RAPID RISK ASSESSMENT

# Multidrug-resistant tuberculosis in migrants, multi-country cluster

Second update, 24 March 2017

## Conclusions and options for response

A multi-country cluster of multidrug-resistant tuberculosis (MDR TB) involving 25 migrants has been delineated by whole genome sequencing (WGS). All cases have a recent history of migration from Somalia (22 cases) and Eritrea (2 cases) and Ethiopia (1). Cases have been reported by Germany (13), Switzerland (8), Austria (2), Finland (1) and Sweden (1). WGS analysis of the 25 cluster isolates supports the hypothesis of cases being part of a chain of recent transmission likely to have taken place either in their country of origin or in a place along their migration route to the country of destination. Based on the currently available information, it is not possible as yet to rule out that transmission occurred in the European Union (EU) or European Free Trade Area (EFTA).

It therefore remains important to investigate exposure risk factors rapidly, including travel itinerary and history of possible contacts among patients and share this information, to further assess whether transmission may have taken place in the EU/EFTA, during migration or in the country of origin, and thus inform appropriately targeted prevention and control measures.

Although the number of cases detected so far suggests that there is only a limited risk of this cluster becoming a widespread event in Europe, more cases may yet be identified in association with this cluster.

Only three of the eight cases in Switzerland were detected through the screening for symptoms used for asylum seekers in Switzerland. Thus, early case finding of active TB and drug susceptibility testing, especially in newly arriving migrants from the Horn of Africa, is important in order to identify and treat active cases and to provide preventive treatment or monitoring for those diagnosed with latent tuberculosis infection.

## Source and date of request

ECDC internal decision, 14 March 2017.

## Public health issue

This second update provides information regarding the risk of EU transmission of an MDR TB clone initially detected in seven asylum seekers from the Horn of Africa who currently reside in Switzerland. Recommendations are given to improve the understanding and the public health impact of this cluster for the EU.

## Consulted experts

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# Disease background information

Multidrug-resistant tuberculosis (MDR TB) is defined as tuberculosis (TB) disease caused by a *Mycobacterium tuberculosis* complex strain resistant to at least rifampicin and isoniazid [1]. MDR TB is an urgent public health priority in Europe, with significant health and cost implications associated with the expensive and prolonged treatment often required [2]. Inadequate or incomplete TB treatment is the main risk factor for the development of resistance among TB cases and is usually associated with intermittent drug use, errors in medical prescription, poor patient adherence and low quality of TB drugs [3].

Options for prevention of TB infection among contacts of MDR TB cases are limited and require an individual risk assessment, taking into consideration:

- the risk of progression to TB disease;
- the drug susceptibility pattern of the source case; and
- the risk of adverse drug events [4,5].

Migrants seeking refuge from conflict or deprived areas may be at increased risk of TB and MDR TB because of the collapse of health service infrastructure in these contexts. Some migrant groups, including refugees, refused asylum seekers, victims of trafficking and undocumented migrants may be at particularly high risk of (MDR) TB due to exposure to destitution, poor social conditions (e.g. overcrowding, poor living conditions, incarceration or detention and homelessness), exposure to other migrants from high-incidence countries affected by MDR TB along their migration route or after entry in the host country, or co-infection (e.g. with human immunodeficiency virus) [2].

The burden of tuberculosis in high-income countries disproportionally affects the foreign-born migrant population and transmission is documented to predominantly occur within migrant communities or indigenous communities, and less between migrant and indigenous communities [2,6]. Active disease occurs in five to ten percent of those infected within a few months to many years after infection and, in up to ten per cent per year, in HIV-positive people.

# Event background information

In December 2016, Switzerland initially reported to the European Commission a cluster of seven MDR TB cases in newly arrived migrants from Somalia (5 cases), Eritrea (1) and Ethiopia (1). The Commission informed the Member States through an Early Warning and Response System (EWRS) message. In response to the EWRS notification Germany, Austria, Finland and Sweden reported cases linked to this cluster by WGS. Switzerland later reported an eighth case. As of 14 March, isolates from 25 cases are part of the WGS cluster and are reported from Germany (13), Switzerland (8), Austria (2), Finland (1) and Sweden (1). All cases have a recent history of migration from Somalia (22 cases), Eritrea (2) and Ethiopia (1).

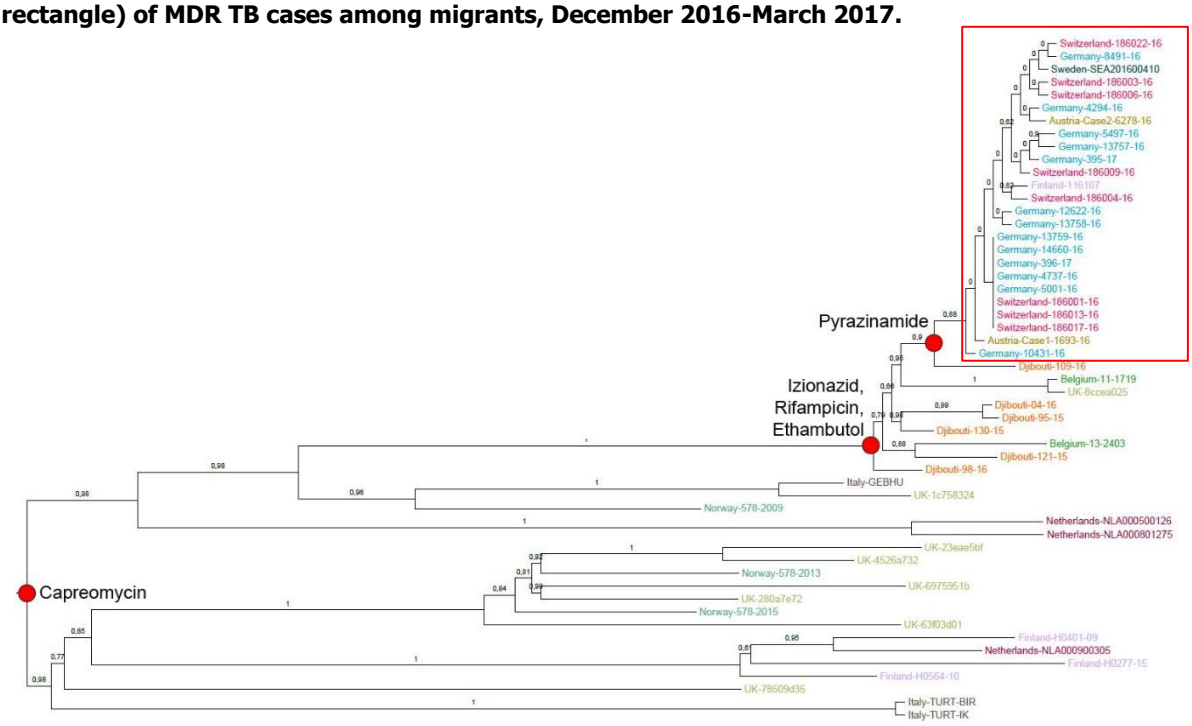
The German National Reference Laboratory for Mycobacteria (Forschungszentrum Borstel, Germany) used for WGS analysis a single-nucleotide polymorphism (SNP) pipeline covering 1 157 potential variable positions in the *Mycobacterium tuberculosis* genome. All cases in the cluster are not differing by WGS analysis by more than one SNP (Figure 1). In addition, Germany reports one culture-negative probable case with an epidemiological link to confirmed cases, one culture-positive case with an epidemiological link to confirmed cases and the same drug susceptibility pattern as the cluster (but WGS is not possible) and one putative case with WGS pending. France reports two cases under investigation with WGS pending.

Typing data from 2 828 MDR TB isolates reported to ECDC, covering the period 2003 to 2015 show that the cluster strain is rare. Only two MDR TB isolates with the same MIRU-VNTR 24 loci pattern have been reported, both from Belgium. The first case had Somalia as their country of origin and was diagnosed in 2011 and the second one had Djibouti as their country of origin and was diagnosed in 2013.

A difference in less than 6 SNPs among isolates may indicate recent transmission according to the European Reference Laboratory Network for Tuberculosis [7]. The isolates in the current cluster are separated by only one SNP, indicating a common source of infection within the past two to three years.

The outbreak cluster cases are 6 SNPs or more from the closest cases who are originating from Djibouti, therefore suggesting a divergence originating in the Horn of Africa more than three years ago.

**Figure 1. Maximum likelihood tree of MDR-TB cases by country of isolation, cluster (in the red rectangle) of MDR TB cases among migrants, December 2016-March 2017.**




*Note: 0.02 substitutions per site. Branches labelled with bootstrap values from 1,000 resamples.*

The maximum likelihood tree analysis above shows the evolution of the isolates, indicating for example that the isolate Djibouti 109-16 and the outbreak isolates are sharing one immediate ancestor.

Available data suggest that the origin of the cluster strain stems from the Horn of Africa. Further comparisons of WGS profiles of the cluster cases and additional circulating strains in Africa could support the clarification of ancestral relationship and make it possible to find a probable date of divergence for the cluster strain.

A preliminary analysis of the interviews of the cases in Switzerland shows that most cases reported symptoms at arrival or before, suggesting that transmission probably did not occur in Switzerland. Six of the refugees had a long stay in Bani Waleed (Libya) in precarious conditions favourable for TB transmission.

# ECDC threat assessment for the EU

According to data published in the latest WHO TB report, the estimated incidence of TB in Somalia was 274 per 100 000 in 2015. According to the same source MDR TB was estimated to be the cause in 8.7% of new TB cases and to be identified in 47.0% of previously-treated TB cases in Somalia. According to IOM, 2.1% of the refugees in Europe, i.e. about 10 000 people, are coming from Somalia. The clustering of case strains by WGS within one SNP difference suggests a recent transmission likely to have taken place either in their country of origin or in a place along their migration route to the country of destination or in the country of destination. Therefore, with the available information, it is not yet possible to rule out that transmission occurred in the European Union (EU) or European Free Trade Area (EFTA).

Infected persons who do not have active TB are not infectious. However, they are at risk of developing active TB disease and becoming infectious. The lifetime risk of reactivation TB for a person with documented latent TB infection (LTBI) is estimated to be 5 to 10%, with the majority developing TB disease within the first five years after initial infection [8].

Although the clearest risk of transmission within the EU/EEA is within the affected migrant population and the TB incidence in a foreign-born population does not have a significant influence on overall TB incidence in the indigenous population in the EU/EFTA, a low risk of transmission to the indigenous population cannot be discounted [2]. Therefore, while there remains a risk of additional cases being detected among newly arrived migrants, the risk of transmission to EU/EFTA resident populations is low.

All four countries involved in the multi-country cluster implement migrant screening [9]. However, only three of the eight cases in Switzerland were detected through the screening for symptoms used for asylum seekers in Switzerland. Thus, early case finding of active TB and drug susceptibility testing, especially in newly arriving migrants from the Horn of Africa, is important in order to identify and treat active cases and to provide preventive treatment or monitoring for those diagnosed with latent tuberculosis infection [10].

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