



RAPID RISK ASSESSMENT

Invasive cardiovascular infection by *Mycobacterium chimaera* associated with 3T heater-cooler system used during open-heart surgery

18 November 2016

Conclusions and options for response

Since 2011, 52 cases of invasive cardiovascular infection caused by *Mycobacterium chimaera* have been detected in patients who had previously undergone open-heart surgery in Europe: France, Germany, Ireland, the Netherlands, Spain, the UK and Switzerland. Cases have also been reported in the US, Canada, Australia and Hong-Kong SAR.

Isolation of *M. chimaera* in heater-cooler units (HCUs) and in air samples suggests aerosolisation of water from the HCUs in the operating room as the most likely source of infection. Contamination of the 3T heater-cooler system, at the manufacturing site in Germany, has been identified as the most plausible source, explaining most but not all of invasive *M. chimaera* infections linked to this device. Contamination during use at the hospital as well as involvement of other heater-cooler system models are also possible.

Relocation of HCUs to be outside of the operating room or other ways of strict separation of the HCU from the air volume of the operating room, appear to be the safest measures. However, this solution may not be feasible in every centre. In such cases, if maintaining the HCU in the operating room is considered the only option, it should be placed at maximum distance from the operating table, the vent exhaust directed and channelled away from the patient and, if possible, close to the room air suction exhaust. However, this option may not be sufficient to eliminate the risk. Replacement of 3T HCUs manufactured before September 2014 with new devices of the same or other brands can be considered as a mitigating strategy, but it should be noted that the potential risks associated with other models remain to be defined.

Centres using 3T HCUs should follow strictly the instructions for use, and in particular those for cleaning and decontamination, issued by the manufacturer. Establishing a quality control process with written procedures including traceability of the HCU used in each operation is also advisable.

Healthcare providers (including cardiologists, pulmonologists, rheumatologists, infectious disease specialists, ophthalmologists, haematologists and primary care providers) caring for patients who have undergone open-heart surgery or other surgery involving cardiopulmonary bypass, such as heart and / or lung transplantation, should be vigilant for cases of endocarditis or other cardiovascular, deep surgical site, or disseminated infection that are of unidentified origin, and for other granulomatous disease, including those with the characteristics of sarcoidosis, and consider testing such cases specifically for slow-growing NTM, such as *M. chimaera*.

Other measures that EU/EEA countries may consider include informing patients who have undergone open-heart surgery involving exposure to 3T HCUs before the implementation of mitigation measures about the risk of acquisition and the signs and symptoms of infections with NTM, and in particular *M. chimaera*, especially if they were operated on in a centre that has detected a case of *M. chimaera* previously. Consideration should also be given to ensuring the ready availability of information for healthcare providers and patients that is accessible on line and may also be disseminated in the form of a letter to the patient, or a patient information leaflet, or as frequently asked questions (FAQ).

An ECDC protocol is available for [retrospective case detection, laboratory diagnosis and environmental testing of *Mycobacterium chimaera*](#). Clinical and mycobacterial diagnostic investigations should be available and accessible for patients at risk after cardiovascular surgery to ensure prompt diagnosis and treatment." Microbiological testing of water and air samples, for the detection of *M. chimaera* and other NTM is technically challenging, with a high likelihood of false negative results. Nevertheless, clinical vigilance, prospective case detection and notification of invasive cardiovascular infection caused by *M. chimaera* after open-heart surgery and selective environmental testing may be considered in the coming years in order to monitor the effectiveness of control measures and ensure timely diagnosis and treatment for infected patients.

Regulatory bodies in charge of licensing and agencies monitoring the safety of such devices should be aware of the association of invasive cardiovascular infections caused by *M. chimaera* and other NTM with HCUs and options for regulatory action should be considered. Relevant information should be disseminated to all centres performing open-heart surgery or other surgery involving extracorporeal circulation. Devices containing water circuits or using water during operation or maintenance and used in sensitive clinical areas should be carefully evaluated for the risk of contamination by NTM.

Source and date of request

ECDC internal decision, 11 November 2016.

Public health issue

Update the assessment of risk of invasive cardiovascular infection by *Mycobacterium chimaera* associated with heater-cooler units used during open-heart surgery in Europe.

Consulted experts

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Disease background information

Mycobacterium chimaera is a slow-growing non-tuberculous mycobacterium (NTM) that was identified as a species within the *Mycobacterium avium* complex in 2004 [1]. Identification requires molecular diagnostic testing.

Mycobacterium chimaera has been associated with lung infections in patients with underlying lung disease, such as chronic obstructive pulmonary disease. Colonisation of water sources and systems, with formation of biofilm is possible.

In 2014, airborne transmission of *M. chimaera* from heater-cooler units (HCUs) was reported for the first time. HCUs are used to regulate the temperature of the blood and of the cardioplegia solution during extracorporeal circulation and use filtered water as a heat exchanger [2]. Water is contained in tanks and circulated through a closed circuit to the heart-lung unit. The device is connected to the membrane oxygenator through tubing and is usually situated in the operating room. The water in the circuit does not come into contact with the patient, but the circuit is not airtight and cooling of the water is accomplished with a fan.

Event background information

This section includes information from published reports, as well as unpublished information communicated through the Early Warning and Response System (EWRS), the Epidemic Intelligence Information System (EPIS) platform, during teleconferences and from a survey of the EU/EEA countries.

Since 2011, cases of invasive cardiovascular infection caused by *M. chimaera* have been reported in patients who had previously undergone open-heart surgery using HCUs in seven EU/EEA countries. In April 2015, ECDC published a rapid risk assessment on the potential risk of invasive cardiovascular infection by *M. chimaera* associated with the use of HCUs [3], which is updated in this document in view of accumulating new evidence.

Case detection

Since 2011, 52 cases of post-surgical cardiovascular infection caused by *M. chimaera* have been reported in Europe: France (two cases), Germany (five cases), Ireland (four cases), the Netherlands (four cases), Spain (one case), UK (25 cases), and Switzerland (10 cases). Ten deaths have been reported to date among these patients but not all deaths have been attributed to the infection. Cases have also been reported in the US, Canada, Australia and Hong-Kong SAR [4-10].

In the majority of cases, patients had undergone cardiac valve replacement/reconstruction and/or the insertion of an aortic vascular graft in the five years prior to diagnosis. Patients who have undergone other operations that involve cardiopulmonary bypass, including heart and / or lung transplantation or introduction of ventricular assist devices (VAD), are also be at risk [11]. The majority of infections were endocarditis, graft infection and disseminated infection, but cases of sternal osteomyelitis have also been reported. Disseminated infection can be indolent, with diverse presentations, such as bacteraemia, granulomatous hepatitis, nephritis, splenomegaly, chorioretinitis, osteomyelitis and bone marrow involvement with cytopenia [12] and may mimic sarcoidosis. The reported interval from operation to infection ranges from three months to five years, with a median interval of 19 months [13]. These infections are difficult to treat, requiring combination antimicrobial therapy and surgical intervention and have a high rate of treatment failure and fatal outcome [12].

Denmark, France, Hungary, Ireland, the Netherlands, Norway, Sweden, and the UK have done retrospective and/or prospective case finding (e.g., through hospital patient registries and laboratories, physician notification and awareness raising for increased diagnostic testing of possible cases). The retrospective case finding went back from five years (Denmark, France, Sweden, one hospital in Norway) to 13 years (Ireland).

Denmark, Norway, Hungary and Sweden did not detect any case through active case finding. No case has been notified in Austria, Slovakia, Latvia and Poland, but active case finding has not been performed. No data are available from case finding or environmental investigation in other Member States.

To date, no cases of post-operative invasive infection caused by *M. chimaera* associated with 3T HCUs manufactured after September 2014 have been reported.

Environmental testing

Investigators in Denmark, France, Ireland, the Netherlands, Sweden, Switzerland and the UK performed microbiological testing of HCUs for *Mycobacterium chimaera*, and 3T devices contaminated with *M. chimaera* were identified in all of them. In Slovakia, samples taken from HCUs were negative for *M. chimaera*. In the UK, the Netherlands, Sweden and Switzerland, some HCUs tested positive for *M. chimaera* after decontamination by the manufacturer. In Scotland, *M. chimaera*-contaminated 3T HCUs were identified that had been manufactured after September 2014.

Denmark, France, Germany, Ireland, the Netherlands and UK have performed whole-genome sequencing of the isolates. Results are pending.

Of note, all cases of invasive cardiovascular infection by *M. chimaera* reported until now have been associated with the use of 3T HCUs. Culture of air samples from the operating room when these 3T HCUs were in use, have grown *M. chimaera*, indicating that these HCUs were responsible for the production of bio-aerosols [2,14,15], making airborne transmission the most probable route. Devices from other manufacturers have also been found to be contaminated by *M. chimaera* and other microorganisms in Denmark, the Netherlands and Germany. However, to date results from investigations of air contamination associated with these other HCUs are not available.

Contamination of HCUs used in extracorporeal membrane oxygenation (ECMO) has also been detected. However, this was not associated with contamination of the air surrounding the devices, possibly because the water circuits of these devices are air-tight. To date, no infections have been linked to the use of ECMOs [2,16].

Contamination of HCUs with other waterborne pathogens, including other NTM (e.g. *M. chelonae*, *M. goodii*, *M. fortuitum* or *M. scrofulaceum*, *M. goodii*, *M. kansasii* and *M. lentiflavum*), *Legionella* spp., non-fermenting Gram-negative bacteria and fungi has also been detected and is of concern, although until now only one case of sternal wound infection by *Legionella* spp. has been reported in Switzerland. The variety of different pathogens identified in HCUs indicates also a risk of contamination within hospitals. Further investigations into the association of HCUs with infections by these pathogens are required to address this risk.

Risk mitigation measures

Epidemiological and microbiological investigations of clinical and environmental isolates from Europe and the US, supported by preliminary results from whole-genome sequencing comparative analysis, indicated that the most likely source of *M. chimaera* infection were 3T HCUs contaminated at the production site during the manufacturing process [4,17,18] and that 3T HCU-produced aerosols with *M. chimaera* can reach the operating table despite ultraclean air ventilation [14,19].

In August 2014, the manufacturer of 3T HCUs implemented, among other measures, a device disinfection process of new devices prior to shipment [20].

Testing conducted by the manufacturer in August 2014 found *M. chimaera* contamination on the production line and water supply at the 3T manufacturing facility. The 3T devices manufactured at this facility were distributed worldwide. In response to the *M. chimaera* findings in August 2014, the manufacturer added cleaning and disinfection procedures to the production line in September 2014.

In September 2014, in response to *M. chimaera* contamination of 3T HCUs, the manufacturer introduced a modification in the post-production process, updated the instructions for use and issued relevant field safety notices, with a last update on 13 October 2016 [21]. The updated instructions address decontamination and enhanced maintenance protocols of 3T HCUs. A deep-cleaning process is also provided by the manufacturer. However, although the modified instructions have been associated with a decrease in colony counts [22,23], eradication of *M. chimaera* has not been consistent. In addition, FDA reported on *M. chimaera*-contaminated 3T HCUs produced after September 2014, although it is not known whether these were contaminated at the manufacturing site or at the healthcare facility where they were used.

In April 2015, ECDC published a Rapid Risk Assessment and, in August 2015, a protocol for case detection, laboratory diagnosis and environmental testing [24].

In the U.S., the Centers for disease Control and Prevention published a guidance document for health departments, health care facilities and providers, and patients [25]. The Food and Drug Administration, (FDA) among other measures, recommended immediate device removal if any 3T HCU, accessory or component tests were positive for *M. chimaera* or have been associated with cases of *M. chimaera* infection; and to strongly consider transitioning away from use of 3T HCUs manufactured before September 2014 until the manufacturer has implemented risk-mitigation strategies, limiting their use to emergency and/or life threatening situations if no other HCU is available [26].

National regulatory authorities for medical devices have been notified across Europe, and a number of control measures have been implemented. The manufacturer's cleaning and disinfection protocol is being used as a basis for local protocols. Several national authorities have recommended removing the HCUs from the operating rooms, and this has been implemented in some countries such as Denmark, Ireland, France and the Netherlands. However, in other countries (Germany, the UK), practical difficulties were encountered e.g. with the length of the tubing required to connect to the membrane oxygenator, that prevented the full implementation of this measure. In many cases the HCUs have been placed as far from the patient as possible with the HCU exhaust directed away from the operating table and /or to the exhaust outlet of the room air ventilation system. Custom-made housing for 3T HCUs has also been designed and implemented in Denmark and Switzerland. In some hospitals in Norway HCUs were placed from the beginning outside of the operating room. The University Hospital Zurich designed a custom-built special housing for the 3T HCU connected to the air exhaust of the operating theatre, an intervention that was expensive and technically demanding [22].

National health authorities have notified a broad panel of clinicians, scientific and professional societies through meetings, articles and information letters or documents. Information for patients and the public has also been provided in the form of information leaflets and press releases [13,27,28].

There is limited information on the effectiveness of patient notification. From the experience of one hospital in the U.S., almost 200 patients could not be reached by phone among 1 500 exposed patients. Among the patients that were notified, 131 underwent evaluation at an "NTM" clinic, without any cases being detected. Two cases at the same hospital were identified through healthcare provider notification [29].

ECDC threat assessment for the EU

The risk of invasive infection by *M. chimaera* in patients having undergone open-heart surgery has been estimated to be 0.4 – 16 per 10 000 patient-years [2,13]. Given a background risk of 1.2% for surgical site infection in the first year after cardiac valve operations and a cumulative 5-year incidence of prosthetic valve endocarditis of 3.2-5.7% [30], the risk of invasive infection by *M. chimaera* is considered low. However, this risk is likely to be underestimated, due to the long interval between operation and diagnosis, as well as the technical difficulty of diagnosing this infection. Decisions to delay surgery until this risk is mitigated should take into account the risk of delaying surgery on an individual basis for each patient.

The manufacturer introduced risk mitigation measures in September 2014, including updated cleaning and disinfection procedures and modifications of the production line. Isolation of NTM from 3T HCUs manufactured after September 2014 indicate that the risk has not yet been eliminated [2,19,26]. To date, there have been no reported cases of *M. chimaera* infection associated with 3T HCUs manufactured after September 2014.

The risk of infection by *M. chimaera* and other pathogens associated with HCUs other than the 3T remains unknown, but is plausible and depends on the potential for aerosol formation. Further study of HCUs and other devices containing water circuits and used in surgery and other sensitive clinical areas need to be performed to inform the estimation of this risk.

Conclusions and options for response

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