REGION KRONOBERG

Clinical and microbiological characteristics of tuberculosis relapses in Sweden

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Introduction

Globally in 2022, an estimated 10.6 million people developed active tuberculosis (TB) and 1.3 million people died from the disease (1). Pulmonary tuberculosis is the most common disease presentation. However, in 10-30% of TB cases the disease is extrapulmonary, affecting for instance lymph nodes, GI tract, bone or central nervous system (2). TB mortality without treatment is estimated to 50% (3). On the other hand, treatment success rates are increasing: 88% of patients with drug-susceptible TB reportedly recover following treatment with the standard quadruple regimen of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol (1). Drug resistance can impact treatment outcomes, as exemplified in a meta-analysis from 2023 reporting a pooled treatment success rate of 78% (95% CI; 74-83%) in TB patients infected by an *M. tuberculosis* strain mono-resistant to Isoniazid (4).

A minority of TB patients who undergo treatment eventually experience disease recurrence (2, 5). The World Health Organization defines 'recurrence' as the diagnosis of a new episode of symptomatic TB disease after having been declared cured at treatment completion. The recurrent disease is either an exogenous reinfection with a different *M. tuberculosis* strain or a relapse due to endogenous reactivation of the original strain (6). The two causes of recurrence can be separated through molecular genotyping of the *M. tuberculosis* strains, revealing the original genotype at endogenous relapse and a different genotype at exogenous reinfection (2). A recurrent TB incidence rate of 2.26 per 100 person years at risk were reported in a systematic review from 2021, whereof 70% were defined as endogenous relapses based on molecular typing of *M. tuberculosis* strain at both disease episodes. However length of follow-up was found to impact rates of relapse versus reinfection, since relapse is more common in the earlier stages after initial treatment completion while reinfection tends to constitute a majority of later recurrence cases (7). In a systematic review from Qiu et al published in 2022, recurrent disease within 2 years from initial TB onset is associated with endogenous relapse rather than exogenous reinfection (8).

In a systematic review from 2018, Rosser et al. report an overall median percentage of 3.4% recurrent infections among TB patients in low burden countries, with a median follow-up of 7.8 years. An overall median percentage of 81% of recurrent cases were considered endogenous relapses rather than reinfection – in contrast to high incidence settings where exogenous reinfection is considered the most common cause of recurrent TB (2, 5). The domination of endogenous relapse in low-endemic settings is supported by a Finnish cohort study from 2016,

identifying 80% of recurrent TB cases between 1995-2013 as endogenous relapses after paired molecular genotyping by whole genome sequencing (WGS) (9).

Sweden is considered a low incidence setting with 362 reported TB cases in 2023 (10). A regional cohort study including all culture verified TB cases in the Stockholm County area (n=2552) between 1996-2016 showed a percentage of 0.7% cases of recurrent infection. WGS of paired *M. tuberculosis* samples among recurrent cases revealed endogenous relapse in 71% (12/17) of cases, with a median duration between disease episodes of 2.4 years (IQR 1.1-4.7 years) (11).

A variety of risk factors for TB recurrence have been suggested. One systematic review indicates that for example male gender, origin from a high-incidence country and, for pulmonary TB, pre-treatment sputum smear-positivity could be associated with recurrence (including reinfection and relapse) in low-endemic regions (5). A Finnish cohort study from 2017 found no significant difference regarding risk of recurrence between pulmonary and extrapulmonary TB at 1 or 2 years of follow-up, but a significantly higher recurrence risk in pulmonary TB >6 years after initial disease (12). Regarding exogenous reinfection, the risk factors HIV coinfection and Beijing family genotype have been suggested (8). Norrby et al. showed initial mono drug resistance in 33% (4/12) of verified endogenous relapse cases and initial multi drug resistance in 16% (2/12) cases. No case of acquired drug resistance at relapse was found (11). A more recent systematic review published in 2024 conclude that MDR (multi-drug resistance) and the use of fixed-dose combination tablets for TB treatment are significantly associated with TB recurrence (again including both reinfection and relapse). However, significant associations between endogenous relapse and risk factors such as mono-resistant mycobacterial strains or smear positivity at pulmonary TB diagnosis could not be determined due to few studies, lack of reliable data and low level of certainty (13). This highlights the need for further studies on the subject.

Increased knowledge regarding risk factors associated with recurrent TB in general and endogenous TB relapse in particular is essential to identify patients in need of closer monitoring and follow-up to optimize chances of lasting cure. On the other hand, patients without risk factors could potentially be candidates for the new shorter TB treatment regimen mentioned in World Health Organization tuberculosis treatment guidelines from 2022 (14). To our knowledge, the characteristics and potential risk factors of recurrent tuberculosis, particularly due to verified endogenous relapse, in a national Swedish setting have not yet been studied.

Aim

The aims of this study are to assess the incidence of endogenous TB relapse in Sweden over the last 15 years, and to characterize the Swedish endogenous TB relapse cohort based on clinical and microbiological data.

Research questions

1. What was the incidence of recurrent TB infections in Sweden between the years 2009-2024? What proportion of all TB cases experience recurrence? What proportion of recurrent cases and of all cases were culture verified with identical *M. tuberculosis* strains at both disease episodes (considered verified endogenous TB relapse)?
2. Is the proportion of endogenous relapse higher in pulmonary or extrapulmonary TB?
3. What proportion of culture-verified endogenous pulmonary TB relapse cases were sputum smear positive at initial diagnosis?
4. What was the median duration from initial TB diagnosis until endogenous TB relapse?
5. Is the proportion of mono- or multi-drug resistance at initial TB diagnosis higher within the endogenous TB relapse subgroup compared to the subgroup of TB cases without reported recurrence?
6. Is the proportion of endogenous TB relapse higher in the subgroup with drug resistance at initial/only TB diagnosis compared to the subgroup with drug sensitive strain?
7. Are there indications of acquired drug resistance in cases of endogenous relapse with the original *M. tuberculosis* strain?

Methods

Study design & population

This project is designed as a retrospective cohort study. The study will include individual data on all patients reported with recurrent TB (i.e. a person reported with TB at least twice in the Swedish national registry of communicable disease surveillance called SmiNet) in Sweden during 15 years between 2009-2024. The inclusion period was defined with regard to the incompleteness of available SmiNet data reported prior to 2009. Reporting cases of active TB in SmiNet is mandatory according to the Communicable Disease Act, enabling a comprehensive data registry. All culture-verified *M. tuberculosis* isolates in Sweden are sent to the Public Health Agency of Sweden for molecular epidemiological genotyping. Patients with culture positive endogenous TB

relapse verified through molecular genotyping will be included for all analyses. See "Planned data analysis per research question" below for details on inclusion of all recurrent TB cases and group level data of all reported TB cases as denominators for research question no. 1, 2, 5 and 6. Individuals diagnosed with TB and/or initiated on treatment outside Sweden during at least one of the TB episodes will be excluded at baseline due to insufficient available information.

Data collection

Following approval of ethical application, data extraction from the Swedish national registry of communicable disease surveillance (SmiNet) and from the Public Health Agency's separate molecular typing database will be requested. Group level data will be extracted from SmiNet including total number of reported TB cases during study period, total number of pulmonary and extrapulmonary TB cases and total number of TB cases with drug susceptible versus drug resistant *M. tuberculosis* strain. The following demographic individual patient data will be collected: age at primary diagnosis and relapse, biological gender, country of birth, Swedish region of residence at TB diagnosis, suspected route of transmission, suspected country of contagion. Collected disease related data will include the following variables from both disease episodes: date of onset of TB symptoms, date of TB diagnosis, TB disease site(s), infectivity at diagnosis, date of treatment initiation, treatment duration, date of treatment completion, status regarding reported cure at treatment completion. Microbiological data from both disease episodes will include type of diagnostic sample/site of sample collection, status of diagnostic samples regarding culture, PCR and microscopy, resistance pattern and molecular typing of the *M. tuberculosis* strain. Extracted patient data will be pseudonymized using serial numbers.

Data analysis

For data analysis Excel software and IBM SPSS Statistics software will be utilized. Descriptive measures such as proportions and median values with interquartile ranges will be calculated, and statistical tests for binary variables will be performed to compare proportions within subgroups. Data results will be presented in frequency tables as well as in pie and bar charts using softwares Excel and GraphPAD. Since this study does not include any controls, results will be compared to what has been previously described in the literature. Doing so, the low generalizability of our results and the limited reliability of comparison to other differently designed studies will be considered.

Planned data analysis per research question

1. The proportion of recurrent TB will be calculated through dividing the number of recurrent cases by the total number of TB cases during study period. Cases of endogenous TB relapse will be identified through comparison of molecular typing data between disease episodes within the individual patient. The endogenous TB relapse proportion within the group of recurrent TB and the total group of TB cases will be calculated as described above.
2. The proportion of endogenous TB relapse within the pulmonary TB recurrence subgroup and the overall pulmonary TB group respectively will be calculated as described above. The endogenous TB relapse proportions within corresponding extrapulmonary TB denominator groups will be assessed identically. For binary variable comparison of proportions between pulmonary and extrapulmonary subgroups, Fisher's exact test will be used with a significance level of 0.05.
3. The proportion of sputum smear positivity at initial pulmonary TB diagnosis within the endogenous TB relapse group will be calculated as described above.
4. To assess duration from initial TB diagnosis until endogenous relapse, median time between disease episodes will be calculated and reported together with interquartile ranges.
5. The proportion of mono- and multi-drug resistance within the endogenous TB relapse subgroup and within the non-recurrence TB subgroup will be calculated as described above. For comparison of proportions between groups, Fisher's exact test will be used with a significance level of 0.05.
6. The proportion of endogenous TB relapse within the subgroup of drug-susceptible *M. tuberculosis* strain at initial TB diagnosis (denominator including both non-recurrent TB and first disease episode of recurrent TB) will be compared to the proportion of endogenous relapse within the drug-resistant *M. tuberculosis* subgroup (denominator as above) using Fisher's exact test with a significance level of 0.05.
7. Indications of acquired drug-resistance at endogenous relapse will be assessed through comparing the proportion of drug-resistant *M. tuberculosis* strain at initial TB infection to the proportion of drug-resistance at TB relapse, within the culture-verified endogenous relapse subgroup.

Ethical considerations

Ethical application was approved by the Swedish Ethics Review Authority in February 2025 (approval number: 2024-08690-01-724341). Due to recently introduced limitations regarding data

access, an updated ethics application including supplementary information on participating researchers was submitted early April 2025. After ethical clearance and submission of data extraction request, the Public Health Agency of Sweden will transfer group-level data and pseudonymized individual data on patients registered in SmiNet with recurrent. No social security numbers will be extracted or accessible to the participating researchers and no individual medical charts will be studied. The data transfer will be performed in line with the agency's secure data management routines. Following approval by Region Kronoberg security unit personnel, the electronic pseudonymized data file will be stored in a password protected storage media within the secure network of Region Kronoberg. A code key will be kept at the Public Health Agency of Sweden for 6 months. Informed consent will not be obtained since collected patient data do not enable identification of individuals.

Time plan

December 2024: Ethics application submitted
February 2025: Approval of ethics application.
April 2025: Submission of updated ethics application (see "Ethical considerations")
April - May 2025: Estimated approval of updated ethics application
April - May 2025: Extraction of pseudonymized data from Swedish Public Health Agency
May - June 2025: Data analysis
June - July 2025: Project report writing

Financing

The project will be performed in the context of a medical sciences course for residents in Region Kronoberg. Ethical application submission will be funded through research grants of the supervisors.

References

1. World Health Organization. Global tuberculosis report 2023. Geneva; 2023. Contract No.: CC BY-NC-SA 3.0 IGO.
2. Swedish Infectious Medicine Association. National clinical tuberculosis guidelines. 2023.
3. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4):e17601.
4. Alemu A, Bitew ZW, Diriba G, Seid G, Moga S, Abdella S, et al. Poor treatment outcome and associated risk factors among patients with isoniazid mono-resistant tuberculosis: A systematic review and meta-analysis. PLoS One. 2023;18(7):e0286194.
5. Rosser A, Marx FM, Pareek M. Recurrent tuberculosis in the pre-elimination era. Int J Tuberc Lung Dis. 2018;22(2):139-50.
6. World Health Organization . Definitions and reporting framework for tuberculosis 2013 revision, updated December
2014 and January 2020. Geneva: World Health Organization. Available from: https://www.who.int/publications/i/item/9789241505345 .
7. Vega V, Rodriguez S, Van der Stuyft P, Seas C, Otero L. Recurrent TB: a systematic review and meta-analysis of the incidence rates and the proportions of relapses and reinfections. Thorax. 2021;76(5):494-502.
8. Qiu B, Wu Z, Tao B, Li Z, Song H, Tian D, et al. Risk factors for types of recurrent tuberculosis (reactivation versus reinfection): A global systematic review and meta-analysis. Int J Infect Dis. 2022;116:14-20.
9. V. Korhonen PWS, M. Haanperä, N. Casali, P. Ruutu, T. Vasankari and H. Soini. Whole genome analysis of Mycobacterium tuberculosis isolates from recurrent episodes of tuberculosis, Finland, 1995–2013. Clin Mircrobiol Infect. 26 March 2016;2016; 22: 549-554.
10. Public Health Agency of Sweden. Notifiable communicable diseases in Sweden 2023 - epidemiological annual report. 2024 May 8. Contract No.: 24070.
11. Norrby M, Groenheit R, Mansjö M, Zedenius I, Vesterbacka J, Lindquist L, et al. Whole genome sequencing of recurrent tuberculosis in Stockholm County 1996–2016. Journal of Public Health and Emergency. 2020;4:31-.
12. Korhonen V, Soini H, Vasankari T, Ollgren J, Smit PW, Ruutu P. Recurrent tuberculosis in Finland 1995-2013: a clinical and epidemiological cohort study. BMC Infect Dis. 2017;17(1):721.
13. Vega V, Cabrera-Sanchez J, Rodriguez S, Verdonck K, Seas C, Otero L, et al. Risk factors for pulmonary tuberculosis recurrence, relapse and reinfection: a systematic review and meta-analysis. BMJ Open Respir Res. 2024;11(1).
14. World Health Organization. Consolidated guidelines on tuberculosis. Module 4: treatment. . Geneva; 2022.