Journal Pre-proof
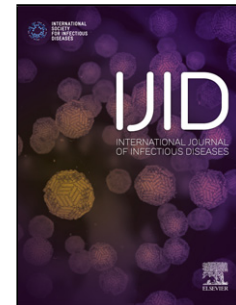
Isoniazid-monoresistant tuberculosis in France: risk factors, treatment outcomes and adverse events

Marwa Bachir, Lorenzo Guglielmetti, Simone Tunesi, Typhaine Billard-Pomares, Sheila Chiesi, Jérémy Jaffré, Hugo Langris, Valérie Pourcher, Frédéric Schramm, Nadine Lemaître, Jérôme Robert, on behalf of the Isoniazid Resistance Group<ce:author-group id="aug0010">, O. Bouchaud, T. Billard-Pomares, E. Carbonnelle, F. Mechaï, H. Nunes, M. Pellan, A-S. Morin, C. Dumesnil, J. Dumoulin, A-L. Roux, M. Jachym, D. le Du, D. Marigot-Outtandy, S. Abgrall, V. Chambrin, C. Guillet, B. Fantin, A. Galy, J-W. Decousser, J.D. Lelièvre, S. Gallien, B. Nebbad-Lechani, L. Deconinck, S. Bulifon, N. Fortineau, B. Wyplosz, F. Cohen, N. Lemaitre, B. Crestani, N. Grall, C. Pierre-Audigier, C. Rioux, Y. Yazdanpanah, C. Le Jeunne, P. Morand, N. Roche, J. Pavie, P. Loulergue, V. Delcey, E. Lecorché, A-L. Munier, F. Mougari, P. Sellier, E. Bille, A. Ferroni, R. Guéry, A. Hummel, J. Lourenco, A. Aubry, I. Bonnet, E. Caumes, C. Londner, F. Morel, K. Lacombe, V. Lalande, J-L. Meynard, N. Veziris, N. De Castro, B. Denis, M. Lafaurie, J-M. Molina, A. Canestri, L. Lassel, G. Pialoux, C. Verdet, A-L. Nardi, M. Gominet, E. Catherinot

Please cite this article as: { doi: https://doi.org/

Isoniazid-monoresistant tuberculosis in France: risk factors, treatment outcomes and adverse events

Marwa BACHIR[1], Lorenzo GUGLIELMETTI[1,2], Simone TUNESI[3], Typhaine BILLARD-POMARES[4], Sheila CHIESI[1], Jérémy JAFFRÉ[2], Hugo LANGRIS[5], Valérie POURCHER[6,7], Frédéric SCHRAMM[8], Nadine LEMAÎTRE[9], Jérôme ROBERT[1,2] on behalf of the Isoniazid Resistance Group.

Affiliations :

[1] Centre d'Immunologie et des Maladies Infectieuses, Sorbonne – Université, INSERM, (U1135 – E2) Paris, France

[2] Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux antituberculeux, Bactériologie-Hygiène, AP-HP.Sorbonne Université, Site Pitié, Paris, France

[3] Service de Médecine interne, hôpital Jean Verdier, AP-HP. Université Paris 13, Bondy, France

[4] Laboratoire de Microbiologie Clinique, CHU Avicenne, AP-HP. Université Paris 13, Bobigny, France

[5] Normandie Université, UNICAEN, CHU de Caen Normandie, Service de bactériologie, 14000 Caen, France

[6] Service des Maladies Infectieuses et Tropicales, AP-HP.Sorbonne Université, Site Pitié, Paris, France

[7] Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), Inserm UMR_S 1136, Paris, France

[8] Laboratoire de Bactériologie, CHU de Strasbourg, Strasbourg, France

[9] Service de Bactériologie-Hygiène, Centre de Biologie-Humaine, CHU d'Amiens, Amiens, France

Running title: isoniazid-monoresistant tuberculosis in France

Declarations of interest: none

Corresponding author:

Marwa Bachir

Tel: +33156016951

Email address: marwa.bachirelrufaai@aphp.fr

Postal address: 4 rue de la Chine, 75020 PARIS, FRANCE

Word Count: 2909 words

Highlights

- No specific risk factors for isoniazid-monoresistant tuberculosis were identified.
- Routine implementation of line probe assay on clinical sample is warranted.
- HR-TB treatment outcomes are comparable to DS-TB's in France.

Abstract (182 words):

Objectives

Isoniazid-monoresistant tuberculosis (HR-TB) is the most prevalent form of drug-resistant TB worldwide and in France and is associated with poorer treatment outcomes compared to drug-susceptible TB (DS-TB). The objective of this study was to determine the characteristics of HR-TB patients in France and to compare outcomes and safety of treatment for HR-TB and DS-TB.

Methods

A case-control multicentre study was performed to identify risk factors associated with HR-TB and to compare treatment outcomes and safety among HR-TB patients and DS-TB patients.

Results

Characteristics of 99 HR-TB diagnosed and treated in university hospitals of Paris, Lille, Caen and Strasbourg were compared to 99 DS-TB's. Female sex (OR=2.2; 1.0-4.7), birth in the West-Pacific WHO region (OR=4.6; 1.1-18.7) and resistance to streptomycin (OR=77.5; 10.1-594.4) were found to be independently associated with HR-TB. Rates of treatment success did not differ significantly between HR-TB and DS-TB.

Conclusions

Factors associated with HR-TB are not relevant enough to efficiently screen TB patients at risk of HR-TB. The systematic implementation of rapid molecular testing on clinical samples remains the only effective way to make the early diagnosis of HR-TB and adapt the treatment.

Key-words: *tuberculosis, isoniazid, drug resistance, risk factors, epidemiology*

1. Introduction

Isoniazid-resistant, rifampicin-susceptible tuberculosis (HR-TB) is the most prevalent form of drug-resistant TB worldwide (besides streptomycin resistance) with estimates rising up to 7% among new TB cases and to 8 to 11% among previously treated TB cases (World Health Organization, 2018; Dean et al., 2020). HR-TB is associated with a higher risk of acquiring further drug resistance and in particular of evolving towards multidrug-resistant TB (MDR-TB), defined by resistance to both isoniazid and rifampicin (Menzies et al., 2009; Jacobson et al., 2011; Gegia et al., 2012).

Yet, HR-TB has been relatively overlooked and little attention has been paid to this particular form of drug-resistant TB. Until recently, monoresistance to isoniazid was considered to have little or no impact on treatment outcome. Several studies, however, have shown that HR-TB is associated with higher rates of treatment failures compared to drug-susceptible (DS) TB.

In a recent systematic review and meta-analysis, Gegia et al. (2017) showed a great disparity in terms of treatment failure rates for HR-TB across studies, ranging from 2% to 66%, probably explained at least partially by the high variability in the sample size of the studies.

Overall, however, the pooled rates of failure, relapse, and acquired drug resistance with the WHO standard treatment regimen were significantly higher for HR-TB than for DS-TB: 11% (95% CI 6–17), 10% (5–15) and 8% (3-13) respectively, in patients with HR-TB and 2% (1–13), 5% (2–7) and 1% (1-2) in those with DS-TB. In this study, multidrug-resistance strains accounted for 96% (93-99) of acquired drug-resistance among HR-TB.

Along with rifampicin, isoniazid is a cornerstone of the standardized first-line anti-TB treatment due its early bactericidal activity. Hence, it is not surprising that resistance to isoniazid undermines treatment efficacy. Up to recently, no consensus was reached on the optimal

treatment of HR-TB. It is only in 2018 that WHO guidelines recommend a specific, evidence-based regimen for HR-TB, i.e. a 6-month regimen including rifampicin, ethambutol, pyrazinamide, and fluoroquinolones (World Health Organization, 2018).

In France, the incidence of HR-TB is approximately 3 times higher than that of MDR-TB, accounting for 5% of all TB cases (i.e. circa 300 cases yearly) (CNR-MyRMA, 2019). Other Central and Western European countries reported similar estimates (Bang et al, 2010; Jenkins et al., 2011). Of concern, the French National Reference Center for Mycobacteria (CNR-MyRMA) has reported an increasing number of HR-TB cases between 1995 and 2008 among young patients born in France after 1980 with no history of prior treatment for TB. In this study, an increase of primary resistance to isoniazid was observed in younger patients among all cohorts (Meyssonnier et al., 2012). Yet, in France, there are so far no well-identified risk factors associated with HR-TB and no data concerning treatment outcomes of HR-TB cases.

The primary objective of our study was to identify the characteristics of patients with HR-TB in France in order to screen those with higher probability of resistance and to adapt treatment early. Our secondary objectives were to compare treatment outcomes and safety among HR-TB patients and DS-TB patients.

2. Materials and Methods

2.1 Study design

We designed a retrospective, multicentre case-control study where patients affected by HR-TB (case-patients) were compared to those affected by DS-TB (control-patients), defined as susceptible to both isoniazid and rifampicin. Both cases and controls had at least one culture positive for *Mycobacterium tuberculosis* complex and were diagnosed in French university hospitals belonging to the AZAY-mycobacteria network from January 1, 2016, to December 31, 2017. The latter network was set up in 1994 by microbiologists for the surveillance of primary and secondary drug-resistant TB. At that time, the network included 36 laboratories across 12 out of 13 regions of metropolitan France (Guerrin-Tran et al., 2006). For practical reasons, only patients reported to the network in the Ile-de-France (Paris and its suburbs), and three other regions (cities of Lille, Caen, and Strasbourg), were included. For each HR-TB patient, one DS-TB patient was randomly selected among culture-positive TB patients in the same participating center. Proportional random sampling, stratified by center, was performed using OpenEpi (www.openepi.com). A retrospective analysis of AZAY-mycobacteria network data over 10 years revealed that HR-TB cases were twice less often born in France than susceptible TB cases (15% and 31% respectively). Based on this assumption, with a 1:1 ratio of case-control and considering "birth in France" as the main variable, we calculated that between 80 and 100 patients in each group were needed to detect a difference between both groups with a statistical power of more than 80%, and a α risk of 5%.

2.2 Data collection

A standardized questionnaire was created to extract data from medical files. Data concerned demographic, clinical, radiological, and microbiological characteristics at baseline, as well as treatment, treatment outcomes, and severe adverse events. Data was entered using *Epidata*.

2.3 Treatment outcomes and safety definitions

Treatment outcomes for HR-TB and DS-TB were defined according to WHO definitions (World Health Organization, 2013). Adequate treatment for HR-TB cases was defined as prolongation of ethambutol or pyrazinamide during the continuation phase, as suggested with caution by WHO in 2014, based on observed practices (World Health Organization, 2014), or the addition of a fluoroquinolone according to 2018 WHO guidelines (World Health Organization, 2018). For DS-TB, the standardized 4-drug regimen was considered as adequate. Adverse events were graded according to the severity scale of the *Common Terminology Criteria for Adverse Events* (CTCAE) v 5.0. Adverse events were considered as severe if they were grade 3 or higher, or if they led to the permanent discontinuation of at least one TB drug.

2.4 Statistical analysis

Demographic, clinical, and radiological baseline characteristics of case- and control-patients were compared by using Fisher's exact and Wilcoxon-Mann-Whitney non-parametric tests for categorical and quantitative variables, respectively. Factors independently associated with HR-TB cases, favorable treatment outcomes, and with severe adverse events, were identified using multivariable logistic regression. Explanatory variables were initially included if associated with the dependent variable with $p \leq 0.2$ in bivariate analysis. Relevant or potentially confounding variables, as described in literature, were also included. The final model was identified using a stepwise backward selection process of explanatory variables and goodness-of-fit was assessed with the Hosmer and Lemeshow test. The final models were the most parsimonious, i.e. with the most significance and the least variables.

Missing observations were imputed using multiple imputation with the assumption that they followed a missing-at-random pattern. MICE function on R.Studio was used to create ten imputed datasets, with a proportion of missing observation ranging from 1% (streptomycin resistance) to 55% (albumin) according to the variable. All statistical analysis was performed using R.Studio version 1.2.5. All statistical tests were bilateral, and significance was determined as $p \leq 0.05$.

2.5 Ethics

The study was approved by the ethic committee of the Bligny Hospital (Briis-sous-Forges, France) in October 2018 and included in the treatment registry of Assistance Publique des Hôpitaux de Paris under the following registration number: 20190822142246.

3. Results

3.1 Assessment of HR-TB cases characteristics

Overall, 99 cases (HR-TB) and 99 controls (DS-TB) were included, with a great majority of cases notified in the Paris region (85), followed by Strasbourg (9), Caen (3) and Lille (2). Median age was similar among HR-TB and DS-TB patients (35 and 36 years, respectively). Among all characteristics (Table 1), HR-TB patients were more likely than DS-TB patients to be born in the WHO West-Pacific region (14.1% versus 3.0%; p=0.01) and to harbor isolates resistant to streptomycin (42.4% vs 1.0%; p<0.001). On the contrary, DS-TB patients were more likely than HR-TB patients to have psychiatric disorders (6.1% vs 0%; p=0.03) and to be smokers (39.4% vs 25.2%) although the difference was not statistically significant (p=0.06). HR-TB and DS-TB patients were not significantly different when comparing all other variables, including HIV-coinfection (9.1% for both groups), prior history of treatment (10.1% vs 6.1%), comorbidities, and clinical and radiological characteristics of TB (localization, presence of lung cavities, disseminated TB).

In a logistic regression model including sex, birth in the WHO West-Pacific region, resistance to streptomycin, miliary tuberculosis, and psychiatric disorders (Table 2), three factors remained independently associated with HR-TB: female sex (OR=2.2; 95% confidence interval 1.0-4.7), birth in the WHO West-Pacific Region (OR=4.6; 1.1-18.7) and resistance to streptomycin (OR=77.5; 10.1-594.4).

3.2 Treatment outcomes

The median time between first symptoms and TB diagnosis was 80 days (interquartile range IQR, 48-157) for HR-TB patients and 72 days (IQR, 41-156) for DS-TB patients (p= 0.6).

The median time between first symptoms and treatment initiation was 83 days (IQR, 53-157) for HR-TB patients and 73 days (IQR, 45-160) for DS-TB patients (p=0.6). Overall, only 72 HR-TB (72.7%) received an adequate treatment: 16 according to 2014 WHO guidelines, with a prolongation of ethambutol and pyrazinamide during the continuation phase (13), and 56 according to 2018 WHO guidelines (World Health Organization, 2018), with the addition of a fluoroquinolone. All DS-TB received an adequate treatment with the 4-drugs standardized regimen. The difference in the proportion of adequate treatment was statistically significant between the two groups (p<0.001). A total of 75.8% of HR-TB patients achieved treatment success (10.1% cured and 65.7% treatment completed) as compared to 80.8% (4.0% cured and 76.8% treatment completed) among DS-TB patients. This difference was not statistically significant. Two HR-TB cases experienced treatment failure, including one who acquired MDR TB, and 4 died, whereas among DS-TB no treatment failure was observed and 5 died (Table 3). Follow-up information 12 months after treatment completion was available for 83 (42%) of the 198 patients. Overall, 1 and 3 relapses were identified among HR-TB and DS-TB patients, respectively.

In multivariable analysis (Table 4), when adjusting for age, sex, immunosuppression, smoking, prior history of TB treatment, radiological characteristics, adequate treatment and HR-TB, three factors were independently associated with favorable treatment outcome: absence of lung cavity (OR=2.6; 1.1-6.3), absence of miliary TB (OR=5.2; 1.4-18.4) and adequate treatment (OR=8.8; 2.9-28.3). HR-TB was not associated with treatment outcome.

3.3 Safety

Severe adverse events were significantly more frequent among HR-TB compared to DS-TB (OR=2.8; 1.0-9.2) with 16 (16.2%) and 7 (7.1%) events reported, respectively, among 15 cases and 6 controls (p=0.04) (Table 5). Hepatotoxicity was by far the most prevalent in both groups

(9 (9.1%) in HR-TB and 3 (3.0%) in DS-TB patients), followed by cytopenia and peripheral neuropathy (3 cases for each). When adjusting for age, sex, extra-pulmonary TB, immunosuppression, smoking and adequate treatment in multivariable logistic regression, isoniazid-monoresistance was no longer associated with the occurrence of severe adverse effects (OR= 2.0; 0.7-5.8) (data not shown).

4. Discussion

In our study, we have shown that HR-TB cases were more likely to be female, born in WHO West-Pacific Region and to be infected with streptomycin-resistant strains, when compared to DS-TB. Treatment outcomes were similar between HR-TB and DS-TB, however, inadequate treatment was more frequent amongst HR-TB. In addition, HR-TB treatment was associated with higher rates of treatment-emergent severe adverse events, although this difference was not significant after accounting for other explanatory variables.

The purpose of this study was to identify factors independently associated with HR-TB in France, to enable the early screening of TB patients at risk of isoniazid-monoresistance. Though several studies conducted in different countries have tried to address this question, no risk factor associated with HR-TB has been clearly identified so far (Vadwai et al., 2011; Vinnard et al., 2011; Munang et al., 2015; Báez-Saldaña et al., 2016; Salindri et al., 2018). In Western European countries, outbreaks of HR-TB cases have been recently described, associated with specific local factors (Ruddy et al., 2004; Hernán García et al., 2016). To our knowledge, female sex has not been described as correlated to isoniazid monoresistance before and we found no further explanation that could currently corroborate this result. The WHO West-Pacific Region, including 27 countries, among which China, Cambodia, and the Philippines, has been recently described as a high-incidence region for HR-TB. In their modelling study, Yuen et al. (2015) estimated indeed that around 12% of all incident TB cases in children were isoniazid-resistant worldwide, with a majority of them occurring in the West-Pacific (28 170 [95%IC: 20 865 to 35 921]) and Southeast Asia WHO Regions (38 507 [IC95% :29 709 - 47 869]). Although the West-Pacific Region seems to account for a large number of isoniazid-resistant TB cases, the estimates do not differentiate between isoniazid-monoresistant and multidrug-resistant TB.

Moreover, the highest proportions of isoniazid-resistant TB cases remain in Europe, rising up to 25% of all TB cases among children, substantially higher than in the West-Pacific region (around 15%). Consequently, we did not expect birth in the West-Pacific Region to be independently associated with isoniazid-monoresistant TB in our study. This result can be explained by a higher proportion of West-Pacific-born TB cases in 2016 and 2017 in France, compared to previous years. Indeed, West-Pacific-born TB patients represented 2.1% of all TB cases registered by the network in the last 10 years and 2.8% of those with isoniazid resistant strains during that period.

The association between resistance to isoniazid and resistance to streptomycin has already been described, with no further biological explanation found to this association. Since streptomycin is no longer used in routine for the modern treatment of TB, resistance to this antibiotic is likely a marker of "old" strains still circulating. Nevertheless, it is possible that in some regions of the world, latter use of streptomycin led to higher prevalence of streptomycin resistance, as in West-Pacific-born TB cases.

Considering the risks of unfavorable outcome and of multidrug-resistant strains selection when inadequately treated, early detection and treatment adaptation of HR-TB cases are needed. A previous modeling study suggested that the use of rapid molecular testing for the combined detection of isoniazid and rifampicin resistance on clinical samples would enable a 50% reduction of acquired multidrug-resistant TB, compared to the detection of rifampicin-resistance alone (Romanowski et al., 2019). In our study, the three factors associated with HR-TB are not discriminatory enough to effectively screen TB patients at risk of having isoniazid-resistant strains. Female gender is obviously not very helpful. Resistance to streptomycin, although strongly associated with resistance to isoniazid, is identified when the phenotypic drug susceptibility pattern is available. Finally, the retrospective analysis of AZAY-network data

showed that only a very small proportion of HR-TB cases notified during the last two decades, were West-Pacific born (2.9%). Hence, in the absence of efficient screening criteria, early detection and treatment adaptation for HR-TB cases among newly diagnosed cases will rely on systematic use of rapid molecular testing for both isoniazid and rifampicin on clinical sample. As for early detection of rifampicin resistance, it may be reasonable to implement early detection on clinical sample only in smear-positive TB cases, where a positive test has a higher likelihood to be relevant; in addition, these patients with higher bacillary load are more contagious and at higher risk of selecting multidrug-resistant strains. Nevertheless, line-probe assays (FluoroType ®MTBDR, GenoType MTBDR*plus*, BD MAX^{TM} MDR-TB) are so far the only rapid molecular testing available to identify HR-TB at an early stage ; however, they are currently not implemented as a routine diagnostic tool and often remain limited to reference laboratories where they are mostly performed on strains (Sulis et al., 2020). Without easy-to-use tools for early HR detection, it is foreseen that a large number of HR-TB cases will be overlooked and receive standard DS-TB regimen.

In our study, there was no statistically significant difference in treatment outcomes between HR-TB and DS-TB, although a trend toward worse outcomes for HR-TB and one case of acquired MDR strain were noticed. This could mean that our study lacked power to show any difference. Nevertheless, adequate treatment, which implies the early detection of HR-TB strains and the adaptation of the treatment regimen, was independently associated with treatment success. Our findings support the relevance of adapting, as soon as possible, the treatment regimen in patients harboring HR-TB strains. Although international guidelines currently recommend the addition of a fluoroquinolone in the treatment of HR-TB, prolonged treatment with rifampicin, ethambutol, and pyrazinamide, as suggested by the WHO in 2014, was considered as equally adequate. In a recent retrospective cohort study comparing the latter treatment regimen with and without fluoroquinolone, no significant difference in outcome was

shown, suggesting a comparable efficiency of both regimens on HR-TB strains (OR= 0.99, 95% CI 0.53–1.85; p = 0.97) (Stagg et al., 2019).

In addition, severe adverse events, in particular hepatotoxicity, were more frequent among HR-TB compared to DS-TB patients. This is not unexpected, considering that a majority of HR-TB patients received a treatment regimen with either a prolonged duration of pyrazinamide or the addition of a fluoroquinolone, all drugs that have known liver toxicity. However, after adjusting for patient and disease characteristics, this difference was not statistically significant.

This study has several limitations, most importantly its retrospective design which implies potential information bias. The case-control design was chosen because HR-TB remains a rare disease in France. Nevertheless, multicentric data and proportional random sampling have limited this bias. Proportional random sampling was supposed to reduce the "quality effect" of a medical team. It is also possible that patients in other regions of France or not managed in university hospitals have different characteristics.

5. Conclusion

In conclusion, our study has identified several risk factors which are independently associated with HR-TB. However, these factors are not sufficient to efficiently identify TB patients at risk of being infected with HR strains. Early detection of HR-TB should therefore rely mainly on the systematic implementation of rapid molecular testing, in particular for smear-positive TB cases**.** This is particularly relevant, in light of our findings that adequate treatment regimens were associated with better treatment outcomes.

Declaration of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Báez-Saldaña R, Delgado-Sánchez G, García-García L, Cruz-Hervert LP, Montesinos-Castillo M, Ferreyra-Reyes L, et al. Isoniazid Mono-Resistant Tuberculosis: Impact on Treatment Outcome and Survival of Pulmonary Tuberculosis Patients in Southern Mexico 1995-2010. PLoS ONE. 2016;11(12):e0168955.
https://doi.org/10.1371/journal.pone.0168955.

Bang D, Andersen PH, Andersen ÅB, Thomsen VØ. Isoniazid-resistant tuberculosis in Denmark: Mutations, transmission and treatment outcome. J Infect. 2010;60(6):452–7.
https://doi.org/j.jinf.2010.03.017.

Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux (CNR-MyRMA). Rapport annuel d'activité. 2018.

Dean AS, Zignol M, Cabibbe AM, Falzon D, Glaziou P, Cirillo DM, et al. Prevalence and genetic profiles of isoniazid resistance in tuberculosis patients: A multicountry analysis of cross-sectional data. PLoS Med. 2020;17(1):e1003008.
https://doi.org/10.1371/journal.pmed.1003008.

Gegia M, Cohen T, Kalandadze I, Vashakidze L, Furin J. Outcomes among tuberculosis patients with isoniazid resistance in Georgia, 2007–2009. Int J Tuberc Lung Dis. 2012;16(6):812–6.
https://doi.org/10.5588/ijtld.11.0637.

Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. Lancet Infect Dis. 2017;17(2):223–34.
https://doi.org/10.1016/S1473-3099(16)30407-8.

Guerrin-Tran E, Thiolet J-M, Rousseau C, Henry S, Poirier C, Che D, et al. An evaluation of data quality in a network for surveillance of Mycobacterium tuberculosis resistance to antituberculosis drugs in Ile-de-France region-2001-2002. Eur J Epidemiol. 2006;21(10):783–5.
https://doi.org/10.1007/s10654-006-9069-y.

Hernán García C, Moreno Cea L, Fernández Espinilla V, Ruiz Lopez Del Prado G, Fernández Arribas S, Andrés García I, et al. Outbreak of isoniazid-resistant tuberculosis in an immigrant community in Spain. Arch Bronconeumol. 2016;52(6):289–92.
https://doi.org/10.1016/j.arbres.2015.07.014.

Jacobson KR, Theron D, Victor TC, Streicher EM, Warren RM, Murray MB. Treatment Outcomes of Isoniazid-Resistant Tuberculosis Patients, Western Cape Province, South Africa. Clin Infect Dis. 2011;53(4):369–72.
https://doi.org/10.1093/cid/cir406.

Jenkins HE, Zignol M, Cohen T. Quantifying the Burden and Trends of Isoniazid Resistant Tuberculosis, 1994–2009. PLoS ONE. 2011;6(7):e22927.
https://doi.org/10.1371/journal.pone.0022927.

Menzies D, Benedetti A, Paydar A, Royce S, Pai M, Burman W, et al. Standardized Treatment of Active Tuberculosis in Patients with Previous Treatment and/or with Mono-resistance to Isoniazid: A Systematic Review and Meta-analysis. PLoS Med. 2009;6(9):e1000150.
https://doi.org/10.1371/journal.pmed.1000150.

Meyssonnier V, Veziris N, Bastian S, Texier-Maugein J, Jarlier V, Robert J. Increase in primary drug resistance of Mycobacterium tuberculosis in younger birth cohorts in France. J Infect. 2012 Jun;64(6):589–95.
https://doi.org/10.1016/j.jinf.2012.01.013.

Munang ML, Kariuki M, Dedicoat M. Isoniazid-resistant tuberculosis in Birmingham, United Kingdom, 1999-2010. QJM. 2015;108(1):19–25.
https://doi.org/10.1093/qjmed/hcu139.

Romanowski K, Campbell JR, Oxlade O, Fregonese F, Menzies D, Johnston JC. The impact of improved detection and treatment of isoniazid resistant tuberculosis on prevalence of multi-drug resistant tuberculosis: A modelling study. PLoS One. 2019;14(1):e0211355.
https://doi.org/10.1371/journal.pone.0211355.

Ruddy MC, Davies AP, Yates MD, Yates S, Balasegaram S, Drabu Y, et al. Outbreak of isoniazid resistant tuberculosis in north London. Thorax. 2004 Apr;59(4):279–85.
https://doi.org/10.1136/thx.2003.010405.

Salindri AD, Sales R-MF, DiMiceli L, Schechter MC, Kempker RR, Magee MJ. Isoniazid Monoresistance and Rate of Culture Conversion among Patients in the State of Georgia with Confirmed Tuberculosis, 2009–2014. Ann Am Thorac Soc. 2018 Mar;15(3):331–40.
https://doi.org/10.1513/AnnalsATS.201702-147OC.

Stagg HR, Bothamley GH, Davidson JA, Kunst H, Lalor MK, Lipman MC, et al. Fluoroquinolones and isoniazid-resistant tuberculosis: implications for the 2018 WHO guidance. Eur Respir J. 2019;54(4):e1900982.
https://doi.org/10.1183/13993003.00982-2019.

Sulis G, Pai M. Isoniazid-resistant tuberculosis: A problem we can no longer ignore. PLoS Med. 2020;17(1):e1003023.
https://doi.org/10.1371/journal.pmed.1003023.

Vadwai V, Shetty A, Soman R, Rodrigues C. Determination of risk factors for isoniazid monoresistance and multidrug-resistant tuberculosis in treatment failure patients. Scandinavian Journal of Infectious Diseases. 2012 Jan 1;44(1):48–50.
https://doi.org/10.3109/00365548.2011.611169.

Vinnard C, Winston CA, Wileyto EP, MacGregor RR, Bisson GP. Isoniazid-resistant tuberculous meningitis, United States, 1993-2005. Emerg Infect Dis. 2011;17(3):539–42.
https://doi.org/10.3201/eid1703.101715.

World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 and January 2020). 2013.

World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. 2014.

World Health Organization. WHO treatment guidelines for isoniazid-resistant tuberculosis: Supplement to the WHO treatment guidelines for drug-resistant tuberculosis 2018.

Yuen CM, Jenkins HE, Rodriguez CA, Keshavjee S, Becerra MC. Global and Regional Burden of Isoniazid-Resistant Tuberculosis. Pediatrics. 2015 Jul;136(1):e50-59. https://doi.org/10.1542/peds.2015-0172.

Tables

Table 1. Comparison of the characteristics of the 99 case-patients with isoniazid-monoresistant tuberculosis (HR-TB) and 99 control-patients with drug-susceptible tuberculosis (DS-TB).
WHO = World Health Organization; OR = Odds Ratio; 95% C.I. = 95% confidence interval

Characteristics	HR-TB (n=99) N (%)	DS-TB (n=99) N (%)	OR (95% C.I.)	p
Male sex	69 (69.7)	78 (78.8)	1.6 [0.8 – 3.3]	0.19
Smoker	25 (25.2)	39 (39.4)	0.5 [0.3 – 1.0]	0.06
Alcohol addiction	7 (7.1)	13 (13.1)	0.5 [0.2 –1.4]	0.16
Intravenous drug use	1 (1.0)	1 (1.0)	1.0 [0.0 – 79.3]	1.00
HIV-positive	9 (9.1)	9 (9.1)	0.9 [0.3 – 2.9]	1.00
Immunosuppression	9 (9.1)	17 (17.2)	0.5 [0.2 – 1.2]	0.14
History of prior TB treatment	10 (10.1)	6 (6.1)	1.7 [0.5 – 6.0]	0.43
Place of birth (WHO regions)				
- European Region	24 (24.2)	34 (34.3)	0.6 [0.3 – 1.2]	0.16
- West-Pacific Region	14 (14.1)	3 (3.0)	5.2 [1.4 – 29.4]	0.01
- South-East Asian Region	6 (6.1)	6 (6.1)	1.0 [0.3 – 3.9]	1.00
- African Region	41 (41.4)	44 (41.4)	0.9 [0.5 – 1.6]	0.77
- East-Mediterranean Region	9 (9.1)	9 (9.1)	1.0 [0.3 – 3.0]	1.00
- American Region	3 (3.0)	2 (2.0)	1.5 [0.2 – 18.5]	1.00
Born in France	17 (17.2)	26 (26.3)	0.6 [0.3 – 1.2]	0.17
Pulmonary TB	82 (82.8)	75 (75.8)	1.5 [0.7 – 3.3]	0.29
Sputum smear positivity	46 (46.5)	42 (42.4)	1.2 [0.6 - 2.1]	0.67
Bilateral pulmonary involvement	50 (50.5)	49 (49.5)	0.8 [0.4 – 1.7]	0.61
Presence of ≥1 lung cavity	41 (41.4)	34 (34.3)	1.2 [0.6 – 2.4]	0.41
Miliary TB	11 (11.1)	5 (5.1)	2.1 [0.6 -8.2]	0.19
Pleural effusion	20 (20.2)	24 (24.2)	0.8 [0.4 – 1.7]	0.60
Extra-pulmonary TB	43 (43.4)	44 (44.4)	1.0 [0.5-1.7]	1.00
Pulmonary and extra-pulmonary TB	54 (54.5)	42 (42.4)	1.6 [0.9 – 3.0]	0.12
Disseminated TB (≥ 3 localizations)	12 (12.1)	11 (11.1)	1.1 [0.42 – 2.92]	1
Resistance to pyrazinamide	5 (5.1)	1 (1.0)		0.26
Resistance to ethambutol	0	0	N.A.	N.A.
Resistance to streptomycin	42 (42.4)	1 (1.0)		<0.001

Table 2. Factors associated with isoniazid-monoresistance among 99 case-patients with isoniazid-monoresistant tuberculosis and 99 control-patients with drug-susceptible tuberculosis: multivariable logistic regression.
WHO = World Health Organization; OR = Odds Ratio; 95% C.I. = 95% confidence interval

Explicative variable	OR (95% C.I.)	*p*
Sex (female)	2.2 [1.002 – 4.7]	0.05
Birth in WHO West Pacific Region	4.6 [1.1 – 18.7]	0.03
Psychiatric troubles	0.0	0.99
Miliary tuberculosis	3.2 [0.9 – 10.7]	0.07
Resistance to streptomycin	77.5 [10.1 – 594.4]	<0.001

Table 3. Treatment outcomes according to World Health Organization definitions of 99 case-patients with isoniazid-monoresistant tuberculosis (HR-TB) and 99 control-patients with drug-susceptible tuberculosis (DS-TB)

Treatment outcomes	HR-TB (n=99) N (%)	DS-TB (n=99) N (%)	*p*
Cured	10 (10.1)	4 (4.0)	0.16
Treatment completed	65 (65.7)	76 (76.8)	0.11
Treatment success **(cured and treatment completed)**	75 (75.8)	80 (80.8)	0.49
Treatment failure	2 (2.0)	0 (0.0)	0.50
Death	4 (4.0)	5 (5.1)	1.00
Lost to follow-up	16 (16.2)	12 (12.1)	0.54
Not evaluated	2 (2.0)	2 (2.0)	1.00

Table 4. Factors associated with treatment success among all patients (99 case-patients with isoniazid-monoresistant tuberculosis and 99 control-patients with drug-susceptible tuberculosis cases and controls): bivariate and multivariable logistic regression.

	n	Treatment success (%)	Bivariate OR (95% C.I.)	Multivariable OR (95% C.I.)	*p*
Sex					
Male	147	76.9	Ref.		
Female	51	82.3	1.4 (0.59-3.61)	1.0 (0.37-2.74)	0.98
Immune status					
Immunocompetent	172	79.6	Ref.		
Immunosuppressed	26	69.2	0.6 (0.22-1.66)	0.4(0.13-1.24)	0.10
Smoking history					
Non-smoker	117	83.8	Ref.		
Smoker or ex-smoker	64	75.0	0.6 (0.26-1.33)	0.5(0.20-1.20)	0.12
Treatment history					
New	181	79.0	Ref.		
Previously treated	16	75.0	0.8 (0.22-3.59)	0.8 (0.21-3.91)	0.79
TB clinical form					
Extra-pulmonary	41	85.4	Ref.		
Pulmonary	157	76.4	0.6 (0.18-1.48)	0.5 (0.21-1.32)	0.19
Disseminated TB					
Localized (<3 localizations)	175	77.7	Ref.		
Disseminated (≥3 localizations)	23	82.6	1.4 (0.42-5.82)	1.8 (0.50-8.60)	0.40
Lung cavities					
Presence of any cavity	75	70.7	Ref.		
Absence of cavities	123	82.9	2.0 (0.96-4.23)	2.6 (1.10-6.31)	0.03
Miliary					
Presence of miliary	16	50.0	Ref.		
Absence of miliary	179	81.0	4.2 (1.28-13.95)	5.2 (1.40-18.40)	0.01
H-susceptibility					
DS-TB	99	80.8	Ref.		
HR-TB	99	75.8	0.7 (0.35-1.54)	1.8 (0.70-5.18)	0.23
Treatment					
Inadequate	31	54.8	Ref.		
Adequate	167	82.6	3.9 (1.58-9.48)	8.8 (2.91-28.32)	<0.001

Table 5. Severe adverse events occurrence among 99 case-patients with isoniazid-monoresistant tuberculosis (HR-TB) and 99 control-patients with drug-susceptible tuberculosis (DS-TB).

Severe adverse event	HR-TB	DS-TB
Hepatotoxicity	9 (56.3%)*	3 (42.8 %)**
Cytopenia	3 (18.8%)	0
Anaphylactic shock	1 (6.2%)	0
Peripheral neuropathy	1 (6.2%)*	2 (28.6 %)
Optical neuritis	1 (6.2%)	0
Psychiatric disorders	1 (6.2%)	0
Cutaneous rash	0	2 (28.6 %)**
Total	*16 (100%)*	*7 (100%)*

* of which one case of hepatotoxicity and peripheral neuropathy; ** of which one case of hepatotoxicity and cutaneous rash.