



## Short report

## Prevalence of IGRA-positivity and risk factors for tuberculosis among injecting drug users in Estonia and Latvia



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## ABSTRACT

**Background:** Illegal drug use and HIV are independent risk factors for tuberculosis (TB) among injecting drug users (IDU). Estonia and Latvia have experienced high rates of TB as well as IDU and HIV outbreaks. There is a lack of knowledge about TB among IDUs in these countries. The purpose of the current study was to estimate the prevalence and risk factors of *Mycobacterium tuberculosis* (MTB) infection among IDUs in Estonia and Latvia.

**Methods:** Participants for this cross-sectional study were recruited from syringe exchange programmes using respondent-driven sampling. For assessing infection with MTB interferon-gamma release assay (IGRA) was used.

**Results:** The study included 375 participants from Estonia and 313 from Latvia. The prevalence of IGRA-positivity among IDUs was 7.7% in Estonia and 25.6% in Latvia. HIV-prevalence was 62% in Estonia and 23% in Latvia. In both countries, IGRA-positivity rates did not differ between HIV-positive and HIV-negative participants. IGRA-positivity was independently associated with a prior diagnosis of TB in Estonia and with imprisonment (ever within a lifetime) and preceding contact with a TB patient in Latvia.

**Conclusion:** Our findings indicate there is an urgent need for a more vigorous approach in providing IDUs with TB screening services.

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## Introduction

The dissemination of HIV among drug users, knowing that HIV is the most potent risk factor for tuberculosis (TB) among adults, makes drug users a critical risk-group to target for TB screening (Hwang, Grimes, Beasley, & Graviss, 2009). Little is known about *Mycobacterium tuberculosis* (MTB) infection and TB among IDU in Eastern Europe where injection drug use has been the main driver of the fastest growing HIV epidemic (European Centre for Disease Prevention & Control/WHO Regional Office for Europe, 2010).

In 2009, Estonia (population 1.3 million) and Latvia (population 2.3 million), both located in North-Eastern Europe, had TB incidence rates of 24/100,000 and 36/100,000, respectively. In 2009, the proportion of TB patients co-infected with HIV was 9.4% in Estonia and

6.9% in Latvia (Rüütel, Trummal, Salekešin & Pervilhac, 2011; State Registry of Tuberculosis Patients, 2011).

Estonia and Latvia also had the highest numbers of newly diagnosed HIV cases per 100,000 population in the European Union (European Centre for Disease Prevention & Control/WHO Regional Office for Europe, 2010). In Estonia, the adult injecting drug use prevalence (among 15–44 year olds) is estimated to be 2.4%; HIV-prevalence rates as high as 70% have been reported among IDUs (Rüütel et al., 2011). In Latvia, the respective percentages are 1.2% (among 15–64 year olds) and 22.6% (The National Health Service, 2011). The overlap of IDU and HIV epidemics, as well as historically high rates of TB, raises a concern that the rates of active TB could increase among this vulnerable population.

Interferon-gamma release assays (IGRA) are relatively new diagnostic tools for TB. They were developed to support the diagnosis of latent TB infection (LTBI). IGRAs are best used in conjunction with an overall risk assessment in order to identify individuals for whom preventative treatment should be considered (European Centre for Disease Prevention, 2011). The purpose of the current study was to

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estimate the prevalence and risk factors of IGRA-positivity (as an indicator of LTBI), amongst current IDUs.

## Materials and methods

### Setting and subject sample

Data collection for this cross-sectional anonymous survey took place in two cities in Estonia: Tallinn (capital city) and Kohtla-Järve (North-Eastern Estonia), and in one city in Latvia: Riga (capital city), in 2007. These regions have the highest rates of HIV and IDU in both countries (Rützel et al., 2011; Infectology Center of Latvia, 2011). Participants were recruited from community-based and government-funded syringe exchange programmes (one site in every city).

Respondent-driven sampling (RDS) was used for the recruitment of IDUs. RDS is a chain referral sampling method designed for the recruitment of hidden populations where the sampling frame is not known; this method reduces bias generally associated with such recruitment (Malekinejad et al., 2008). Individuals were eligible to participate if they were  $\geq 18$  years of age, provided written informed consent and reported injecting drug use in the two months prior to enrollment.

### Study instruments and procedures

- (1) All potential participants were assessed for study eligibility. To ensure IDU-status, the skin of study subjects was checked for injection marks and/or subjects were asked to describe the process of preparing drugs for injection.
- (2) Participants completed an interviewer-administered structured questionnaire, which was modified from multiple questionnaires and included questions on socio-demographics, history of drug use, imprisonment, TB, TB contacts, current symptoms and health complaints, and contacts with the services for TB (Des Jarlais, Perlis, Stimson, Poznyak & WHO Phase II Drug Injection Collaborative Study Group, 2006; Salomon et al., 1999; Wolfe et al., 1995).
- (3) Blood samples were collected for infectious diseases (HIV, TB) seromarkers testing.
- (4) All participants were instructed for peer recruitment and everybody was asked to invite three peers to participate.
- (5) A dual incentive system was used: (i) For study participation; and (ii) for recruiting peers. One incentive comprised a super-market gift voucher with a value of 6.4 EUR in Estonia, and a value of 7.0 EUR (equivalent to 5 LVL) in Latvia.

### Laboratory testing

- (1) Venous blood was tested for the presence of HIV antibodies using: (i) In Estonia – Vironostika HIV Uniform II Ag/Ab (BioMerieux); positive cases were confirmed with INNO LIA HIV I/II Score Westernblot. (ii) In Latvia – Vironostika HIV Uniform II Ag/Ab (BioMerieux) and Genscreen Plus HIV Ag–Ab (BioRad, France); all positive cases were confirmed with the same test systems.
- (2) For assessing infection of *MTB*, QuantiFERON-TB Gold (Cellestis Europe) was used. This technology is based on the measurement of interferon-gamma secreted from stimulated T-cells previously exposed to *MTB* (Cellestis, n.d.).

### Data analysis

Descriptive statistics were used to characterise participants by study site and IGRA test results. Associations between participant

characteristics and IGRA test results were evaluated using either the Wilcoxon rank-sum test or the Fisher exact test, followed by univariate and multivariable logistic regressions. For multivariable logistic regression, IGRA-positivity was adjusted for gender, age, and factors significantly associated in the univariate regression. All analyses were conducted for each country separately. Statistical analyses were performed using STATA 10.0 (StataCorp LP., College Station, TX) and SPSS 17.0.

### Ethical approval

The study was approved by the Tallinn Medical Research Ethics Committee in Estonia and the Ethics Committee of the State Agency of Tuberculosis and Lung Diseases in Riga, Latvia.

## Results

### Participants

A total of 208 participants in Tallinn, 170 in Kohtla-Järve and 335 in Riga were tested with IGRA. The number of indeterminate test results was the following: 1 in Tallinn (HIV-negative), 2 in Kohtla-Järve (both were HIV-positive), and 22 in Riga (11 HIV-positive and 11 HIV-negative). No major differences were observed (data not shown) between background data of participants from Tallinn and Kohtla-Järve, and therefore the data from these two sites in Estonia were analysed and presented together.

The following analysis includes only those 375 respondents from Estonia (207 from Tallinn and 168 from Kohtla-Järve), and 313 from Riga, Latvia, whose IGRA test results were either positive or negative.

### Participant characteristics

A total of 85% of the participants in Estonia and 72% in Latvia were male. The median age of participants in Estonia was 26 years (range 18–54 years) and median duration of injecting drug use was 8 years (range 0–30 years). The median age of participants in Latvia was 28 years (range 18–55 years) and median duration of injecting drug use was 8 years (range 0–38 years). In Estonia, 52.8% of participants and 47.9% in Latvia reported having been in prison at least once.

### Tuberculosis and HIV

In Estonia, 21.8% of participants and in Latvia, 39.6% reported they had, at some point, lived, worked or studied with somebody who had TB, with 1.9% of participants in Estonia and 8.6% in Latvia having had TB themselves. The proportion of participants that reported symptoms related to TB (i.e. cough for more than 2 weeks and/or blood in sputum), was 10.9% in Estonia and 41.5% in Latvia. In Estonia 61.5% ( $n = 230$ ) and in Latvia 23.0% ( $n = 72$ ) were tested positive for HIV during the study.

The percentage of participants testing positive IGRA was 7.7% in Estonia and 25.6% in Latvia. Percentage positive for both IGRA and HIV was 4.0% in Estonia and 5.1% in Latvia. In Estonia, the prevalence of IGRA-positivity among HIV-positive participants was 9.0% and among HIV-negative participants, 6.5% ( $p = 0.4$ ). In Latvia, the prevalence of IGRA-positivity among HIV-positive respondents was 22.2% and among HIV-negative, 26.6% ( $p = 0.2$ ).

### Correlates of IGRA-positivity

Univariate analysis identified several factors associated with IGRA-positivity in both countries (Table 1). Multivariable logistic regression analysis showed that in Estonia, IGRA-positivity was

**Table 1**  
Univariate analysis of factors associated with IGRA-positivity among injecting drug users in Estonia and Latvia, 2007.

Characteristic	Estonia				Latvia			
	Total N=375	IGRA– N=346 n (%)	IGRA+ N=28 n (%)	Odds ratio (95% CI)	Total N=313	IGRA– N=233 n (%)	IGRA+ N=80 n (%)	Odds ratio (95% CI)
Gender								
Male	317	292 (92.1)	25 (7.9)	1.00	226 (72.2)	163 (72.1)	63 (27.9)	1.00
Female	57	54 (94.7)	3 (5.3)	0.65 (0.19–2.22)	87 (27.8)	70 (80.5)	17 (19.5)	0.63 (0.34–1.15)
Age								
≤Median age <sup>a</sup>	197	185 (94.4)	11 (5.6)	1.00	165 (52.7)	131 (79.4)	34 (20.6)	1.00
>Median age	178	160 (89.9)	18 (10.1)	1.9 (0.87–4.15)	148 (47.3)	102 (68.9)	46 (31.1)	1.74 (1.04–2.90)
Duration of IDU								
≤Median duration <sup>b</sup>	212	194 (91.5)	18 (8.5)	1.00	164 (52.4)	128 (78.0)	36 (22.0)	1.00
>Median duration	163	152 (93.3)	11 (6.8)	0.78 (0.36–1.70)	149 (47.6)	105 (70.5)	44 (29.5)	1.49 (0.89–2.48)
Imprisonment								
No	177	167 (94.4)	10 (5.6)	1.00	163 (52.1)	136 (83.4)	27 (16.6)	1.00
Yes	198	179 (90.4)	19 (7.7)	1.77 (0.80–3.92)	150 (47.9)	97 (64.7)	53 (35.3)	2.75 (1.62–4.68)
Contact with TB patient								
No	262	243 (92.8)	19 (7.2)	1.00	189 (60.4)	154 (81.5)	35 (18.5)	1.00
Yes	73	66 (90.4)	7 (9.6)	1.36 (0.55–3.64)	124 (39.6)	79 (63.7)	45 (36.3)	2.51 (1.49–4.21)
TB ever								
No	368	342 (92.9)	26 (7.1)	1.00	286 (91.4)	222 (77.6)	64 (22.4)	1.00
Yes	7	4 (57.1)	3 (42.9)	9.87 (2.10–46.44)	27 (8.6)	11 (40.7)	16 (59.3)	5.05 (2.23–11.42)
TB symptoms <sup>c</sup>								
No	334	309 (92.5)	25 (7.5)	1.00	183 (58.5)	139 (76.0)	44 (24.0)	1.00
Yes	41	37 (90.2)	4 (9.8)	1.34 (0.44–4.05)	130 (41.5)	94 (72.3)	36 (27.7)	1.21 (0.73–2.02)
HIV-infection								
Neg	144	131 (91.0)	13 (9.0)	1.00	241 (77.0)	177 (73.4)	64 (26.6)	1.00
Pos	230	215 (93.5)	15 (6.5)	0.70 (0.32–1.52)	72 (23.0)	56 (77.8)	16 (22.2)	0.79 (0.42–1.48)

<sup>a</sup> Median age: 26 years in Estonia; 28 years in Latvia.

<sup>b</sup> Median duration of injecting drug use: 8 years in both countries.

<sup>c</sup> Having cough more than 2 weeks, and/or blood in sputum.

independently associated with TB history (AOR 8.98 (1.87–43.21)) and in Latvia, with imprisonment (AOR 2.00 (1.09–3.64)) and contact with a TB patient (AOR 1.93 (1.11–3.36)).

## Discussion

To the best of our knowledge, this is the first study from Eastern Europe to report the prevalence of MTB infection among IDUs. Our results were based on IGRA testing, and although there is no standard procedure for detecting LTBI, studies have consistently reported that IGRAs are highly sensitive and specific for detecting TB infection (Menzies, Pai & Comstock, 2007) and feasible and acceptable for use among IDUs under routine programmatic conditions (Dewan et al., 2006).

In the present study, the prevalence of IGRA-positivity among IDUs was 7.7% in Estonia and 25.6% in Latvia. Unfortunately, there are no data available from either country to compare these results to other population groups (i.e. general population). With regard to HIV infection, there were no differences in the prevalence of IGRA-positivity among HIV-infected and uninfected individuals.

In Estonia, IGRA-positivity has been independently associated with TB diagnosis in the past. In Latvia, the factors independently associated with IGRA-positivity were imprisonment and previous contact with a TB patient. Historically, in both countries, TB rates in prisons have been high (Rützel et al., 2011; State Registry of Tuberculosis Patients, 2011). In Estonia, TB control in prisons has improved in the last decade; TB screening (via X-ray) is mandatory upon imprisonment; the absolute number of TB cases diagnosed in prisons has decreased alongside an increase in the proportion of cases diagnosed upon entry. Therefore, it can be assumed that there are fewer undiagnosed and infectious TB cases in prisons in Estonia (Rützel et al., 2011). Even though the number of TB cases diagnosed

in prisons in Latvia has also decreased in the last decade, more than half of those cases are detected during imprisonment. This may be due to the limited TB screening available in the Latvian penitentiary system – in most prisons, X-ray equipment is not accessible, while screening on admission relies on questionnaires and complaints, which are not the most sensitive of testing methods (Zellweger, 2006). These differences in TB control may partly explain why IGRA-positivity was associated with imprisonment in Latvia but not in Estonia.

## Limitations

The cross-sectional design of our study does not allow us to draw temporal inferences between MTB infection and the risk factors we examined. Although the study used RDS to enroll participants, the recruitment was conducted in government-funded syringe exchange programmes and therefore our results may not be generalisable of all IDUs in the region. The small sample size may further decrease the precision of estimates. In Estonia, data collection took place in spring; in Latvia in the fall and early winter; thus, the prevalence of health complaints may have been influenced by the different seasons. Information obtained about TB contacts may be prone to recall bias. Moreover, we were not able to confirm whether any of the participants who were IGRA-positive had active TB.

An increase in TB prevalence among relatively young individuals, such as IDUs, who often have active social lives may have serious individual health and public health consequences and may lead to the spread of TB infection. Therefore, those having or who are at risk of having HIV infection should be closely monitored for TB even in countries where TB prevalence is low (Van Deutekom et al., 1993). Despite the high rates of HIV, TB and IDU in both countries,

there has not yet been a major overlap between these three groups. However, the findings from our study indicate there is an urgent need for a more vigorous approach to providing TB screening services for IDUs. Syringe exchange programmes can be strategic partners in reaching this vulnerable and socially marginalised group.

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### Conflict of interest

None.

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