RAPID COMMUNICATION

# Interim laboratory testing guidelines for the detection of non-tuberculous Mycobacterium (NTM) infections in post-operative patients exposed to heater-cooler units

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## Abstract

The advice contained in this document should be read in conjunction with relevant federal, provincial, territorial and local legislation, regulations, and policies. Recommended measures should not be regarded as rigid standards, but principles and recommendations to inform the development of guidance.

This advice is based on currently available scientific evidence and adopts a precautionary approach where the evidence is lacking or inconclusive. It was approved for publication on December 5, 2016. It is subject to review and change as new information becomes available.

The main changes to this version include additions to: Case load reported to date, Sarcoidosis-like disease as an Indicator, Whole Genome Sequencing effort, links to Provincial and Territorial Lab Services and Health Canada reporting.

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## Scope

This document outlines laboratory testing criteria and specimens to be collected for symptomatic persons with history of exposure to heater-cooler units during cardiothoracic heart surgery performed from November 1st, 2011 onward.

## Background

A recent outbreak of *Mycobacterium chimaera* has been detected globally in patients who have undergone cardiothoracic heart surgery while in the presence of contaminated heater-cooler units. At this point in time, 52 cases of non-tuberculosis Mycobacterium (NTM) have been detected in Europe, and 2 within Canada (11).

There are many areas of uncertainty with respect to: 1) the magnitude and factors affecting infection risk, 2) clinical presentations of disease and 3) ideal management of devices.

At this time the risk to patients is thought to be low as evidenced by small number of cases reported globally. Risk estimates will be supplied as more information becomes available.

The Canadian Public Health Laboratory Network and its partners are working to support the laboratory response through the production of these *interim* recommendations.

This guidance document will focus on 1) defining patients at risk to establish criteria for testing and 2) recommendations related to the sample collection and testing for detection of *M. chimaera* in patients.

## Clinical presentations* associated with post-operative non-tuberculous Mycobacterium infection

The majority of patients present three months to five years (median 18 months) after the index surgery, with symptoms of fever, fatigue, shortness of breath, night sweats, joint or muscle pain and unexplained weight loss (1,3,7). Cardiac manifestations include prosthetic valve endocarditis (PVE), prosthetic vascular graft infection (PVGI), paravalvular abscess, and pseudo and mycotic aneurysms (7.10). Extracardiac manifestations include bone infection (osteomyelitis, spondylodiscitis), sternotomy wound infection, mediastinitis, hepatitis, and bloodstream infection (BSI) (3,7,10). Ocular manifestations due to emboli (panuveitis, multifocal chorioiditis, chorioretinitis) are observed in approximately 50% of patients (3). Immunologic manifestations include arthritis, cerebral vasculitis, pneumonitis, myocarditis, granulomatous nephritis) (7,10). Splenomegaly is observed in approximately 80% of cases (3) as well as bone marrow involvement with cytopenia. Recent recommendations have raised awareness for granulomatous diseases, particularly those that resemble sarcoidosis (11). There have been case reports of *M. chimaera* patients who were initially diagnosed with sarcoidosis.

## Patient testing criteria

### Criteria 1: Risk exposure

Patients must have had cardiothoracicsurgery in the past. Due to the prolonged incubation time, patients who have had surgery from November of 2011 onward would be considered to meet this criterion.

Caveat: Some isolated reports involve patients without cardiothoracic surgery, but in a room with an active heater-cooler unit on standby. While these patients are not routinely felt to be at risk, such patients could be considered for NTM testing if a compatible clinical syndrome was present (see below).

*Prior presentations: Published literature from Germany (5 cases)(2) Switzerland (6 cases)(1) and the United Kingdom (17 cases)(9) demonstrate that the majority of patients presented with endocarditis, paravalvular abscess, site infection or bacteremia associated with artery bypass graft, valve replacement or repair. Common accompanying signs and symptoms were fatigue, fever, hepatitis, renal insufficiency, splenomegaly and pancytopenia.

### Criteria 2: Compatible clinical syndrome

Overall patients tend to present with non-specific symptoms, making the distinction of NTM infection from other, more common causes of these symptoms difficult. To that end, a compatible syndrome is defined as presence of:

- **Constitutional**: recurrent or prolonged fever, fatigue, shortness of breath, weight loss, night sweats, joint or muscle pain
- **Cardiac**: prosthetic valve endocarditis and/or prosthetic vascular graft infection
- **Extracardiac**: bone infection, sternotomy surgical wound infection, mediastinitis, hepatitis, bloodstream infection, ocular infection (panuveitis, multifocal chorioiditis, chorioretinitis)
- **Immunologic/embolic**: splenomegaly, cytopenia
- **Infants**: febrile episodes and failure to thrive

Symptoms must have either: 1) appeared post-surgery or, 2) if present prior to surgery, must have significantly worsened following surgery AND symptoms should have been present ≥ three weeks. Persistence of these non-specific symptoms beyond three weeks helps to eliminate other infections that generally are diagnosed or resolved within that time span. In the absence of a diagnosis (both infectious and non-infectious) patients with unexplained symptoms should be investigated for possible *M. chimaera* infection.

### Important testing considerations

- Asymptomatic individuals who have undergone cardiothoracic surgery should not undergo testing for M. chimaera, based on current evidence.
- It may be impractical to wait ≥3 weeks, either due to severe illness or when patient follow-up will be complex due to frailty or geographic access. Under these exceptional circumstances, one can consider proceeding to NTM testing without waiting.

#### Specimens

The following specimens should be submitted for mycobacterial cultures from eligible patients, as identified by the testing recommendations:

Clinical samples from sterile sites (**Table 1**), such as, but not restricted to, blood, purulent drainage, or fresh tissue should be sent for mycobacterial culture and acid fast bacilli (AFB) smear with accompanying requisition (**Appendix 1**: Links to local laboratory services). Please note, *M. chimaera* is a slow growing organism and detection through culture can take up to 6-8 weeks incubation. If it is early in the infection, *M. chimaera* may not be detected.

Positive cultures identified as *M. avium-intracellulare* complex microorganisms must be sent forward to a reference laboratory for 16S (or alternative such as hsp65/ITS) gene sequencing to confirm as *Mycobacterium chimaera* species at https://cnphi.canada.ca/gts/reference-diagnostic-test/5054?labId=1004. Sending pure culture on solid or in a liquid (minimum 4mL) medium is optimal for the reference laboratory.

Isolates potentially tied to this outbreak are currently undergoing whole genome sequencing as part of a national collaborative effort. Results are pending.

**Table 1: Clinical testing for identifying potential cases of non-tuberculous Mycobacterium (NTM) following cardiac surgery**

| Clinical symptoms/ exposure | Specimen and testing recommendations |
|---|---|
| **Asymptomatic**<br>**AND**<br>Cardiothoracic surgery after Nov 1, 2011 | None |
| **Symptomatic**[1]<br>• Constitutional: recurrent or prolonged fever, fatigue, shortness of breath, weight loss, night sweats<br>• Cardiac: prosthetic valve endocarditis and/or prosthetic vascular graft infection<br>• Extracardiac: bone infection, sternotomy surgical wound infection, mediastinitis, hepatitis, bloodstream infection, ocular **infection (panuveitis, multifocal chorioiditis, chorioretinitis)**<br>• Immunologic/embolic: splenomegaly, cytopenia<br>• Infants: febrile episodes and failure to thrive<br>**AND**<br>• Open-chest surgery 3 months to 5 years prior to illness onset | • Blood: Request mycobacterial blood culture at local, commercial or reference laboratory as available (Appendix 1)<br>- Specific incremental yield of multiple blood cultures is not known at present. A set of 2 cultures collected 12 hours apart is a reasonable option with more specific recommendations to follow as data becomes available. NTM isolation from a sterile site is highly likely to be clinically significant (12)<br>• Tissue (including bone), and fluid**:** Request mycobacterial culture and acid fast staining at local, commercial or reference laboratory as available<br>- Aseptically collect and submit in sterile container without fixative<br>• Submit to laboratory with appropriate requisition indicating patient history<br>• Refer culture to reference laboratory as necessary for species level discrimination |

[1] Symptomatic is defined as: **Investigation of NTM infection in patients with prolonged illness (≥3 weeks) AND absence of alternative diagnosis through routine investigation to eliminate common etiologic agents**

### Testing of heater-cooler units and surrounding environment

The authority to advise on the testing of heater-cooler units resides with Health Canada (http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/60662a-eng.php#issue-problem).

### Reporting of adverse events from medical devices

Health Canada encourages healthcare professionals to report any cases of patient infection thought to be associated with the use of devices. The Medical Devices Problem Report Form and Guidelines (http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/md-im/index-eng.php) can be found on the Health Canada Web site.

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## Conflicts of interest

None

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## Appendix 1: Link to provincial laboratory services

| Province | Link to Laboratory Services | Laboratory Contact(s) |
|---|---|---|
| **British Columbia** | http://www.bccdc.ca/health-professionals/professional-resources/laboratory-services | mel.krajden@bccdc.ca<br>mabel.rodrigues@bccdc.ca |
| **Alberta** | http://www.provlab.ab.ca/guide-to-services.pdf | greg.tyrrell@albertahealthservices.ca<br>cary.shandro@albertahealthservices.ca |
| **Saskatchewan** | http://sdcl-testviewer.ehealthsask.ca/ | paul.levett@health.gov.sk.ca<br>dfarrell@health.gov.sk.ca |
| **Manitoba** | http://dsmanitoba.ca/ | arendina@dsmanitoba.ca<br>dswidinsky@dsmanitoba.ca |
| **Ontario** | http://www.publichealthontario.ca/en/ServicesAndTools/LaboratoryServices/Pages/Index.aspx | frances.jamieson@oahpp.ca<br>kevin.may@oahpp.ca |
| **Quebec** | https://www.inspq.qc.ca/lspq/repertoire-des-analyses | hafid.soualhine@inspq.qc.ca |
| **Newfoundland** | www.publichealthlab.ca. | jessica.kafka@easternhealth.ca<br>robert.needle@easternhealth.ca |
| **Nova Scotia** | http://www.cdha.nshealth.ca/pathology-laboratory-medicine/laboratory-client-support-center | david.haldane@nshealth.ca<br>darlene.mcphee@nshealth.ca |
| **New Brunswick** | | hope.mackenzie@HorizonNB.ca<br>janet.reid@HorizonNB.ca |
| **Northwest Territories** | | caroline_newberry@gov.nt.ca |
| **Nunavut** | | smarchand@gov.nu.ca |