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ECDC SURVEILLANCE

Tuberculosis molecular surveillance status report, focusing on rifampicin and multi-drug resistance in the EU/EEA

March 2025

Summary

The European Centre for Disease Prevention and Control (ECDC) has analysed whole genome sequencing (WGS) profiles of rifampicin resistant (RR)- and multi-drug resistant (MDR) *Mycobacterium tuberculosis* strains, collected between 2020 and 2023 in the European Union (EU) and European Economic Area (EEA). The results were added to tuberculosis (TB) WGS data collected during the period 2017–2019 as a part of an EU/EEA pilot project on TB molecular surveillance.

Analysis of 2 726 RR/MDR TB isolates with complete WGS data showed:

- a sub-optimal typing coverage at EU/EEA level. Only 11 countries contributed, with 751 strain sequences during the period 2020–2023;
- wide variation in the sequencing coverage. The highest sequencing coverage was achieved in 2018 (69.0%), while the lowest coverage was observed in 2023 (17.1%);
- a decreasing clustering proportion from 2020. The lowest clustering percentage was observed in 2023 (21.2%) and the highest in 2020 (62.0%);
- the identification of 68 cross-border molecular clusters, comprising 650 RR/MDR TB strains in total. Only 18 clusters included 10 or more strains, involving two to ten countries in each cluster;
- limitations due to the incompleteness of data for some non-mandatory variables (e.g. country of birth/nationality). As a consequence, in-depth analyses of cluster dynamics and possible transmission routes within the clusters was not possible;
- successful lineage assignment in 97.3% of the strains. The most prevalent lineages were Beijing (N=1 033, 37.9%), Mainly T (N=561, 20.6%) and Haarlem (N=320, 11.7%). Due to the low number of countries submitting WGS data during the period 2020–2023, Beijing lineage appeared to be a dominant strain, however this should be interpreted with caution.

The COVID-19 pandemic had a significant impact on TB laboratory services in the EU/EEA [1], and the engagement of the EU/EEA countries remains low, 10 countries in 2023 compared to 23 countries in 2018 and 2019.

In conclusion, despite the support and IT infrastructure available at ECDC, efforts are still needed to consolidate the WGS-based surveillance of TB in the EU/EEA in order to achieve the 2017–2019 level as a minimum (i.e. typing coverage above 50%). A higher WGS typing coverage will contribute to a better understanding of rifampicin RR/MDR TB strain diversity, early detection and tracing of trans-national outbreaks and the mapping of transmission routes across Europe, as well as changes in the resistance pattern and mechanism.

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Background

Genotyping has become a standard tool in tuberculosis control programmes for countries within the European Union (EU) and European Economic Area (EEA) and is gaining recognition as the gold standard for TB transmission studies and outbreak investigations. Approximately half of the TB reference laboratories in the EU/EEA are using WGS to characterise drug resistance profiles and to assess the genetic relatedness of the *Mycobacterium tuberculosis* strains isolated at country level [2].

In September 2017, the European Centre for Disease Prevention and Control (ECDC) initiated a 30-month (2017−2020) pilot project on the use of WGS for molecular typing and characterisation of *Mycobacterium tuberculosis* complex isolates in the EU/EEA. This pilot project generated evidence on the use of WGS for a better understanding of rifampicin resistant (RR)- and multi-drug resistant (MDR) TB strain diversity. The results will aid early detection and tracing of trans-national outbreaks and the mapping of transmission routes across Europe. In addition, analysis and reporting standards were established, along with WGS methodology standards to ensure data comparability within EU/EEA [3].

The pilot project showed that a WGS-based surveillance system is not only feasible but can efficiently clarify the dynamics of in-country and cross-border RR/MDR-TB transmission across EU/EEA countries. The results of this study highlight that the establishment of an EU/EEA centralised WGS-based surveillance system for TB will require the strengthening of national integrated systems (including WGS, microbiology and epidemiological data) performing prospective WGS surveillance. In addition, it will also be necessary to develop clear procedures to facilitate international collaboration for the investigation of cross-border clusters. Therefore, following ECDC's decision to introduce WGS-based surveillance into routine TB surveillance activities, the TB module has been developed on the EpiPulse[1] platform for analysis and visualisation of TB WGS data.

Building upon the lessons learned from the pilot WGS project, ECDC has provided additional technical support to EU/EEA countries interested in using WGS for molecular characterisation of RR/MDR TB strains isolated between 2020 and 2023. This support included the provision of sequencing services for the EU/EEA countries lacking additional capacity for WGS, as well as online support with data uploads to The European Surveillance System (TESSy) and data analysis in EpiPulse. All WGS results obtained as a result of this support were included in TESSy.

In addition, ECDC requested EU/EEA countries performing routine WGS for RR/MDR TB strains to submit the WGS data of RR/MDR TB strains isolated between 2020 and 2023 to TESSy, as a first step towards systematic TB molecular surveillance.

Aim

The aim of this report is to provide an overview of the dynamics and geographical distribution of RR/MDR TB strains in the EU/EEA, focussing on the strains isolated in 2020−2023, and to perform molecular cluster identification, including WGS data collected in 2017−2019, as part of an EU/EEA pilot project on TB molecular surveillance.

Overview

Data

The isolate data were extracted from TESSy on 22 October 2024. The database contains 2 726 RR/MDR TB isolates with complete WGS data, reported during the period 2017−2023. During the period covered by the EUMySeqTB project (2017−2019), 23 countries submitted 1 975 sequences to TESSy, while during the period 2020−2023, 751 sequences were submitted by nine countries (Table 1).

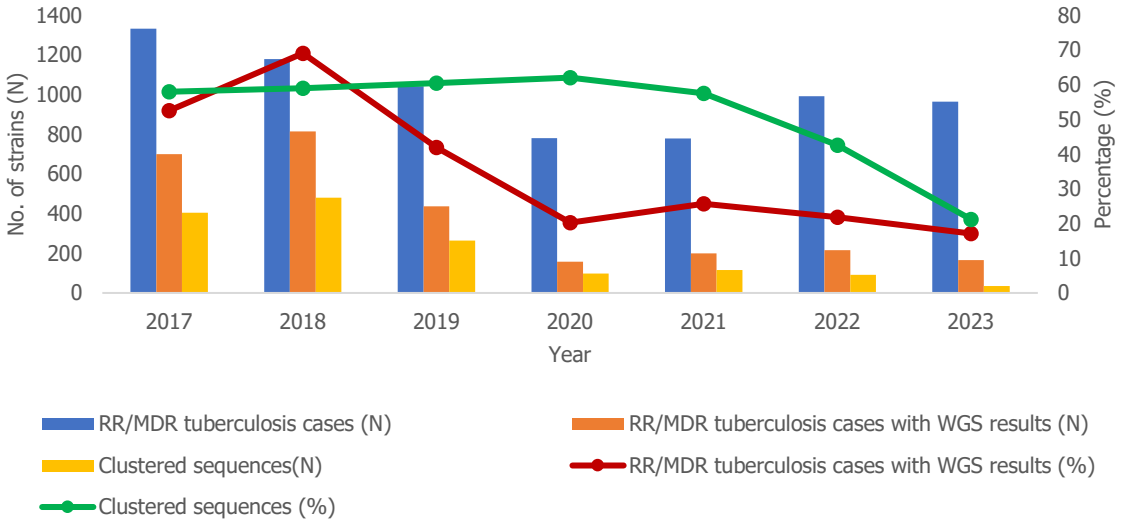
[1] ECDC's EpiPulse platform is available at: https://epipulse.ecdc.europa.eu

Table 1. Number of RR/MDR TB strains with WGS data reported to TESSy, 2017–2023

Country	Year							Total
	2017	2018	2019	2020	2021	2022	2023	
Austria		18	6					24
Belgium	5	8	6					19
Bulgaria	24	24	16					64
Croatia		2	1					3
Czechia	5	8	11	3	11			38
Denmark		4	3					7
Estonia	29	28	24	21	21	16	19	158
Finland	4	4	2				5	15
France	8	61	25					94
Germany	70	93	15					178
Hungary	3	12	4	13	16	15	11	74
Ireland	6	6	8	3	7	9	4	43
Italy	63	40	20	21	26	5	15	190
Latvia	18	33	33					84
Lithuania	80	63	53	39	49	69	62	415
Netherlands	10	6	6			8	16	46
Norway	3	6	2				16	27
Poland	27	53	10	41	51	68		250
Portugal	12	19	4					35
Romania	306	298	174					778
Slovakia	1	3	2					6
Slovenia	1							1
Spain	15	35	12	16	13	11	15	117
Sweden	9	10	5	7	7	16	6	60
Total	**699**	**834**	**442**	**164**	**201**	**217**	**169**	**2 726**

The data for 169 strains isolated in 2023 were reported by 10 countries. During the period 2017–2023, the number of notified RR/MDR TB cases showed a decreasing trend from 1 332 to 964 in 2023, following the trend in TB notifications (unpublished data for 2023) [4]. The highest sequencing coverage was achieved in 2018 (69.0%), while the lowest coverage was observed in 2023 (17.1%). The lowest clustering percentage was observed in 2023 (21.2%) and the highest in 2020 (62.0%).

Figure 1. Sequencing coverage and clustering percentage of RR/MDR tuberculosis, EU/EEA, 2017–2023



Clusters

Cluster identification was performed using the ECDC pipeline by comparing the 2 891 Core Genome Multi-locus Sequence Typing (cgMLST) loci. A cross-border molecular cluster was defined as two or more *M. tuberculosis* isolates from at least two EU/EEA Member States with less than six allelic differences (AD). In this analysis the emphasis was on cross-border molecular clusters which included at least one isolate from 2020 or later.

Among the RR/MDR TB strains covering the period from 2017 till 2023, 68 cross-border molecular clusters were detected and a total of 650 RR/MDR TB strains were clustered. The cluster size varied between two and 73 strains involving two to ten countries. Only 18 clusters included 10 or more strains in total (Table 2).

Table 2. Cross-border molecular clusters with strains isolated during the period 2020–2023

Cluster ID	Number of isolates	Countries*
2021-09.TB.17.Beijing	73	DE(4), EE(22), HU(1), LT(46)
2021-09.TB.41.Beijing	64	BE(1), CZ(3), DE(1), EE(1), FR(2), IT(5), LT(1), NL(1), PL(48), SK(1)
2021-09.TB.11.mainlyT	37	IT(20), RO(17)
2021-09.TB.37.mainlyT	34	AT(1), IT(3), RO(30)
2021-09.TB.31.Beijing	32	IE(2), LT(28), PL(2)
2021-09.TB.46.LAM	28	LT(27), NO(1)
2021-09.TB.214.Beijing	26	DE(2), IT(2), LT(2), PL(19), SE(1)
2021-09.TB.10.Beijing	22	DE(1), CZ(1), LT(18), PL(1), SE(1)
2021-09.TB.50.Ural	19	DE(1), RO(18)
2021-09.TB.49.mainlyT	18	BE(1), DE(1), RO(16)
2021-09.TB.57.Beijing	17	CZ(1), DE(5), IT(1), LT(5), LV(1), PL(4)
2021-09.TB.120.Euro-American	16	AT(4), DE(7), FR(1), IT(4)
2021-09.TB.24.mainlyT	14	DE(1), RO(13)
2021-09.TB.55.Beijing	14	CZ(3), DE(1), EE(1), ES(1), PL(5), SE(3)
2021-09.TB.66.Haarlem	13	IT(2), RO(11)
2021-09.TB.09.Euro-American	12	DE(5), IT(5), NL(1), SE(1)
2021-09.TB.153.X-type	10	ES(9), SE(1)
2021-09.TB.19.mainlyT	10	AT(1), RO(9)
2021-09.TB.03.LAM	9	ES(3), IT(6)
2021-09.TB.23.Euro-American	9	DE(1), FR(2), IT(3), SE(3)
2021-09.TB.234.H37Rv-like	9	HU(8), IT(1)
2023-04.TB.29.Beijing (2.2.1)	9	AT(1), CZ(1), DK(1), PL(6),
2021-09.TB.169.LAM	8	EE(1), IE(1), LT(1), LV(5)
2021-09.TB.26.Ural	8	PT(1), DE(2), IT(4), RO(1)
2021-09.TB.43.LAM	8	LV(4), FR(1), NL(1), EE(2)
2021-09.TB.38.Beijing	7	DE(3), IT(1), FR(1), AT(1), SE(1)
2021-09.TB.206.Ural	6	ES(3), LT(3)
2021-09.TB.45.Beijing	6	AT(3), DE(2), SE(1)
2021-09.TB.109.Haarlem	5	IT(1), RO(4)
2021-09.TB.280.Beijing	5	BE(2), PL(3)
2021-09.TB.33.Ural	5	IE(1), LT(4)
2021-09.TB.29.LAM	5	ES(1), NL(1), IT(3)
2021-09.TB.79.Haarlem	5	FR(1), RO(4)
2021-09.TB.89.TUR	5	BG(4), SI(1)
2021-09.TB.207.Ural	4	PL(3), DE(1)
2021-09.TB.266.TUR	4	BG(2), DE(2)
2021-09.TB.47.mainlyT	4	DE(1), RO(3)
2021-09.TB.116.Beijing	3	IT(1), PL(1), SE(1)
2021-09.TB.15.mainlyT	3	IT(1), RO(2)
2021-09.TB.168.mainlyT	3	DE(1), RO(2)
2023-04.TB.32.Mainly T (4.7)	3	HR(1), HU(2)
2021-09.TB.245.Haarlem	3	NO(1), RO(2)
2021-09.TB.277.Beijing	3	IT(2), SE(1)
2021-09.TB.30.Euro-American	3	DE(1), FR(1), IT(1)
2021-09.TB.90.mainlyT	3	IT(1), RO(2)
2021-09.TB.100.Euro-American	2	NL(1), PL(1)
2021-09.TB.111.Delhi-CAS	2	FI(1), SE(1)
2021-09.TB.122.mainlyT	2	IT(1), RO(1)
2021-09.TB.140.LAM	2	ES(1), FR(1)
2021-09.TB.159.LAM	2	BE(1), ES(1)
2021-09.TB.161.Haarlem	2	IT(1), RO(1)

Cluster ID	Number of isolates	Countries*
2021-09.TB.251.Beijing	2	FR(1), IT(1)
2021-09.TB.264.Euro-American	2	DE(1), IT(1)
2021-09.TB.290.Beijing	2	LT(1), NL(1)
2021-09.TB.293.LAM	2	ES(1), PT(1)
2021-09.TB.296.Beijing	2	FR(1), NL(1)
2021-09.TB.61.mainlyT	2	BG(1), DE(1)
2021-09.TB.75.Beijing	2	DE(1), LT(1)
2021-09.TB.82.mainlyT	2	BG(1), FR(1)
2021-09.TB.97.Ural	2	SK(1), PL(1)
2023-04.TB.16.Beijing (2.2.1)	2	DE(1), PL(1)
2023-04.TB.12.Beijing (2.2.1)	2	CZ(1), PL(1)
2023-04.TB.21.Beijing (2.2.1)	2	LT(1), NL(1)
2023-04.TB.26.Haarlem (4.1.2.1)	2	DE(1), FR(1)
2023-04.TB.41.Beijing (2.2.1)	2	DE(1), IT(1)
2023-04.TB.42.Mainly T (4.8)	2	PL(1), RO(1)
2023-04.TB.44.Beijing (2.2.1)	2	AT(1), HU(1)
2024-05.TB.01.Beijing (2.2.1)	2	EE(1), FI(1)

** The two-letter country codes are assigned according to the ISO 3166 country code standards (https://www.iso.org/obp/ui/#search)*

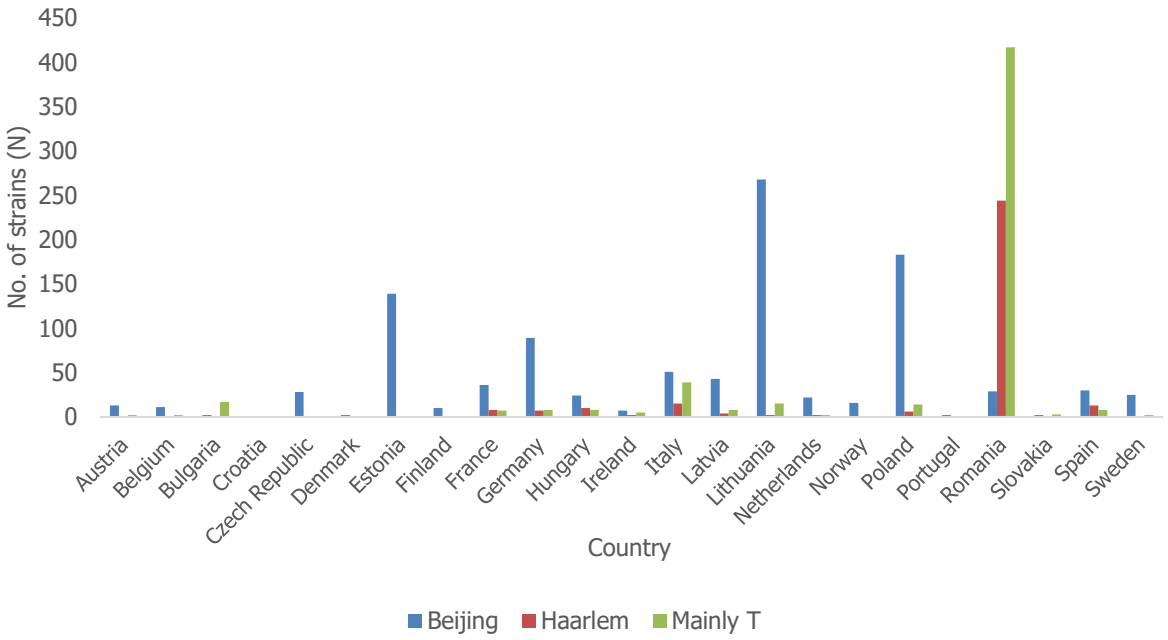
Of 2 726 RR/MDR TB strains, 2 653 (97.3%) had a successful lineage assignment. The most prevalent lineages were Beijing (N=1 033, 37.9%), Mainly T (N=561, 20.6%) and Haarlem (N=320, 11.7%) (Table 3).

Table 3. Genotypic lineages of RR/MDR TB strains by year

Lineage	Year							Total
	2017	2018	2019	2020	2021	2022	2023	
Beijing	211	254	137	94	109	137	91	1 033
Mainly T	176	224	119	12	15	7	8	561
Haarlem	125	105	68	6	8	3	5	320
LAM	53	89	34	19	19	24	16	254
Ural	36	35	34	10	16	18	18	167
Euro-American	36	46	20	6	9	3	3	123
Delhi-CAS	11	18	7	3	2	1	3	45
S-type	20	13	4	1		1	5	44
TUR	15	16	6		1			38
X-type	1	9	3	2	4	6		25
East African-Indian	5	10	4		1			20
H37Rv-like	3	2	1	4	3	1		14
Cameroon	5			1				6
East-Asian			1					1
Uganda			1					1
West-African		1						1
Not assigned	2	12	3	6	14	16	20	73
Total	**699**	**834**	**442**	**164**	**201**	**217**	**169**	**2 726**

The three most prevalent lineages are not equally distributed across the EU/EEA. During the period 2017–2023, Haarlem and Mainly T were most prevalent in Romania, which reported 245 (76.6.9%) of the 320 Haarlem strains reported in the EU/EEA, and 418 (74.5%) of the 561 Mainly T strains. During the same period, the Beijing lineage was predominant in the other EU/EEA countries that submitted data. However, these results should be interpreted with caution due to the low number of countries submitting WGS data during the period, including Romania (Figure 2).

Figure 2. Beijing, Haarlem and Mainly T lineages isolated in 2017–2023



Conclusions

The first six months of the COVID-19 pandemic had a significant impact on TB laboratory services in the EU/EEA, due to the challenges with procuring supplies and reagents, staff unavailability linked to either COVID-19-related sickness or self-isolation, lockdowns and re-deployment. Nearly all national reference laboratories in the EU/EEA experienced a sharp reduction in workload (i.e. reduced number of incoming specimens) in both primary and reference activities [1]. This may have contributed to the sub-optimal level of the sequencing coverage at EU/EEA level during the period 2020–2023, because the end of the COVID-19 pandemic was not declared until 5 May 2023, and there might be not have been sufficient time for laboratories to fully recover yet. As a minimum, sequencing coverage should reach the level of the 2017–2019 period (at least 50%) in order to allow for in-depth analysis of cluster dynamics and possible transmission routes within the EU/EEA. Further efforts are therefore needed in the countries, along with technical support from ECDC and other EU initiatives, to consolidate TB WGS-based surveillance activities in the EU/EEA.

Next steps

ECDC will continue to provide technical support to the EU/EEA Member States for participation in RR/MDR TB molecular surveillance activities (e.g. data reporting to the molecular surveillance module of TESSy and the use of EpiPulse for analysis and visualisation of data).

ECDC welcomes your feedback! Please send any comments or suggestions you may have to tubeculosis@ecdc.europa.eu.

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