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Tuberculosis in people of Ukrainian origin in the European Union and the European Economic Area in 2019-2022

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- Aus der Sektion Medizin-

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Abbreviations

ANOVA – analysis of variance

BCG – Bacillus Calmette–Guérin

CI 95% - 95 % confidence interval

COB – country of birth

COVID-19 – coronavirus disease 2019

CTZ – citizenship

ECDC – European Centre for Disease Prevention and Control; ECDC

EEA – European Economic Area

EU – European Union

Eurostat – Statistical Office of the European Union

DR-TB – drug-resistant tuberculosis

DS-TB – drug-sensitive tuberculosis

DST – drug susceptibility testing

LTBI – latent tuberculosis infection

Mtb – *Mycobacterium tuberculosis*

NAAT – nucleic acid amplification test

RR- / MDR-TB – rifampicin-resistant/ multidrug-resistant tuberculosis

SARS-CoV-2 – severe acute respiratory syndrome coronavirus type 2

TB – tuberculosis

TESSy – The European Surveillance System

(pre-) XDR-TB – (pre-) extensively drug-resistant tuberculosis

UK – United Kingdom of Great Britain and Northern Ireland

UNHCR – United Nations High Commissioner for Refugees

WHO – World Health Organization

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1. Introduction

1.1 Tuberculosis - general terms and global trends

Tuberculosis (TB) is an infectious disease caused by pathogens of the *Mycobacterium tuberculosis* (*Mtb*) complex. The standard route of transmission is via the inhalation of infectious aerosols (1). Therefore, the most common manifestation site is pulmonary; however, other organ systems can also be affected (2). After contact with the pathogen, a small proportion of those exposed develop active disease. Others contain the infection but remain hosts of viable bacteria and may develop active disease at a later stage and are therefore considered latently infected (LTBI). In the majority of those exposed, active disease does not occur (3 – 7). The risk of transmission, infection and progression to active disease is strongly influenced by environmental and host factors. Socio-demographic determinants such as living and working conditions, access to healthcare, social support systems and financial security play a decisive role. Marginalized population groups are often disproportionately affected by TB (8 – 10).

In 2014, the decision-making body of the World Health Organization (WHO) adopted a set of goals summarized under the title "End TB strategy", with the aim of lowering the global TB burden (11, 12). One year later, in alignment with the End TB milestones, the United Nations included the target to contain the TB epidemic by 2030 in the Sustainable Development Goals (13). In the following years, TB notification rates across the European Union and the European Economic Area (EU/EEA) gradually declined as programmatically foreseen. However, with the spread of SARS-CoV-2 in the region and the extensive challenges that healthcare services were confronted with at the start of the coronavirus pandemic, TB notification rates decreased disproportionately in 2020 (**Figure 1**) (14). This trend suggests a significant increase of the diagnostic gap, which jeopardizes the achievements of the End TB strategy with regard to case finding and the initiation of treatment (15).

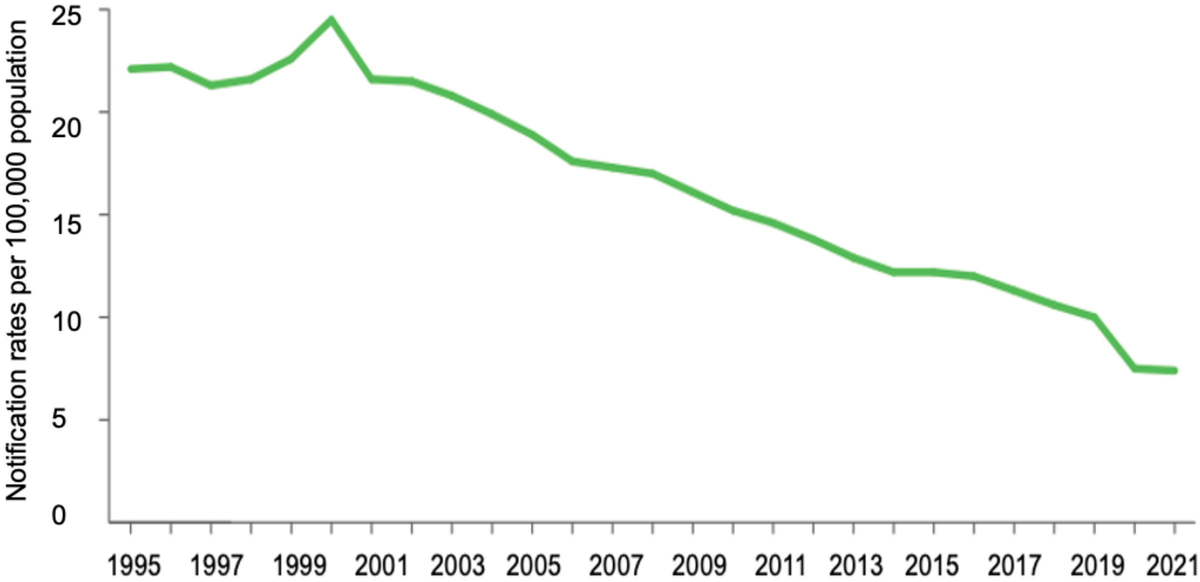

Figure 1: Tuberculosis notification rates per 100,000 population in the EU/EEA, 1995 - 2021.

Source: Tuberculosis surveillance report 2023, Figure 3.2.1 (14). Adopted according to CC BY-4.0.

Currently, on a global scale, TB is the infection with the second-highest mortality rate from a single pathogen after SARS-CoV-2. It is estimated that 10.6 million people worldwide developed TB in 2022 (16).

1.2 Tuberculosis treatment and drug-resistance

The standard therapy for TB consists of an intensive two-month course of combination treatment comprising the drugs rifampicin, isoniazid, ethambutol and pyrazinamide, followed by a continuation treatment with rifampicin and isoniazid for four additional months (17).

TB infections caused by *M. tuberculosis* strains resistant to the first-line therapeutics rifampicin (RR-TB) or rifampicin and isoniazid (multidrug-resistant; MDR-TB) affected an estimated total of 410,000 people worldwide in 2022. The number of MDR/RR-TB cases correctly diagnosed and accordingly treated was only 171,650 in the same year. This number corresponds to about 43% of the estimated number of affected cases. Closing this gap through universal coverage of drug-susceptibility testing and increased availability of second-line drugs is one of the progress indicators within the End TB strategy (16, 18).

MDR/RR-TB strains of *M. tuberculosis* that exhibit additional resistance to second-line drugs from the fluoroquinolone group (levofloxacin or moxifloxacin) are referred to as pre-XDR-TB (pre-extensively drug-resistant). *M. tuberculosis* bacteria that are also resistant to another therapeutic agent from the second-line drugs in group "A" (bedaquiline and linezolid) are referred to as XDR-TB (extensively drug-resistant) pathogens (19).

Despite new diagnostic and therapeutic options offering quicker detection of mutations associated with resistance and all-oral treatment regimens, antibiotic resistance continues to be a challenge in the care of TB patients worldwide (20, 21). Especially affected are a number of countries in the WHO European Region, including Ukraine and the Russian Federation (16).

1.3 Tuberculosis in the European Union and the European Economic Area in the context of migration

The differences in notification rates among individual member states of the European Union (EU) and the European Economic Area (EEA) are considerable, ranging from 48.7 TB cases per 100,000 population in Romania to 2.5 per 100,000 in Liechtenstein. However, the total EU/EEA TB notification rate of 8 cases per 100,000 population is low in global comparison and only two countries in the region – Romania and Lithuania – reported more than 20 TB cases per 100,000 population in 2022 (30).

Among EU/EEA countries with incidence of less than 20 TB cases per 100, 000 population, native cases (i.e., cases in patients born in the respective country) are rare due to the low risk of exposure and transmission. Therefore, patients with a migratory background arriving in a low-incidence setting from countries with a higher TB disease burden represent the majority of cases in TB statistics (**Figure *2***) (22–

25). Transmission from foreign-born index cases to the native population is uncommon and does not play a significant role in the EU/EEA TB epidemiology (26).

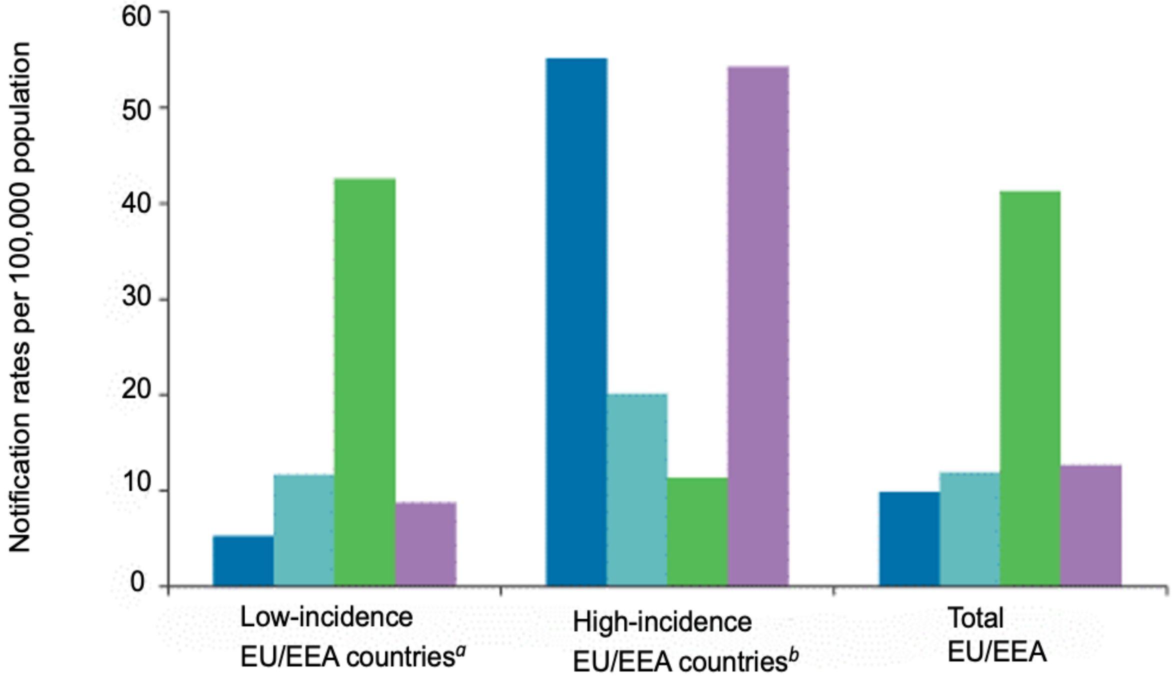

Figure 2: Tuberculosis cases per 100,000 population according to origin. EU/EEA, 2003 – 2017.

Dark blue: native TB cases; light blue: other EU/EEA origin; green: non-EU/EEA origin; purple: total.

[a] Countries with TB incidence of <20 cases per 100 000 population.

[b] Countries with TB incidence of ≥20 cases per 100 000 population.

Source: Hollo et al., 2016 (22). Adapted according to CC BY-4.0.

Limited access to healthcare services, language barriers, housing insecurity, stigmatization, loss of earnings during treatment and a lack of social and financial support are aggravating factors in the efforts to reduce the TB burden among people with migratory background. Addressing these issues as part of a multifaceted, sociomedical, patient-centred approach is an important step towards further pursuit of the End TB targets in the EU/EEA (27 - 29).

1.4 Tuberculosis in Ukraine

In Ukraine, the notification rate was successfully reduced from over 100 cases per 100,000 population to 64.6 / 100,000 in the period from 2012 to 2019. In 2020, a substantial drop to 44.5/ 100,000 was reported with the onset of the COVID-19 pandemic, followed by a discrete increase to 45.5 and 49.3/ 100,000 in 2021 and 2022, respectively (**Figure *3***) (30).

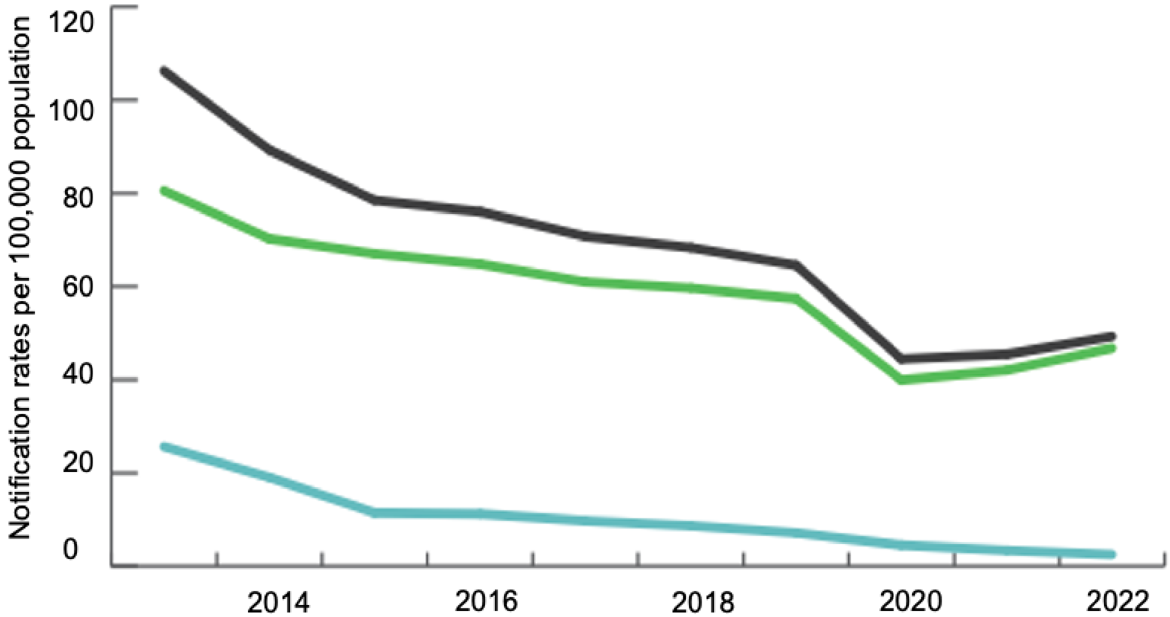

Figure 3: Tuberculosis notification rate per 100,000 population in Ukraine, total and stratified by previous treatment history, 2012 – 2022.

Black line: total; green line: new and relapse cases; blue line: other cases;

Source: Tuberculosis surveillance report 2024 (30). Adapted according to CC BY-4.0.

This level continues to be more than six times higher than the total EU/EEA notification rates observed in recent years. Further, this discrepancy is more pronounced in the case of the estimated incidence rates, which, in 2022, were 90/ 100,000 population in Ukraine and 8.6/ 100,000 in the EU/EEA (30).

Of particular concern is the high proportion of infections caused by MDR/RR-TB strains in the country. Due to the alarming levels of drug-resistance, Ukraine has been classified by the WHO as a high priority country in this regard (16). In 2022, the proportion of RR-TB cases in Ukraine amounted to 28.3% (n = 3647) of all bacteriologically confirmed pulmonary TB cases with drug susceptibility results. In the EU/EEA, this proportion was only 5.0% (n = 933) (30).

1.5 Tuberculosis in the context of the Russia – Ukraine war

After the Russian invasion of Ukraine in February 2022, millions of Ukrainians were displaced both internally and externally. By the end of the same year, over four million had been granted temporary protection status in EU/EEA countries, according to data from the Statistical Office of the European Union (Eurostat) (**Figure 4**) (31). As a result, the size of the Ukrainian population in the region increased significantly.

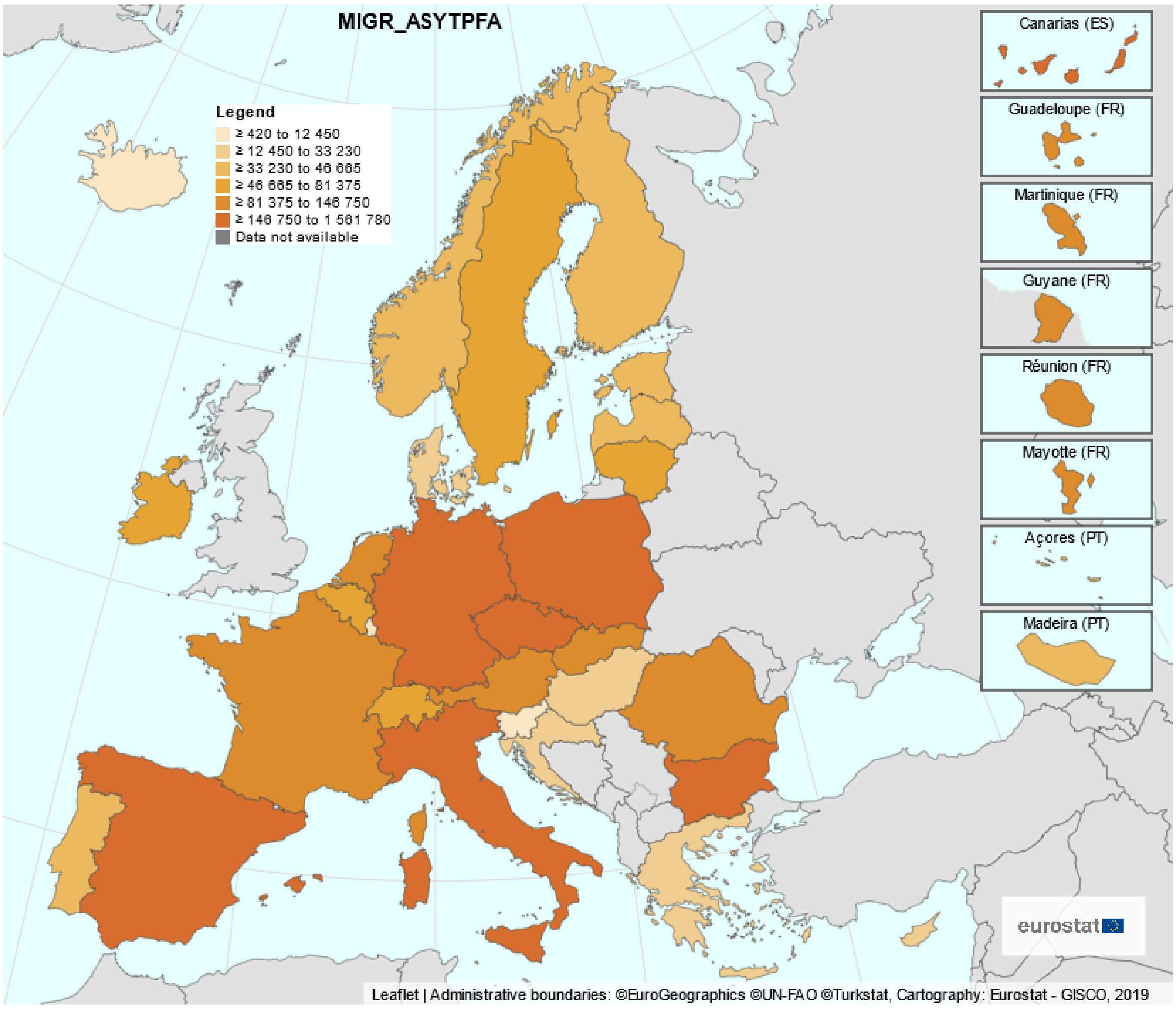

Figure 4: Number of approved temporary protection status applications in people holding Ukrainian citizenship as of 31.12.2022.

Source: Eurostat, MIGR_ASYTPFA (31). Cited under CC BY-NC-SA 3.0 IGO

The European Centre for Disease Prevention and Control (ECDC) and the WHO refrained from recommending general TB screening in Ukrainians fleeing the conflict. Mandatory TB screening is generally recommended for migrants and asylum seekers arriving from countries with notification rates over 100 notified TB cases per 100,000 population. Furthermore, long migratory journeys are associated with higher TB rates due to additional exposure risks along the route (32, 33). Since these factors do not apply to the Ukrainians seeking refuge after the start of the conflict, screening programs for the general Ukrainian population were expected to results in a low TB yield. The ECDC recommendations for screening were therefore limited to specific high-risk groups (34). In various EU/EEA countries, screening measures were implemented to different extents (35). The legal basis for access to medical care is provided for Ukrainian refugees under the temporary protection plan (36). However, Ukrainians can enter many EU/EEA countries without visa and data on undocumented migrants from Ukraine, both pre-war as well as after the start of the armed conflict, are scarce. Therefore, many are likely to not have profited from the temporary protection status (37).

1.6 Research objective

The goal of this study is to assess the TB burden among Ukrainians in the European Union and the European Economic Area. The study period covers four years, from 2019 to 2022, with the aim of evaluating the impact of the first year of the Russia – Ukraine war on the TB epidemiology among Ukrainians (defined as people born in Ukraine or holding a Ukrainian citizenship) in the region, while also considering the influence of the coronavirus pandemic.

Specifically, the following parameters will be evaluated within the defined timeframe:

- The absolute numbers of notified TB cases in the EU/EEA.
- The notification rates per 100,000 Ukrainian population.
- The demographic, clinical and microbiological characteristics of TB cases in Ukrainians in the EU/EAA.

Assessing the burden of disease in this population is an important step in developing evidence-based TB prevention, care and control measures tailored to the needs of this migrant population. Ultimately, this information should help guide public health practitioners and clinicians in their decision-making process and improve care for the affected population group. Additionally, evaluating the disease dynamics in the context of crises could help strengthen emergency preparedness structures in the region.

2. Materials and methods

2.1 Surveillance Data

Tuberculosis is a notifiable disease in Ukraine as well as in the EU/EEA member states. Public health authorities are notified in the event of laboratory detection or clinically justified suspicion. Tuberculosis notification data from the EU/EEA countries are submitted to the European Centre for Disease Prevention and Control (ECDC) and entered into The European Surveillance System (TESSy), where they are classified according to various demographic, clinical and microbiological criteria (30). This information is used to monitor epidemiological developments in the region. The EU/EEA countries transmit their data either at the case-specific level or as aggregated data. This enables targeted filtering according to variables of particular interest. The TESSy database thus allows for a detailed cross-national analysis of TB epidemiology.

2.2 Study countries

Surveillance data from the following countries were obtained:

- All member states of the European Union (EU):
  Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden.
- The three additional member states of the European Economic Area (EEA):
  Iceland, Liechtenstein, Norway.

Data from Liechtenstein for 2019 were not transferred to TESSy. Additionally, the TB surveillance data from Latvia for 2019 and 2020 were not transmitted to TESSy due to a technical malfunction and were obtained directly through the Latvian Ministry of Health for this study.

The analysis was performed on the 30 EU/ EEA countries listed above.

Data from the United Kingdom of Great Britain and Northern Ireland (UK) were not included due to its withdrawal from the EU/EEA in 2020.

2.3 Surveillance dataset parameters

The dataset included information on demographic, anamnestic, microbiological and clinical variables for all TB cases reported in the EU/EEA region.

All notified cases were included, encompassing new and relapse TB cases (incident cases) as well as other cases with a previous TB history that do not meet the relapse criteria. Cases were further categorized by their geographical origin as Ukrainian, EU/EEA native, non-EU/EEA and non-Ukrainian cases or unknown. The origin of a case is recorded based on the citizenship (CTZ) or the country of birth (COB) of the affected patient. The reporting country determines which of the two options is used to report cases in national and supranational surveillance platforms (e.g., TESSy) (30). As the definition of origin is not uniform across the study countries, the dataset included both cases in Ukrainian citizens and cases involving people born in Ukraine but potentially holding different citizenship. Where available, the time of entry into the reporting EU/EEA country was also provided. Additional demographic information included the sex and age group of TB cases.

The site of disease was documented as pulmonary or extrapulmonary. Pulmonary cases can affect the lungs and, simultaneously, other organ systems (e.g., miliary disease). Cases with pleural or mediastinal lymph-node presentation are classified as extrapulmonary in the absence of parenchymal lung involvement. Other common extrapulmonary manifestation sites include the gastrointestinal, skeletal and genitourinary systems (38).

Furthermore, cases were categorized according to their previous TB history, discriminating between new cases and those with previously diagnosed and treated TB. For cases with a previous TB history, no further differentiation between relapse cases (i.e., those with a recurrent episode after a successful first treatment) and other pre-treated cases was possible. The dataset also included information on HIV co-infection status, where available.

Laboratory confirmation is required to ensure correct diagnosis and treatment and allows for drug resistance testing and appropriate treatment. Confirmation status was reported according to the 2018 European Commission criteria for the classification of TB cases as possible, probable or confirmed. Possible cases are reported based on clinical criteria and pathogen identification is not available. Confirmed cases require the isolation of a pathogen of the *M. tuberculosis* complex (excluding *Mycobacterium bovis,* BCG) from a clinical specimen or, alternatively, the detection of *M. tuberculosis* on nucleic acid amplification test (NAAT) in combination with positive microscopy. Probable cases are identified based on clinical criteria and either positive NAAT or positive microscopy (39). Regarding the microbiological parameters, information on the availability and the extent of the drug susceptibility testing (DST) was included (DST performed – yes or no; DST for rifampicin only – yes or no). Resistance status was pre-categorized as RR, MDR, pre-XDR or XDR. Cases are reported once in their highest grade of resistance; for example, cases with resistance to both rifampicin and isoniazid were reported only once as MDR-TB cases, rather than being coded twice as RR and MDR cases. The same logic was applied to (pre-) XDR-TB cases. (Pre-) XDR-TB cases for the entire study period were coded according to the updated WHO definitions from 2021 (19). Data on susceptibility status of single drugs were not available except for rifampicin. Drug-resistant (DR)-TB refers to cases resistant to any drug or combination of drugs.

Treatment outcomes were reported as successful, failed, defaulted (lost to follow-up), fatal, still on treatment and unknown or transferred (not evaluated). Final data on outcomes are available with a delay of one year for drug-susceptible (DS) cases and two years for DR cases. Therefore, the most recent information on outcomes in this dataset was available for 2021 or 2020, depending on the susceptibility status.

The case information for this study was exported exclusively in the form of aggregated data. Potentially identifiable personal information was not included.

2.4 Population statistics

To calculate the notification rate of TB among Ukrainians in the countries of the EU/EEA, the total number of Ukrainians in each country during the specified period is required in addition to the number of cases per country.

The notification rate, standardized per 100,000 Ukrainian migrant population, was calculated as follows:

$$notification\ rate = \frac{number\ of\ notified\ cases\ (n)}{population\ size}\ x\ 100,000$$

National statistical institutes and the Statistical Office of the European Union (Eurostat) were identified as possible sources for obtaining foreign population data for the 30 EU/EEA countries. Due to the better availability of datasets classified by citizenship, population statistics on Ukrainian citizens were used in the denominator of the formula above for the primary analysis, instead of data classified by country of birth. Where information was available from both Eurostat and national statistical services, the Eurostat datasets were preferred. These are largely uniform for the EU/EEA countries and offer the advantage of improved comparability between countries and individual years, as they are subject to similar regulations.

The following Eurostat datasets were used in this study:

- MIGR_POP1CTZ - the migrant population with usual residence in the reporting country (by citizenship as of January 1st for the same year) (40).

In cases where this dataset was incomplete (Greece 2019-2022, France 2022, Croatia 2019-2022, Cyprus 2019-2022, Malta 2019-2022 and Poland 2019-2022), the data were retrieved from the following dataset:

- MIGR_RESVALID or MIGR_RESVAS - valid residence permit holders (by citizenship as of December 31st for the following year) (41).

In one case, data were obtained from a national register (Estonia, 2021) (42).

For 2022, in addition to one of the datasets listed above, the following dataset was added:

- MIGR_ASYTPFA - Ukrainian citizens with temporary protection status as of December 31st 2022 (31).

Furthermore, in countries where TB cases are reported based on the country of birth of affected patients, population datasets categorised by country of birth were compiled, if available (40), to explore the potential influence of this factor on the calculated notification rates. However, data by country of birth were largely missing for 2022, as the information on temporary protection is collected based on citizenship only (31).

2.5 Ethics

This analysis relies strictly on anonymized, retrospective data acquired through routine surveillance. Additionally, the project was reported to the Ethics Committee of the University of Lübeck and approved on August 15, 2023. It is registered under the number 2023-593.

2.6 Data analysis and visualization

Descriptive analysis was carried out using commercially available statistical software (StataCorp LLC, Version 18).

Absolute numbers, proportions and rates are reported by year, country, origin, resistance profile, HIV status and other clinical or microbiological parameters and stratified by age and gender, where feasible. Significance testing of differences between time points or groups was performed using either the analysis of variance test (ANOVA), negative binomial regression or chi^2 test. Sensitivity testing for the calculated rates was performed in a population defined by citizenship versus country of birth. Data visualization was carried out using Stata LLC, the ECDC MAp Maker tool (EMMa), Excel and Canva Inc.

3. Results

3.1. Population size

In 2019, 2020 and 2021, there were approximately 1.2 million, 1.3 million, and 1.2 million Ukrainian citizens residing in the EU/EEA, respectively. By the end of 2022, this number surged to a total of 5.8 million.

Ten EU/EEA countries – Austria, Bulgaria, Czechia, Germany, Italy, Netherlands, Poland, Spain, Slovakia and Romania – recorded a Ukrainian population of over 100,000 citizens in 2022. A summary of the population size per country can be found in the appendix (8.1 Population data).

- Stratification by age and sex

The male-to-female ratio among Ukrainian citizens in the region was balanced from 2019 to 2021, with values of 0.9, 0.8 and 0.9, respectively, indicating a larger female subpopulation. In 2022, the proportion of females in the population further increased, leading to a decline of the male-to-female ratio to 0.6. Stratification by sex was partially unavailable for France, Hungary, Ireland and Malta.

Due to inconsistencies in the age grouping of the individual population datasets, age stratification was performed in 3 groups: 14 years or younger, 15 to 64, and 65 years of age or older. The highest population growth in 2022 was recorded in the female group aged 15 to 64, followed by the male population in the same age group. In 2022, over a million Ukrainian citizens in the region were under 15 years of age. The smallest proportion of the population consisted of males aged 65 years or older (**Figure 5**).

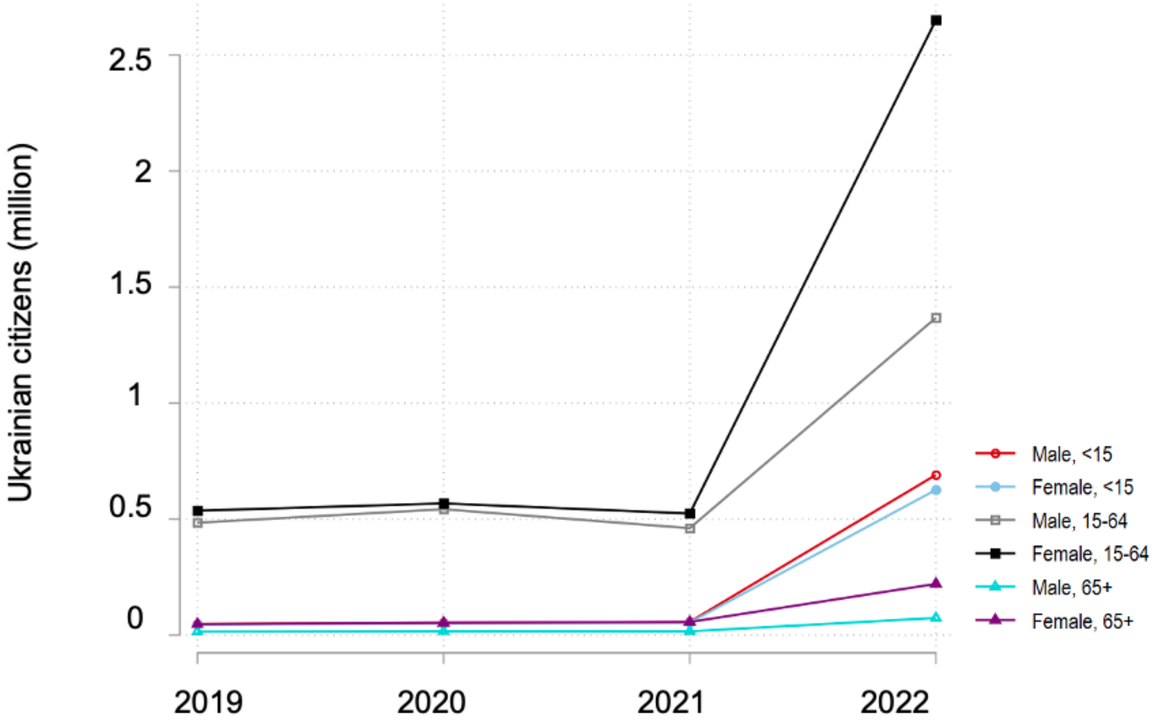

Figure 5: Stratification of the Ukrainian population in the EU/EEA by age and sex, 2019 – 2022.

Population data by citizenship (31, 40 – 42).

3.2 Absolute case numbers

Of the 30 EU/EEA countries included in the analysis, 27 reported at least one case of TB in a patient of Ukrainian origin during the four-year study period. Zero cases of Ukrainian origin were reported from Bulgaria, Croatia or Liechtenstein. In total, this resulted in 1,382 notified TB cases in the region. More than half of these cases were reported in 2022 (n = 780). In the previous three years, the absolute numbers of notified TB cases were as follows – 2019: n = 235, 2020: n = 164; 2021: n = 203 (mean 2019-2021 n = 201, CI 95 %: 112 – 289). Differences in the crude numbers were significant between the years when weighted according to the population size (**Table 1**).

Table 1: Notified TB cases of Ukrainian origin and change (%) between years, EU/EEA 2019 – 2022.

	Ukrainian citizens, EU/EEA	Ukrainian cases, EU/EEA	% change to the previous year	p-value [a]
2019	1,199,185	235	-	-
2020	1,306,104	164	-30.2	< 0.0001
2021	1,192,058	203	+23.8	0.0036
2022	5,818,113	780	+284.2	< 0.0001

[a] p-values were obtained with a chi^2 statistic for trend in proportion.

Population data by citizenship (31, 40 – 42).

Furthermore, the number of EU/EEA countries reporting 5 or more cases almost doubled in 2022 (n = 18, 60.0%) compared to the baseline value of 10 countries (33.3%) in 2019.

Three countries – Czechia, Germany and Poland – contributed the highest absolute number of notified cases and combined accounted for 56.6% (n = 133), 68.9% (n = 113), 64.0% (n = 130) and 71.3% (n = 556) of all Ukrainian cases in the EU/EEA (**Figure 6**).

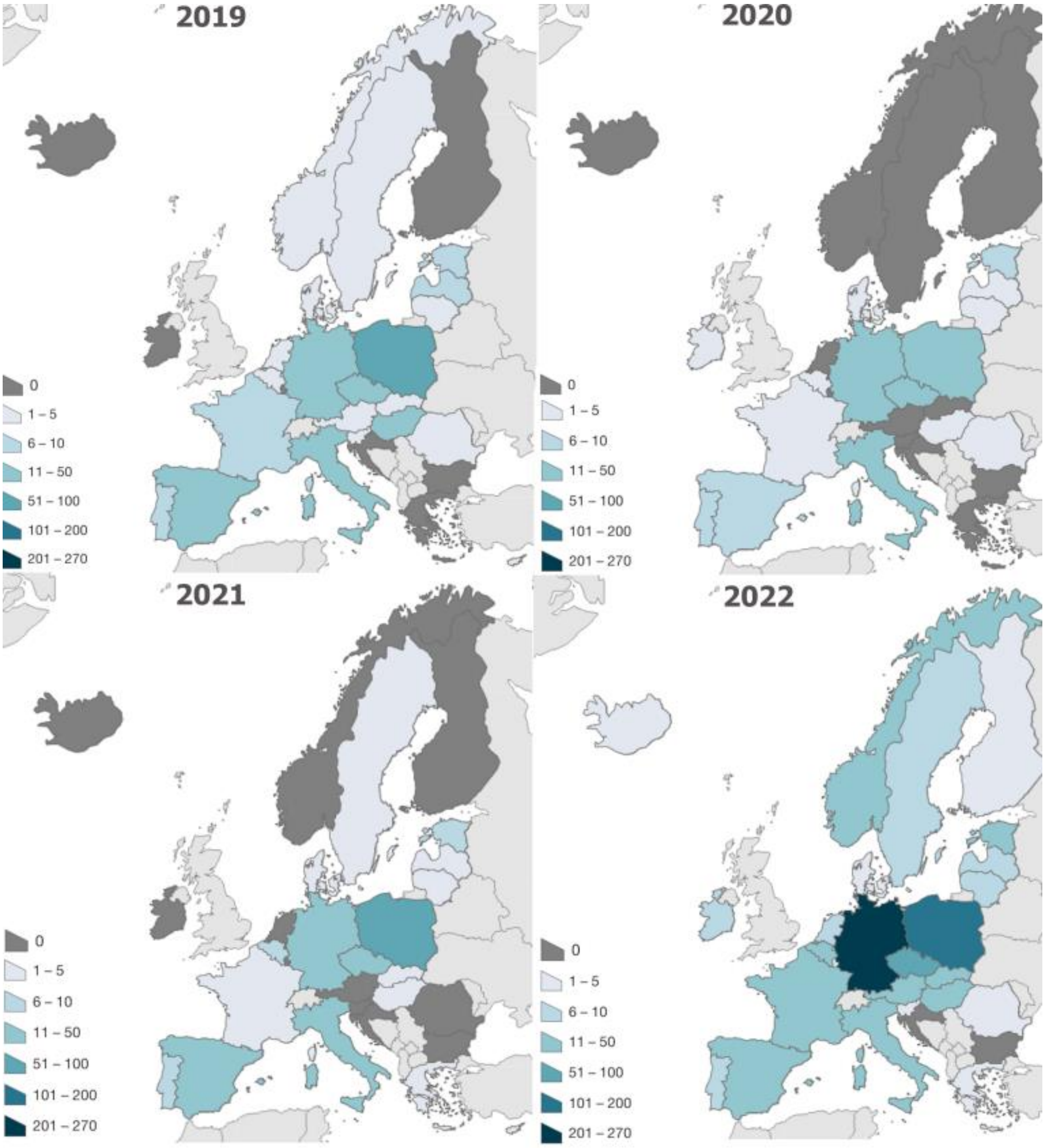

Figure 6: Notified TB cases (n) in Ukrainians in the EU/EEA, 2019-2022. Countries displayed in light grey are not EU/EEA member states as of January 2024. Source: Stoycheva et al., 2024 (43). Adapted according to CC BY-4.0.

In 2022, the highest number of cases was reported in Germany, with 270 cases of Ukrainian origin, corresponding to an almost ten-fold increase to the mean value of the previous three years (mean n = 33; CI 95%: 17.3 – 49.3).

Data completeness regarding the year of entry of the patient into the respective EU/EEA reporting country was overall low. The time of entry was available in 18.3%

(n = 43), 15.2% (n = 25), 12.3% (n = 36) and 16.2% (n = 126) of the cases. When provided, the year of relocation of the affected TB patient to the reporting EU/EAA country and the year of TB diagnosis overlapped in 34.9% (n = 15), 24.0% (n = 6), 22.2% (n = 8) and 69.8% (n = 88) of the cases in 2019 – 2022.

Compared to all cases notified in the EU/EEA, the cases of Ukrainian origin remained a rather small proportion of 2.2% (n = 780) in 2022. However, this was an almost four-fold increase compared to the previous years (2019: 0.51%, 2020: 0.48% and 2021: 0.60% of all cases notified in the EU/EEA) (**Figure 7**).

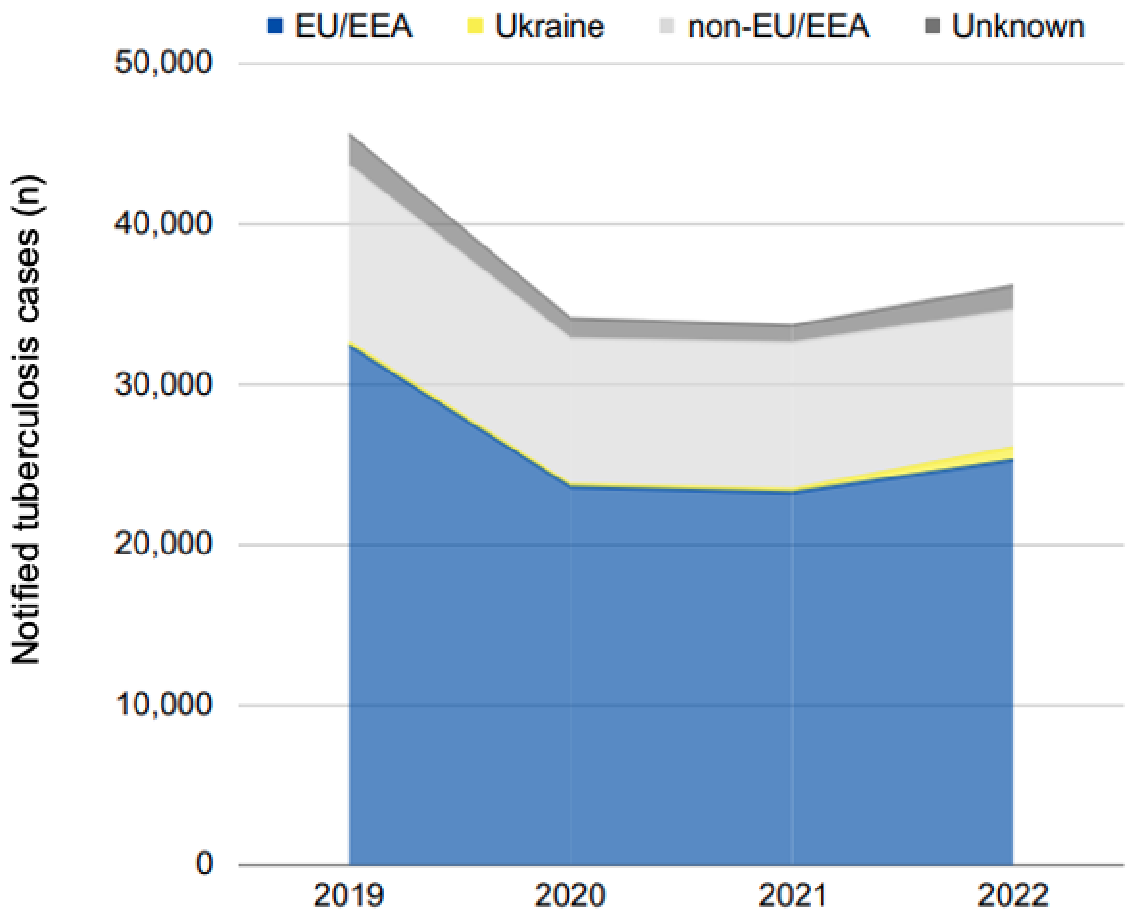

Figure 7: Distribution of origin among notified TB cases (n) in the EU/EEA per year, 2019 – 2022.

Source: Stoycheva et al., 2024 (43). Adapted according to CC BY-4.0.

- Stratification by age and sex

Overall, cases were predominantly male, with a male-to-female ratio of 2.0, 1.5, 2.5, and 1.4 between 2019 and 2022. This sex distribution of the notified cases among

Ukrainians in the EU/EEA resembled the distribution in Ukraine, with the exception of 2022, when the ratio was 1.4 in the EU/EEA compared to 2.9 in Ukraine (30). This indicates a higher proportion of female cases in the EU/EEA compared to Ukraine.

More than half of all Ukrainian migrant cases were reported in the age group from 25 to 44 years. The number of notified cases in the age group under 15 years slightly increased in 2022 to 6.2% (n = 48) of all cases among Ukrainians, compared to an average of 1.3% (mean n = 3; CI 95% -1 – 6) in the previous years (**Table 2**).

Table 2: Age distribution in Ukrainian TB cases in the EU/EEA, 2019 - 2022.

	2019		2020		2021		2022		Total
Age group	n	%	n	%	n	%	n	%	n
< 15	3	1.3	1	0.61	4	2.0	48	6.2	56
15-24	16	6.8	12	7.3	8	3.9	77	9.9	113
25-44	130	55.3	84	51.2	109	53.7	392	50.3	715
45-64	62	26.4	45	27.4	70	34.5	214	27.4	391
≥65	24	10.2	22	13.4	12	5.9	49	6.3	107
Total	235		164		203		780		1,382

3.3 Comparison with WHO case estimates

The notified TB cases were compared to estimates calculated using a publicly available calculator for expected TB cases in the Ukrainian migrant population. These estimates were based on the demographic data recorded in the temporary protection dataset for 2022, without considering the number of usually resident Ukrainians in the EU/EEA countries. The calculator is provided by the WHO Regional Office for Europe (**Figure 8**) (44).

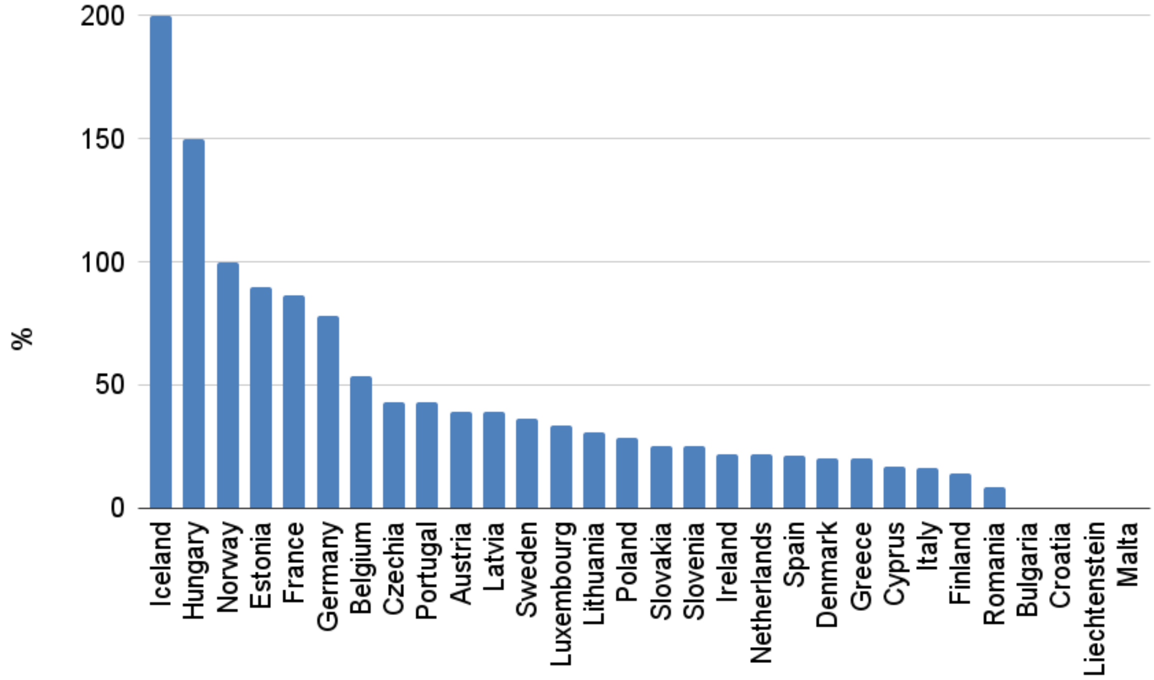

Figure 8: Notified cases as percentage (%) of the estimated TB cases in Ukrainians per country, 2022.

For 23 of the 30 EU/EEA countries, the notified cases were over 50% lower than the expected values (Figure 8). In two countries – Iceland (n < 5) and Hungary (n = 21) – the notified cases were higher than the expected number of cases. For Norway, the reported case numbers and the calculated estimates were identical (n = 16).

3.4 Tuberculosis notification rates

Notification rates were calculated for all countries and time points separately as well as for the EU/EEA region in total. At the EU/EEA level, the notification rates per 100,000 population displayed a sinusoidal pattern, with a baseline value of 19.6 per 100,000 in 2019, a substantial decrease in 2020 (12.6/ 100,000), renewed increase in 2021 (17.0/ 100,000) and a lower value in 2022 (13.4/ 100,000). The overall trend was negative and the range was significantly lower compared to the level reported in Ukraine throughout the period (**Figure 9**) (30).

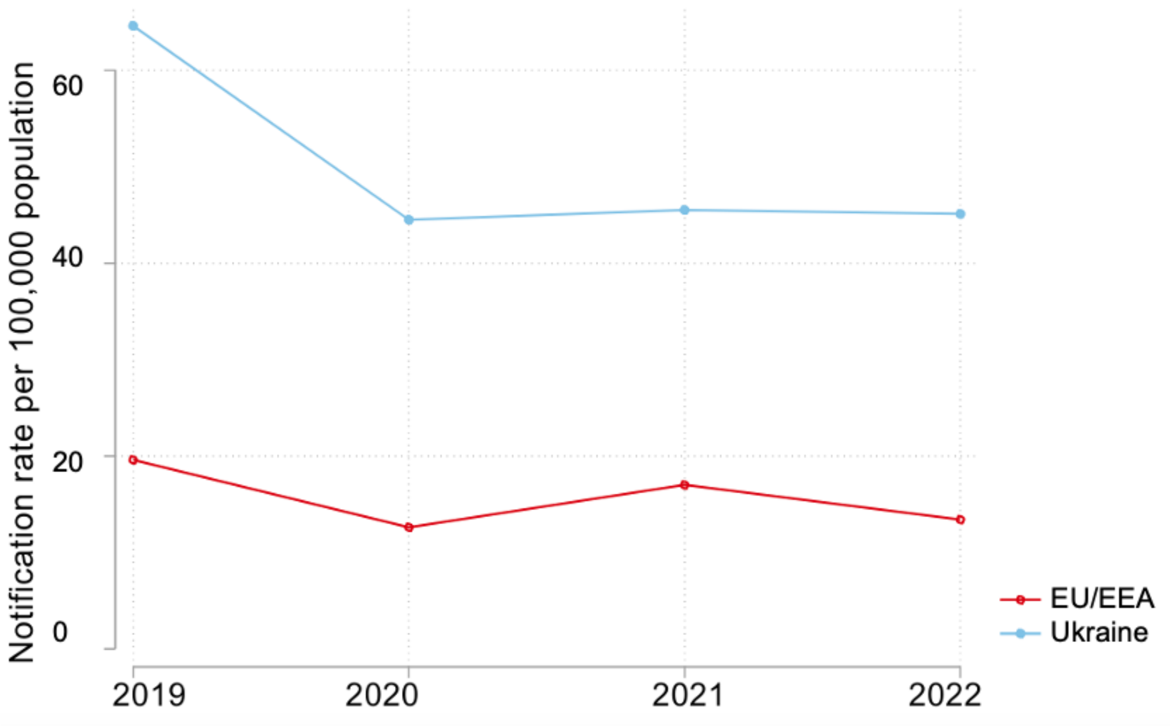

Figure 9: Tuberculosis notification rates per 100,000 population in Ukraine and among Ukrainian citizens in the EU/EEA.

Notification rate in Ukraine (30).

Population data (31, 40 – 42).

At the country level, the total notification rates showed a right-skewed distribution, with values ranging from 0 to 187.3 per 100,000 population, displaying substantial variations. The notification rates for all countries with 5 or more cases are provided below. Over the four years from 2019 to 2022, the proportion of EU/EEA countries with a notification rate of zero fluctuated from 30.0% (n = 9) to 50.0% (n = 15), 40.0%, (n = 12) and 13.3% (n = 4). All countries with notification rates over 50 per 100,000 had a small Ukrainian population size of less than 15,000 citizens. In the five countries with consistently large Ukrainian populations of over 100,000 citizens throughout the study period - Czechia, Germany, Italy, Poland and Spain - the TB notification rates remained below 30 per 100,000 Ukrainian citizens from 2019 to 2022 (**Figure 10**).

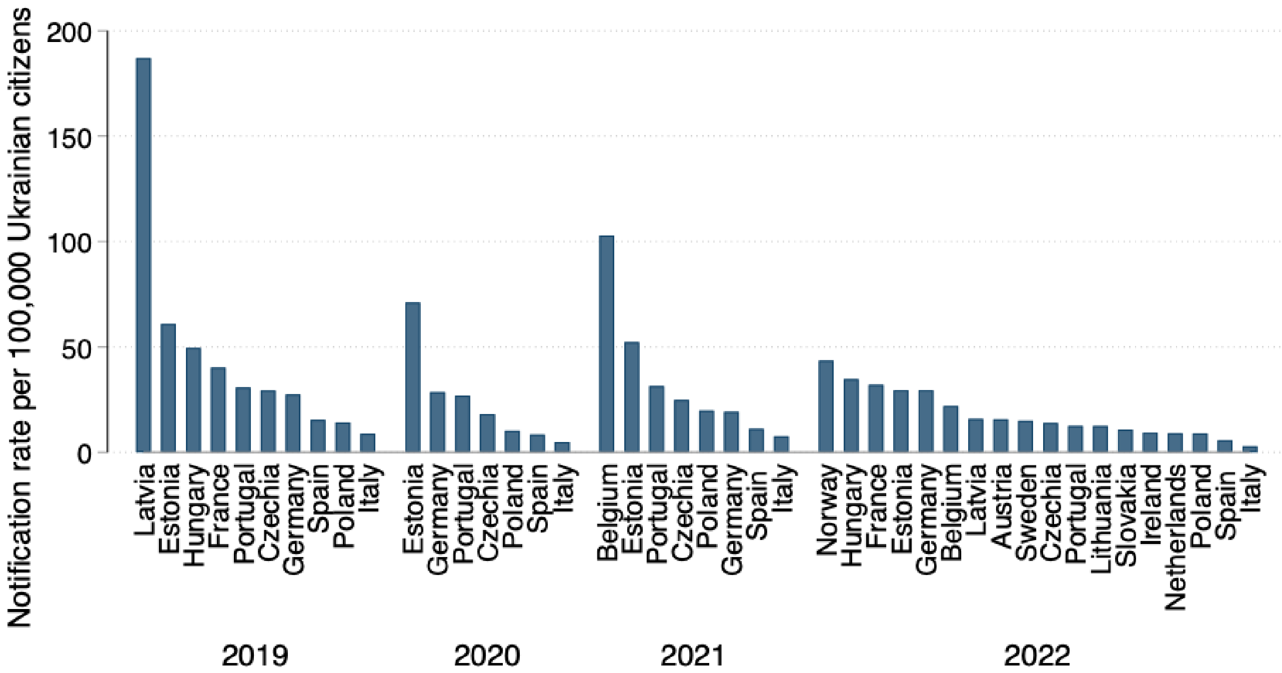

Figure 10: Tuberculosis notification rates per 100,000 Ukrainian citizens in countries with 5 or more cases per time point.

Population data (31, 40 – 42).

Source: Stoycheva et al., 2024 (43). Adapted according to CC BY-4.0.

- Stratification by age and sex

Notification rates stratified by age and gender were calculated at the EU/EEA level to avoid distortion due to small population sizes in individual countries. Similar to the pattern of notification rates in Ukraine (30), the highest rates were found in males in the age groups between 15 and 64 years and 65 years or older (**Figure 11**).

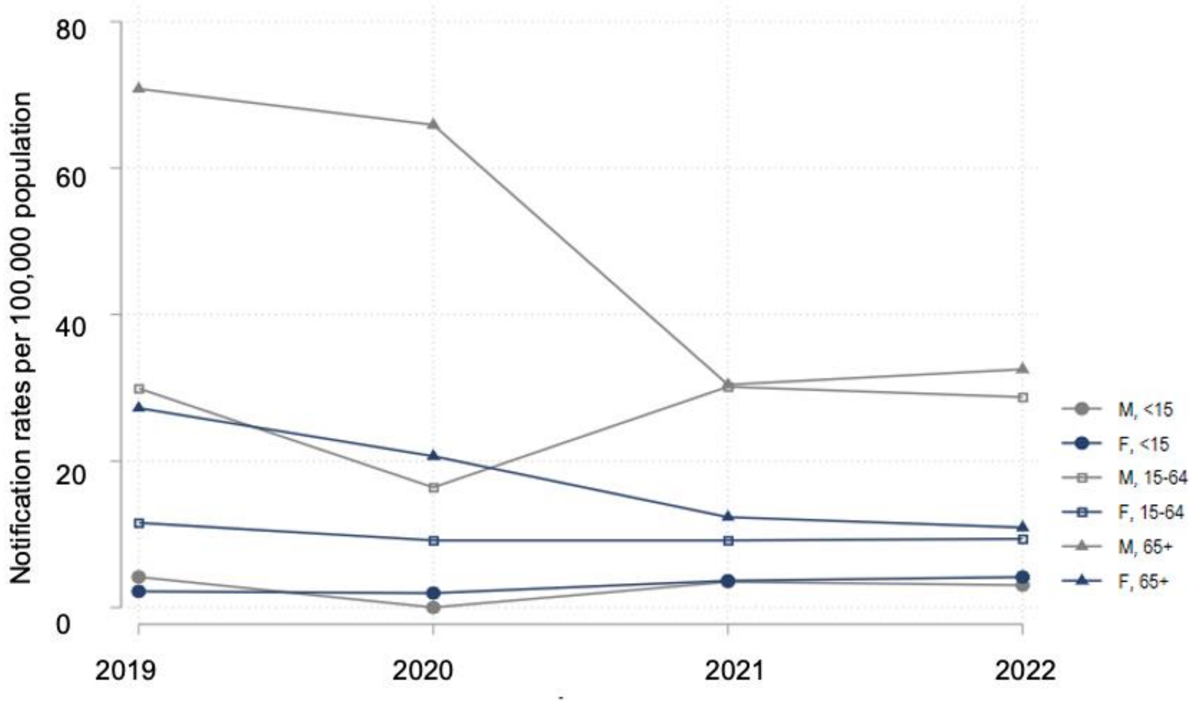

Figure 11: Tuberculosis notification rates per 100,000 Ukrainian citizens stratified by age and sex. EU /EEA level, 2019 - 2022.

Male – M; Female – F;

Population data (31, 40 – 42).

3.5 Notification rates in a Ukrainian population defined by country of birth

Multiple countries in the EU/EEA report case origin based on the country of birth. To assess possible differences in TB notification rates between Ukrainian populations defined by citizenship (CTZ) and those defined by country of birth (COB), datasets based on COB were additionally used. The notification rates calculated with these datasets were compared to those calculated in populations strictly defined by CTZ. Substantial differences were observed in Latvia, Romania and Slovakia in 2019 (**Figure 12**), where the Ukrainian population defined by COB appeared to be considerably larger than the population defined by CTZ.

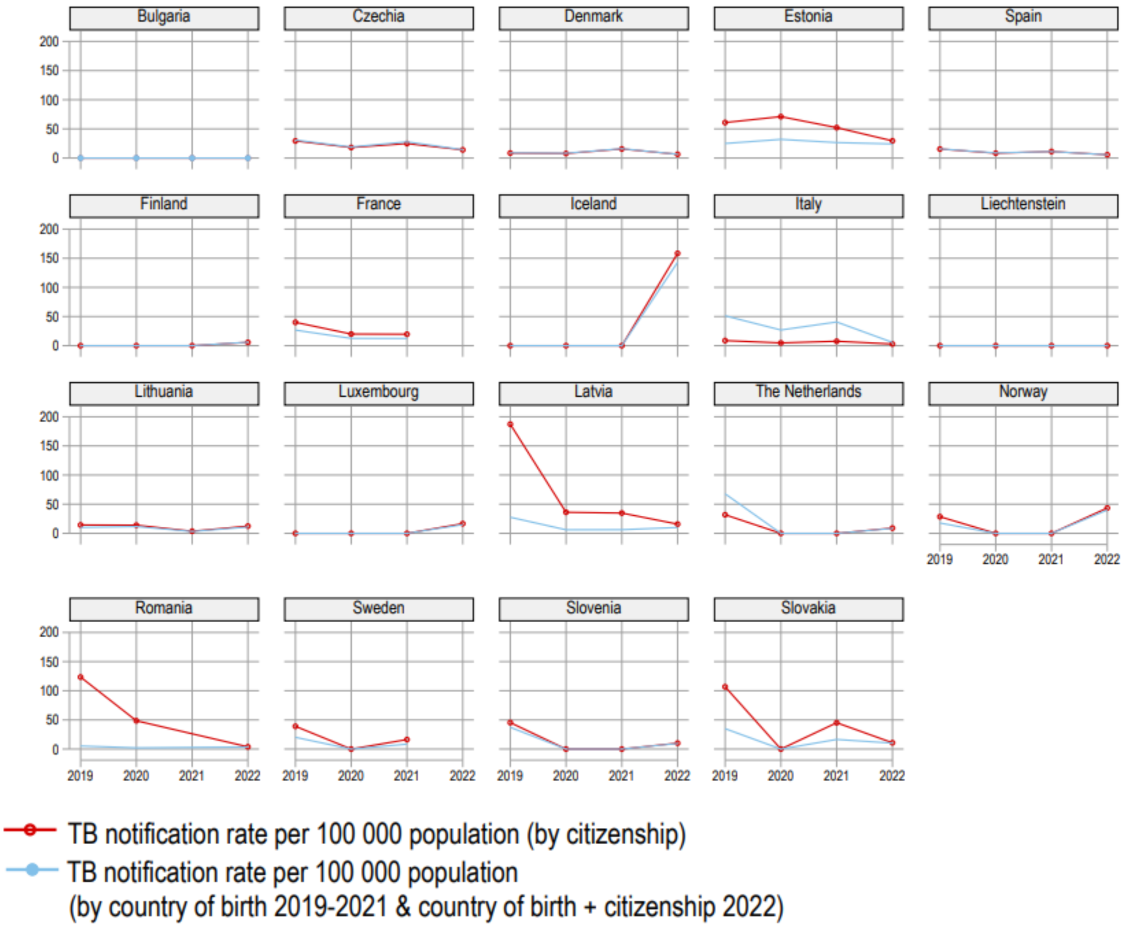

Figure 12: Comparison of TB notification rates in a population defined by country of birth and country of citizenship.
Population data (31, 40 – 42).

Among the three countries with the highest total number of notified TB cases – Czechia, Germany and Poland – the difference in rates by COB versus CTZ was negligible for Czechia; for Germany, population data by COB were not available and Poland reports the origin of TB cases according to CTZ; therefore, rates by COB were not calculated for Poland.

At EU/EEA level, total notification rates calculated using available COB datasets combined with CTZ datasets (where data by COB were missing) were comparable to the rates calculated using only CTZ data (21.2 versus 19.6; 13.3 versus 12.6; 19.0 versus 17.0; 13.7 versus 13.4;).

A sensitivity analysis was performed on country-specific rates using negative binomial regression, comparing populations defined strictly by COB versus CTZ. The regression of country-specific notification rates showed slightly lower levels by COB, with overlapping CI 95% (**Figure 13**). Data for 2022 were not included due to the lack of population data defined strictly by COB.

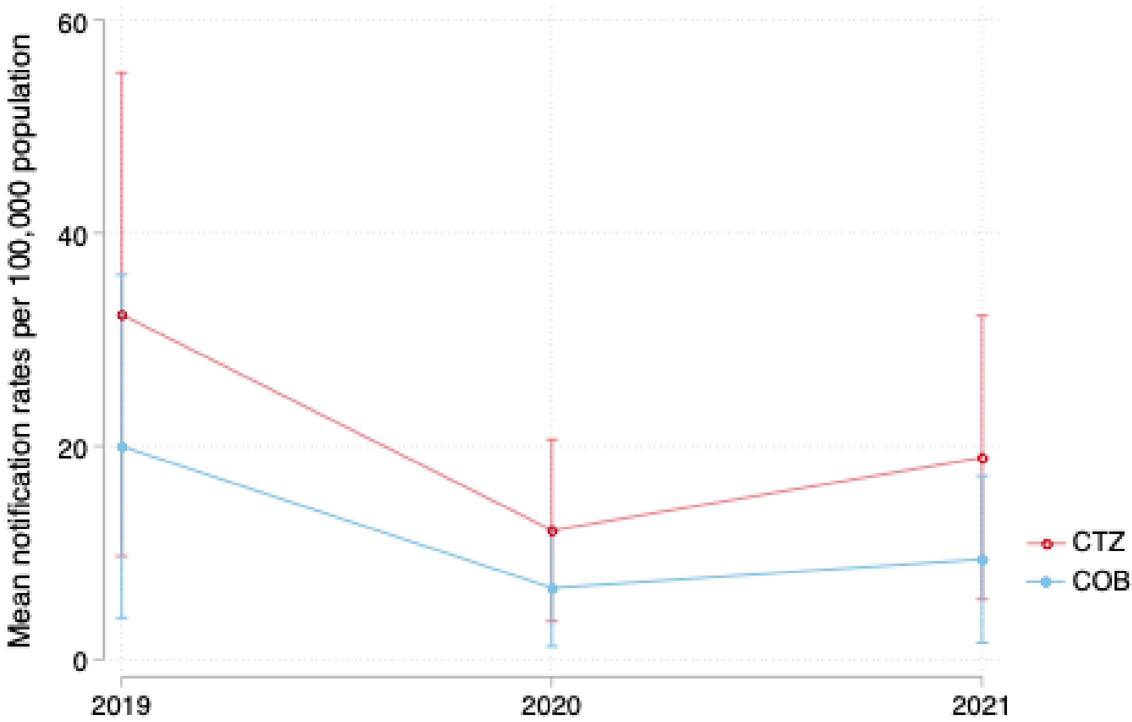

Figure 13: Sensitivity analysis of mean EU/EEA country-specific notification rates per 100,000 Ukrainian population with 95% confidence intervals, 2019 - 2021.
Ukrainian population defined by citizenship (CTZ; red) versus population defined by country of birth (COB; blue).
Population data (31, 40 – 42).

3.6 Laboratory confirmation and drug susceptibility testing

Between 2019 and 2022, laboratory confirmation was available overall for 80.3% of the notified cases. Variations between the years (2019: n = 185, 78.8%; 2020: n = 133, 81.1%; 2021: n = 169, 83.3%; 2022: n = 608, 77.9%) were non-significant on ANOVA test (F (3, 1378) = 1.05, p = 0.369)). Probable cases, where the combination of both positive microscopy and NAAT or culture confirmation was not available, were rare (2019: n = 16, 2020: n = 9; 2021: n = 15; 2022: n = 63).

Among the laboratory-confirmed cases, a form of DST was performed in all cases. The proportion of cases with DST for rifampicin only was 17.5% (n = 31), 12.9% (n = 17), 16.0% (n = 27) and 12.5% (n = 76), respectively.

In pulmonary cases in Czechia, Germany and Poland, data on laboratory confirmation were missing in 13.1% (n = 42) in Germany, 11.4% (n = 40) in Poland and 3.3% (n = 6) in Czechia. Overall, the highest proportion of pulmonary TB cases lacking information on laboratory confirmation was observed in Hungary, with 43.6% (n = 17 of 39 cases in total).

- Stratification by age and sex

Overall, the proportion of laboratory confirmation was 81.0% (n = 702) in men and 76.3% (n = 392) in women. The difference in laboratory confirmation status between the sexes was significant (chi^2, p = 0.037), irrespective of the manifestation site.

Stratified by age, the lowest proportion of laboratory confirmation was observed in the age group under 15 years, at 25.0% (n = 14 of 56 cases in total). In this age group, further 8 cases were classified as probable, with the remaining 34 cases (60.7%) lacking pathogen detection. The highest proportion of confirmed cases was observed in the age group from 15 to 24 years, at 83.2% (n = 94 of 113 cases in total).

3.7 Manifestation site

The manifestation site was predominantly pulmonary, accounting for 91.5% of all cases (n = 1,257). The fluctuations between the individual years were minor (range: 90.6% - 92.0%). Specific details on the affected organ system in extrapulmonary cases were not provided. In total, 116 cases of extrapulmonary TB were notified. In 9 cases the manifestation site was not provided.

The proportion of extrapulmonary cases classified as neither laboratory confirmed nor probable (i.e., cases without pathogen identification) was significantly higher than the proportion among pulmonary cases (31.9%, n = 37 extrapulmonary versus 11.1%, n = 140 pulmonary) (chi^2 test, p <0.001).

- Stratification by age and sex

89.5% (n = 460) of all female cases and 91.2% (n = 797) of all male cases were affected by pulmonary disease, indicating a similar sex distribution of the manifestation site in the study population (chi^2 test, p = 0.126). The male-to-female ratio of extrapulmonary cases was positive in the age groups up to 44 years and negative in the age groups of 45 years or more. Significant changes of sex distribution between the study years were not observed.

42.9% (n = 24) of all cases under 15 years (n = 56) were extrapulmonary. This proportion was significantly higher than the proportion of extrapulmonary cases in all other age groups (chi^2 test, p = 0.000).

3.8 HIV co-infections

Data on HIV status were largely missing. Information was not available for any time point for Austria, Finland, France, Germany, Poland and Sweden. For the other EU/EEA countries, the dataset was only partially complete regarding HIV status information. Overall, data on the HIV status were provided in 30.2% (n = 71), 26.8% (n = 44), 32.5% (n = 66) and 20.3% (n = 159) of all cases (mean 2019-2022: 27.5%; n = 85). Where data were available, the proportion of positive cases was 12.6% (n = 9) in 2019, 18.1% (n = 8) in 2020, 10.6% (n = 7) in 2021 and 13.2% in 2022 (n = 21) (mean 2019-2022: 13.6%, n = 11). Differences between the time points were not significant on ANOVA (df(3), F(0.45), p = 0.72).

- Stratification by age and sex

Of the total 45 cases with a positive HIV co-infection status recorded from 2019 to 2022, 33 (73.33%) were male and 36 (80.00%) were between 25 and 44 years old.

3.9 Previous TB history

The majority of the notified cases were new diagnoses in previously unaffected individuals (77.2%, n = 1,067). Only 11.3% of all cases (n= 156) had a recorded history of prior TB and in 11.5% (n = 159) no information on previous diagnosis or treatment status was available. The proportion of previously treated cases gradually increased from 6.4% (n = 15) in 2019 and 7.9% (n = 13) in 2020 to 11.8% (n = 24) in 2021 and 13.3% (n = 104) in 2022. This increase was significant in ANOVA (df(3), F(4.45), p = 0.0041). Overall, the proportion of previously treated cases was higher among DR-TB cases compared to DS-TB cases (23.0% versus 8.0%; chi^2, p=0.000) (**Figure 14**).

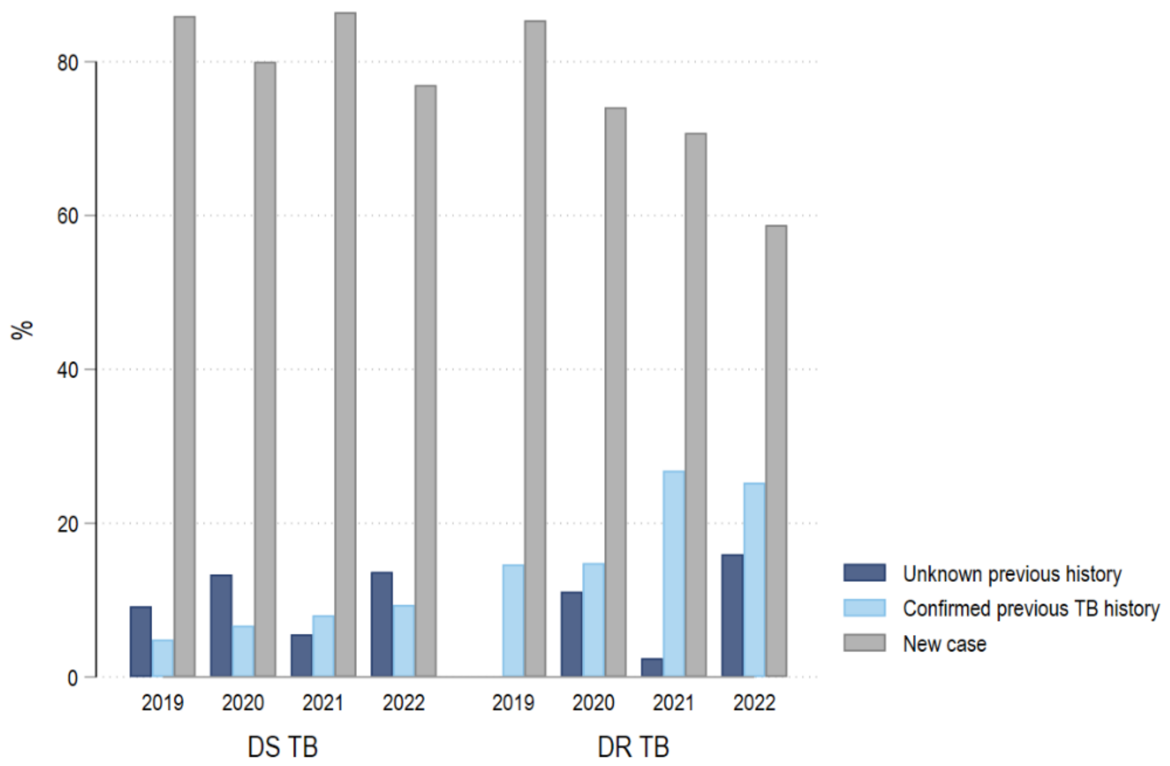

Figure 14: Treatment history in drug-susceptible TB cases (DS-TB) and drug-resistant TB cases (DR-TB) in Ukrainians in the EU/EEA, 2019 – 2022.

Treatment success rates were comparable between new and previously treated cases (16.8%, n = 179 versus 16.0%, n = 25). However, information on treatment outcome was not available for the majority of cases (see 3.11).

- Stratification by age and sex

The proportion of male cases was higher among previously treated cases compared to new cases (69.9%, n = 109 versus 62.0%, n = 662).

The highest proportion of previously treated cases was found in the age group between 45 and 64 years (12.5%, n = 49). However, previously treated cases were found also among younger age groups: under 15 years and between 15 and 24 years. Combined, these two age groups accounted for 6.4% of all previously treated cases (n = 10) and 13.2% of all new cases (n = 141).

3.10 Drug-resistance surveillance

Drug-resistant TB cases were classified according to their highest level of resistance into four mutually exclusive categories: RR-TB, MDR-TB, pre-XDR-TB and XDR-TB. In total, 305 cases with any of the defined types of resistance were reported between 2019 and 2022 (**Table 3**), corresponding to 22.1% of all cases reported in the region during the four-year period. The highest total numbers of DR- TB cases were reported in Poland (n = 99), Germany (n = 93) and Czechia (n = 23).

Table 3: Drug-resistant TB cases in Ukrainians in the EU/EEA, 2019 – 2022.

	MDR/RR-TB	Pre-XDR-TB[a]	XDR-TB [a]	Total	% of all laboratory confirmed [b]	% of all
2019	39	4	0	43	23.2%	18.3%
2020	22	5	0	27	20.3%	16.5%
2021	32	9	0	41	24.3%	20.2%
2022	152	38	4	194	31.9%	24.9%

Cases are only listed once, according to their highest level of resistance.

[a] (Pre-) XDR-TB cases according to 2021 WHO definitions (19).

[b] Laboratory confirmation according to European Commission 2018 definitions (39).

Compared to the baseline year of 2019, the proportion of DR-TB cases among all notified cases significantly increased (chi^2, p = 0.037). However, the increase in proportion from 2021 to 2022 was not significant (chi^2, p = 0.164). Similarly, the differences in proportions of laboratory confirmed DR-TB cases were significant between 2019 and 2022 but not between 2021 and 2022 (chi^2, p = 0.237 versus p = 0.572).

In total, among cases with previous TB history, the proportion of DR-TB was 44.9% (n = 70 of 156 cases). In new cases, this proportion was significantly lower at 18.7% (n = 200 of 1067 cases without prior TB) (chi^2, p < 0.001). Overall, 200 of the 305 DR-TB cases recorded throughout the four years were in previously unaffected individuals without a prior TB diagnosis or treatment.

Within the context of all DR-TB cases of various origins notified in the EU/EEA, the Ukrainian cases with drug-resistance corresponded to of 4.2% (n = 43), 3.5% (n = 27) and 5.5% (n = 41) between 2019 and 2021. Notably, in 2022, this proportion substantially increased to 19.7% of all DR-TB cases notified within the EU/EEA (n = 194 of 986 DR-TB cases) (**Figure 15**).

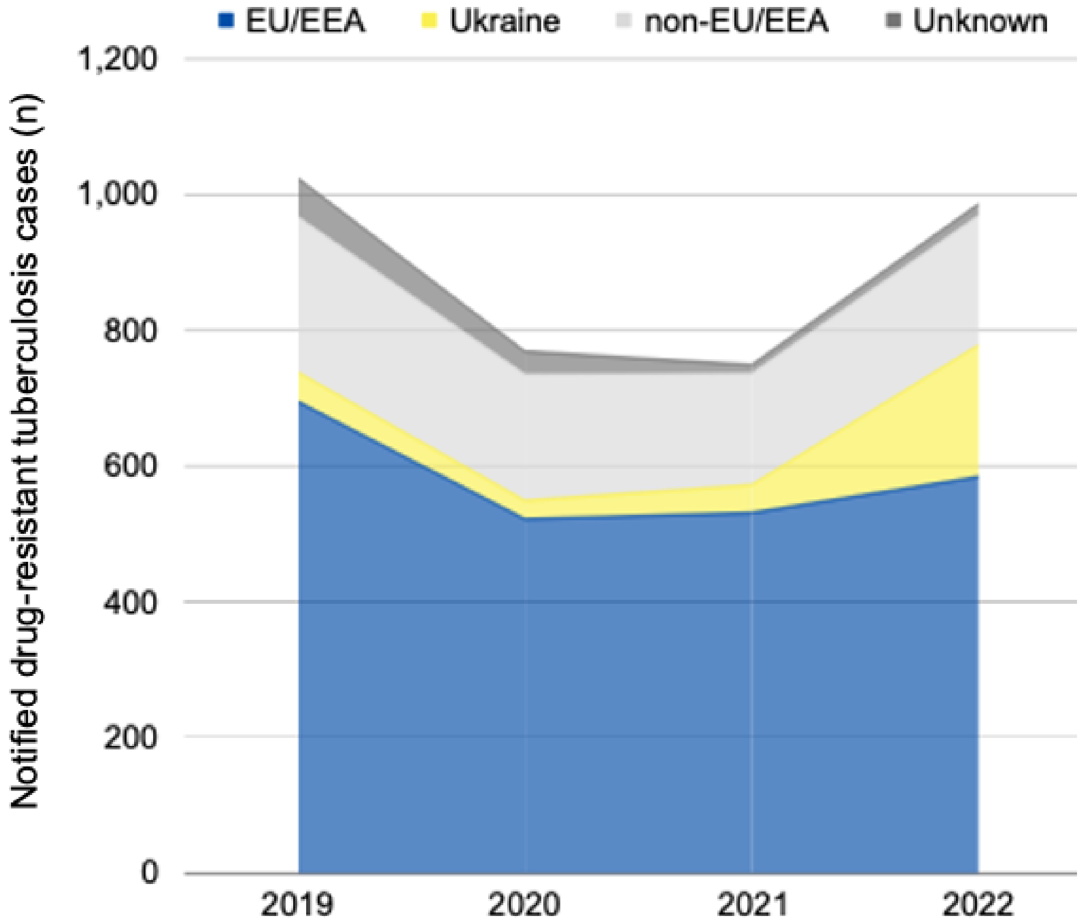

Figure 15: Distribution of origin among DR-TB cases (n) notified in the EU/EEA, 2019 – 2022.

Source: Stoycheva et al., 2024 (43). Adapted according to CC BY-4.0.

- Stratification by age and sex

Overall, the total male-to-female ratio of Ukrainian DR-TB cases was at 1.99. Expressed as a proportion of all cases within each sex, DR-TB cases were 19.8% (n = 102) in females and 23.4% (n = 203) in males. The available data suggested that the observed differences in proportion of DR-TB cases between the sexes were not significant (chi^2 test, $p = 0.122$). In 2022 specifically, among all female cases, 24.9% (n = 79) were DR-TB, while the proportion among male cases was identical at 24.8% (n = 115). This suggests affliction higher than the mean expected level among females in 2022, though the increase was not statistically significant (chi^2, p= 0.128).

The highest proportion of DR-TB cases was observed in the age group from 25 to 44 years at 26.4% (n = 188 of 711), followed by the age group from 45 to 64 years with 20.8% (n = 81 of 389 cases) and 19.5% in the age group from 15 to 24 years (n = 22 of 113 cases). In the age group under 15 years, 5.4% of the cases were affected by DR-TB (n = 3 of 56 cases).

3.11 Treatment outcomes

Due to the nature of the data, information on treatment outcomes is available with a delay of one year for DS-TB and two years for DR-TB. Therefore, outcome data were evaluated for the completed 2019 and 2020 cohorts only. Overall, the treatment outcome status was recorded as "unknown" or "transferred out" in 44.9% and 7.3% of all cases (n = 179 and 29 of 399 in total) and "defaulted" in 4.8% (n = 39 of 399). Among cases with outcomes different than "unknown", "transferred", and "defaulted", the success rates were 73.7% (n = 73) in 2019 and 74.0% (n = 54) in 2020 (**Table 4**).

Table 4: Treatment outcomes of Ukrainian TB cases notified in the EU/EEA, 2019 – 2020.

Treatment outcome [a]	2019		2020		Total	
	n	%	n	%	n	%
Success	73	31.1	54	32.9	127	31.8
Failed	0	0	1	0.6	1	0.25
Defaulted (lost to follow-up)	10	4.3	9	5.5	19	4.8
Died	8	3.4	10	6.1	18	4.6
Still on treatment	18	7.7	8	4.9	26	6,5
Transferred (not evaluated)	21	8.9	8	4.9	29	7.3
Unknown (not evaluated)	105	44.7	74	45.1	179	44.9
Total	235		164		399	

[a] Data from 2021 and 2022 not evaluated.

Analysis stratified by drug-resistance status and demographic structure was not performed due to the overall low number of cases with available information on clinical outcome.

4. Discussion

The aim of this study was to assess the TB burden among Ukrainians in the EU/EEA from 2019 to 2022. Results show overall moderate total notification rates of less than 20 cases per 100,000 Ukrainian citizens at EU/EEA level throughout the period. Lockdowns and restrictions in routine care and active TB case finding due to the onset of the coronavirus pandemic are reflected in a decrease of absolute numbers and rates in 2020. Furthermore, the first year following the Russian invasion of Ukraine in February 2022 saw an almost fourfold increase in notified cases among Ukrainians in the EU/EAA. Over the period from 2019 to 2022, a significant increase in drug-resistance among Ukrainian TB patients in the EU/EEA was observed. These developments suggest substantial challenges to the End TB strategy in the region.

Compared to the previous year, the number of TB cases of Ukrainian origin notified in the EU/EEA and recorded in the TESSy database decreased by 30% in 2020. This decrease was slightly higher, yet comparable with the one reported by ECDC for the total EU/EEA region (30). Notably, the population size and demographic structure of Ukrainian citizens in the EU/EEA remained stable from 2019 to 2020. The sharp decline of national, supranational and global TB notification rates at the onset of the coronavirus pandemic is considered disproportionate and suggests an increase in the diagnostic gap rather than a desired programmatic decline in TB incidence (14, 16). At the start of the pandemic in 2020, access to diagnostic and routine healthcare services was severely restricted due to capacity issues, contact regulations and fear of increased exposure to COVID-19 at health facilities (45). While some protective impact from contact restrictions and public mask-wearing is assumed to have resulted in a reduction of TB transmission, this effect does not influence household transmissions and does not compensate for delayed diagnoses due to limited access to healthcare services (46). The 7,000 estimated excess TB deaths in the WHO European Region for the period 2020-2022 are a clear indicator of this negative development (30). At a global level, the excess TB mortality is estimated to have reached almost half a million individuals over three years (16). The downscaling of routine care and elective procedures to redirect resources to COVID-19-related services similarly led to a decrease in cancer incidence across all cancer types and to a post-pandemic increase in late-stage cancer diagnoses (47, 48). Socially vulnerable groups have been reported to be disproportionately affected (45). The aftermath of the pandemic highlights weak links in healthcare and underscores the need for better emergency response structures, resilient health systems and intensified community engagement. The under-detection of TB cases during the coronavirus pandemic will likely have a lasting impact on communities affected by TB and on the global TB epidemic (15).

The full-scale Russian invasion of Ukraine on February 24th 2022 and the subsequent attacks on civilian infrastructure, including health facilities, led to further weaking of an already vulnerable health system in Ukraine and resulted in the displacement of millions of Ukrainian residents into neighbouring countries within the European Region (36, 49). As of July 2024, approximately six million Ukrainian refugees remain displaced across Europe, according to the United Nations High Commissioner for Refugees (UNHCR) (49). With an estimated TB incidence more than ten times higher than the estimated incidence in the EU/EEA (30), people in Ukraine are at a higher risk of being affected by TB than EU/EEA residents. The analysis of TESSy data on TB notifications among Ukrainians in the EU/EEA revealed an increase in the total number of notified cases in 2022, a direct consequence of the mass population displacement following the start of the conflict. However, cases of Ukrainian origin remained a small portion of all TB cases notified in the EU/EEA. Additionally, despite the nearly fourfold increase in notified TB cases, the TB notification rate per 100,000 did not increase, remaining below the pre-pandemic level and even decreasing in 2022. This finding can be explained by the demographic distribution of the Ukrainian migrant population in 2022, which showed the largest increase in the female group and also included over 1 million minors under 15 years (31, 40 – 42). These demographic groups are less commonly affected by TB compared to adult male individuals in Ukraine and in the EU/EEA (30). Another possible explanation for the comparatively low notification rates could be the different socio-economic backgrounds of Ukrainians fleeing the war in 2022; however, statistics on the socio-economic status in this population were not available.

Comparing the notified TB case numbers with estimates based on WHO calculations (44) for the specific age and sex structure of the migrant population in

2022, 23 of the 30 EU/EEA countries reported numbers more than 50% lower than the expected values. Despite the large uncertainties in the estimated numbers, under-detection and/or under-reporting are likely. The notification rate of 43.5 per 100,000 calculated for Norway was closest to the value reported in Ukraine and the notified TB case numbers also accurately corresponded to the WHO estimates for expected cases. In Norway, over 90% of the Ukrainian population that received temporary protection status in 2022 was screened for TB (50), which explains the high detection rates in the country. However, even in this setting, the notification rate remained below 50 per 100,000 population, corresponding to a number needed to screen of 2,299 to detect one case. This number was closer to the one reported in a general inpatient population in a low to moderate TB incidence setting than to the number reported in other migrant populations (51).

Different EU/EEA countries applied diverse TB screening strategies for Ukrainian refugees, resulting in a patchwork of policies (35, 50, 52 - 56). A few countries had no TB screening policies for Ukrainian refugees in place. Notification rates in host countries with general or partial TB screening recommendations for Ukrainian refugees were almost twice as high compared to those without such policies (53). However, fears of stigmatisation and low technical preparedness in some EU/EEA member states were reported (52, 54, 55). The ECDC and the WHO Regional Office for Europe prioritize screening in risk populations and refrain from extending the recommendation for screening to the broader Ukrainian migrant population due to similar considerations (34). Additionally, mandating general TB screening for Ukrainians, without applying this regulation to other large migrant groups in the EU/EEA from countries with similar incidence rates and DR-TB prevalence, such as the Russian Federation, Romania, and other Eastern European, Central Asian and African countries (16, 30), would be inconsistent and would contribute to existing stigmatization concerns.

Throughout the entire period from 2019 to 2022, TB notification rates among Ukrainians in the EU/EEA significantly differed from those in Ukraine. Studies on migrant populations have previously demonstrated that the TB burden in people of foreign origin in the new country of residence often differs from the level observed in the country of origin (25). While the harmonization of screening strategies across the EU/EEA countries could be a reasonable approach and can be introduced for specific criteria (e.g., TB incidence in the country of origin exceeding 100 per 100,000 population) (57), a more flexible local surveillance-guided approach that takes into consideration both the local incidence in foreign-born communities and the incidence in the country of origin is equally important. This is especially true in a developing humanitarian situation and can help guide interventions (58). Such an approach could further take into account the TB incidence in the host country – a factor that also shows high variability in the EU/EEA, ranging from an estimated 2.2 per 100,000 in Greece to 52.0 per 100,000 in Romania (30).

Overall, a systematic general screening for TB in Ukrainian migrants does not seem justified given the estimated and notified incidence in Ukraine, the low notification rates among Ukrainians in the EU/EEA and the overall low screening yield in 2022. Resources should therefore be allocated to risk groups and settings as well as to other priority areas with high relevance – such as the diagnostics and treatment for DR-TB.

An increase in the absolute number of DR-TB cases of Ukrainian origin was anticipated in 2022 due to the rise in total notified TB case numbers. The DR-TB proportion of 24.9% of all Ukrainian cases in the EU/EEA is comparable to that observed in the broader European region (53) and the one reported in Ukraine (30). Notably, the proportion of DR-TB among Ukrainian cases in the EU/EEA significantly increased in 2022 compared to the start of the study period, leading to an overrepresentation of Ukrainian DR-TB cases among all DR-TB cases notified in the region. In 2022, almost one in five DR-TB cases in the EU/EEA was of Ukrainian origin. Furthermore, the majority of DR-TB cases were in individuals without previous TB history, underscoring the importance of drug-susceptibility testing as well as early recognition, treatment and retention in treatment to effectively limit the transmission of DR-TB strains.

To meet the 2030 End TB targets, the EU/EEA must achieve a TB notification rate of 2.4 per 100,000 population. As of the end of 2021, the projected decline has been reported to fall short of meeting the 2030 targets both in terms of notification rates (calculated as approximation for incidence) and mortality rates (59). Fluctuations due to unforeseen events such as the coronavirus pandemic and the prolonged armed conflict are likely to have a long-lasting impact on the TB epidemiology in the region and will slow down the progress towards achieving the End TB goals. The high levels of drug-resistance in Ukrainians with TB and the fact that the highest increase in DR-TB is observed by the WHO in the European Region (16) further emphasize the importance of *M. tuberculosis* drug-susceptibility testing in the countries of the region. With almost one out of three confirmed Ukrainian TB patients and a quarter of all notified TB cases of Ukrainian origin in the EU/EEA being affected by DR-TB, resistant strains must always be expected in this patient population.

This analysis has several limitations. Most notably, the findings of the study rely on routinely collected notification data and thus on the accurate reporting. Under-reporting as well as under-diagnosing may lead to significant epidemiological misinterpretation of the TB burden among the studied population.

Furthermore, the high mobility of migrant populations in general and especially the displaced Ukrainian population following the Russian invasion, may have resulted in an over- or underestimation of the denominator for the calculation of notification rates. The population size also serves as the basis for calculating case estimates with the WHO calculator. Therefore, uncertainty regarding the size of the population also increases the uncertainty of the calculation of these estimates.

Additionally, due to the non-uniform reporting strategies and definitions regarding the origin of TB cases across the EU/EEA, some cases were classified by country of birth, while others were reported based on citizenship. Population datasets for the primary analysis were selected based solely on citizenship, leading to a mismatch for several countries and potentially affecting the comparability of results between EU/EEA countries.

Data on socio-economic background was not available. Given the significant role of social determinants in the transmission and progression of TB infections, this additional information could have provided more accurate estimates and allowed for a stratified analysis adjusted for these risk factors.

The limited availability of data on the entry time point of TB patients into the reporting EU/EEA country constrains the ability to differentiate between long-term foreign residents and such with recent history of displacement, particularly due to the Russia-Ukraine war. As a result, a causal connection between the increase in notified TB cases and the conflict can be assumed but not confirmed. After the decrease in TB case notifications and notification rates in 2020, the rebound of diagnostic services following the coronavirus pandemic in may have also contributed to the increase in registered TB case numbers across the region in 2022.

Lastly, the data were provided and analysed in aggregated form. Drug-resistance status was pre-classified and susceptibility status for individual drugs was not available. Information regarding the drug-resistance levels for specific anti-TB agents would be valuable for the allocation of diagnostic and therapeutic resources across the region.

Despite its limitations, this study provides valuable insights into the TB epidemiology of the Ukrainian migrant population in the low-incidence setting of the EU/EEA countries. The results suggest a substantial TB case-detection gap among the Ukrainian migrant population due to the onset of the coronavirus pandemic in 2020. The absolute increase in TB cases of Ukrainian origin in 2022 is indicative of the effect of the conflict on TB epidemiology in the region. The TB notification rates per 100,000 Ukrainian citizens, not only in 2022 but also in the previous years, suggest a lower affliction or a lower case-detection among the Ukrainian migrant population compared to the general population in Ukraine. However, when compared to the general EU/EEA population, Ukrainian migrants were more commonly affected by TB. Furthermore, high-levels of drug-resistance were observed among Ukrainian cases in the EU/EEA. These findings underline the importance of the accessibility of qualified medical care and the increased awareness regarding the higher prevalence of TB in this patient subpopulation among health providers. However, general active screening is not justified due to the comparatively low expected screening yield.

Achieving the End TB goals for the EU/EEA region is closely linked to the availability of patient-centred and inclusive health services for migrants. Improved strategies for timely diagnosis, initiation of appropriate drug combination and retention in treatment could include offers for general medical examinations in the first months after arrival, broader availability of linguistically and culturally appropriate ambulatory services as well as enhanced communication among healthcare providers and public health institutions across the region. To address the increased levels of resistance, emphasis should be placed on drug-susceptibility testing, the availability of second-line drugs and retention in treatment among Ukrainians.

Finally, intensified peace efforts are needed to continue the fight against TB in Ukraine and in the broader region.

5. Summary

Ukraine has a tuberculosis (TB) notification rate substantially higher than that of the European Union and the European Economic Area (EU/EEA) and is a high-priority country concerning drug-resistant (DR-) TB. In recent years, Ukraine has faced two unprecedented challenges: the coronavirus pandemic and the onset of the Russia – Ukraine war in 2022, which led to the displacement of millions of Ukrainians across the EU/EEA countries. The effect of these events on the TB epidemiology among Ukrainians residing in the EU/EEA countries was evaluated.

Surveillance data from the EU/EEA member states were obtained for 2019, 2020, 2021 and 2022. Notification rates were calculated using population statistics. Crude and stratified absolute numbers, rates and proportions are presented and evaluated.

The absolute number of notified TB cases among Ukrainians in the EU/EEA declined to n = 164 with the start of the coronavirus pandemic and increased to n = 780 in 2022. Three EU/EEA countries – Czechia, Germany and Poland contributed the highest numbers of TB cases of Ukrainian origin. Total EU/EEA notification rates among Ukrainian migrants remained below 20 per 100,000. The lowest rate of 12.6 per 100,000 was calculated for 2020 and is indicative of the decrease in diagnostic capacities at the start of the coronavirus pandemic. A second decline, to a rate of 13.4 per 100,000 was observed in 2022, likely reflecting the different sociodemographic profile of the population fleeing the conflict. Under-detection of cases is also a plausible contributing factor; however, general screening is not justified due to the low expected yield and concerns about stigmatization. Notably, the number and proportion of DR-TB cases among Ukrainians increased over the study period. In 2022, almost 20% of all DR-TB cases in the EU/EEA were of Ukrainian origin.

In conclusion, while the overall notification rates among Ukrainian migrants in the EU/EEA remain at levels below 20 per 100,000, the absolute number of notified TB cases surged almost fourfold in 2022. Furthermore, the proportion of DR-TB among Ukrainian cases in the EU/EEA significantly increased. Targeted migrant-sensitive healthcare services are important for the achievement of the End TB goals in the region.

6. Zusammenfassung

6.1 Einleitung

In der Ukraine konnte die Tuberkulose (TB)-Melderate im Zeitraum von 2012 bis 2022 von über 100 Fällen pro 100.000 Einwohner auf 49,3 halbiert werden. Dennoch weist das Land jedoch weiterhin eine über sechsmal höhere Melderate im Vergleich zur Europäischen Union (EU) und zum Europäischen Wirtschaftsraum (EWR) auf. Darüber hinaus gilt die Ukraine als Hochprioritätsland in Bezug auf antibiotikaresistente TB-Formen. Im Jahr 2022 betrug der Anteil der Rifampicin-resistenten (RR-) Fälle in der Ukraine 28,3% (n = 3647) von allen bakteriologisch gesicherten pulmonalen TB-Fällen mit vorliegender Empfindlichkeitsprüfung für Rifampicin. In der EU/im EWR lag dieser Anteil bei lediglich 5,0% (n = 933) (30).

Nach dem Beginn des Konflikts zwischen Russland und der Ukraine im Februar 2022 erhielten nach Daten des Statistischen Amtes der Europäischen Union (Eurostat) bis zum Stichtag 31.12.2022 über vier Millionen Ukrainer einen temporären Schutzstatus in den EU-/EWR-Ländern (31). Infolgedessen stieg die Größe der ukrainischen Population in der Region deutlich an.

6.2 Zielsetzung

Ziel dieser Arbeit ist es, die aktuelle TB-Epidemiologie unter Ukrainern in der EU und im EWR zu erfassen. Der Untersuchungszeitraum für die Studie umfasst vier Jahre, von 2019 bis 2022. Die Einflüsse der COVID-19 Pandemie und des ersten Jahres des Russland-Ukraine-Krieges sollen dabei abgebildet werden. Durch die Ermittlung der Krankheitslast in dieser Population soll die Versorgung der betroffenen Personengruppen verbessert werden.

6.3 Methoden

Für TB-Erkrankungen gilt sowohl in der Ukraine als auch in den EU-/EWR-Mitgliedsstaaten eine Meldepflicht bei Nachweis oder begründetem Verdacht. Dadurch ist die Datenlage zu TB-Erkrankungen in der Region sehr gut. TB-Meldungen aus den EU-/EWR-Ländern werden an das Europäische Zentrum für die Prävention und die Kontrolle von Krankheiten (engl.: European Centre for Disease Prevention and Control; ECDC) übermittelt. Die Daten werden anschließend in das

Europäische Surveillance System (engl.: The European Surveillance System; TESSy) eingepflegt und nach demographischen, anamnestischen, mikrobiologischen und klinischen Variablen klassifiziert. Die TESSy-Datenbank ermöglicht somit eine länderübergreifende Analyse. Zusätzlich wurden Daten aus Lettland direkt vom lettischen Nationalen Institut für Public Health für 2019 und 2020 bezogen, da diese aufgrund von Übertragungsfehlern über TESSy nicht verfügbar waren. Die TB-Meldungen aller EU-/EWR-Mitgliedsstaaten für den Zeitraum von 2019 bis 2022 wurden in die Studie eingeschlossen.

Zur Berechnung der TB-Melderate wurde zudem die Gesamtzahl der Ukrainer im jeweiligen Land hinzugezogen. Für die Populationsstatistik wurde die Zahl der registrierten ukrainischen Staatsbürger verwendet. Menschen, die in der Ukraine geboren sind, aber eine andere Staatsbürgerschaft besitzen, wurden somit in der primären Analyse nicht berücksichtigt. Eine Sensitivitätsanalyse in einer nach Geburtsland definierten Population wurde ergänzend durchgeführt. Populationsdatensätze wurden über Eurostat bezogen (31, 40, 41). Für Estland wurden zusätzlich Daten über das nationale statistische Amt bezogen (42).

6.4 Ergebnisse

Zwischen 2019 und 2022 wurden in der Region insgesamt 1.382 TB-Fälle ukrainischer Herkunft registriert. Über die Hälfte dieser Fälle (n = 780) wurde im Jahr 2022 verzeichnet. Deutschland, Polen und Tschechien meldeten die höchsten Zahlen sowohl für 2022 als auch für die ersten drei Studienjahre. Drei Länder – Bulgarien, Kroatien und Liechtenstein – verzeichneten keine TB-Fälle ukrainischer Herkunft.

Ein Rückgang der TB-Meldungen von 30,2%, von 235 auf 164, wurde in der ukrainischen Population in der EU/im EWR im Jahr 2020 verzeichnet. Nach einem Anstieg der Meldezahlen, nahezu auf das Ausgangsniveau im Jahr 2021, wurde schließlich im Jahr 2022 ein fast vierfacher Anstieg auf 780 Fälle beobachtet. Die meisten TB-Fälle wurden in der Altersgruppe zwischen 25 und 45 Jahren registriert. Männer waren durchgehend häufiger betroffen. Im Jahr 2022 war das Verhältnis von männlichen zu weiblichen Fällen ausgeglichener als im Vergleich zu den ersten drei Studienjahren.

Die Gesamt-EU/EWR-Melderaten unter Ukrainern lagen im gesamten Zeitraum im Bereich unter 20 Erkrankungen pro 100.000 und waren somit durchgehend niedriger als die Melderaten in der Ukraine (2019: 64,6/ 100.000 – 2022: 49,3/ 100.000). Die höchste EU/EWR-Rate wurde 2019 verzeichnet (19,6/100.000). Im Jahr 2020 spiegelte sich der Rückgang der Fallmeldungen auch in den Melderaten pro 100.000 wider. So wurde der tiefste Gesamtwert von 12,6/ 100.000 im Jahr 2020 verzeichnet. In den Jahren 2021 und 2022 kam es zu einem Anstieg auf 17,0/ 100.000 und einem erneuten Rückgang der Rate, sodass der Gesamtwert im Jahr 2022 bei 13,4 pro 100.000 ukrainische Staatsbürger lag.

Die Melderaten unter ukrainischen Migranten in den einzelnen EU/EWR-Ländern zeigten eine hohe Variabilität. Abgesehen von einzelnen Ausnahmen wurden mehrheitlich Werte berechnet, die niedriger waren als die Melderate in der Ukraine. Die Melderaten in den 5 Ländern mit den größten ukrainischen Populationen über den gesamten Zeitraum – Deutschland, Italien, Polen, Spanien und Tschechien – lagen durchgehend im Bereich zwischen 10 und 30 Erkrankungen pro 100.000 ukrainische Staatsbürger. Stratifiziert nach Alter und Geschlecht wurde die höchste Rate bei Männern in der Altersgruppe von 65 Jahren oder älter beobachtet.

Die absolute Zahl der TB-Erkrankungen, verursacht durch resistente Mykobakterien-Stämme, stieg von 43 Fällen im Jahr 2019 auf 194 Fälle im Jahr 2022 an. Der prozentuale Anteil resistenter Formen unter den ukrainischstämmigen Erkrankungen nahm von 2019 bis 2022 signifikant zu. So waren 2022 24,9% aller Fälle oder 31,9% der laborgesicherten Infektionen durch resistente TB-Formen verursacht. Im Kontext aller in der EU/im EWR registrierten resistenten TB–Fälle waren 19,7% ukrainischer Herkunft.

Behandlungsergebnisse lagen für 2022 und 2021 aufgrund der zeitversetzten Übermittlung dieser Daten teilweise nicht vor. In den 2 Jahren zuvor waren über die Hälfte der Fälle als „lost-to follow-up“ und/ oder „nicht evaluiert“ gekennzeichnet.

6.5 Diskussion

In der Auswertung der TB-Meldedaten des ECDC unter Ukrainern in der EU/im EWR spiegeln sich die Ereignisse der letzten Jahre durch den Rückgang der Fallzahlen in 2020 und die Zunahme der Meldungen im Jahr 2022 nach der Invasion

Russlands in die Ukraine wider. Der Rückgang der Fallmeldungen und der Notifikationsraten pro 100.000 Einwohner im Jahr 2020 entspricht der globalen Tendenz zu Beginn der Corona-Pandemie (15) und weist auf die Einschränkung der diagnostischen Kapazitäten hin. Die Reduktion der Notifikationsraten pro 100.000 bei gleichzeitig steigenden Fallmeldungen im Jahr 2022 kann im Kontext der veränderten Populationsstruktur mit einem hohen Anteil an Jugendlichen und weiblichen Personen gewertet werden (31). Darüber hinaus ist eine unterschiedliche sozioökonomische Zusammensetzung der Migrantenpopulation im Jahr 2022 denkbar. Die Diskrepanz zwischen geschätzten und beobachteten Fallzahlen könnte jedoch auch auf eine Unterdetektion hinweisen. Ein generelles Screening ist mit höheren Detektionsraten assoziiert (53), allerdings wird das generelle Screening teilweise als diskriminierend und stigmatisierend wahrgenommen und ist in vielen Ländern der Region finanziell und personell nicht gewährleistet (52, 54, 55). Angesichts der moderaten Melderaten in der Ukraine sowie in EU/EWR-Ländern mit eingeführtem Screening für ukrainische Migranten ist davon auszugehen, dass ein generelles Screening trotz erhöhter Detektionsraten zu einem vergleichsweise niedrigen Ertrag führen würde. Gezieltes TB-Screening in Risikopopulationen sowie generelle medizinische Untersuchungen werden hingegen klar von ECDC und WHO befürwortet (34).

Der hohe Anteil an antibiotikaresistenten TB-Fällen unter Ukrainern in der EU/im EWR ist vergleichbar mit dem Resistenzanteil in der Ukraine (30) und betont die Wichtigkeit der mikrobiologischen Diagnosesicherung und der adäquaten Therapie.

6.6 Ausblick

Niederschwellige, sprachlich und kulturell angepasste sowie an den Lebensumständen orientierte Versorgungsstrukturen sind notwendig, um die End-TB-Ziele in der EU/im EWR zu erreichen. Besondere Aufmerksamkeit sollte der Fallidentifizierung, der Empfindlichkeitsprüfung sowie der Initiierung und Kontinuität einer adäquaten Therapie in der ukrainischen Population gewidmet werden, insbesondere aufgrund des hohen Anteils an Resistenzen. Für eine nachhaltige und konsequente Senkung der TB-Belastung unter Ukrainern sind vor allem auch die Stabilität und der Frieden in der Region entscheidend.

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8. Appendix

8.1 Population data

		2019	2020	2021	2022
Austria	MIGR_ASYTPFA(1.0)				89,465
	MIGR_POP1CTZ(1.0)	11,162	11,585	11,898	12,673
Belgium	MIGR_ASYTPFA(1.0)				61,900
	MIGR_POP1CTZ(1.0)	5,335	5,630	5,835	6,187
Bulgaria	MIGR_ASYTPFA(1.0)				146,750
	MIGR_POP1CTZ(1.0)	6,625	7,577	8,972	10,055
Cypress	MIGR_ASYTPFA(1.0)				12,450
	MIGR_RESVAS(1.0)	3,903	4,186	4,151	4,573
Czechia	MIGR_ASYTPFA(1.0)				457,685
	MIGR_POP1CTZ(1.0)	129,284	143,129	145,155	170,977
Germany	MIGR_ASYTPFA(1.0)				776,735
	MIGR_POP1CTZ(1.0)	131,051	133,281	134,989	138,203
Denmark	MIGR_ASYTPFA(1.0)				32,565
	MIGR_POP1CTZ(1.0)	11,716	12,722	12,821	13,715
Estonia	MIGR_ASYTPFA(1.0)				41,670
	MIGR_POP1CTZ(1.0)	9,848	11,259		15,934
	RV069			13,405	
Spain	MIGR_ASYTPFA(1.0)				158,300
	MIGR_POP1CTZ(1.0)	103,606	107,576	107,234	105,667
Finland	MIGR_ASYTPFA(1.0)				44,855
	MIGR_POP1CTZ(1.0)	4,593	5,126	5,837	7,202
France	MIGR_ASYTPFA(1.0)				81,375
	MIGR_POP1CTZ(1.0)	19,922	20,009	20,285	
	MIGR_RESVAS(1.0)				18,610
Greece	MIGR_ASYTPFA(1.0)				21,310
	MIGR_RESVAS(1.0)	19,390	19,082	18,745	20,690
Croatia	MIGR_ASYTPFA(1.0)				19,110
	MIGR_RESVAS(1.0)	1,354	2,304	2,464	2,405

Hungary	MIGR_ASYTPFA(1.0)				29,695
	MIGR_POP1CTZ(1.0)	24,197	30,316	27,380	30,707
Ireland	MIGR_ASYTPFA(1.0)				70,495
	MIGR_POP1CTZ(1.0)	2,981	3,373	3,492	3,910
Iceland	MIGR_ASYTPFA(1.0)				2,285
	MIGR_POP1CTZ(1.0)	209	225	237	240
Italy	MIGR_ASYTPFA(1.0)				149,295
	MIGR_POP1CTZ(1.0)	227,867	228,560	235,907	225,307
Liechtenstein	MIGR_ASYTPFA(1.0)				420
	MIGR_POP1CTZ(1.0)	51	44	56	51
Lithuania	MIGR_ASYTPFA(1.0)				65,125
	MIGR_POP1CTZ(1.0)	13,891	21,404	26,898	7,105
Luxembourg	MIGR_ASYTPFA(1.0)				4,915
	MIGR_POP1CTZ(1.0)	912	980	1,007	1,075
Latvia	MIGR_ASYTPFA(1.0)				37,800
	MIGR_POP1CTZ(1.0)	4,806	5,531	5,745	6,371
Malta	MIGR_ASYTPFA(1.0)				1,620
	MIGR_RESVALID(1.0)	1,046	1,174	1,088	1,192
Netherlands	MIGR_ASYTPFA(1.0)				102,895
	MIGR_POP1CTZ(1.0)	6,268	7,042	7,082	7,540
Norway	MIGR_ASYTPFA(1.0)				33,230
	MIGR_POP1CTZ(1.0)	3,498	3,806	3,826	3,553
Poland	MIGR_ASYTPFA(1.0)				1,561,780
	MIGR_RESVAS(1.0)	413,770	476,206	343,775	651,221
Portugal	MIGR_ASYTPFA(1.0)				44,980
	MIGR_POP1CTZ(1.0)	29,218	29,718	28,629	27,195
Romania	MIGR_ASYTPFA(1.0)				100,890
	MIGR_POP1CTZ(1.0)	1,619	2,057	2,172	2,338
Sweden	MIGR_ASYTPFA(1.0)				46,665
	MIGR_POP1CTZ(1.0)	5,116	5,848	6,147	6,674
Slovenia	MIGR_ASYTPFA(1.0)				7,410
	MIGR_POP1CTZ(1.0)	2,202	2,284	2,397	2,434

Slovakia	MIGR_ASYTPFA(1.0)				104,145
	MIGR_POP1CTZ(1.0)	3,745	4,070	4,429	6,494

8.2 Ethical approval

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Aktenzeichen: 2023-593
15.08.2023 / IK

Verkürztes Verfahren - Anzeige
Antragsteller: Prof. Dr. Dr. Christoph Lange
Titel: The impact of migration in the context of the Russia-Ukraine conflict on the epidemiology of tuberculosis infections in the European Union, the European Economic Area and the United Kingdom.
Hier: Ihre Einreichung vom 01.08.2023

Sehr geehrter Herr Lange,

mit Ihrem o.g. Schreiben informieren Sie die Ethik-Kommission über Ihr geplantes Vorhaben.

Die Ethik-Kommission nimmt das Vorhaben zustimmend zur Kenntnis.

Mit freundlichen Grüßen

Prof. Dr. Alexander Katalinic
Vorsitzender der Ethik-Kommission

Allgemeine Hinweise:
Ggf. aufgeführte Hinweise sind zu berücksichtigen. Eine Wiedervorlage ist nicht nötig. Bei Bedarf eines Votums ohne Hinweise sind die angepassten Dokumente als Amendmend vorzulegen. Änderungen sind hervorzuheben.
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Vorgelegte Dokumente
1) 202307_Proposal_v0.4_FZB-TBNET-ECDC TB in Ukrainians EU_EEA_UK_clean.pdf vom 01.08.2023
2) Anzeige_EK_FZB-ECDC-TBNET-TB-Ukraine-EU-EEA-UK.pdf vom 01.08.2023
3) nicht verfügbar - Studieninformation und Einwilligungserklärung.pdf vom 01.08.2023
4) TESSy metadata description.pdf vom 01.08.2023

9. Acknowledgements

First and foremost, I would like to express my gratitude to Prof. CL for his inspirational energy, knowledge and dedication and for his invaluable support.

Furthermore, I would like to thank Dr. DZ for his critical thinking and the excellent scientific input.

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Last but not least, I would like to thank my parents and my grandparents for giving me the opportunity to study and explore the world.

10. Curriculum vitae

Personal details:

Personalien:	Krista Stoycheva Born 20.06.1990 in Pernik, Bulgaria

Formal education:

2010 – 2016	Medical studies, Charité Medical University; Berlin, Germany; State exam and licensure 11.2016
2004 – 2009	Foreign language school; Pernik, Bulgaria

Professional experience:

2023 – 2024	Research assistant/ Safety physician / Doctoral student - Research Center Borstel – Leibniz Lungcenter, Borstel
2022	Research assistant/ Safety physician - Division for infectious disease and tropical medicine – Ludwig Maximilian University, Munich
2017 – 2021	General Practitioner Training - Internal medicine and infectious disease - Accident and emergency
2012 – 2016	Student assistant - German Organ Transplantation Organisation, Berlin

11. Publication and presentations

11.1 Publication

Stoycheva, K., Cristea, V., Ködmön, C., Rosales-Klintz, S., Zenner, D., Vasiliu, A., van der Werf, M., & Lange, C. (2024). Tuberculosis in people of Ukrainian origin in the European Union and the European Economic Area, 2019 to 2022. Euro surveillance: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin, 29(12), 10.2807/1560-7917.ES.2024.29.12.2400094.
https://doi.org/10.2807/1560-7917.ES.2024.29.12.2400094

11.2 Presentations

02.02.2024 – DanGerouS Mycobacteria Meeting; Copenhagen, Denmark.
18.03.2024 – World TB Day Webinar (ECDC/WHO); online.
13.04.2024 – Deutsche Gesellschaft für Innere Medizin; Wiesbaden, Germany.
21.06.2024 – Clinical TB course (Deutsches Zentrum für Infektionsforschung/ Research Center Borstel); Borstel, Germany.