Feidhmeannacht na Seirbhíse Sláinte
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Report of Case Finding Investigation to identify *Mycobacterium chimaera* Infections potentially associated with Heater-Cooler Units used during Cardiothoracic Surgery in Ireland
NIMLT 50944

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Correction

A correction has been made to Table 3 of this report (v1.1).

There was a typographical error in the original report produced (v1.0).

This related to the number of ECMO procedures conducted at St. James's Hospital; the corrected figure is zero and not 61 as originally reported.

HPSC, 27/01/2017

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Abbreviations

ECDC European Centre for Disease Prevention and Control

ECMO Extracorporeal Membrane Oxygenation

EWRS Early Warning and Response System

HCU Heater-cooler unit

HPSC Health Protection Surveillance Centre

HPRA Health Products Regulatory Authority

HSE Heath Service Executive

IHR International Health Regulations

IMRL Irish Mycobacteria Reference Laboratory

ITS Internal Transcribed Spacer

MAC *Mycobacterium avium* complex

NHS National Health Service

NIMLT National Incident Management & Learning Team

NTM Non-tuberculous mycobacterium

PHE Public Health England

PHL Public Health Laboratory

UHI Unique Health Identifier

1. Summary

Background

Mycobacterium chimaera is a slow-growing, environmental non-tuberculous mycobacterium (NTM) that was distinguished as a distinct species in 2004 (1). Studies suggest that it is prevalent in water networks and biofilms (2, 3). Its identification requires molecular methods (3). In a clinical context, it has been linked to lung infections in individuals with underlying lung disease (1, 4, 5).

Early Warning & Response System (EWRS) alerts from Switzerland (July 2014) and the Netherlands (February 2015) regarding cases of *M. chimaera* infection diagnosed after cardiothoracic surgery were issued to EU Member States and circulated to relevant healthcare providers in Ireland by the Health Protection Surveillance Centre (HPSC). In April 2015, the European Centre for Disease Prevention and Control (ECDC) published the first rapid risk assessment (RRA) alerting EU Member States to the potential risk of *Mycobacterium chimaera* infection arising following open heart surgery (6). Subsequently, additional cases of invasive infection after cardiothoracic surgery have been reported in several European countries, namely Germany, France, Spain and the UK (7). Cases have also been reported in the U.S., Canada, Australia and Hong-Kong SAR (7-16). While reported case numbers are low, infections have been severe (e.g., endocarditis, disseminated infection), with some deaths reported. The interval between surgery and diagnosis has been up to five years (17-20), with the earliest identified case diagnosed in 2008 (20).

These infections have been linked to a particular brand of heater-cooler unit (HCU) used during cardiothoracic surgery i.e. LivaNova PLC (formerly Sorin Group Deutschland GmbH). Outbreak investigators found *M. chimaera* in the HCU water circuits and air samples while the HCUs were running, suggesting that the mycobacteria are transmitted to the surgical site following aerosolisation of contaminated water within the HCU (18, 21). This brand of HCU was widely used across Europe, including Ireland (it will be referred to hereafter as a LivaNova/Sorin HCU).

In response to the publication of the ECDC's RRA which was circulated to all acute public hospitals by HPSC in April 2015, a National Incident Management & Learning Team (NIMLT 50944) was established in Ireland in May 2015 to assess the risk to Irish patients. Active prospective and retrospective case finding, device assessment and microbiological investigations were undertaken. This report presents the findings of the case finding investigation.

Methods

Prospective and retrospective case finding was undertaken. In June 2015, the NIMLT wrote to microbiologists, cardiothoracic surgeons and cardiologists to request prospective and retrospective reporting to the Health Protection Surveillance Centre (HPSC) of any potential cases of NTM[1] diagnosed since 2007 following cardiothoracic surgery.

Cases were also retrospectively identified through matching laboratory records of NTM isolates (January 2007 - June 2015) to cardiothoracic surgery/ECMO[2] records (January 2002 – June 2015)[3].

Results

At the time of finalising this report, there have been four confirmed adult cases of invasive infection due to *M. chimaera* since 2007 among patients who had previously undergone cardiothoracic surgery in Ireland. To date, there have been no paediatric cases identified in Ireland. This is in the context of approximately 3,000 cardiothoracic surgeries involving the use of HCUs performed annually in Ireland.

The index case had already been diagnosed with NTM infection and commenced treatment, prior to the first correspondence from the NIMLT, which then pointed to the potential link between the NTM infection and cardiothoracic surgery. That case was also identified through the retrospective review process, whereby cross-matching of microbiology laboratory and cardiothoracic surgery records was carried out by HPSC. Three additional cases have been identified prospectively and notified to HPSC.

The four cases were in adults and all had undergone aortic valve replacement/repair surgery. The patients presented with one or more of the following symptoms; endocarditis, bloodstream infection, disseminated infection, graft infection and skin or soft tissue infection.

All four cases had been exposed to LivaNova/Sorin HCUs during surgery at a single cardiothoracic centre prior to onset of symptoms. The incubation period ranged from 14 months to 39 months. The earliest potential exposure date related to surgery performed in 2012. One patient died. However, the *M. chimaera* infection was determined not to be the primary cause of the patient's death.

[1] *M. chimaera* is a recently characterised species within *Mycobacterium avium* complex (MAC) (2004), and its identification requires molecular diagnostic testing (1). In recent years, the Irish Mycobacteria Reference Laboratory (IMRL) has been able to identify *M. chimaera* by using internal transcribed spacer (ITS) sequencing. However, *M. chimaera* would be reported by most Irish laboratories as MAC or *M. intracellulare*. For this reason, laboratories were requested to report all NTM isolates diagnosed since 2007 to the HPSC.
The following definition of NTM was provided to the laboratories: all mycobacteria except those belonging to:
Mycobacterium tuberculosis complex (i.e. including *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. canetti*, *M. caprae*, *M. micoti* and *M. pinnipedii*). All other mycobacteria not specified above should be reported. These will include *Mycobacterium avium* complex, *Mycobacterium intracellulare* and *Mycobacterium chimaera.*

[2] In addition to their use during cardiothoracic surgery, HCUs are also employed during extracorporeal membrane oxygenation (ECMO). Therefore, patients who underwent this procedure were also included.

[3] This investigation looked for cases of NTM diagnosed from 2007 onwards. As it can take up to five years for symptoms to manifest following surgery (20), laboratory records were cross-checked with cardiothoracic surgery records from 2002 onwards. The rationale for limiting the review to this time period is based on the experience of the UK investigation where the earliest case diagnosed was in 2008.

Conclusions & Recommendations

The small number of confirmed *M. chimaera* infections identified in Ireland to date indicates that the risk to patients is very low, but present. Although case numbers are small, the infections were severe.

Clinicians investigating any patient who has previously undergone cardiothoracic surgery for endocarditis or other infection should consider mycobacterial infection in the differential diagnosis and organise appropriate testing. Furthermore, it is paramount that all healthcare professionals, including cardiothoracic surgeons, cardiologists and microbiologists prospectively notify any potential cases to HPSC.

2. Introduction

2.1 Disease background

Mycobacterium chimaera is a slow-growing, environmental non-tuberculous mycobacterium (NTM) that was first distinguished as a species within the *Mycobacterium avium* complex (MAC) in 2004 (1). Its natural reservoir is not well known, but studies indicate that it is prevalent in water systems and biofilms (2, 3).

Identification of *M. chimaera* is currently only possible through molecular methods and diagnosis is limited to specialised laboratories (3). The Irish Mycobacteria Reference Laboratory (IMRL) can identify *M. chimaera* by sequencing of the internal transcribed spacer (ITS) region between the 16S and 23S genes. However, most Irish microbiology laboratories routinely testing for mycobacteria would be equipped to identify it to the level of MAC or *M. intracellulare* only.

In a clinical context, *M. chimaera* has been associated with lung infections in individuals with underlying lung disease e.g., chronic obstructive pulmonary disease and cystic fibrosis (1, 4, 5).

2.2 Event background

To date, cases of invasive cardiovascular infection caused by *M. chimaera* have been reported in patients who had previously undergone cardiothoracic surgery in Switzerland, the Netherlands, Germany, France, Spain, UK, US, Canada, Australia and Hong-Kong (7-16). As national investigations proceed and awareness increases of a link between *M. chimaera* and infection following cardiac surgery, it may be anticipated that additional cases will be identified and notified.

At the time of finalising this investigation report, there are publications and reports describing cases from several European countries, including ten cases in Switzerland, four in the Netherlands, five in Germany, two in France, one in Spain and 25 cases in the UK (7). Of those 47 patients, six fatal outcomes have been reported to date.

In the US, cases have been identified in Pennsylvania and Iowa. Fifteen cases have been reported in Pennsylvania, six of whom died (8-10).

Patients presented with prosthetic valve endocarditis, vascular graft infection and/or manifestations of disseminated mycobacterial infection, including; embolic and immunological manifestations (splenomegaly, arthritis, osteomyelitis, bone marrow involvement with cytopenia, chorioretinitis, lung involvement, hepatitis, nephritis and myocarditis) (19). The time from surgery to diagnosis ranged from three months to five years (17, 20). While case numbers in all countries are low, severe infections have been reported.

Infections have been attributed to transmission of organisms from contaminated heater-cooler units (HCUs) used in the operating theatre during cardiothoracic surgery (18). HCUs

are used to regulate the temperature of the blood during extracorporeal circulation and use tap water as a heat exchanger. The Swiss investigation identified *M. chimaera* contamination in HCUs, including water samples from the units (18). Air sample cultures were positive *for M. chimaera* when units were running, but negative when units were powered off. Further Swiss investigations have confirmed airborne transmission of *M. chimaera* aerosols from a contaminated HCU (21). These findings have been corroborated by results from a German investigation (22). In summary, the available evidence suggests *M. chimaera*-contaminated HCUs as a potential source of infection, with aerosolisation of water from these devices as the most plausible route of infection.

On 14th July 2014 and 23rd February 2015, alerts from the European EWRS were circulated regarding cases of *M. chimaera* causing endocarditis and invasive infection following cardiothoracic surgery in Switzerland and The Netherlands, respectively.

ECDC began co-ordinating an EU-wide investigation and is gathering information in collaboration with affected countries to assess the public health risk. In April 2015, ECDC published the first rapid risk assessment (RRA) detailing this (6). The RRA was updated in November 2016 (7). ECDC also issued a protocol for case detection, laboratory diagnosis of *M. chimaera* infection and environmental testing for *M. chimaera* potentially associated with HCUs to support the harmonisation of country-specific investigations (23).

The HCU manufactured by LivaNova PLC (formerly Sorin Group Deutschland GmbH), was implicated in the Swiss investigation (this will be referred to as a LivaNova/Sorin HCU throughout this report). This brand is widely used in Europe, including Ireland. In June 2015, LivaNova/Sorin issued a Field Safety Notice (FSN) updating the decontamination regimen for HCUs and recommending microbiological monitoring and removal of highly contaminated devices from service (24). To date, there has been no reported case of *M. chimaera* infection associated with another brand of HCUs, with all cases associated with LivaNova/Sorin devices. However, it is not certain that the risk is limited to these devices and other brands (e.g., Maquet) are also being investigated.

Investigations in Europe and the US suggest a common-source, multi-country outbreak related to contamination of 3T LivaNova/Sorin devices manufactured prior to September 2014 (10, 17, 25).

A study by Haller *et al* suggests that some HCUs may have been contaminated with *M. chimaera* at a single manufacturing site in Germany (17). *M. chimaera* was isolated from five cases in Germany who had been exposed to this brand of HCU, from water samples taken from used HCUs from three different countries (Germany, Switzerland and the Netherlands) and in samples taken from new HCUs and also from the environment at the manufacturing site in Germany. Preliminary typing results indicate that *M. chimaera* isolates recovered at the manufacturing site are almost identical to those detected in the used HCUs from the different countries. Investigations continue, including next generation sequencing of the isolates, which should help differentiate whether cases arose due to contamination of HCUs

at the manufacturing site or at the local site. The positive environmental samples at the manufacturing site prompted a modification of the manufacturing process and follow-up environmental investigations did not detect *M. chimaera*.

In December 2015, the manufacturer informed the Robert Koch Institute (RKI), Germany of positive samples from environmental investigations. Thereafter, Germany issued EWRS and International Health Regulations (IHR) alerts in order to inform the public health authorities in EU/EEA and worldwide of the suspected common source.

A recent U.S. study undertook whole genome sequencing of clinical isolates from eleven patients and five 3T LivaNova/Sorin HCUs from hospitals in Pennsylvania and Iowa, where clusters of infection had been identified (10). The authors found few single nucleotide polymorphism (SNP) differences between outbreak-related isolates compared with hundred-fold larger SNP differences between outbreak-related isolates and an epidemiologically unlinked isolate.

2.3 HCUs in use in Ireland

There are nine cardiothoracic centres in Ireland. When this issue was first identified at European level, four used LivaNova/Sorin HCUs and five used Maquet HCUs (Table 1). The LivaNova/Sorin HCUs in use were models 1T and 3T. The HPRA contacted all cardiothoracic centres again for an update on device use. By November 2016, all nine centres use Maquet HCUs (one centre has retained a LivaNova/Sorin HCU as back-up, but it is not in clinical use).

In addition to their use during cardiothoracic surgery, HCUs are also employed during extracorporeal membrane oxygenation (ECMO).

Table 1. Details of heater cooler units in use in Irish hospitals, as of July 2015 (at the commencement of the investigation)

Manufacturer	Hospital name	Number of devices	Dates delivered
LivaNova/Sorin	Beacon Hospital	2	Sept 2006
	Mater Private Hospital	5	March 2002 July 2006 July 2007 October 2012
	Mater Misericordiae University Hospital	3	April 2007 Sept 2012
	Our Lady's Children's Hospital, Crumlin	2	May 2012
Maquet	Blackrock Clinic	2	2009
	Cork University Hospital	3	2011
	Galway Clinic	2	2008
	St James's Hospital	3	2002 2009
	University Hospital Galway	3	2009

Note: Beacon Hospital, Mater Private Hospital, Mater Misericordiae University Hospital and Our Lady's Children's Hospital Crumlin purchased new HCUs in 2016 (Appendix 1 details the brands of HCUs in use in Irish hospitals in July 2015 and in November 2016).

2.4 National Incident Management & Learning Team

In response to the publication of the RRA by ECDC in April 2015, a HSE National Incident Management and Learning Team (NIMLT) was established in May 2015 to oversee the management of this incident in Ireland (NIMLT 50944). The membership includes representation from the Health Service Executive (HSE), the Health Products Regulatory Authority (HPRA), the Health Protection Surveillance Centre (HPSC), the nine cardiothoracic centres (includes HSE, public voluntary and private hospitals), the Public Health Laboratory (PHL), Cherry Orchard and the Irish Mycobacteria Reference Laboratory (IMRL), located in St. James's Hospital (Appendix 2).

The primary aim of the NIMLT was to assess the risk of *M. chimaera* infection to cardiothoracic surgery patients in Ireland and to identify mitigation strategies for any risk identified. Assessment of risk was addressed through the following:

1. Retrospective and prospective case finding
2. Device assessment: Sampling from the HCUs in use in the nine cardiothoracic centres was carried out. The Public Health Laboratory (PHL), Cherry Orchard determined the presence or absence of MAC in water samples (and air samples). Isolates were then referred to the IMRL for identification to species level using molecular methods
3. Microbiological investigation: The IMRL undertook speciation and further characterisation of isolates from potential cases, as well as environmental isolates. It

also performed next generation sequencing (NGS) of all *M. chimaera* isolates associated with this incident, as well as unrelated isolates for comparison.

2.5 Case finding

This report presents the results of the case finding undertaken at HPSC. This was conducted in parallel to the other strands of the NIMLT's overall investigation. Case finding comprised both prospective and retrospective detection. Its purpose was to identify cases of *M. chimaera* infection among patients who previously underwent cardiothoracic surgery or ECMO involving the use of HCUs in Ireland.

The findings of this study inform the risk of *M. chimaera* infection to Irish patients from contaminated HCUs used during cardiothoracic surgery and ECMO. Furthermore, as this multi-country outbreak continues to unfold, it adds to the evolving knowledge base.

3. Aim and Objectives

Aim

To identify cases of *Mycobacterium chimaera* infection among patients who previously underwent cardiothoracic surgery or ECMO in Ireland, to inform the risk associated with HCUs used during these procedures.

Objectives

1. To identify patients with NTM isolates diagnosed in Irish laboratories on and after 1st January 2007

2. To determine if any of these individuals underwent cardiothoracic surgery or ECMO in the preceding five years i.e. back to 2002

3. To ascertain if any of these individuals meet the case definition, as prescribed in the ECDC protocol

4. For those who meet the case definition, to inform the relevant clinician in order to ensure appropriate follow-up

5. Where clinical isolates are available, to request referral of these isolates to the IMRL for further characterisation

4. Methods

4.1 Case Definition

The case definition, as specified in the ECDC protocol was used (24).

Clinical criteria:

Any of the following:

- Prosthetic valve endocarditis[4]
- Prosthetic vascular graft infection
- Sternotomy wound infection
- Mediastinitis
- Manifestations of disseminated infection including embolic and immunologic manifestations e.g., splenomegaly, arthritis, osteomyelitis, bone marrow involvement with cytopenia, chorioretinitis, lung involvement, hepatitis, nephritis, myocarditis

Exposure criteria:

A patient having undergone surgery requiring cardiopulmonary bypass in the five years prior to the onset of symptoms of infection

Confirmed case:

A patient meeting both the clinical and exposure criteria

AND

M. chimaera detected by culture and identified by DNA sequencing in an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

Probable case:

A patient meeting the clinical and exposure criteria

AND

M. chimaera detected by direct PCR and amplified DNA sequencing from an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

OR

MAC detected by culture or direct PCR from an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

OR

Histopathological detection of non-caseating granuloma and foamy/swollen macrophages with acid fast bacilli in cardiac or vascular tissue in the proximity of the prosthetic material or in specimen from the sternotomy wound

[4] As evidenced by echocardiography (vegetations, new or partial dehiscence of a prosthetic valve, pseudo-aneurysm or an abscess in the tissues surrounding a heart valve)

4.2 Case finding

This case finding investigation comprised both retrospective and prospective detection of cases.

4.2.1 Retrospective case finding

Two approaches were used to retrospectively identify cases.

Firstly, in response to the briefing letter sent by the Director of the HPSC on 23rd June 2015 (Appendix 3), clinicians were requested to notify HPSC if a case had been identified in their hospital.

Secondly, potential cases were identified by matching laboratory records of NTM isolates to cardiothoracic surgery and ECMO records.

This involved the following steps:

a. All microbiology and histopathology laboratories in Ireland retrospectively reported all NTM isolates diagnosed on and after 1st Jan 2007. A MS Excel template was provided (Appendix 4) and this was returned electronically as an encrypted file to the HPSC.

b. The nine cardiothoracic centres were requested to provide details on all patients who underwent cardiothoracic surgery or ECMO on and after 1st January 2002. A MS Excel template was provided (Appendix 5) and this was returned electronically as an encrypted file to the HPSC.

c. At the HPSC, potential cases were identified through matching laboratory records of NTM isolates (January 2007 - June 2015) to cardiothoracic surgery/ECMO records (January 2002 – June 2015) using a series of criteria as outlined below.

d. Additional clinical and microbiological information was sought from the relevant clinicians in order to ascertain whether the patient met the case definition.

e. For those patients who met the case definition, a case report form was completed by the relevant clinician and returned to the HPSC (Appendix 6).

4.2.2 Prospective case finding

In response to the briefing letter sent by the Director of the HPSC on 23rd June 2015 to microbiologists and microbiology laboratories, cardiothoracic surgeons and cardiologists (Appendix 3), cases of NTM infection related to cardiothoracic surgery were prospectively reported to the HPSC.

Clinicians were advised in the briefing letter that patients meeting clinical and exposure criteria without microbiological evidence of other pathogen(s) should be evaluated for mycobacterial infection.

4.3 Data management

4.3.1 Data sources

There is no common national data source that captures all cardiothoracic surgical procedures undertaken in Ireland e.g., the Hospital In-Patient Enquiry (HIPE) system is limited to public hospitals. Therefore, hospital-specific databases maintained by perfusionists and cardiothoracic surgeons of all patients who undergo cardiothoracic surgery and ECMO were used to provide the relevant data to HPSC. The microbiology laboratories that perform diagnostic testing for mycobacteria provided a list of patients with NTM isolates since 2007 from their laboratory information systems.

4.3.2 Data collation and storage

Laboratory and cardiothoracic surgery data were collated in a Microsoft Access database at the HPSC. HPSC data protection and data confidentiality procedures were adhered to. The MS Access database and files received from the laboratories and cardiothoracic centres were stored in a secure location on the HPSC network. Both paper and electronic case report forms received were also stored in secure locations at the HPSC. Access was restricted to members of the investigation team collecting and analysing data. Data entry and analysis was centralised at the HPSC.

4.3.3 Data quality

Following collation of the data from the laboratories and the nine cardiothoracic surgical centres at the HPSC, a number of data quality checks were conducted at this stage.
This included the following:

- checking values of quantitative variables for inconsistencies
- checking values of qualitative variables for inconsistencies
- checking for outliers
- checking for duplicates
- checking for missing values
- logic checks e.g. age > 120 years

4.3.4 Cross-matching of laboratory and cardiothoracic surgery/ECMO data

In order to identify patients with a positive NTM isolate who also had cardiothoracic surgery or ECMO prior to the laboratory diagnosis, a series of matching criteria were applied (Table 2).

Table 2. Criteria used to match laboratory and cardiothoracic surgical records

Matching Level	Variables
1	First Name AND Surname AND DOB AND Sex
2	Medical Record Number AND Hospital Name
3	First Name AND Surname AND DOB
4	Surname AND DOB AND Sex
5	First Name AND Surname AND Sex
6	Surname AND DOB
7	First Name AND DOB
8	First Name AND Surname

Matching at level 1 was the most stringent, with the stringency of the match decreasing thereafter. An automated matching process was initially conducted, using a series of queries developed in MS Access, based on the criteria outlined in Table 2. All potential matches that were flagged were manually reviewed in order to identify the true matches. If it was not clear whether or not it was a true match, the relevant hospital or laboratory was asked to provide additional identifying details. As a quality control measure, this manual review was repeated to validate the results.

4.4 Patient follow-up

In the event that a patient met the case definition, the hospital where the patient underwent surgery was informed. The relevant consultant microbiologists were requested to co-ordinate the completion of a case report form and return to HPSC.

For matching records where it was unclear whether or not a patient met the case definition, HPSC requested the consultant microbiologist at the diagnosing laboratory to co-ordinate a review of the patient's healthcare records to determine if there was any evidence of invasive infection (Appendix 7). Following the clinical review, any patient who did not meet the case definition was excluded from further investigation.

4.5 Data analysis

Descriptive analyses were used to describe the laboratory and cardiothoracic surgery data and any identified cases. The risk of infection to patients was estimated by calculating the crude incidence rate per 10,000 years' post-operative follow-up and the expected number was derived. Data analysis was performed using MS Access, MS Excel and STATA® version 14.1 (StataCorp., Texas, USA).

4.6 Data destruction

Data relating to persons under investigation and identified as not meeting the case definition will be destroyed 12 months following production of the final report. Data relating to cases will be retained for eight years, as per HSE policy (26).

4.7 Ethical considerations

4.7.1 Ethical approval

Ethical approval was not required.

4.7.2 Confidentiality and data protection

The Data Protection Commissioner was consulted by the Chair of the NIMLT, to ensure that the investigation was compliant with data protection legislation.

5. Results

5.1 Retrospective case finding

5.1.1 Laboratory data

There are 39 clinical microbiology laboratories in Ireland. Eighteen of these perform testing for mycobacteria, and the remaining 21 refer their samples to laboratories that provide this diagnostic service. Between January 2007 and June 2015, 2,034 isolates of NTM were detected and subsequently reported to HPSC as part of the look-back investigation (Figure 1). The annual numbers of NTM isolates reported by laboratory are presented in Appendix 8.

5.1.2 Cardiothoracic surgery and ECMO data

Between January 2002 and June 2015, 40,420 cardiothoracic surgeries and 234 ECMO procedures were undertaken across the nine designated cardiothoracic centres (Table 3 and Figure 1). The annual numbers of cardiothoracic surgeries and ECMO procedures, by cardiothoracic centre are presented in Appendix 9.

Table 3. Number of cardiothoracic surgical or ECMO procedures, Ireland: January 2002 – June 2015

Centre	Hospital Type	Manufacturer HCU*	Number CTS†	Number ECMO‡	Total
Beacon Hospital**	Private	LivaNova/Sorin	658	0	658
Blackrock Clinic	Private	Maquet	6,336	0	6,336
Cork University Hospital	Public	Maquet	5,803	0	5,803
Galway Clinic††	Private	Maquet	485	0	485
Galway University Hospital**	Public	Maquet	1,563	0	1,563
Mater Misericordiae University Hospital	Public	LivaNova/Sorin	7,430	103	7,533
Mater Private Hospital	Private	LivaNova/Sorin	8,554	0	8,554
Our Lady's Children's Hospital Crumlin	Public	LivaNova/Sorin	3,406	131	3,537
St. James's Hospital	Public	Maquet	6,185	0	6,185
Total			**40,420**	**234**	**40,654**

*Heater-cooler unit

†Cardiothoracic surgery

‡Extracorporeal membrane oxygenatic

**Procedures commenced in these centres during 2007

††Procedure commenced towards the end of 2004

Overall, the level of completeness of data provided by the cardiothoracic centres to the HPSC was high. However, there were some missing data for a number of variables requested and this is outlined in Table 5.

Table 4. Completeness of key fields on cardiothoracic surgery and ECMO data provided to HPSC

	First Name	Surname	Date of Birth	Gender	Date of Surgery	Date ECMO commenced
Beacon Hospital	✓	✓	✓	✓	✓	N/A
Blackrock Clinic	✓	✓	✓	✓	✓	N/A
Cork University Hospital	✓	✓	✓	✓	✓[a]	N/A
Galway Clinic	✓	✓	✓	✓	✓	N/A
Galway University Hospital	✓	✓	✓[b]	✓	✓	N/A
Mater Misericordiae University Hospital	X[c]	✓	✓	✓	X[d]	✓
Mater Private Hospital	✓	✓	X[e]	X[f]	✓	N/A
Our Lady's Children's Hospital Crumlin	✓	✓	✓	✓	✓	✓
St James's Hospital	✓	✓	✓	✓	✓	N/A

N/A = not applicable

[a]Exact date of surgery not available for 26 patients who underwent surgery between 01/11/2009 and 31/12/2009 in CUH; 01/11/2009 used as approximate date for these patients

[b]DOB missing for 5 GUH patients

[c]First name missing for all MMUH patients

[d]Date of surgery not provided by MMUH – date of discharge provided and used as proxy

[e]DOB missing for MPH patients pre-2006

[f]Gender missing for MPH patients pre-2006

5.1.3 Cross-matching exercise

Figure 1 outlines the number of records reviewed at each step of the retrospective case-finding (look-back) investigation. When the laboratory and cardiothoracic surgical records were compared using an automated method (including "fuzzy logic"), 1,056 potential matches were identified. Following a manual review of these potential matches, only 29 definite matches remained. A detailed review of these 29 matches was undertaken. One confirmed case was identified (this patient had already been identified locally and had commenced treatment for *M. chimaera* infection in the relevant hospital).

Twenty eight matches were excluded. For eight, the laboratory specimen predated cardiothoracic surgery. For one, the isolate was not a NTM. For the remaining 19 matches, NTM had been isolated from either a non-invasive specimen or a tissue sample and although the patient also met exposure criteria of having undergone cardiothoracic surgery, upon formal review of each healthcare record, it was determined that there was no evidence of invasive infection. Therefore, none of the 19 matches met the case definition for *M. chimaera* infection and thus, were excluded from further investigation.

5.2 Prospective case finding

To date, three additional cases have been notified to the HPSC through prospective case finding.

5.3 Cases

At the time of finalising this report, four confirmed cases of invasive *M. chimaera* infection identified in patients who had previously undergone cardiothoracic surgery in Ireland, have been reported to HPSC.

The four cases were in adults and all had undergone aortic valve replacement/repair surgery. The cases presented with one or more of the following symptoms; endocarditis, bloodstream infection, disseminated infection, graft infection and skin or soft tissue infection.

Prior to onset of symptoms, all four cases had been exposed to LivaNova/Sorin HCUs during surgery at a single cardiothoracic centre. The incubation period ranged between 14 months and 39 months. The earliest implicated surgery was performed in 2012 and the most recent was in 2014. One patient died. However, the *M. chimaera* infection was determined not to be the primary cause of death.

No cases in patients exposed to HCUs during ECMO have been reported to date in Ireland.

5.4 Risk of acquiring *M. chimaera* infection after cardiothoracic surgery

To estimate the risk of acquiring *M. chimaera* infection after cardiothoracic surgery, the investigation focused on the cohort of patients who underwent cardiothoracic surgery in Ireland between 2007–2014 (since our investigation focused on cases diagnosed with *M. chimaera* infection since 2007 and an incomplete year's data was available for 2015)

Between 2007 and 2014, 23,321 patients underwent cardiothoracic surgery in Ireland. Assuming each patient is theoretically at risk of developing *M. chimaera* infection for five years after surgery, the total person years at risk for these patients was 102,079 person-years (i.e. as of 17/11/2016). Using this figure and the number of cases identified to date (n=4), this gives a crude incidence rate of 0.4 (95% confidence interval 0.2-1.0) per 10,000 person years post-operative follow-up (Table 6). However, since the four cases of *M.*

chimaera identified in Ireland had undergone surgery involving valve replacement/repair, the estimate of risk should be limited to this cohort of patients. However, full details on the procedure were not available to HPSC for all patients who underwent cardiothoracic surgery. Assuming 50% of patients who underwent cardiothoracic surgery in Ireland had valve repair or replacement surgery, then the crude incidence risk should be doubled (0.8 per 10,000 years' post-operative follow-up) (Table 6).
Restricting the analysis to the cohort of patients exposed to LivaNova/Sorin HCUs during valve replacement/repair, the estimated crude incidence risk is 1.6 per 10,000 years' post-operative follow-up, while the risk to date is effectively zero/negligible for patients exposed to Maquet HCUs (Table 6).

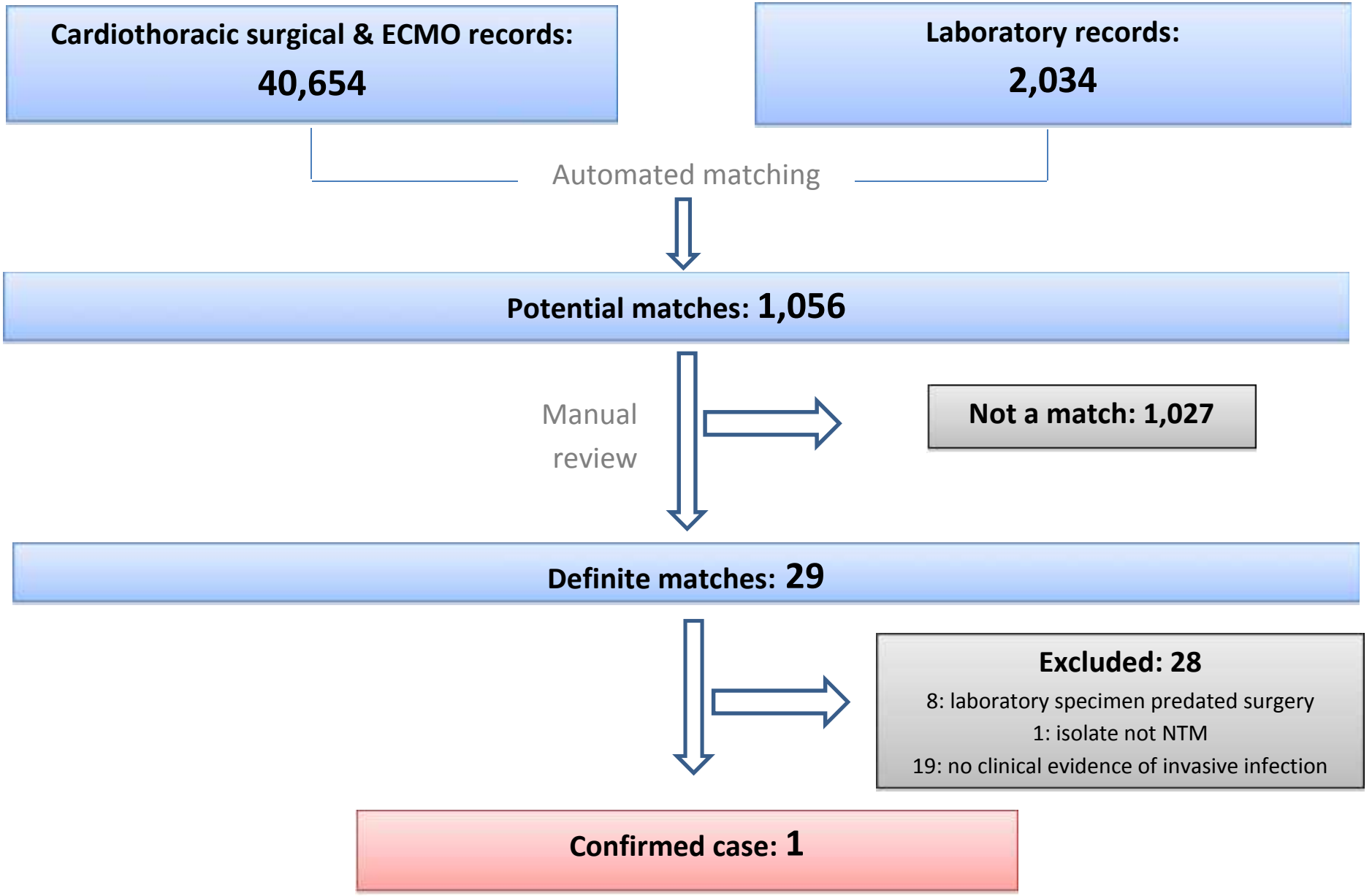
Since the incubation period for *M. chimaera* infection is up to five years, patients who underwent surgery between November 2011 and December 2014 may develop infection in the future. Applying the crude incidence rates calculated above to the residual periods these patients remain at risk (up to December 2019 for some patients), it is estimated that one additional case (point estimate: 0.55; 95% confidence interval 0.2-1.4) could emerge during the remaining follow-up period (Table 5).

Table 5. Incidence rate of *M. chimaera* infections in patients (as of 07/11/2016) who underwent cardiothoracic surgery (CTS) in Ireland, between 2007-2014

	No. of cases	**No. of surgeries**	**Person years at risk to date**	**Crude incidence rate 10, 000 (95% CIs)**	**Residual person years at risk**	**Estimated number of additional cases**
All CTS patients	4	23,321	102,431	**0.39 (0.15-1.0)**	14,163	
CTS patients with valve replacement/repair*	4	11,660.5	51,215	**0.78 (0.30-2.0)**	7,082	0.55 (0.21-1.4)
CTS patients exposed to LivaNova/Sorin HCUs	4	11,333	49,951	**0.8 (0.3-2.1)**	6,703	
CTS patients with valve replacement/repair exposed to LivaNova/Sorin HCUs*	4	5666.5	24,976	**1.6 (0.6-4.2)**	3,352	0.54 (0.2-1.4)
CTS patients exposed to Maquet HCUs	0	11,988	52,480	**0.0 (-)**	7,460	0

*Assuming 50% of patients who underwent CTS had a procedure involving valve replacement or repair

Figure 1. Number of records reviewed at each step of the retrospective case-finding (look-back) investigation



6. Discussion

Risk of *M. chimaera* infection to Irish patients

A national case-finding investigation has to-date identified four cases of *M. chimaera* infection since 2007 among patients who had undergone cardiothoracic surgery or ECMO in Ireland during the preceding five years. This is in the context of approximately 3,000 cardiothoracic surgeries involving the use of HCUs being undertaken per year in Ireland, or in excess of 40,000 such procedures since 2002. Focusing on the cohort who underwent cardiothoracic surgery between 2007 and 2014 and exposed to LivaNova/Sorin HCUs, the crude incidence rate was 0.8 per 10,000 person years post-surgery follow-up (95% confidence interval 0.3-2.1). This indicates a very low but present risk to a selected group of open cardiothoracic surgery patients in Ireland.

For every 10,000 patients undergoing heart surgery to replace a heart valve, approximately 120 could be expected to develop a surgical site infection and between 300 and 600 could develop endocarditis over a five-year period. Within this group, an additional one patient might develop infection because of mycobacteria. Consequently, any potential risk of infection should be balanced against the potential risk of delaying cardiac surgery in a patient for whom it may reflect the optimal treatment (20).

This estimation of potential risk is similar to that identified in England (0.4 per 10,000 person years' post-operative follow-up; based on 100,000 patients who underwent valve repair or replacement surgery between 2007 and 2014 and 17 probable cases identified (20). The UK and Irish investigations indicate a lower risk than the Swiss study, where the first outbreak was investigated and involved six cases between 2008 and 2012 from approximately 600 patients receiving extracorporeal circulation per year (18).

Severity of infection

While the number of cases identified in Ireland to date has been low, the infections were severe. This is in concordance with the experience to date in other countries. The four cases occurred in the absence of severe immunodeficiency. All presented with endocarditis and/or bloodstream infection or disseminated infection. One patient had a fatal outcome, although the *M. chimaera* infection was determined not to be the primary cause of death.

The findings of this investigation add to the emerging evidence that this recently characterised species is more virulent than previously thought (19).

The interval between surgery and diagnosis was lengthy (range: 14 months – 39 months). This is in keeping with the long incubation period described for cases in other countries (17-20).

Model of HCU

All four cases had undergone surgery involving the use of LivaNova/Sorin HCUs. Although it is not yet clear if the risk of mycobacterial infection is limited solely to this one manufacturer, all cases reported to date in this multi-country outbreak have been exposed to LivaNova/Sorin devices. Infections associated with Maquet HCUs (the other brand in use in Ireland) have not been reported to date.

Health Information Systems

This study highlighted a number of deficiencies in the Irish health information infrastructure. Firstly, the absence of a unique health identifier (UHI) in Ireland was underscored during the look-back investigation, resulting in a time-consuming process of cross-matching the laboratory with the surgical records. A UHI would have been facilitated a less complicated and more timely investigation.

A common national data source that captures all cardiothoracic surgical procedures does not exist (e.g. the Hospital In-Patient Enquiry HIPE system does not include private hospitals). Hospital-specific databases maintained by perfusionists and cardiothoracic surgeons were used instead.

Other components of the NIMLT's investigation

The case finding investigation described in this report comprised just one element of the overall work coordinated by the NIMLT 50944. In parallel, the following activities have also been undertaken:

- Measures have been taken to mitigate the risk associated with these HCU devices. Each cardiothoracic surgical centre has undertaken a local risk assessment and implemented appropriate actions to identified risks. These include; enhanced decontamination regimens, deep-cleaning of devices by the manufacturer, decommissioning of contaminated devices and procurement of new machines (the HCUs used by Irish hospitals in November 2016 are detailed in Appendix 1)

- Environmental sampling (i.e. water samples) from the HCUs *in situ* in the nine cardiothoracic surgical centres is ongoing and microbiological testing of these samples is performed by the PHL, Cherry Orchard. The recommended testing schedule is currently once every four weeks for LivaNova/Sorin devices and once every eight weeks for Maquet devices

- Identification and molecular typing by NGS of clinical and environmental isolates is being conducted at the IMRL

- The HPRA has published safety notices and manufacturer's field safety notices. The HPRA is a member of an EU Regulatory Group investigating the incident and requesting manufacturers to develop appropriate short-term and long-term corrective measures. As a member of the NIMLT, the HPRA has advised the NIMLT on international developments and updated advice in this area

- The HPSC is the point of contact with ECDC and communicates international developments on the investigation with the NIMLT

- Furthermore, throughout its investigation, the NIMLT has communicated its findings to the relevant stakeholders. Information and advice have been provided through an advice document for providers of cardiothoracic surgery and a patient information leaflet. A national clinical referral pathway for patients at risk of *M. chimaera* infection has also been developed and distributed to all hospitals and GPs nationally. A voluntary organisations briefing session was organised by the NIMLT in July 2016

Strengths of this study

This was a national case finding investigation with 100% participation from cardiothoracic surgical centres, along with microbiology and histopathology laboratories in Ireland. The retrospective look back component successfully identified the already-confirmed case, thereby indicating the robustness of the study's methodology.

Data quality assurance was emphasised throughout. Data quality checks were conducted, the review of potential matches was undertaken by two investigators and the cross-matching of laboratory and cardiothoracic surgery/ECMO records was repeated to validate results. Communication from the NIMLT and the HPSC to the relevant hospitals during this investigation has been effective in raising clinician awareness and has contributed to the prospective notification of three confirmed cases.

Limitations of study

Retrospective case finding is likely to have under-estimated the number of cases for two reasons. Firstly, prior to this incident, culture for mycobacteria was not part of the routine diagnostic work-up for patients with suspected cardiovascular infection. Secondly, *M. chimaera* is a recently characterised species and identification is currently only possible using specialised molecular diagnostic methods, which are only available in the IMRL. In instances where NTM isolates were not referred to the IMRL for further characterisation or where isolates are no longer available, it was not possible to further speciate the organism.

7. Recommendations

1. Mycobacterial infection should be considered in the differential diagnosis of any patient with a history of open heart surgery or ECMO, who presents with suspected endocarditis or other cardiovascular or relevant infection, with appropriate testing. This is key to ensuring timely diagnosis and correct clinical management of the patient

2. All healthcare professionals, particularly cardiothoracic surgeons, cardiologists, microbiologists and microbiology laboratories should continue to prospectively notify any potential cases to the HPSC

3. A unique health identifier (UHI) should be introduced in Ireland for use across all healthcare settings, regardless of funding source. By facilitating the process of linking datasets, UHIs would be especially valuable in any future similar look-back/case finding investigation

8. Acknowledgements

We would like to thank the staff of the cardiothoracic surgical centres and the microbiology laboratories for providing data to HPSC. Furthermore, we would like to thank Ajay Oza (Surveillance Scientist, HPSC) for his technical expertise in developing the patient matching criteria.

We would also like to acknowledge the expertise and contribution of our colleagues in other EU Member States, particularly Public Health England and Public Health Agency, Northern Ireland, along with ECDC in guiding the format of investigation.

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10. Appendices

Appendix 1. Brands of heater-cooler units in use in Irish hospitals, July 2015 and November 2016

Hospital name	July 2015		November 2016	
	LivaNova/Sorin	Maquet	LivaNova/Sorin	Maquet
Beacon Hospital	**2**	**0**	**0**	**2**
Mater Private Hospital	**5**	**0**	**1***	**2**
Mater Misericordiae University Hospital	**3**	**0**	**0**	**3**
Our Lady's Children's Hospital Crumlin	**2**	**0**	**0**	**2**
Blackrock Clinic	**0**	**2**	**0**	**2**
Cork University Hospital	**0**	**3**	**0**	**3**
Galway Clinic	**0**	**2**	**0**	**2**
St James's Hospital	**0**	**3**	**0**	**2**
University Hospital Galway	**0**	**3**	**0**	**3**
Total	**12**	**13**	**1***	**21**

*One LivaNova/Sorin 3T retained as back-up, not in clinical use

Appendix 2: Membership of National Incident Management and Learning Team 50944

National Lead, HSE Acute Hospital Division	Dr Ciaran Browne (Chair)
Health Protection Surveillance Centre	Dr Karen Burns, Consultant Clinical Microbiologist Dr Darina O'Flanagan, Specialist in Public Health Medicine and Director (Retired May 2016) Dr Joan O'Donnell, Specialist in Public Health Medicine Dr Margaret Fitzgerald, Senior Surveillance Scientist Dr Breda Cosgrove, Specialist Registrar in Public Health Medicine
Public Health Laboratory, Cherry Orchard	Dr Eleanor McNamara, Consultant Microbiologist and Director Dr Anne Carroll, Surveillance Scientist
Irish Mycobacteria Reference Laboratory	Prof Tom Rogers, Consultant Microbiologist and Clinical Director Dr Margaret Fitzgibbon, Chief Medical Scientist
Health Products Regulatory Authority	Dr Joan Gilvarry, Director of Human Products Monitoring Ms Anne Tobin, Medical Device Vigilance Manager Ms Andrea Hanson, Senior Medical Device Vigilance Assessor
National Clinical Head of Medical Devices HSE	Mr Ger Flynn
Beacon Hospital	Dr Philip Murphy, Consultant Microbiologist Mr Marco Arcari, Clinical Perfusionist Ms Leonora Leonard, Infection Prevention & Control
Mater Private Hospital	Dr Margaret Hannan, Consultant Microbiologist Mr Lars Nolke, Consultant Cardiothoracic Surgeon Ms Audrey Doyle, Director of Quality Ms Paula O'Malley, Infection Prevention & Control
Mater Misericordiae University Hospital	Dr Margaret Hannan, Consultant Microbiologist Mr Lars Nolke, Consultant Cardiothoracic Surgeon Mr Noel Lynch, Clinical Perfusionist Ms Breda Corrigan, Assistant Director of Nursing
Our Lady's Children's Hospital Crumlin	Dr Niamh O'Sullivan, Consultant Microbiologist Dr Terence Prendiville, Consultant Paediatric Cardiologist Mr Raymond MacDonnell, Clinical Perfusionist Ms Rachel Kenna, Director of Nursing
Blackrock Clinic	Mr Bryan Harty, Chief Executive Officer Ms Edel Costigan, Quality Manager Mr Paul Hickey, Clinical Perfusionist Ms Carmel Mangan, Director of Nursing

	Ms Joanne Flanagan, Infection Prevention & Control
Cork University Hospital	Prof Michael Prentice, Consultant Microbiologist Mr Eoin Coleman, Clinical Perfusionist Ms Catherine Collins, Clinical Perfusionist Ms Betty Hickey, Assistant Director of Nursing
Galway Clinic	Mr Markus Fischer, Clinical Perfusionist
St James's Hospital	Dr Brian O'Connell, Consultant Microbiologist Mr Paul Fagan, Clinical Perfusionist
University Hospital Galway	Dr Marianne Nolan, Consultant Microbiologist Mr Dave Veerasingam, Consultant Cardiothoracic Surgeon Mr Mark DaCosta, Consultant Cardiothoracic Surgeon Ms Denise Gonoud, Clinical Perfusionist Ms Judith Davitt, Infection Prevention & Control
HSE Communications	Ms Ann McLoone Ms Ann Martin
Health & Social Care Services Northern Ireland	Dr Lorraine Doherty, Assistant Director of Public Health (Health Protection)

Appendix 3: HPSC briefing letter to Microbiologists, Cardiothoracic Surgeons and Cardiologists, June 2015

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

hpsc

To: *Consultant Microbiologists and Histopathologists, Consultant Infectious Diseases Physicians, Consultant Cardiothoracic Surgeons, Consultant Cardiologists, Infection Prevention & Control Nurses, Directors of Public Health, Specialists in Public Health Medicine, ICU physicians, Occupational Health Physicians, Health Products Regulatory Authority, Consultant Respiratory Physicians, Consultant Paediatricians; Dr Philip Crowley, Department of Health, Dr Stephanie O'Keeffe, Dr Kevin Kelleher, Dr Robert Cunney, Professor Thomas Rogers*

CC: *Irish Society of Clinical Microbiologists, Infectious Diseases Society of Ireland, Infection Prevention Society, Irish Cardiac Society*

23 June 2015

Dear Colleagues,

RE: *Mycobacterium chimaera* infection following cardiac surgery.

International Early Warning Response System (EWRS) reports have previously been circulated on 14th July 2014 and 23rd February 2015 regarding cases of *Mycobacterium chimaera* causing endocarditis and invasive infection following cardiac surgery.

Mycobacterium chimaera is a slow-growing non-tuberculous mycobacterium often reported initially as *M. intracellularae* or *M. avium* complex.

Switzerland has reported six *M. chimaera* infections: three cases of endocarditis, one bloodstream infection and two vascular graft infections. Two of the six had fatal outcomes related to the infection. The clinical manifestations included osteomyelitis and involvement of multiple organs such as the eye and spleen. The Netherlands reported one fatal *M. chimaera* infection in a patient following cardiac surgery. A case has also been reported in Germany. On 21 May, Public Health England (PHE) reported that a retrospective investigation identified 13 patients with endocarditis, surgical site infection or disseminated infection with *Mycobacterium chimaera* or other *Mycobacterium avium* complex (MAC) species within four years of surgery involving cardiopulmonary bypass. These patients had surgery in many different hospitals in the UK between 2007 and 2014. A definitive link between the heater cooler units and the patient infections has not been established by the UK investigation. Further microbiological investigations are underway.

Investigation in Switzerland included microbiological examination of environmental samples that identified M. chimaera contamination in heater-cooler units used during cardiac operations,

including water samples from the units. Air sampling cultures became positive for *M. chimaera* when units were running but not if they were turned off. This suggests *M. chimaera*-contaminated heater-cooler units as a potential source of infection.

The European Centre for Disease Prevention and Control (ECDC) is co-ordinating an EU wide investigation and has issued a protocol for use. The HSE is undertaking both a retrospective review and a prospective investigation of possible cases as recommended in the EU protocol. The following case definitions will be used for the investigation:

Case definition

Clinical criteria:
Any of the following:

- Prosthetic valve endocarditis[5],
- Prosthetic vascular graft infection
- Sternotomy wound infection,
- Mediastinitis
- Manifestations of disseminated infection including embolic and immunologic manifestations e.g. splenomegaly, arthritis, osteomyelitis, bone marrow involvement with cytopenia, chorioretinitis, lung involvement, hepatitis, nephritis, myocarditis.

Exposure criteria:
A patient having undergone surgery requiring cardiopulmonary bypass in the 5 years prior to the onset of symptoms of infection

Confirmed case:
A patient meeting the clinical and exposure criteria

AND

M. chimaera detected by culture and identified by DNA sequencing in an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

Probable case:
A patient meeting the clinical and exposure criteria

AND

M. chimaera detected by direct PCR and amplified DNA sequencing from an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

OR

Mycobacterium avium complex (MAC) detected by culture or direct PCR from an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

OR

Histopathological detection of non-caseating granuloma and foamy/swollen macrophages with acid fast bacilli in cardiac or vascular tissue in the proximity of the prosthetic material or in specimen from the sternotomy wound.

The following actions are recommended:

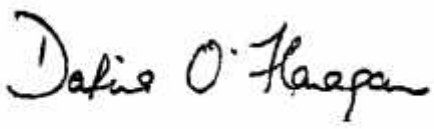
[5] As evidenced by echocardiography (vegetations, new or partial dehiscence of a prosthetic valve, pseudo-aneurysm or an abscess in the tissues surrounding a heart valve)

1. The HPRA has advised Cardiothoracic services using cardiopulmonary bypass to review procedures and evaluate heater cooler devices for potential contamination. The guidance and recommendation outlined by the device manufacturer should be followed.
2. Prospective investigation: Patients requiring investigation for suspected endocarditis or infection related to cardiac surgery should undergo evaluation for mycobacterial infection. Microbiology laboratories, cardiothoracic surgeons and cardiologists should prospectively report any probable cases of non-tuberculous mycobacterial infection related to cardiac surgery to the Health Protection Surveillance Centre and specimens for further diagnostic work-up sent to the National Mycobacterial Reference Laboratory in St James's hospital.
3. Retrospective investigation:
    a. Retrospective testing for MAC/*M. chimaera* of stored microbiological or histopathological samples from cases of culture negative and otherwise unexplained endocarditis or vascular graft infection, including histopathological evidence of mycobacterial infection, should be considered by clinical microbiologists, in conjunction with the investigating clinician. It is appreciated that such historical samples are unlikely to be available for further investigation. It is advisable to review any patients with prosthetic valve endocarditis or other relevant infections after cardiothoracic surgery, who have not had a microbiological diagnosis, to see if mycobacterial investigations may be relevant as this diagnosis would alter management. Liaison with an infection specialist is recommended. Please notify HPSC of any cases identified retrospectively.
    b. Microbiology laboratories, cardiothoracic surgeons and cardiologists should retrospectively report any known cases of non-tuberculous mycobacterial infection diagnosed since 2007. This data file (template to be provided by HPSC to microbiology/ histopathology departments) should be encrypted and sent to HPSC using the following email address myco.chim@hpsc.ie All queries re data encryption should go to Dr Margaret Fitzgerald, senior surveillance scientist at HPSC: margareta.fitzgerald@hse.ie

    Non-tuberculous mycobacteria are all mycobacteria **except** those belonging to**:** *Mycobacterium tuberculosis* complex (i.e. including *M*. *tuberculosis, M*. *africanum*, *M*. *bovis*, *M*. *canetti*, *M*. *caprae*, *M*. *microti* and *M*. *pinnipedii*)

    All other *Mycobacterium* not specified above should be reported. These will include *Mycobacterium avium* complex, *M. intracellularae* and *Mycobacterium chimaera.* These cases will be cross checked with Hospital Inpatient Enquiry (HIPE) data and/or other hospital specific cardiopulmonary bypass databases to check if they have had cardiac surgery in the preceding 5 years. If available, specimens from these cases will then be tested to see if *M. chimaera* is identified. In view of the small number of cases that have been identified in other jurisdictions with larger populations, the number of cases of MAC infection who have had cardiopulmonary surgery in the preceding five years is expected to be very low. However, this anonymised information will be used as part of the international risk assessment of these devices.

4. The Society for Cardiothoracic Surgery (SCTS) in Great Britain and Ireland advises that in most cases the risk from delaying cardiothoracic surgery, including valve replacement or repair is likely to outweigh the infection risk. SCTS advises that surgeons may wish to consider on an individual case basis whether there are any planned procedures that would not be affected by delay.[1] In patients who are being consented for cardiothoracic surgery, SCTS advises that surgeons inform their patients of the specific risk but also that the risk of delaying surgery is significantly greater. The risk of other infections also remains much higher than that of mycobacterial infection.
5. Cardiologist / cardiac surgeons are advised to review any identified cases to discuss with the patients any therapeutic implications.
6. These non–tuberculous mycobacteria are found very widely in the environment, including in tap water. Most people are exposed on a regular basis with no adverse consequences. In the presence of pre-existing lung damage to the respiratory tract, or an impaired immune system these organisms may cause infection of the respiratory tract. Theatre staff should be advised of the issue and if they have pre-existing lung conditions or impaired immune system should be offered occupational health review.



Darina O'Flanagan
Director Health Protection Surveillance Centre

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Appendix 4:

Microbiology and Histopathology laboratory template for reporting cases of non-tuberculous mycobacterium infection* diagnosed on or after 1st January 2007

***For the microbiology laboratory: Non-tuberculous mycobacteria are all mycobacteria except those belonging to Mycobacterium tuberculosis complex (the latter includes *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. canetti*, *M. caprae*, *M. microti* and *M. pinnipedii*).**
All other mycobacteria not specified above should be reported. These will include *Mycobacterium* avium complex, *Mycobacterium intracellulare* and *Mycobacterium chimaera*.
Please report data available now and do not await further speciation

***For the histopathology laboratory: Histopathological detection of non-caseating granuloma and foamy/swollen macrophages with acid-fast bacilli in cardiac or vascular tissue in the proximity of the prosthetic material or in specimen from the sternotomy wound**

Note: Cells shaded in grey for completion by Microbiology and Histopathology laboratory.
Cells shaded in red specific to the Microbiology laboratory and those in blue specific to the Histopathology laboratory

Completed by:	Name of person completing form
Date completed:	Date form completed

Variables included on the template:

1. **Number**
2. **Laboratory name**
3. **Patient First Name**
4. **Patient Surname**
5. **Address 1**
6. **Address 2**
7. **Town/Suburb**
8. **County**
9. **Date of Birth**
10. **Sex** (Male, Female)
11. **Specimen ID**
12. **Specimen type** (e.g. blood, pus, tissue biopsy, implanted prosthetic material etc.)
13. **Specimen collection date**
14. **Acid-fast bacilli seen by microscopy** (Yes/No/Not done)
15. **Organism identified** (*M. chimaera, M. intracellulare*, *M. avium* complex, *Mycobacterium* species)
16. **Method of confirmation** (Culture, PCR, Culture & PCR)
17. **Isolate or specimen referred to Reference Laboratory?** (Yes, No)
18. **If referred, name of Reference Laboratory**
19. **Isolate typed** (Yes, No, Unknown)
20. **Typing method used**
21. **Histopathology summary of microscopic examination**
22. **Histopathologist name**
23. **Hospital number**
24. **Indication for test or clinical condition that prompted test** (if available)
25. **Comments**

Appendix 5:

Template for reporting of patients who underwent surgery involving use of cardiopulmonary bypass on and after January 2002

*Sheet 1 - for reporting of patients who underwent surgery involving cardiopulmonary bypass (CPB) on and after January 2002

*Sheet 2 - for reporting of patients who underwent extracorporeal membrane oxygenation (ECMO) on and after January 2002

Completed by:

Date completed:

Variables included on the template:

Number

Hospital Name

Patient First Name

Patient Surname

Medical Record Number

County of residence (if available)

Date of Birth

Age

Sex (male/female)

Name of procedure involving CPB*

Date of surgery involving CPB†

Name of Surgeon‡

Comments

*Not included in worksheet for reporting ECMO

†For ECMO template, used date ECMO commenced

‡For ECMO template, used name of consultant

Appendix 6: Case Report Form

CASE REPORT FORM

On individuals diagnosed with non-tuberculous Mycobacterium infection on or after 1st January 2007 and who underwent surgery necessitating use of cardiopulmonary bypass in the preceding 5 years

Questions highlighted in grey are essential information that should be completed initially for all cases (initial report) meeting the case definition (provided on the final page of this form)

Questions not highlighted are additional information that can be reported following detailed review of clinical notes (update report). Please **keep** this report in the patient's notes and inform HPSC that you have a case meeting case definition (myco.chim@hpsc.ie). HPSC staff will then take this information by confidential telephone interview.

Initial report ☐ **Update report** ☐

1. Reporter

1.1 Name	
1.2 Job title	
1.2 Organisation	
1.3 Phone number	
1.4 Email address	
1.5 Date completed	(dd/mm/yyyy)

2. Patient Details

2.1 First name		**2.2 Surname**	
2.3 Date of birth	(dd/mm/yyyy)	**2.4 Age** (at time of dx of mycobacterial infection)	
2.4 Sex	**Male** ☐ **Female** ☐		
2.5 Last known address			

3. Organisation Details

3.1 Hospital where mycobacterial infection diagnosed	
3.2 Medical record number of patient in hospital where mycobacterial infection diagnosed	

3.3 Clinician in charge of care when mycobacterial infection diagnosed	
3.4 Microbiologist/ ID Physician contact	
3.5 Infection Control Team contact	
3.6 Date of last admission (irrespective of reason for admission)	
3.7 Clinician in charge of care during last admission	
3.8 Hospital where cardiac surgery performed (if different from 3.1 above)	
3.9 Medical record number of patient in hospital where surgery performed (if different from 3.2 above)	
3.10 Contact at hospital where cardiac surgery performed	

4. Clinical Details

4.1 Clinical presentation of mycobacterial infection	**Endocarditis** ☐ **Disseminated infection** ☐ **Blood stream infection** ☐ **Graft infection** ☐ **Prosthesis infection** ☐ **Skin or soft tissue infection** ☐ **Osteomyelitis** ☐ **Not clinically significant** ☐ **Other** ☐ **If other, please specify:**	**4.2 Organism identified**	***Mycobacterium chimaera*** ☐ ***Mycobacterium intracellulare*** ☐ ***Mycobacterium* avium complex** ☐ ***Mycobacterium* sp.** ☐

4.3 Date of presentation with clinical symptoms relating to mycobacterial infection	(dd/mm/yyyy)
4.4 Did the patient have any significant co-morbidities or immunosuppression at time of presentation?	**Yes** ☐ **No** ☐ If yes, please provide further details below **Significant co-morbidities:** **Immunosuppression:**
4.5 Was further surgery required?	**Yes** ☐ **No** ☐ If yes, please provide further details below **Number of subsequent surgeries:** **Dates of subsequent surgeries:** **Type of subsequent surgery:**
4.6 Details of management of infection (including antibiotics given and length of treatment)	
4.7 Outcome	**Still ill** ☐ **Recovered** ☐ **Died** ☐ If the patient has died, please further details below **Date of death** (dd/mm/yyyy): **Was death attributable to mycobacterial infection?** **Yes** ☐ **No** ☐

5. Laboratory Results

	Date of specimen	**Type of specimen** (e.g. blood, pus, tissue biopsy, implanted prosthetic material etc.)	**Organism identified**	**Laboratory diagnosis date**	**Type of test carried out to characterise the organism**	**Laboratory type**
5.1					WGS** ☐ 16S ☐ Line probe assay ☐ Phenotypic ☐	Local lab ☐ Reference lab ☐ Other ☐
5.2					WGS** ☐ 16S ☐ Line probe assay ☐ Phenotypic ☐	Local lab ☐ Reference lab ☐ Other ☐
5.3					WGS** ☐ 16S ☐ Line probe assay ☐ Phenotypic ☐	Local lab ☐ Reference lab ☐ Other ☐
5.4					WGS** ☐ 16S ☐ Line probe assay ☐ Phenotypic ☐	Local lab ☐ Reference lab ☐ Other ☐
5.5					WGS** ☐ 16S ☐ Line probe assay ☐ Phenotypic ☐	Local lab ☐ Reference lab ☐ Other ☐
5.6					WGS** ☐ 16S ☐ Line probe assay ☐ Phenotypic ☐	Local lab ☐ Reference lab ☐ Other ☐

**WGS: whole genome sequencing

6. **Cardiac Surgery**

6.1 Has this patient had more than one open cardiac surgery procedure in the ten years prior to their mycobacterial infection?	**Yes** ☐ **No** ☐ If yes, please give dates of each surgery and provide further details for each PROCEDURE:

6.2.1 Date of first cardiac surgery procedure	
6.2.2 Hospital	
6.2.3 Name of Surgeon	
6.2.4 Type of theatre surgery carried out in	**Conventional theatre** ☐ **Ultraclean ventilated** ☐ **Other** ☐
6.2.5 Procedures undertaken	
6.2.6 Reason for surgery (i.e. underlying condition)	
6.2.7 Was this a revision procedure?	**Yes** ☐ **No** ☐
6.2.8 Was this an emergency procedure?	**Yes** ☐ **No** ☐
6.2.9 ASA score at time of surgery	**I** ☐ **II** ☐ **III** ☐ **IV** ☐ **V** ☐
6.2.10 Antimicrobial prophylaxis used	
6.2.11 Length of surgery	
6.2.12 Was there delayed closure of the	**Yes** ☐ **No** ☐

sternal wound?	
6.2.13 Was an implant used?	**Yes** ☐ **No** ☐
6.2.14 Type of implant used	
6.2.15 Cardiopulmonary bypass used?	**Yes** ☐ **No** ☐
6.2.16 Make of bypass machine used	
6.2.17 Further details of bypass machine used (e.g., model)	
6.2.18 Length of time on bypass?	
6.2.19 Date of purchase of bypass machine used in the procedure	
6.2.20 Is the same bypass machine in use currently?	**Yes** ☐ **No** ☐ If no, when was it replaced?
6.2.21 If yes, was bypass machine contaminated with same species (Yes/No)	

6.3.1 Date of subsequent cardiac surgery procedure	
6.3.2 Hospital	
6.3.3 Name of Surgeon	
6.3.4 Type of theatre surgery carried out in	**Conventional theatre** ☐ **Ultraclean ventilated** ☐

	Other ☐
6.3.5 Procedures undertaken	
6.3.6 Reason for surgery (i.e. underlying condition)	
6.3.7 Was this a revision procedure?	**Yes** ☐ **No** ☐
6.3.8 Was this an emergency procedure?	**Yes** ☐ **No** ☐
6.3.9 ASA score at time of surgery	**I** ☐ **II** ☐ **III** ☐ **IV** ☐ **V** ☐
6.3.10 Antimicrobial prophylaxis used	
6.3.11 Length of surgery	
6.3.12 Was there delayed closure of the sternal wound?	**Yes** ☐ **No** ☐
6.3.13 Was an implant used?	**Yes** ☐ **No** ☐
6.3.14 Type of implant used	
6.3.15 Cardiopulmonary bypass used?	**Yes** ☐ **No** ☐
6.3.16 Make of bypass machine used	
6.3.17 Further details of bypass machine used (e.g., model)	
6.3.18 Length of time on bypass?	

6.3.19 Date of purchase of bypass machine used in the procedure	
6.3.20 Is the same bypass machine in use currently?	**Yes** ☐ **No** ☐ If no, when was it replaced?
6.3.21 If yes, was bypass machine contaminated with same species (Yes/No)	

6.4 What are routine decontamination processes for bypass machines locally?	
6.5 Any existing concerns or infection control issues around bypass machines locally?	
6.6 Additional information	

7. Case classification

7.1 Classification	**Confirmed** ☐ **Probable** ☐

PLEASE NOTE:
Questions highlighted in grey are essential information that should be completed initially for all cases.

Questions not highlighted are additional information that can be reported following detailed review of clinical notes.

Please continue on a separate sheet if there are additional laboratory specimens or surgical procedures.

This case report form is based on the one developed by Public Health England with some slight modifications.

Case definition (EU definition)

Clinical criteria:

Any of the following:

- Prosthetic valve endocarditis[6]
- Prosthetic vascular graft infection
- Sternotomy wound infection
- Mediastinitis
- Manifestations of disseminated infection including embolic and immunologic manifestations e.g. splenomegaly, arthritis, osteomyelitis, bone marrow involvement with cytopenia, chorioretinitis, lung involvement, hepatitis, nephritis, myocarditis

Exposure criteria:

A patient having undergone surgery requiring cardiopulmonary bypass in the 5 years prior to the onset of symptoms of infection

Confirmed case:

A patient meeting both the clinical and exposure criteria

AND

M. chimaera detected by culture and identified by DNA sequencing in an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material).

Probable case:

A patient meeting the clinical and exposure criteria

AND

M. chimaera detected by direct PCR and amplified DNA sequencing from an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

OR

MAC detected by culture or direct PCR from an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

OR

Histopathological detection of non-caseating granuloma and foamy/swollen macrophages with acid fast bacilli in cardiac or vascular tissue in the proximity of the prosthetic material or in specimen from the sternotomy wound.

[6] As evidenced by echocardiography (vegetations, new or partial dehiscence of a prosthetic valve, pseudo-aneurysm or an abscess in the tissues surrounding a heart valve)

Appendix 7: HPSC Letter to Microbiologists re health record review

Health Protection Surveillance Centre
25-27 Middle Gardiner Street
Dublin 1, Ireland
Ph +353 1 876 5300
Fx +353 1 856 1299
e info@mailx.hse.ie
www.hpsc.ie

Dr xxx
Consultant Microbiologist
Address

07/04/2016

Re: Mycobacterial infections associated with heater-cooler units used in cardiothoracic surgery

Dear Dr XXX,

In 2015, Switzerland, the Netherlands, Germany and the UK reported cases of invasive cardiovascular infection caused by *Mycobacterium chimaera* which were linked to contamination of heater-cooler units used in theatre during cardiothoracic surgery. During the latter half of 2015, a look-back investigation was initiated in Ireland, in order to identify individuals diagnosed with non-tuberculous mycobacterial (NTM) infection who had also undergone cardiothoracic surgery in the preceding five years.

Microbiology laboratories provided the HPSC with details of all NTM isolates cultured between January 2007 and June 2015. Cardiothoracic surgical centres provided data on all patients who underwent surgery between January 2002 and June 2015. Potential cases were then identified through cross-matching the laboratory records with the surgical records. During the look-back process, HPSC's data protection and data confidentiality procedures were adhered to. To maintain patient confidentiality, you have received this letter as an encrypted email using the Cisco Registered Envelope Service (CRES) system.

A patient with a positive culture for NTM reported by your laboratory and who had also undergone cardiothoracic surgery in the five years prior to the positive laboratory result was identified during the look-back investigation. The details of this patient are provided on page 3. The reported NTM was isolated from a specimen taken from a non-invasive site. Based on the information currently available to the HPSC, this would not meet the EU case definition for *M. chimaera* infection (case definition provided on page 4).

However, for completeness of the investigation, I would appreciate if you would review your local microbiology records and in the event that the patient has a healthcare record in your hospital, to request and review this also to ascertain if there was any clinical evidence of unexplained endocarditis, surgical site infection or disseminated infection at any stage post-cardiothoracic surgery.

I would be grateful if you could please inform me of the outcome of this review.
In the event that you do not have access to the healthcare record, I would be grateful if you could provide me with details of the patient's treating physician and/or general practitioner.

Furthermore, the original NTM isolate was not referred to the Irish Mycobacteria Reference Laboratory (IMRL). If the isolate is still available in your laboratory, please refer it to the IMRL for further characterisation, assigning the code "NIMLT 50944" to flag that it is part of the look-back investigation.[7]

For your information, a clinical pathway for patients who are worried about NTM infection or who are suspected of having infective endocarditis is being developed by the National Incident Management and Learning Team (NIMLT). Once this document is finalised, it will be shared with clinicians as it will be a guiding pathway for clinicians with patients requiring follow-up and investigation.

I will be retiring shortly from my post as Director of the HPSC, please liaise with Dr Karen Burns, Consultant Microbiologist, HPSC (karen.burns1@hse.ie) regarding the information requested above.

With kind regards,

Dr Darina O'Flanagan
Director
HSE - Health Protection Surveillance Centre

cc. Dr xxx, Consultant Microbiologist, XX Hospital

[7] This paragraph was inserted in incidences where the original isolate was not referred to IMRL

Patient details:	
Name:	
Date of birth:	
Microbiology details:	
Laboratory name:	
MRN:	
Specimen ID	
Specimen:	
Specimen date:	
Organism originally identified:	
Isolate available at IMRL:	*
IMRL Specimen ID:	
Isolate re-tested at IMRL as part of look-back investigation:	
Organism identified on re-testing:	
Surgery details:	
Hospital name:	
MRN:	
Date of surgery:	
Name of surgeon/consultant:	

Case definition (EU definition)

Clinical criteria:

Any of the following:

- Prosthetic valve endocarditis[8]
- Prosthetic vascular graft infection
- Sternotomy wound infection
- Mediastinitis
- Manifestations of disseminated infection including embolic and immunologic manifestations e.g. splenomegaly, arthritis, osteomyelitis, bone marrow involvement with cytopenia, chorioretinitis, lung involvement, hepatitis, nephritis, myocarditis

Exposure criteria:

A patient having undergone surgery requiring cardiopulmonary bypass in the 5 years prior to the onset of symptoms of infection

Confirmed case:

A patient meeting both the clinical and exposure criteria

AND

M. chimaera detected by culture and identified by DNA sequencing in an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material).

Probable case:

A patient meeting the clinical and exposure criteria

AND

M. chimaera detected by direct PCR and amplified DNA sequencing from an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

OR

MAC detected by culture or direct PCR from an invasive sample (blood, pus, tissue biopsy or implanted prosthetic material)

OR

Histopathological detection of non-caseating granuloma and foamy/swollen macrophages with acid fast bacilli in cardiac or vascular tissue in the proximity of the prosthetic material or in specimen from the sternotomy wound.

[8] As evidenced by echocardiography (vegetations, new or partial dehiscence of a prosthetic valve, pseudo-aneurysm or an abscess in the tissues surrounding a heart valve)

Appendix 8: Number of non-tuberculous Mycobacterium isolates reported by laboratory and year, January 2007 – June 2015

Laboratory	2007	2008	2009	2010	2011	2012	2013	2014	Jan-Jun 2015	Total
AMNCH	8	16	13	17	9	15	14	13	7	**112**
Beacon Hospital	-	-	-	-	3	-	1	-	1	**5**
Beaumont Hospital	2	1	-	1	-	-	2	-	1	**7**
Cork University Hospital	34	87	140	129	30	142	135	54	57	**808**
IMRL	34	46	58	48	57	51	59	61	26	**440**
Mater Misericordiae University Hospital	-	3	5	2	3	2	2	8	1	**26**
National Maternity Hospital, Holles Street	-	-	-	-	-	-	-	1	-	**1**
Our Lady's Children's Hospital, Crumlin	2	1	-	2	1	3	-	2	-	**11**
PHL, Cherry orchard	-	-	1	5	3	4	-	-	-	**13**
Sligo Regional Hospital	4	3	1	-	-	-	-	-	-	**8**
St. James's Hospital	6	32	18	34	37	13	18	20	7	**185**
St. Vincent's University Hospital	17	21	13	19	18	18	15	23	8	**152**
Temple Street Children's University Hospital	1	-	1	-	-	-	1	-	1	**4**
University Hospital Galway	11	8	10	15	11	16	18	22	10	**121**
University Hospital Limerick	4	5	12	9	6	13	19	3	-	**71**
University Hospital Waterford	7	7	11	7	5	11	10	8	4	**70**
Total	**130**	**230**	**283**	**288**	**183**	**288**	**294**	**215**	**123**	**2,034**

Appendix 9: Number of cardiothoracic surgical or extracorporeal membrane oxygenation procedures reported by centre and year, January 2002 - June 2015

Cardiothoracic Centre	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Jan-Jun 2015	Total
Beacon Hospital	-	-	-	-	-	12	38	88	97	101	86	83	87	66	**658**
Blackrock Clinic	503	584	484	508	484	494	466	424	392	422	448	469	425	233	**6,336**
Cork University Hospital	217	481	472	443	468	426	437	484	447	432	426	378	419	273	**5,803**
Galway Clinic	-	-	4	24	38	39	37	47	67	55	49	53	43	29	**485**
Galway University Hospital	-	-	-	-	-	52	134	175	212	201	194	196	234	165	**1,563**
Mater Private	662	645	827	779	467	657	678	658	568	627	588	521	547	330	**8,554**
Mater Misericordiae University Hospital	871	793	769	571	516	473	456	451	377	410	518	527	460	341	**7,533**
Our Lady's Children's Hospital Crumlin	173	171	170	228	253	257	277	293	333	342	328	323	272	117	**3,537**
St James's Hospital	567	570	528	451	413	401	374	385	411	421	391	374	454	445	**6,185**
Total	**2,993**	**3,244**	**3,254**	**3,004**	**2,639**	**2,811**	**2,897**	**3,005**	**2,904**	**3,011**	**3,028**	**2,924**	**2,941**	**1,999**	**40,654**