

RAPID RISK ASSESSMENT

Extensively drug-resistant (XDR) tuberculosis – multi-country cluster, Romania

Update, 21 October 2016

Main conclusions and options for response

A cluster involving four cases of extensively drug-resistant tuberculosis (XDR TB) has been detected in students attending the University of Medicine and Pharmacy in Oradea Municipality, Bihor County, Romania.

One case was diagnosed in a contact exposed outside of Romania, and three cases are in students in the same year of study in Romania. The first case recorded in this outbreak was an Israeli citizen, who was a student in Romania and later confirmed with TB in Israel in August 2015. Two of the cases are UK residents who attended the Romanian university; one was diagnosed in Romania in October 2015 (case 2), and the other was diagnosed in the UK in September 2016. An additional case has been diagnosed in a family contact of case 2 in the UK.

Contact tracing identified 87 exposed contacts who are at risk of developing XDR TB disease. These cases are being followed up to identify and adequately treat active TB cases among them as well as testing for latent tuberculosis infection (LTBI) using tuberculin skin tests (TST). Contacts identified with LTBI may receive preventive treatment depending on the drug susceptibility profile of the XDR TB strain. They should also be closely monitored with clinical observation to ensure the early detection of XDR TB and prevent further transmission.

More cases may be expected in association with this cluster. It is therefore important to trace all contacts of any additional cases in order to identify and treat active cases and provide preventive treatment or monitoring for those diagnosed with LTBI.

ECDC decided to produce this update after new information on the event background become available. The main conclusions and options for response remain unchanged from the version dated 19 October 2016.

Source and date of request

ECDC internal decision, 21 October 2016.

Public health issue

Multi-country cluster of extensively drug-resistant tuberculosis (XDR TB) among students at the Faculty of Medicine and Pharmacy in Oradea Municipality, Romania, 2015–2016.

Consulted experts

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Experts from the following institutions contributed to this risk assessment: World Health Organization (WHO) Regional Office for Europe and Odette Popovici (National Institute of Public Health – National Centre for Communicable Disease Surveillance and Control, Romania).

ECDC acknowledges the valuable contributions of all experts. Although experts from the WHO Regional Office for Europe reviewed the risk assessment, the views expressed in this document do not necessarily represent the views of WHO Regional Office for Europe. All experts have submitted declarations of interest and a review of these declarations did not reveal any conflicts of interest.

Disease background information

Extensively drug-resistant tuberculosis (XDR TB) is defined as tuberculosis (TB) caused by a strain resistant to rifampicin and isoniazid, which is also resistant to fluoroquinolone (FQ) or any of the second-line injectable drugs, such as capreomycin, kanamycin, or amikacin. Cases with XDR TB may be virtually untreatable, depending on the level of resistance to second-line drugs and the capacity of the health system. Moreover, conditions affecting the patient's immunity can contribute to high rates of morbidity and mortality associated with XDR TB [1].

Inadequate or incomplete TB treatment is the main risk factor for the development of resistance among TB cases, and it is usually associated with intermittent drug use, errors in medical prescription, poor patient adherence and low quality of TB drugs [2].

Although clear evidence is not yet available, given the level of threat posed by XDR TB, it is considered prudent to systematically investigate contacts of known or suspected cases of XDR TB to prevent the transmission of XDR TB strains in the community [1, 3].

In contacts of XDR TB cases, prevention options for the development of disease are limited and require an overall individual risk assessment, taking into consideration:

- risk of progression to TB disease;
- drug susceptibility pattern of the source case;
- risk of adverse drug events [5, 6].

If preventive treatment is not considered feasible, XDR TB infected contacts should be closely monitored with clinical observation to ensure early detection of XDR TB and to prevent further transmission [6]. Children under five and people of all ages living with HIV should be evaluated every six months for two years.

Since with XDR TB there is a higher probability of death, failure, longer hospitalisation, longer treatment duration and delayed microbiological (sputum smear and culture) conversion than with multi-drug resistant tuberculosis (MDR TB), the early diagnosis and aggressive management of XDR TB provides the best chance of positive outcome, although prevention is still paramount [7].

Event background information

A cluster involving four cases of XDR TB has been detected, affecting three students attending the University of Medicine and Pharmacy in Oradea Municipality, Bihor County, Romania. One contact case has also been diagnosed. The three students are in their third year of study. The presumed index case (case 1) is a student from Israel, and two students (case 2 and case 3) are from the United Kingdom (UK). The fourth case (case 4) is a contact of case 2 in the UK. To date, no cases have been detected yet among Romanian students/faculty personnel who are known contacts of the index case.

The first case recorded in this outbreak (case 1) had been diagnosed with XDR TB in June 2015 in Israel, and this fact was notified to the Romanian National Centre for Communicable Diseases Surveillance and Control on 15 October 2015 by the IHR National Focal Point (NFP) for Israel. On 19 October 2016, the Israeli authorities shared the drug resistance test results with the Romanian National Centre for Communicable Diseases Surveillance and Control and ECDC. The resistance pattern is as follows: rifampicin resistant (R), isoniazid R, ethambutol R, pyrazinamide sensitive (S), streptomycin R, ciprofloxacin R, amikacin R, capreomycin R, ethionamide R, cycloserine R, ofloxacin R, clarithromycin intermediate (I) and clofazimine I. Before leaving for Romania in July 2014, the presumed index case was tested negative for LTBI by TST (0 mm). In July 2015, the TST was repeated, showing an induration (palpable, raised, hardened area or swelling) of 13 mm.

Romanian authorities initiated contact tracing in October 2015 and identified 59 contacts among students, teachers and didactic auxiliary personnel of a wide range of nationalities: Romania (17), Finland (12), UK (9), Germany (4), Israel (3), Nigeria (3), Sweden (3), Mauritius Islands (2), Austria (1), Italy (1), Palestine (1), Poland (1), Hungary (1) and the United Arab Emirates (1). All underwent chest X-rays and 46 who had sputum tests were negative for Mycobacterium tuberculosis. As TST is only performed in persons under 19 years of age in Romania, only two contacts had a tuberculin skin test (PPD 5U). One TST result was considered negative (4 mm) and the other positive (20 mm).

This TST positive student (case 2) returned to the UK where treatment was initiated in March 2016. The date of XDR confirmation is not known, but treatment was modified for XDR in June 2016. Case 2 was considered non-infectious by the attending pulmonologist in the UK and returned to Romania.

As part of the contact tracing initiated in the UK around case 2, the brother of case 2 was diagnosed with XDR TB (case 4) and three other members of case 2's family were diagnosed with LTBI. Public Health England (PHE) notified the Romanian authorities about case 4.

On 30 September 2016, the UK notified the Romanian National Centre for Communicable Diseases Surveillance and Control of an additional case of XDR TB related to this cluster (case 3). The student in question was one of the 59 contacts of case 1 traced in October 2015, at which time the case had been reported to have a negative chest X-ray.

The notification of case 3 to the Romanian authorities triggered the resumption of the epidemiological investigations in Romania and all the contacts were re-evaluated.

Case 1, case 2 and case 3 were in contact with each other at the university. Case 2 and case 3 lived on the same floor in the same building.

The contact tracing initiated in September 2016 increased the number of contacts to follow-up to 87. Out of the 28 newly identified contacts, 10 were students (6 from Israel, 3 from Finland, 1 from USA) and 18 were University employees. Ten contacts involved in the first contact investigation had already left Romania, and therefore the results of their first screening were communicated to the respective authorities in their countries of origin: Finland, Germany, Sweden and the UK.

Chest X-ray examination of 68 contacts was negative for 66 contacts. The remaining nine contacts will be investigated during week 42. Sputum microscopy was initiated for 46 contacts and 27 tested negative, while 19 are still pending. The genetic GeneXpert RIF/TB test was performed for 26 contacts and all were negative. Cultures were prepared for 45 contacts and results are pending.

The whole genome sequencing performed in UK revealed that the isolates from case 2, case 3 and case 4 are closely related (0 SNPs difference) and that the isolates share the same novel mutation in codon 1588 of *rpoB* gene. The microbiological results of the index case were shared with the Romanian National Centre for Communicable Diseases Surveillance and Control and ECDC. Strains from Bihor County, Romania, will be sent to the WHO Supranational Reference Laboratory in Sweden, which expressed its availability for further laboratory investigations. All laboratory data will be further analysed.

The event was notified to WHO on 13 October 2016 through the IHR contact point for Romania.

On 14 October 2016, the IHR NFP for the UK shared drug resistance test results of the isolated strain: rifampicin resistant (R), isoniazid R, ethambutol R, pyrazinamide R, ciprofloxacin R, amikacin R, kanamycin R, para-aminosalicylic acid sensitive (S), prothionamide R, capreomycin R, linezolid S, moxifloxacin R and ofloxacin R.

ECDC threat assessment for the EU

The *Mycobacterium tuberculosis* strain identified in the cluster associated with the University of Medicine and Pharmacy in Oradea Municipality, Bihor County, Romania has caused XDR TB in three university students and a contact. Infected persons who do not present with symptoms of 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 [4]. Current contact tracing activities should mitigate the risks of further transmission. However, more cases may be identified through ongoing or future contact tracing.

Conclusions and options for response

More cases may be expected in association with this cluster. It will therefore be important to trace all contacts of any such additional cases in order to identify and treat active cases and to provide preventive treatment or monitoring for those diagnosed with LTBI.

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