavioral factors that interfere with the occurrence of diseases, and these factors are attributed to the persistence of infectious diseases such as TB in the population, even today. Numerous specialized studies strengthen the hypothesis of associating social vulnerability with TB emergence and distribution in the community. Therefore, the development of more accurate estimates of pediatric TB cases is an urgent need for public policy scheduling and resource allocation and, consequently, for reducing morbidity and mortality from TB among children.*

Keywords: *Tuberculosis, children, erythema nodosum, multidisciplinary team, depression.*

How to cite: Mihailov, O. M., Mihailov, R., Dinu, C., & Ciubara, A. B. (2024). The importance of involving a multidisciplinary team in the management of a patient diagnosed with TB, associating erythema nodosum. *BRAIN. Broad Research in Artificial Intelligence and Neuroscience*, 15(1), 193-207. <https://doi.org/10.18662/brain/15.1/545>

1. Introduction

TB in children (under 15 years of age) has often been considered a minor problem by national TB control programmes (Marais, 2018). The low bacterial load of TB in children, which confers a lower risk of disease transmission, has made the identification and treatment of TB and tubercular infection in this age group a lower priority than in older people. It was only in 2012 that the WHO TB programme began publishing estimates of the number of pediatric cases and deaths by TB. These estimates have become progressively more robust with the incorporation of data from National TB Inventory studies conducted in countries with high TB rates and the inclusion of information on BCG coverage and HIV status of children affected by TB. (WHO, 2021). Although, on the one hand, young children suffer more often from transmissible TB than adolescents and adults, they are at greater risk of falling ill and of severe forms of TB, especially children under 5 years of age and without BCG vaccine. (Marais, 2018). The diagnosis of TB in children is hampered by low bacillary load in children or inadequate access to more sensitive diagnostic tests, leading to incorrect reporting of TB cases and deaths among children, not only due to underdiagnosis and underreporting, but also, less often, to overdiagnosis. Diagnostic techniques classically used in adults have low sensitivity and specificity when used for children, and the confirmation by bacteriological identification is not always possible. In addition, often the treatment was carried out without isolating the mycobacteria, based on a triad that refers to the clinical and radiological picture, tuberculin test positivity and contact with an adult with bacilliferous TB. The low positivity of bacteriological tests can be explained by the fact that, in general, TB in children is paucibacillary, the damage being most often extrapulmonary, therefore, most often they are unable to voluntarily expectorate sputum. An alternative method of obtaining sputum is gastric lavage collection, a relatively invasive method that requires a 3-day hospitalization (Cano et al., 2017; Untu et al., 2015).

The estimated mortality of children with TB who do not receive specific treatment is 22% (up to 43% in children younger than 5 years), compared to 0.9% in treated children. It is estimated that nearly 1 million children develop TB each year (Jenkins, 2017). However, most of these children have never been diagnosed or treated for their disease, and there were approximately 208,000 child deaths from TB globally in 2019. According to a mathematical modeling study, an estimation of 239,000 children under 15 died of TB worldwide in 2015, and 80% of those deaths occurred in children under

5. Therefore, the development of more accurate estimates of pediatric TB cases is an urgent need for public policy scheduling and resource allocation and, consequently, for reducing morbidity and mortality from TB among children. In this context, the article by Yerramsetti et al. (2021) in *The Lancet Global Health* is very welcome. The authors developed a mathematical model to estimate pediatric TB incidence and underreporting in 185 countries from 2013 to 2019, accounting for more than 99% of all pediatric TB notifications in the world. They propose a different estimation method that takes into account several factors known to influence pediatric risks of infection and TB disease (HIV, malnutrition, and non-BCG vaccination), adding new parameters to previous models proposed by others (Yerramsetti, 2021). In their proposed new mathematical model for pediatric TB incidence, Yerramsetti et al. (2021) estimated that malnutrition, lack of BCG vaccination, and HIV infection could account for about 25% of new TB cases in children. This information becomes even more relevant when we consider that the countries with the highest TB rate and TB -HIV coinfection, which are among the poorest or most socially unequal in the world, are the ones likely to suffer the most from the COVID-19 pandemic (Yerramsetti, 2021). The COVID-19 pandemic has led to an 18% reduction in the number of new TB cases reported, to reduction of access to TB diagnosis and treatment, and an increase in the estimated number of TB deaths (more than 1.5 million in 2020) (The World Bank, 2021). The economic consequences of the pandemic have generated more poverty and inequality, which could directly increase malnutrition rates in children and, consequently, the risk of TB in this age group. BCG vaccine coverage in many countries has been severely impacted by the COVID-19 pandemic, with even a 50% drop in BCG vaccination seen in some areas (Lassi et al., 2003; Lupu et al., 2017).

1.1 Erythema nodosum, a consequence of TB in children

Erythema nodosum (EN) is a type of panniculitis, which presents clinically as red nodules, of different sizes, sensitive, frequently located in the tibia and less often on the forearms and thighs at the level of the subcutaneous tissue (Boonchai et al., 1998). It is a type IV hypersensitivity reaction to various stimuli, such as drugs, infections and malignant diseases (Requena & Yus, 2008). The incidence of EN presenting with TB is largely considered to be rare, as it is usually associated with other diseases. It should be noted that in countries where TB is an endemic disease, the prevalence of EN increases in direct correlation with the prevalence of TB. Apart from TB, other systemic causes such as sarcoidosis and inflammatory bowel disease must also be considered, as they comprise 25% of all cases. In addition, EN

can be caused by the consumption of drugs, especially sulfonamides and amoxicillin; this accounts for about 15% of presentation cases. Erythema nodosum usually begins with a prodromal state, and this occurs one to three weeks before the onset of painful, erythematous rash. This state of prodrome can then lead to specific symptoms such as arthralgia with or without arthritis, weight loss, malaise, and fever. A patient presenting with symptoms similar to arthritis and EN may be described as secondary due to TB; this is called Poncet's disease, a rare presentation of TB (Bjorn-Mortensen et al., 2016). Therefore, a patient with erythema nodosum should have an extensive diagnostic evaluation in order to consider and exclude numerous differential diagnoses, and especially in this case TB should be excluded. More surprisingly, recent data from Denmark showed a strong association of EN with TB diagnosis within a month from diagnosis. Almost 50% of cases with positive gamma interferon release test according to mycobacterium TB infection and EN, subsequently received a diagnosis of active TB. The study concludes that either EN is a strong predictor of TB or an early symptom of primary extrapulmonary TB and certainly requires thorough evaluation and careful follow-up (Chen et al., 2013). Similarly, Mert et al. (2011) reported that among the clinical forms of TB, primary TB is the only one that would cause erythema nodosum, commonly found in young children and adolescents. It can manifest itself even before the appearance of a dermal reaction to tuberculin. For these reasons, all patients with erythema nodosum should be stratified according to the risk of exposure to TB. Investigations should include TST, chest X-ray and sputum analysis with acid-resistant bacilli.

1.2 The psychological impact of TB-treatment

Adolescents aged 10-19 years require increased attention during TB treatment because they are at increased risk of dropout due to fear of social isolation for the most part (Irwin & Johnson, 2005).

One known fact of major importance is that TB treatment affects patients' mental health. Among adolescents, depression is the main problem, which causes therapeutic dropout along with low self-esteem.

A recent collection of testimonies from children in the global MDR-TB community described a number of psychosocial challenges they face, including persistent stigma, dropout, mental illness, and lack of financial, emotional, and parental support. From their statements, we can mention the following: the large number of pills they have to take daily, the size of the pills that makes their administration quite difficult, their bitter taste, their side effects such as dizziness and epigastralgia, nausea, which contribute to dropping out the TB treatment (Dodd et al., 2018).

The psychosocial needs of adolescents with TB were discussed by TB-care providers during in-depth interviews conducted in Zimbabwe by Moscibrodzki et al. (2021). It was stressed that identifying mental health problems is insufficient to meet the needs of adolescents as age-appropriate mental health services are lacking.

Prolonged isolation at home or hospitalization for a long period during TB treatment also contributes to mental health challenges for adolescents (Kulldorf & Nagarwalla, 1995).

In most countries, infection control is achieved through home isolation that often lasts longer than the infectious period, children and adolescents having to interrupt school attendance, social gatherings.

Isolation and hospitalization may have more pronounced effects on adolescents and children with TB than other age groups. They are deeply sensitive to social exclusion and the effects of isolation, stigma and discrimination can have long-lasting consequences (Deacon & Stephney, 2017).

Chiang et al. (2021) observed that the social isolation required by TB treatment led to low esteem, sadness and depression, the same emotions being felt in hospitalized TB patients who cannot receive visits from family or friends (isolation, negative emotions and symptoms of depression).

The mental health of TB-infected children and adolescents can also be affected by the responsibility not to pass on the disease, hence a tension or a break in family dynamics might occur. In most families, children noticed how they tried to find a culprit for TB transmission, hence the feeling of burden of not passing it on to another family member (Irwin & Johnson, 2005).

The negative impacts of TB disease on family relationships were substantially amplified by long hospital stays. Notably, the distance between hospitalized children and family members can be particularly difficult for their mental health. Throughout the literature, it has been clear that they rely on family members for emotional comfort when they feel disappointed and need reassurances that they will be able to heal once treatment is over.

The current treatment regimen for MDR-TB is problematic in terms of duration, complexity and adverse events associated with drugs. Although any long-lasting effects do not seem to exist in younger children, they, like all children, would strongly benefit from a shorter and more manageable treatment regimen. Finally, psychosocial support of both children and their carers is needed to mitigate the potential negative effects of stigma. Multi-level interventions should aim to provide a support framework for children and their families, starting from diagnosis and continuing in outpatient treatment of the child (Vega et al., 2004).

1.3 Clinical case

A 12-year-old female patient from rural areas, normally developed physically and neuropsychologically, is hospitalized for tuberculin hyperergy IDR5U PPD = 12mm, following to TB contact with her father (bilateral lung TB, BK positive) and nodular lesions at bilateral anterior tibial level and forearm.

From the personal physiological and pathological history, we note that she is the first child born at term by natural birth, without signs of fetal suffering, birth weight 3000 grams, Apgar score 8, was naturally fed for 6 months, subsequently diversified at 6 months, vaccinated according to the national immunization schedule. At the age of 11, the patient had chickenpox.

From family medical history, it is worth mentioning the 37-year-old father, known to have bilateral pulmonary TB, currently hospitalized at the Galati Pulmonology Hospital. At the objective clinical examination, we mention a satisfactory general condition, hyperemic nodular lesions, some purplish in color, painful on palpation at bilateral anterior tibial level and at the level of the forearm, with a discreet hyperemic pharynx and saburral tongue.



Figure 1. Hyperemic and purplish nodular lesions at the anterior tibial level
Source: Authors' personal data

Paraclinical examinations revealed a biological inflammatory syndrome: Fibrinogen 499 mg/dl, ESR 30mm/30 min, and the blood count revealed a neutrophilia 72.7%, while the biochemistry showed changes only in serum creatinine, with a value of 0.42 mg/dl. Complete urine examination revealed the frequency of flat epithelial cells, leukocytes and mucus with a relatively common microbial flora, while urine culture was below 1000 CFU/ml.

The microscopic BK examination and culture from sputum was BAAR negative. Also, at the examination for the identification of germs in sputum, no pathogenic germs developed under aerobiosis conditions, and no yeast colonies were identified from mycosis. The nasal exudate revealed the absence of beta hemolytic Streptococcus and Staphylococcus aureus. The RT-PCR test for detecting SARS-COV 2 infection was negative.

Following imaging investigations (cardiopulmonary radiography), enlarged bilateral volume hilums were observed.

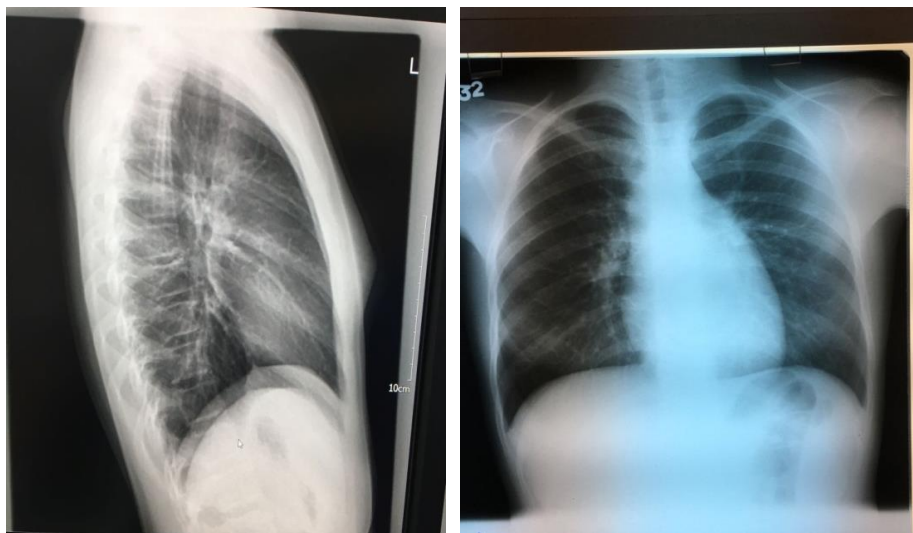


Figura 2. Cardiopulmonary radiography-postero-anterior and lateral radiography
Source: Authors' personal data

Patient: M.M.A.

Relevant data from **the Interview on aspects of family, school, social environment and healthy behavior**

Following the initial evaluation interview and observation, we note:

- The patient describes a balanced, supportive family climate, living in rural areas, with her parents and younger brother (9 years). She

denies drinking alcohol or aggression in the family. The father is currently hospitalized in the adult ward of our hospital. The teenager maintains daily telephone contact with family members.

- At school level, she reports good adaptation to the change of school cycle (she is currently in the fifth grade), with satisfactory results and without tensions in the relationship with teachers or colleagues. She says she is concerned about the possibility of attending online school classes during her admission, wanting to be informed on what is taught in school. Given that she is enrolled in a class with simultaneous teaching (fifth and seventh grade), where the conditions for carrying out teaching activities have some shortcomings, we consider addressing this issue through a proposal submitted to the County School Inspectorate to allow the patient to attend online classes or to be adequately supported in terms of recovering the school subject.
- Social interactions are age-specific, with a group of friends with whom she also keeps in touch during hospitalization through online social networks.
- The patient denies sleep or eating disorders, as well as other problems related to a healthy lifestyle.
- She describes as difficult adjusting to hospitalization: „I miss my family”, to which the special context determined by the fact that her anniversary is coming next is added.

CERQ (Cognitive Emotion Regulation Questionnaire) is a multidimensional questionnaire, built to identify cognitive-emotional coping strategies, that a person uses after experiencing certain negative events or situations. Compared to other coping questionnaires, which do not explicitly distinguish a person's thoughts from their actual activity (what they are doing), CERQ refers exclusively to the thoughts a person has when he/she lives a negative experience and are overwhelmed by emotions, identifying dysfunctional cognitive-emotional coping strategies and thus contributing to their correction in psychological counseling/personal development programs.

The CERQ questionnaire measures the frequency of use of certain strategies through 9 rating scales (Schenker et al, 2022):

- Self-blame (thoughts according to which the entire responsibility for the lived situation belongs to oneself, guilt is also attributed to them and concerns arise about thoughts that refer to the mistakes he/she makes; he/she is intensely concerned with his/her own sense of

guilt, this coping strategy can be associated with psychopathological symptoms).

- Acceptance (thoughts due to which they resign themselves to what has happened and accept the situation, thinking that it can no longer be changed and that life goes on; although acceptance in itself is a beneficial process for most events, a very high level can lead to resignation, in the sense of inability to influence events, a negative feeling of “not being able to change things in any way”; a high score can be associated with psychopathological symptoms, especially when the latter relate to events that have not been accepted / assimilated mentally. A low score is also associated with emotional problems, in the context of an inability or poor capacity for adaptive psychological anchoring to reality/concrete situation (in case of negative life events).
- Rumination (constantly thinking and/or being preoccupied with the feelings and thoughts they associate with a negative event, a high score being definitely associated with emotional problems or psychopathological symptoms).
- Positive refocus (strategy that involves thinking about other, more pleasant things, instead of thinking about the negative event experienced. Studies show that this strategy can have positive effects on our well-being; a (lower) score may be associated with a reduced level of emotional well-being)
- Refocus on planning (it is a strategy that involves thinking about the steps to take to cope with a negative event or thinking about a plan to change a situation; it is a functional cognitive coping strategy, provided that the person faces the situation. When a person scores high on this strategy without taking action, this score can be associated with certain emotional problems (thoughts without action); a very low score is almost certainly associated with the presence of problems)
- Positive reassessment (it mentally associates a positive meaning to a negative event in terms of personal development, thinking that the event will make him/her stronger, looking for its positive aspects. It is a workable strategy, provided that something is really done to solve the problem. When a person scores high on this strategy without taking action, this score is associated with certain emotional problems. A low level can be associated with certain problems).

- Putting things into perspective (functional thoughts that reduce the severity of the event by comparing it to other events, emphasizing that there are worse things in the world; a low score indicates less use of functional thoughts that reduce the severity of the event by comparing it to other events, without emphasis on the fact that there are worse things in the world).
- Catastrophizing (thinking recurrently about how terrible the event was and that it is the worst thing that could have happened, that it is much worse than what happened to others; a high score is almost certainly associated with emotional problems or psychopathological symptoms).
- Blaming others (thoughts of blaming others for what happened to him/her, holding others responsible for what happened, and/or thinking about mistakes others have made in this regard).

Following the administration of CERQ, the patient achieved the following scores and levels at which she uses the different cognitive emotional coping strategies measured:

- Self-blame: score 4; very low level
- Acceptance: score obtained 4; very low level
- Rumination: score obtained 4; very low level
- Positive refocus: score 8; below average level
- Refocus on planning: score 4; very low level
- Positive reassessment: score 6; low
- Putting things into perspective: score 6; very low level
- Catastrophizing: score 4; low
- Blaming others: score 5; medium level

1.4 Conclusions

- The risk of developing TB is highest when there is already a positive TB and BK positive member in the family, especially among grade 1 relatives.
- Another important risk factor in TB transmission is represented by the living conditions and origin environment, in our case, the patient lived in rural areas, in a house with 2 rooms and 4 people, a rather crowded environment and favorable at the same time to transmission of TB infection due to unsatisfactory ventilation and also smoking is a important risk. The patient is not an active smoker, but her parents are, which includes her in the category of passive

smoker. This exposure contributes to the group of risk factors for developing TB.

- The low socio-economic status has an important contribution to the rate of dropping out of treatment.
- Prolonged isolation from family and friends during hospitalization contributes to changes in patients' mental health, in our case, the patient said she misses her family.
- Because the viral load in children is low, the risk of transmitting the disease is low, as in our case where microscopic examination and culture of BK from sputum were BAAR negative.
- The risk of developing a complicated form of TB and resistant to treatment is increased in unvaccinated children, in our case, the patient being vaccinated according to the national immunization schedule up to the current age.

1.5 Discussions and conclusions exposed from the point of view of psychological analysis

Starting from the idea that the hospitalization situation is almost always an unpleasant event in a person's life, especially in the case of long-term hospitalizations, as well as considering the patient's age (in the psychovulnerable/sensitive stage of adolescence) and also her discomfort experiences, the more difficult adaptation in the first days after admission - noted during the initial interview, it was chosen that after administering and scoring the Cognitive Emotion Regulation Questionnaire, to take into account from the perspective of a psychological counseling intervention the strategies used to a lesser extent by the patient in processing negative life events (scores below average, low or very low), but which may be associated with the presence of psychological problems, namely: Acceptance; Positive refocus; Refocusing on planning; Positive reassessment and putting it into perspective.

Accordingly, psychological counseling took into account the development of adaptive coping strategies (age-appropriate acceptance, mentally assimilated; positive refocus; refocus on planning; positive reevaluation; putting into perspective) and discouraging maladaptive ones (self-blame; rumination; catastrophizing; blaming others). It is important to mention in this context that the intervention took into account both the specialized assistance provided by the psychologist in individual sessions and its completion through the contribution of the medical staff (physician, nurses, students) in daily contact with the patient. The multidisciplinary approach of the case, through discussions between the members of the

therapeutic team mentioned above, led to a favorable evolution in the psychological state of the patient, who reported after 8 days from admission an improvement in the psycho-emotional state, implicitly of the adaptation to hospitalization and optimism: “At first I missed my family, but now I got used to it; I was even talking to my mom that I didn't even know when time had passed.” We hope to strengthen within our hospital this multidisciplinary model of intervention, which, in light of the results obtained so far, we consider to be a model of good practices, with a positive impact on the evolution of the TB patient, especially on underage patients found in development.

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.

References

- Ammassari, A., Murri, R., Pezzotti, P., Trotta, M. P., Ravasio, L., De Longis, P., ... & AdICONA Study Group. (2001). Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 28(5), 445-449.
- Bjorn-Mortensen, K., Ladefoged, K., Simonsen, J., Michelsen, S. W., Sørensen, H. C. F., Koch, A., ... & Soborg, B. (2016). Erythema nodosum and the risk of tuberculosis in a high incidence setting. *International Journal of Circumpolar Health*, 75(1), 32666 <https://doi.org/10.3402/ijch.v75.32666>
- Boonchai MD, W., Suthipinittharm MD, P., & Mahaisavariya MD, P. (1998). Panniculitis in tuberculosis: a clinicopathologic study of nodular

- panniculitis associated with tuberculosis. *International journal of dermatology*, 37(5), 361-363 <https://doi.org/10.1046/j.1365-4362.1998.00299.x>
- Cano, A. P. G., Romanelli, M. T. N., Pereira, R. M., & Tresoldi, A. T. (2017). Tuberculose em pacientes pediátricos: como tem sido feito o diagnóstico?. *Revista Paulista de Pediatria*, 35, 165-170.
<https://www.scielo.br/j/rpp/a/GHVVJCMxG5Z8FwGfGvyqVLz>
- Chen, S. A., Chen, J., Chen, L., Zhang, Q. A., Luo, X., & Zhang, W. (2013). Mycobacterium tuberculosis infection is associated with the development of erythema nodosum and nodular vasculitis. *PLoS one*, 8(5), e62653
<https://doi.org/10.1371/journal.pone.0062653>
- Chiang, C. H., Tang, P. U., Lee, G. H., Chiang, T. H., Chiang, C. H., Ma, K. S. K., & Fang, C. T. (2021). Prevalence of Nontuberculous mycobacterium infections versus Tuberculosis among autopsied HIV patients in Sub-Saharan Africa: a systematic review and meta-analysis. *The American Journal of Tropical Medicine and Hygiene*, 104(2), 628.
- Deacon, H., & Stephney, I. (2007). *HIV/AIDS, stigma and children: A literature review*. Cape Town: HSRC press
- Dodd, P. J., Yuen, C. M., Becerra, M. C., Revill, P., Jenkins, H. E., & Seddon, J. A. (2018). Potential effect of household contact management on childhood tuberculosis: a mathematical modelling study. *The Lancet Global Health*, 6(12), e1329-e1338. [https://doi.org/10.1016/S2214-109X\(18\)30401-7](https://doi.org/10.1016/S2214-109X(18)30401-7)
- Instituto Brasileiro de Geografia e Estatística. Censo demográfico 2010: resultados gerais da amostra.
- Irwin, L. G., & Johnson, J. (2005). Interviewing young children: Explicating our practices and dilemmas. *Qualitative health research*, 15(6), 821-831.
<https://doi.org/10.1177/1049732304273862>
- Jenkins, H. E., Yuen, C. M., Rodriguez, C. A., Nathavitharana, R. R., McLaughlin, M. M., Donald, P., ... & Becerra, M. C. (2017). Mortality in children diagnosed with tuberculosis: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, 17(3), 285-295 [https://doi.org/10.1016/S1473-3099\(16\)30474-1](https://doi.org/10.1016/S1473-3099(16)30474-1)
- Jenkins, H. E., Tolman, A. W., Yuen, C. M., Parr, J. B., Keshavjee, S., Pérez-Vélez, C. M., ... & Cohen, T. (2014). Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *The Lancet*, 383(9928), 1572-1579 [https://doi.org/10.1016/S0140-6736\(14\)60195-1](https://doi.org/10.1016/S0140-6736(14)60195-1)
- Kulldorff, M., & Nagarwalla, N. (1995). Spatial disease clusters: detection and inference. *Statistics in medicine*, 14(8), 799-810
<https://doi.org/10.1002/sim.4780140809>
- Lassi, Z. S., Naseem, R., Salam, R. A., Siddiqui, F., & Das, J. K. (2021). The impact of the COVID-19 pandemic on immunization campaigns and programs: a

- systematic review. *International journal of environmental research and public health*, 18(3), 988 <https://doi.org/10.3390/ijerph18030988>
- 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 si Interventie Socială*, 56, 123-132
- Marais, B. J., Gie, R. P., Schaaf, H. S., Hesselning, A. C., Obihara, C. C., Starke, J. J., ... & Beyers, N. (2004). The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era [State of the Art]. *The International Journal of Tuberculosis and Lung Disease*, 8(4), 392-402.
- Marais, B. J. (2018). Preventing tuberculosis in household contacts crucial to protect children and contain epidemic spread. *The Lancet Global Health*, 6(12), e1260-e1261. [https://doi.org/10.1016/S2214-109X\(18\)30449-2](https://doi.org/10.1016/S2214-109X(18)30449-2)
- Mert, A., Bilir, M., Tabak, F., Ozaras, R., Ozturk, R., Senturk, H., ... & Aktuglu, Y. (2001). Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. *Respirology*, 6(3), 217-224, <https://doi.org/10.1046/j.1440-1843.2001.00328.x>
- Moscibrodzki, P., Enane, L. A., Hoddinott, G., Brooks, M. B., Byron, V., Furin, J., ... & Chiang, S. S. (2021). The impact of tuberculosis on the well-being of adolescents and young adults. *Pathogens*, 10(12), 1591 <https://doi.org/10.3390/pathogens10121591>
- Requena, L., & Yus, E. S. (2008). Erythema nodosum. *Dermatologic clinics*, 26(4), 425-438doi: 10.1016/j.det.2008.05.014. PMID: 18793974.
- 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
- Untu, I., Chirita, R., Bulgaru-Iliescu, D., Chirila, B. D., Ciubara, A., & Burlea, S. L. (2015). Ethical implications of bio-psycho-social transformations entailed by the aging process. *Revista de cercetare si interventie sociala*, 48.
- Vega, P., Sweetland, A., Acha, J., Castillo, H., Guerra, D., Fawzi, S., & Shin, S. (2004). Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, 8(6), 749-759.
- WHO, G. (2020). Global tuberculosis report 2020. *Glob. Tuberc. Rep*, 2020
- WHO, G. (2021). Global tuberculosis report 2021. *Glob. Tuberc. Rep*, 2021
- Yerramsetti, S., Cohen, T., Atun, R., & Menzies, N. A. (2022). Global estimates of paediatric tuberculosis incidence in 2013–19: a mathematical modelling analysis. *The Lancet Global Health*, 10(2), e207-e215 [https://doi.org/10.1016/S2214-109X\(21\)00462-9](https://doi.org/10.1016/S2214-109X(21)00462-9)

