

## ORIGINAL RESEARCH

# OVERVIEW OF TUBERCULOSIS PREVENTIVE TREATMENT AMONG CHILDREN IN SURABAYA

Gambaran Pemberian Terapi Pencegahan Tuberkulosis Pada Anak di Kota Surabaya

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## ABSTRACT

**Background**: A high prevalence of tuberculosis (TB) infection rates is followed by high rates of TB infection in children. The TB Preventive Treatment (TPT) for children with Isoniazid (INH) is one of the primary activities to improve TB cases by finding them early to prevent the transmission of TB to children. Purpose: This study aimed to describe the implementation of TPT with prophylactic INH among children in Surabaya. Methods: This research was a descriptive observational study with a case series design using secondary data on the provision of TPT in children, child TB cases in Surabaya City in 2016-2018, and a network of partnerships with hospitals/clinics/doctors' private practices for the prevention and control of TB in the city of Surabaya in 2016-2018 as the population. The data were collected by in-depth interviews with the holders of the TB prevention and control program of Surabaya. The data were analyzed by comparing and describing the targets and achievements of the INH administration in children. Results: The implementation of INH for children in Surabaya is not optimal and has not reached the targets. The networking of health facilities with providers for the provision of TPT with INH for children is still low in Surabaya City. Conclusions: Delivery of INH for children in Surabaya has been implemented and has increased, however, it is not optimal because it has not reached the targeted districts/municipalities that determined.

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## ABSTRAK

**Pendahuluan:** Tingginya prevalensi angka infeksi TBC juga diikuti dengan tingginya angka infeksi TBC pada anak. Profilaksis pencegahan TBC anak dengan Isoniazid (INH) merupakan salah satu kegiatan yang diprioritaskan untuk meningkatkan temuan kasus TBC lebih dini sehingga dapat mencegah penularan TBC How to Cite: Aprilidyawati, R, Wahjuni, C. U., & Yuliandari, R. D. (2020). Overview of tuberculosis preventive treatment among children in Surabaya. *Jurnal Berkala Epidemiologi*, 8(3), 275–282. https://dx.doi.org/10.20473/jbe.v8i320 20. 275–282 anak. **Tujuan:** Penelitian ini bertujuan untuk menggambarkan pelaksanaan pemberian terapi pencegahan tuberkulosis dengan profilaksis Isoniazid (INH) pada anak di Kota Surabaya. Metode: Penelitian ini merupakan penelitian deskriptif observasional dengan desain case series menggunakan data sekunder pemberian profilaksis pencegahan dengan Isoniazid (INH) pada anak, kasus TBC anak di Kota Surabaya tahun 2016-2018, dan jejaring kemitraan dengan RS/Klinik/Praktik Dokter dalam Pencegahan dan Pengendalian TBC di Kota Surabaya Tahun 2016-2018 sebagai populasi. Pengumpulan data dilakukan dengan Indepth Interview kepada pemegang Program Pencegahan dan Pengendalian TBC Kota Surabaya. Data dianalisis dengan membandingkan dan mendeskripsikan antara target dan capaian pemberian TPT INH pada anak. Hasil: Pelaksanaan pemberian TPT INH pada anak di Kota Surabaya masih belum optimal dan belum mencapai target. Jejaring kemitraan fasilitas layanan kesehatan dalam melakukan pemberian TPT INH pada anak masih rendah di Kota Surabaya. Kesimpulan: Pemberian TPT INH pada anak di Kota Surabaya sudah dilaksanakan dan mengalami peningkatan hasil capaian walaupun hasilnya masih belum optimal karena belum mencapai target Kab/Kota yang telah ditentukan.

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## **INTRODUCTION**

Tuberculosis is a contagious disease caused by *Mycobacterium tuberculosis*. The source of infection is patients who have pulmonary TB with positive Acid Resistant Bacteria (BTA+) that, when coughing, sneezing, or talking, eject a droplet of *Mycobacterium tuberculosis*. Children have a very high risk of infection when in contact with BTA (+) adults (Egere et al., 2016).

Tuberculosis is an infectious disease with the highest number of cases in the world; in 2017 alone, it was estimated that there were 10 million new cases and 1.6 million deaths. Therefore, it takes effort to prevent even one of them by giving isoniazid (INH) (Lee et al., 2019). Prophylactic treatment for tuberculosis with INH is the prevention given to someone who has been proven not to suffer from tuberculosis (TB) and is in contact with TB patients, and it is also given to children. As much as 50%–60% of children who live with adult patients with pulmonary TB with a positive sputum smear will be infected with TB, and 10% of that percentage will have TB (Datiko, Yassin, Theobald, & Cuevas, 2017).

The purpose of giving prophylactic treatment for TB is to reduce the burden of TB in children and anyone with immune deficiencies because these high-risk groups are infected with TB. Tuberculosis preventive treatment (TPT) exerts protective effects by administering INH for at least six months and can reduce the risk of TB in children (Gegia, Winters, Benedetti, van Soolingen, & Menzies, 2017).

Doctors determine who can be given preventive therapy with INH, and further administration may be performed by a doctor, clerk, or officer Directly Observed Treatment, Short-course of TB. The INH drug can be administered at all levels of health care, including private health care practices. Prophylactic INH is given to children found to have been in contact with TB especially for children aged <5 years, children who are human immunodeficiency virus (HIV)-positive, and children with a condition of immune disorder (Dlamini, Ji, & Chien, 2019).

The screening and management of contact investigation have great potential to reduce the morbidity and mortality of TB in children. This can prevent the development of infectious disease with early initiation of preventive therapies (Nyathi et al., 2019). Several studies have shown that microscopic examination (sputum smear), culture, and X-Pert *Mycobacterium tuberculosis*/rifampicin (Cepheid, Sunnyvale) can significantly detect and diagnose TB with bacteriological confirmation (Swaminathan & Ramachandran, 2015). The dose of TPT with INH is 10 mg/kg once daily (maximum 300 mg/day). The INH medication is taken once daily on an empty stomach. The duration of TPT INH given is six months (one month = 28 days of treatment) with a record of the child's clinical state. If there are follow-up symptoms of TB, the child is examined for the diagnosis of TB, and if the child proves to be tubercular, TPT INH is stopped and anti-TB drugs are given (Ministry of Health RI, 2016).

Giving TPT INH to children is one indicator of the success of a contact investigation, of which a target is, among others, the success rate of TPT administration of INH, which can be determined through the total number of children who received the full TPT INH divided by the number of children who received INH. The failure rate of TPT INH administration can also be measured by the number of children failed during the provision of TPT INH divided by the number of children who got the TPT INH (Ministry of Health RI, 2016). Table 1 shows that there are groups of children who are given TPT INH therapy. This group of children is children under five years of age (toddlers) who have contact with TB patients but don't proven to be sick with TB or a child over 5 years of age with a positive HIV status and a positive result on examination of exposure or latent TB infection (ILTB) (Ministry of Health RI, 2016).

#### Table 1

Age	HIV	Check- up result	Governance
Toddler	(+) / (-)	ILTB	TPT INH
Toddler	(+) / (-)	exposed	TPT INH
> 5 years old	(+)	ILTB	TPT INH
> 5 years old	(+)	exposed	TPT INH
> 5 years old	(-)	ILTB	Observation
> 5 years old	(-)	exposed	Observation
~			

Source: Ministry of Health RI (2016)

The provision of prophylactic treatment for the prevention of TB in children remains a challenge in many countries, especially countries with a high burden of TB and HIV. However, the coverage of TPT INH is still low and, in 2016, only reached 2.4%–73% (Nyathi et al., 2019). This study aimed to describe the implementation of TPT with prophylactic INH among children in Surabaya.

#### METHODS

This research was a descriptive observational study with a case series design using secondary data on the provision of TPT with INH in children, child TB cases in Surabaya City in 2016-2018, and the network of hospitals/clinics/ private doctors' practices in the prevention and control of TB in Surabaya in 2016–2018 as the study population. The inclusion criteria of this study were children being given TPT INH for the prevention of TB in 2016–2018. It is said that it is included in the inclusion criteria if the child has a history of contact with pulmonary TB patients and has received TPT INH in health service facilities such as Public Health Centers (PHC), hospitals, clinics, and private doctors' practices. The completeness of TPT INH administration was not observed in this study.

The secondary data collection was done in the Prevention and Control of Infectious Diseases Section, Division of Disease Prevention and Control, Health Department of Surabaya. The data were collected by in-depth interviews with the holders of the TB prevention and control program of Surabaya. The data were tabulated, analyzed by comparing and describing the targets and achievements of the INH administration in children with the information derived from the The data analysis consisted literature. of univariables to present the data in a frequency distribution table. This research fulfilled the research ethics requirements as proven by a letter issued by the Universitas Airlangga, Faculty of Dental Medicine Health Research Ethical Clearance Commission. No. 493/HRECC.FODM/VII/2019.

#### RESULTS

Figure 1 shows that the cases of TB each year continue to increase and the child TB cases do as well. The high number of TB cases in children has not been followed by the implementation of the provision of maximum prophylactic treatment due to various obstacles, such as reporting and TB services that have not been integrated due to a high rate of rejection from the families and weak commitment.

Figure 1 shows that, overall, the trend of TB cases is increasing every year and that TB cases in children in Surabaya have been seen to rise significantly, especially in 2017. The trend of TB cases in children is the same as the trend of BTA+ pulmonary TB cases. One of the reasons that this

happens is because of the low prevention of TB preventive therapy with INH among children, and there is a need for awareness and compliance in parents in the implementation of prevention of TB infection in children.

Table 2 shows that most children were noted to be suffering from TB in a hospital or advanced health care facility. This means that the early detection of TB in children has not been optimal. Giving prophylactic drugs for the prevention of TB among children is not easy to do, and there is still a lack of commitment in the provision of TPT INH. Denial from the families (parents) of children who will be given TPT INH is still high because the families do not think that their children get sick and, thus, do not need to be given TPT INH. It also shows that there are no clinics or physician practices that provide preventive therapy of TPT INH among children in the prevention of TB.



Source: Surabaya City Health Office (2019)

Figure 1. TB Case picture in Surabaya 2016-2018

#### Table 2

Distribution of Children with TB in Health Service Facilities Based in Surabaya City in 2016–2018

Children TB cases	Year		
	2016	2017	2018
PHC	93	94	57
Hospital	249	371	381
Clinic	0	0	0
Private Doctors' Practices	0	0	0
Total	342	465	438
G G 1 G' II	1.1 0.00	(2010)	

Source: Surabaya City Health Office (2019)

Table 3 shows that the achievement of children being given TPT INH increased significantly in 2017, whereby the percentage of

achievement was close to the target. In 2018, the TPT INH achievement declined and was well below the national target. Research has shown that doing active case finding in households will amount to higher achievement than passive case finding because actively seeking the source of infection prevention can be done from the beginning to avoid infecting others.

Table 3 showed that the percentage target of TPT INH administration in children increased gradually in 2016; the target of TPT INH administration was 25% of the 914 children who should be given TPT INH, but only 5.25% (12 children) were given TPT INH. These achievements only met about 21% of the target set.

In 2017, the target was increased to 35% of the estimated 1,041 children who should get the TPT INH, but only 28.85% (105 of 364) received the TPT INH. Although they did not reach the target, these achievements increased significantly compared to the previous year, meeting about 82% of the target set. There was a significant increase in 2017, while, in 2018, there was a decline in achievement whereby the target was increased to 45% of the estimated 1,041 children who should get the TPT INH but only reached 16.64% (93 of 559 children). These achievements only met about 36% of the target set, a decrease from the achievements in the previous year (Table 3).

#### Table 3

Overview of the Scope and Target of TPT INH Among Children in Surabaya in 2016–2018

0						
Torract	Year					
Target	2016	2017	2018			
Estimated Number	914	1,041	1,243			
of Children TPT						
INH						
Target TPT INH	228	364	559			
among Children						
% Target	25%	35%	45%			
TPT INH Among Children						
Amount	12	105	93			
% Achieved	5.26%	28.85%	16.64%			

Source: Surabaya City Health Office (2019)

Table 4 shows that the achievement is still below the national target program due to the nonoptimal provision of prophylactic treatment delivery and the outcomes of TB in children are also influenced by non-optimal health service facilities such as hospitals, clinics, and private doctors' practices that perform preventive TB therapy among children. It can be seen from Table 4 that, in 2016, there were only 12 PHC that provided TPT INH and that, in 2017 and 2018, all PHC had given TPH INH (63 PHC). There were no hospitals doing TPT INH in 2016; there were 33 hospitals in 2017, and 31 hospitals in 2018. No clinic or private doctors' practices provided TPT INH among children from 2016 to 2018.

According to Table 4, the new TPT INH administration program in children has been conducted since 2016, therefore, the coverage of TPT INH throughout the health service facilities is still low. Based on Table 4, all health centers in the city of Surabaya have done TPT INH administration in children since 2017, but the hospitals did not entirely implement TPT INH administration in children. Furthermore, in 2018, it looks like the number of hospitals that perform TPT INH decreased. Clinics and physician practices did not entirely implement TPT INH administration from 2016 to 2018. In the case of TB in children, it is mostly transmitted by adult patients with TB. This is because most children do not produce sputum, and cough droplets released by children are far fewer in number than those of adults. When they cough, the adults' patients can expel 3,000–3,500 bacilli of *Mycobacterium tuberculosis*, and they can sneeze up to one million bacilli of *Mycobacterium tuberculosis*. However, the transmission of children can still occur. therefore, the significance of the TB case (+) as a whole is also in line with the significance of the increasing child TB cases (Karo et al., 2019).

TB in children is mostly obtained from contact with smear-positive adults. This is because the symptoms of TB in children generally do not produce sputum so that it has less effect on other children (Prieske, Krüger, Aehle, Bauer, & Granacher, 2018).

## DISCUSSION

#### Table 4

Distribution of Health Service Facilities That Gave TPT INH Therapy in the Surabaya City in 2016–2018

Information	Year		
Information	2016	2017	2018
Σ Health Care Facilities (Fasyankes)			
PHC	63	63	63
Hospital	59	59	59
Clinic	279	331	279
Private Doctors' Practices	5,060	8637	8751
Did TPT INH			
PHC	12	63	63
Hospital	0	33	31
Clinic	0	0	0
Private Doctors' Practices	0	0	0
% TPT INH			
PHC	19	100	100
Hospital	0	56	53
Clinic	0	0	0
Private Doctors' Practices	0	0	0
Not TPT INH			
PHC	51	0	0
Hospital	59	26	28
Clinic	279	331	279
Private Doctors' Practices	5,060	8637	8751
% No TPT INH			
PHC	81	0	0
Hospital	100	44	47
Clinic	100	100	100
Private Doctors' Practices	100	100	100
Source: Surabaya City Health Office (2019)			

Effectiveness of INH for the prevention of TB has been observed. Currently, INH preventive therapy is recommended to prevent TB infection in children and TB/HIV in people living with HIV. Prophylactic INH has a greater protective effect on TB disease because it can reduce the likelihood of the development of TB becoming active in children by 69% (Zunza, Gray, Young, Cotton, & Zar, 2017).

The overview of TPT INH administration in children in the city of Surabaya in 2016–2018 in all health care facilities needed to be improved because it was not optimal. Based on this research, it can be seen that the image of TPT INH administration in children in Surabaya is still below the target districts/municipalities that have been determined. Giving TPT INH to children as prevention was first conducted in 2016 in Surabaya, but the health service facilities networking with the Surabaya City Health Department did not fully perform the TPT INH administration in children. Isoniazid is a drug that can reduce the number of cases of active TB in HIV patients by 40% (Pal et al., 2018).

The provision of TPT INH for the prevention of TB disease, especially in children, is still not optimal due to several things. Dewi, Damsar, & Azwar (2019) argued that there are structural constraints in the response to TB, including health service facilities, health personnel, unavailability of preventive prophylactic INH treatment in children, and constraining agents like the lack of public knowledge and less active drug supervisor.

The problem that arises is related to the provision of TPT INH, namely the lack of commitment between health service facilities (both government and private) and the Surabaya City Health Office in terms of eradicating and preventing TB problems. Thus, there is a need to increase the commitment between the health service facility providers, government, and society in terms of overcoming the problem of TB. This is very influential on TB prevention and treatment programs and in the provision of TPT INH in children as well. There are results that are directly proportional to the number of health care providers providing INH preventive therapy to children with the achievements: the lower the number of health care facilities that provide preventive TB treatment services, the lower the achievements. This also applies to the program of TPT INH TB preventive therapy in children (Dodd, Yuen, Sismanidis, Seddon, & Jenkins, 2017).

Implementation of TB preventive therapy in children using INH has been done globally, but

there are barriers to screening children before giving INH TB, especially in endemic areas, affecting the INH administration itself (Swindells et al., 2019). This is in line with the reduced number of health service facilities that performed TPT INH administration in children in 2018 (Jenkins, 2016). Moonan et al (2018) argued that the initiation and implementation of TPT among children has historically been poor. However, incremental progress towards elimination is possible with careful evidence-guided policy development, planning, and implementation. Implementing partners and stakeholders should consider addressing several key operational research questions to inform their policy and practice. To achieve elimination, the national TB program must take a phased multipronged approach to TB prevention and care.

Dewi, Damsar, & Azwar (2019) mentioned the need for awareness and compliance of parents in the implementation of the prevention of TB infection in children. In Table 3, there are estimates regarding children who should be given the prophylactic treatment of TB INH in Surabaya and the percentage of children who should be the target of TPT INH in Surabaya. The approximate amount of specified targets used as indicators of achievement of the implementation of TPT INH administration in children shows that the achievement is still not optimal every year because it is still below the target districts/municipalities that have been determined.

The high amount of rejection from the patients' families (parents) who think that their children do not get sick and do not need to be given the drug also became one of the problems. Therefore, it is necessary to optimize the provision of information, education, and communication to the general public related to INH for prevention of TB disease, especially in children, so that rejections coming from the children's parents can be avoided. Giving IEC can be done by any one of them by the cadres (Susetyowati, Ningtyias, & Prasetyo, 2018).

Joint commitment between health facilities, health cadres, and local health offices is needed in dealing with health problems and in overcoming TB problems. This supports research conducted by Diallo et al (2018) that stated that the lack of provision of TPT INH for the prevention of TB in children is because there is still denial from families (parents) and lack of commitment. It is necessary to increase the understanding of the community related to TPT INH in children and change the perception of people that drugs should only be given to someone who has symptoms, so it is hoped that the rejection that occurs can be reduced or avoided because giving TPT INH to children is prevention given to children. who are asymptomatic or do not cause TB symptoms (Gupta et al., 2019). The low number of hospitals/clinics/private doctors' practices that perform TPT INH administration in children make the target TPT INH administration in children in Surabaya always under the national target. It takes commitment from both the government and health professionals to implement the prevention of TB in children (Romanowski et al., 2019).

## **Research Limitation**

A limitation of this study is that this study only used secondary data but did not did not check the data of existing health service facilities. Additionally, this study was limited to the years 2016–2018, and the existing data simply reported the data of the health service facilities. The TPT INH administration, related logistics, and completeness of the TPT INH treatment itself were not further investigated in this study.

## CONCLUSION

The Provision of TPT INH to children in Surabaya has been implemented and has increased the performance result. However, in the last three years, the results are not optimal because the treatment has not reached the target districts/cities that have been determined. The implementation and reporting of the TPT INH administration also need to be optimized for many health service facilities that are not networked in the provision of TPT INH because an increase in the number of health care facilities that implement and report giving TPT INH in children will increase the achievement of providing TPT INH for children so that the target can be achieved.

The commitment to the prevention of TB needs to be improved to maximize the number of achieved implementations of TPT INH administration in children. It is suggested that further research examine the completeness of TPT INH treatment in children, i.e., whether children get complete TPT INH for six months (180 doses) and the logistics related to INH itself.

## **CONFLICT OF INTEREST**

The authors declare that no conflict of interest in this study.

## AUTHOR CONTRIBUTION

All authors participate actively in this article and are responsible for the content of writing of the article. RA: preparation, writing original draft, research design selection, editing, and revision of the article. CUW: supervision, editing, and revision of the article. RDY: supervision, editing and revision of the article.

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## REFERENCES

- Datiko, D. G., Yassin, M. A., Theobald, S. J., & Cuevas, L. E. (2017). A community-based isoniazid preventive therapy for the prevention of childhood tuberculosis in Ethiopia. *International Journal of Tuberculosis and Lung Disease*, 21(9), 1002– 1007. https://doi.org/10.5588/ijtld.16.0471
- Dewi, S., Damsar, & Azwar. (2019). Analisis kendala implementasi program penanggulangan tuberkulosis di Kecamatan Meral Kabupaten Karimun. *Jurnal Ilmu Sosial dan Ilmu Politik*, 9(1), 28–48.
- Diallo, T., Adjobimey, M., Ruslami, R., Trajman, A., Sow, O., Obeng Baah, J., ... Menzies, D. (2018). Safety and side effects of rifampin versus isoniazid in children. *New England Journal of Medicine*, 379(5), 454–463. https://doi.org/10.1056/NEJMoa1714284
- Dlamini, N. C., Ji, D. Der, & Chien, L. Y. (2019). Factors associated with isoniazid resistant tuberculosis among human immunodeficiency virus positive patients in Swaziland: a case-control study. *BMC Infectious Diseases*, 19(1), 1–8. https://doi.org/10.1186/s12879-019-4384-6
- Dodd, P. J., Yuen, C. M., Sismanidis, C., Seddon, J. A., & Jenkins, H. E. (2017). The global burden of tuberculosis mortality in children: a mathematical modelling study. *The Lancet Global Health*, 5(9), e898–e906. https://doi.org/10.1016/S2214-109X(17)30289-9
- Egere, U., Sillah, A., Togun, T., Kandeh, S., Cole, F., Jallow, A., ... Kampmann, B. (2016). Isoniazid preventive treatment among child

contacts of adults with smear-positive tuberculosis in the Gambia. *Public Health Action*, 6(4), 226–231. https://doi.org/10.5588/pha.16.0073

- Gegia, M., Winters, N., Benedetti, A., van Soolingen, D., & Menzies, D. (2017). Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, 17(2), 223–234. https://doi.org/https://doi.org/10.1016/S1473-3099(16)30407-8
- Gupta, A., Montepiedra, G., Aaron, L., Theron, G., McCarthy, K., Bradford, S., ... Weinberg, A. (2019). Isoniazid preventive therapy in HIVinfected pregnant and postpartum women. *New England Journal of Medicine*, 381(14), 1333–1346.

https://doi.org/10.1056/NEJMoa1813060

- Jenkins, H. E. (2016). Global burden of childhood tuberculosis. *Pneumonia*, 8(1), 1–7. https://doi.org/10.1186/s41479-016-0018-6
- Karo, B., Kohlenberg, A., Hollo, V., Duarte, R., Fiebig, L., Jackson, S., ... van der Werf, M. J. (2019). Isoniazid (INH) mono-resistance and tuberculosis (TB) treatment success: analysis of European surveillance data, 2002 to 2014. *Eurosurveillance*, 24(12), 1–13. https://doi.org/10.2807/1560-7917.ES.2019.24.12.1800392
- Lee, M.-R., Huang, H.-L., Lin, S.-W., Cheng, M.-H., Lin, Y.-T., Chang, S.-Y., ... Chong, I.-W. (2019). Isoniazid concentration and NAT2 genotype predict risk of systemic drug reactions during 3HP for LTBI. *Journal of Clinical Medicine*, 8(6), 812. https://doi.org/10.3390/jcm8060812
- Ministry of Health RI. (2016). *Minister of health RI's regulation number 67 of 2016 concerning tuberculosis control.* Jakarta: Ministry of Health RI.
- Moonan, P. K., Nair, S. A., Agarwal, R., Chadha, V. K., Dewan, P. K., Gupta, U. D., ...
  Khaparde, S. D. (2018). Tuberculosis preventive treatment: the next chapter of tuberculosis elimination in India. *BMJ Global Health*, 3(5), e001135. https://doi.org/10.1136/bmjgh-2018-001135
- Nyathi, S., Dlodlo, R. A., Satyanarayana, S., Takarinda, K. C., Tweya, H., Hove, S., ... Harries, A. D. (2019). Isoniazid preventive therapy: Uptake, incidence of tuberculosis and survival among people living with HIV in Bulawayo, Zimbabwe. *PLoS ONE*, *14*(10), 1–12.

https://doi.org/10.1371/journal.pone.0223076

- Pal, R., Hameed, S., Sabareesh, V., Kumar, P., S., Fatima, Singh, & Z. (2018). Investigations into isoniazid treated mycobacterium tuberculosis by electrospray mass spectrometry reveals new insights into its lipid composition. Journal of Pathogens, 2018. 1 - 14. https://doi.org/10.1155/2018/1454316
- Prieske, O., Krüger, T., Aehle, M., Bauer, E., & Granacher, U. (2018). Effects of resisted sprint training and traditional power training on sprint, jump, and balance performance in healthy young adults: a randomized controlled trial. *Frontiers in Physiology*, 9, 1–10.

https://doi.org/10.3389/fphys.2018.00156

- Romanowski, K., Campbell, J. R., Oxlade, O., Fregonese, F., Menzies, D., & Johnston, J. C. (2019). The impact of improved detection and treatment of isoniazid resistant tuberculosis on prevalence of multi-drug resistant tuberculosis: A modelling study. *PLoS ONE*, 14(1), 1–15. https://doi.org/10.1371/journal.pone.0211355
- Surabaya City Health Office. (2019). *Health* profile of Surabaya City at 2018. Surabaya City Health Office. Surabaya.
- Susetyowati, H. M., Ningtyias, F. W., & Prasetyo, A. (2018). The role of cadres in improving the succes of preventive treatment programs with isoniazid (PP INH) in Jember. *Multidisciplinary Journal*, 1(1), 17–20.
- Swaminathan, S., & Ramachandran, G. (2015). Challenges in childhood tuberculosis. *Clinical Pharmacology & Therapeutics*, 98(3), 240–244.

https://doi.org/10.1002/cpt.175

- Swindells, S., Ramchandani, R., Gupta, A., Benson, C. A., Leon-Cruz, J., Mwelase, N., ... Chaisson, R. E. (2019). One month of rifapentine plus isoniazid to prevent HIVrelated tuberculosis. *New England Journal of Medicine*, 380(11), 1001–1011. https://doi.org/10.1056/NEJMoa1806808
- Zunza, M., Gray, D. M., Young, T., Cotton, M., & Zar, H. J. (2017). Isoniazid for preventing tuberculosis in HIV-infected children (review). *Cochrane Database of Systematic Reviews*, (8), 1–32. https://doi.org/10.1002/14651858.CD006418 .pub3