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INFORMATION DE SECURITE – MISE A JOUR

Risques de mycobactérie en chirurgie Cardiaque
Désinfection et nettoyage des Générateurs thermiques Sorin

Référence	**9611109-11/11/16-008-C**
Dispositifs concernés :	Système de perfusion Sorin Group – Générateurs thermiques 1T et 3T, et dispositifs Flex Therm (Références catalogue : 16-02-50, 16-02-80, 16-02-81, 16-02-82, 16-02-83, 16-02-85, 16-02-95, 16-70-00)
Date:	11 Novembre 2016
A l'attention de :	Spécialistes de l'hygiène, Responsables de salle d'opération de Chirurgie Cardiaque, Responsables risque/ sécurité, Distributeurs, Cliniciens, Perfusionnistes et autres utilisateurs de ces dispositifs
Motif	LivaNova diffuse une mise à jour de l'information de sécurité en raison d'informations récentes publiées aux Etats Unis.

Cher Client,

Au cours des deux dernières années, LivaNova[1] et l'ensemble de la communauté de la chirurgie cardiaque ont beaucoup appris sur le risque nouvellement identifié d'infection par des Mycobactéries non Tuberculeuses ("MNT"), lors de chirurgie à cœur ouvert. Les MNT sont très répandues dans la nature et se retrouvent couramment dans le sol, l'eau naturelle, les systèmes de distribution d'eau potable et les réseaux de plomberie des habitations et des bâtiments, en particulier dans les circuits de circulation d'eau chaude des hôpitaux et des habitations. Les MNT ne sont généralement pas dangereuses, mais dans de rares cas, elles peuvent causer des infections chez les patients très malades ou des individus ayant un système immunitaire affaibli.

En tant que leader sur le marché des générateurs thermiques, LivaNova s'engage pour la sécurité des patients et le support aux utilisateurs de nos appareils. Nous prenons très au sérieux le risque rare mais préoccupant d'infection potentielle par les MNT. Nous nous sommes engagés à assurer la confiance des professionnels de santé dans nos Générateurs Thermiques, qui sont des éléments essentiels des procédures de chirurgie cardiaque. A cet égard, nous souhaitons vous fournir une mise à jour sur ce problème important de notre industrie.

Comme vous le savez peut-être, le 13 octobre 2016, aux Etats-Unis, le Center for Disease Control and Prevention (CDC) et la Food and Drug Administration (FDA) ont publié plusieurs communications au sujet des infections par Mycobactéries non Tuberculeuses (MNT) associées à l'utilisation des Générateurs Thermiques. L'article Morbidity and Mortality Weekly Report ("MMWR") du CDC décrit les résultats d'une analyse génomique d'échantillons obtenus de patients atteints d'infections MNT causées par la Mycobacterium chimaera (**Annexe 1**). Comme l'article MMWR le spécifie, les données présentées ne sont

[1] LivaNova PLC est une société holding au Royaume-Uni, propriétaire exclusive de plusieurs filiales, dont Sorin Group Deutschland GmbH et Sorin Group USA, Inc. Dans le présent document, le nom de marque LivaNova fait référence à toutes ces entités.

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pas nouvelles. En effet, elles semblent plutôt corroborer les conclusions précédemment présentées dans l'article d'Haller, et. al., publié par EuroSurveillance, en avril 2016. (**Annexe 2**).

Cependant, sur la base des données présentées dans cette publication récente, LivaNova souhaite transmettre de manière proactive ses recommandations d'action en France, où il existe des options qui ne sont pas disponibles aux États-Unis. Ces recommandations sont les suivantes :

1. Les Générateurs Thermiques connus ou suspectés d'être contaminés avec M. chimaera, d'après le programme de test de l'établissement, ou d'autres informations connues de l'hôpital, devront être retirés de la salle d'opération, ou, si cela est faisable, ne devront plus être utilisés, dès que possible. Nous vous recommandons de vous rapprocher de votre représentant LivaNova dans le but d'organiser le service de désinfection profonde avant une nouvelle utilisation.

2. Pour les établissements dont les dispositifs ne sont pas connus pour être contaminés par M. chimaera, nous recommandons les actions suivantes :

    a. Suivre les instructions d'utilisations des Générateurs Thermiques et plus particulièrement celles relatives au nettoyage et à la désinfection. Appliquer ces instructions est essentiel pour limiter le risque potentiel causé par l'utilisation de ces dispositifs non stériles.

    b. Si la configuration du bloc opératoire le permet, diriger ou dévier l'échappement du Générateur Thermique loin du patient, par exemple, d'après la notification de sécurité "Risques de mycobactéries en chirurgie cardiaque » (**Annexe 3**), vers le conduit d'évacuation de la salle d'opération.

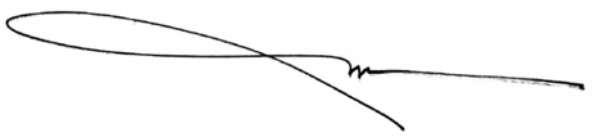
    c. Effectuer des contrôles de la qualité de l'eau d'après la notification de sécurité "Risques de mycobactéries en chirurgie cardiaque » (**Annexe 3**).

    d. Utiliser de nouveaux accessoires, tubes et connecteurs pour éviter la re-contamination lors de l'utilisation d'un autre Générateur Thermique. N'oubliez pas que la contamination du dispositif peut émaner d'autres sources, comme une contamination environnementale ou le contact avec des accessoires contaminés.

LivaNova continue de travailler en collaboration avec l' Autorité compétente de notre pays dans le but de développer des solutions pour diminuer les risques potentiels de contamination par M. chimaera.

Veuillez remplir le formulaire de réponse client fourni en Annexe 4, et le renvoyer selon les instructions figurant sur le formulaire. Nous vous remercions de votre coopération sur ce sujet.

Sincères salutations,



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Annexe 1

MMWR

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Notes from the Field: Mycobacterium chimaera Contamination of Heater-Cooler Devices Used in Cardiac Surgery — United States

Weekly / October 14, 2016 / 65(40);1117–1118

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In the spring of 2015, investigators in Switzerland reported a cluster of six patients with invasive infection with *Mycobacterium chimaera*, a species of nontuberculous mycobacterium ubiquitous in soil and water. The infected patients had undergone open-heart surgery that used contaminated heater-cooler devices during extracorporeal circulation (*1*). In July 2015, a Pennsylvania hospital also identified a cluster of invasive nontuberculous mycobacterial infections among open-heart surgery patients. Similar to the Swiss report, a field investigation by the Pennsylvania Department of Health, with assistance from CDC, used both epidemiologic and laboratory evidence to identify an association between invasive *Mycobacterium avium* complex, including *M. chimaera,* infections and exposure to contaminated Stöckert 3T heater-cooler devices, all manufactured by LivaNova PLC (formerly Sorin Group Deutschland GmbH) (*2*). *M. chimaera* was described as a distinct species of *M. avium* complex in 2004 (*3*). The results of the field investigation prompted notification of approximately 1,300 potentially exposed patients.* Although heater-cooler devices are used to regulate patients' blood temperature during cardiopulmonary bypass through water circuits that are closed, these reports suggest that aerosolized *M. chimaera* from the devices resulted in the invasive infections (*1*,*2*). The Food and Drug Administration (FDA) and CDC have issued alerts regarding the need to follow updated manufacturer's instructions for use of the devices, evaluate the devices for contamination, remain vigilant for new infections, and continue to monitor reports from the United States and overseas (*2*).

Whole genome sequencing was completed on isolates from 11 patients and from five Stöckert 3T heater-cooler devices from hospitals in Pennsylvania and Iowa, two of the states where clusters of infections were identified (*2*). Samples from heater-cooler devices included swabs from the interior of the device, water drained from the devices, and air samples collected while a device was operating. Single nucleotide polymorphisms (SNPs) were identified after comparing patient and device samples against sequence data from an *M. chimaera* reference isolate. Results from pairwise comparisons among all sequences across a core genome of approximately 5 million base pairs revealed a maximum of 38 SNPs between any two isolates related to the outbreak investigation, versus a minimum of 2,900 SNPs between any single outbreak isolate and the epidemiologically unlinked isolate (sequence files available from the National Center for Biotechnology Information: Pennsylvania isolates Bioproject PRJNA344472; Iowa isolates Bioproject PRJNA345021; epidemiologically unlinked isolate RefSeq Assembly Accession GCF_001307335.1).

These results strongly suggest a point-source contamination of Stöckert 3T heater-cooler devices with *M. chimaera*. A recent report from Germany noted that preliminary typing results of *M. chimaera* from heater-cooler devices from three different European countries were almost identical to samples obtained from the manufacturing site, further supporting the likelihood of point-source contamination (*4*). Additional sequence comparisons between patient specimens and device samples obtained from facilities from various regions in the United States are ongoing. Sequence comparisons between U.S. and European samples, as well as samples from the manufacturing site, could provide additional information for evaluating the possibility of point-source contamination at the heater-cooler manufacturing site. Efforts are currently ongoing to obtain and compare European sequencing results.

Although thousands of patients in the United States have been notified regarding potential exposure to contaminated heater-cooler devices, the number who were exposed might be much larger. Over 250,000 procedures using cardiopulmonary bypass are performed in the United States each year (*5*). Stöckert 3T heater-cooler devices represent approximately 60% of the U.S. market (*2*). CDC and FDA are continuing their efforts to increase provider and patient awareness of the risk. CDC has issued guidance on identifying patients at risk to ensure timely diagnosis and treatment of these indolent and often unrecognized infections (*2*). FDA is continuing to gather information, issue communications, and assess the situation from both public health and regulatory perspectives (*6*).†

Acknowledgments

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* https://www.wellspan.org/news/story/15810 .

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† http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/UCM520191.htm .

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Annexe 2

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Contamination during production of heater-cooler units by *Mycobacterium chimaera* potential cause for invasive cardiovascular infections: results of an outbreak investigation in Germany, April 2015 to February 2016

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Invasive infections with *Mycobacterium chimaera* were reported in patients with previous open chest surgery and exposure to contaminated heater-cooler units (HCUs). We present results of the surveillance of clinical cases and of contaminated HCUs as well as environmental investigations in Germany up until February 2016. Clinical infections occurred in five male German cases over 50 years of age (range 53–80). Cases had been exposed to HCUs from one single manufacturer during open chest surgery up to five years prior to onset of symptoms. During environmental investigations, *M. chimaera* was detected in samples from used HCUs from three different countries and samples from new HCUs as well as in the environment at the manufacturing site of one manufacturer in Germany. Our investigation suggests that at least some of the *M. chimaera* infections may have been caused by contamination of HCUs at manufacturing site. We recommend that until sustainable measures for safe use of HCUs in operation theatres are implemented, users continue to adhere to instructions for use of HCUs and Field Safety Notices issued by the manufacturer, implement local monitoring for bacterial contamination and continuously check the websites of national and European authorities for current recommendations for the safe operation of HCUs.

Introduction

In July 2014, the Federal Office of Public Health Switzerland (FOPH) reported about patients with *Mycobacterium chimaera* infections, who had previously undergone open-chest heart surgery with exposure to contaminated heater-cooler units (HCUs) [1]. Several other reports and publications have suggested since that HCUs produced by one manufacturer in Germany may be a source of *M. chimaera* infections that occurred in Switzerland, Germany, the Netherlands and United Kingdom [2-5].

HCUs are commonly used in cardiac surgery during extracorporeal circulation in order to regulate the temperature of the blood and to provide temperature-controlled water for cardioplegia. HCUs have water tanks that provide temperature-controlled water to external heat exchangers. Since *M. chimaera* was detected in air samples close to operating HCUs, airborne transmission is believed to be the most likely transmission mechanism in the *M. chimaera* cases after open chest surgery [4,6].

M. chimaera is a slow-growing nontuberculous mycobacterium (NTM) belonging to the *M. avium* complex (MAC). It was first reported by Tortoli et al. in 2004 as a closely to *M. intracellulare*-related distinct species [7]. Identification requires molecular diagnostic testing [8]. *M. chimaera* may cause lung infections especially in patients with underlying lung disease as well as disseminated infections in immunocompromised patients and was found in skin and bone infections. In the environment, it was identified in biofilms and detected in water sources such as household water [9].

Among others, the report by the FOPH about the outbreak investigations in Switzerland and the reports about cases in Germany and the Netherlands led to increased surveillance efforts and outbreak investigations in Europe [3,10]. Here we present the results of the surveillance of clinical cases, of the surveillance of contaminated HCUs and of environmental investigations in Germany.

Table 1

Cases with symptomatic *Mycobacterium chimaera* infection, notified between April 2015 and February 2016, Germany (n=5)

Case number	Age (years)	Sex	Cardiac surgery centre	Type of surgery (exposure)	Prosthetic material	Site of infection	Death due to infection	Incubation period (years)[a]
1	80	Male	A	Aortic valve replacement	Yes	Endocarditis	No	<1
2	75	Male	B	CABG	No	Spondylodiscitis	No	5
3	65	Male	C	Aortic valve replacement	Yes	Valvular aortic endocarditis, paravalvular leak and abscess	Yes	3
4	67	Male	C	CABG and aortic valve replacement	Yes	Paravalvular abscess[c]	No[b]	4
5	53	Male	C	Aortic valve replacement	Yes	Endocarditis and cerebral abscesses	No	3

CABG: coronary artery bypass grafting.

[a] Time between exposure to open chest surgery involving use of an HCU and clinical diagnosis.

[b] Currently in palliative care.

[c] Endocarditis lenta and change of aortic valve in September 2013.

Methods

Definitions

For our investigations we used the following case definitions: a confirmed case was defined as a patient having undergone surgery with extracorporeal circulation in the five years before onset of symptoms of NTM infection AND in whom *M. chimaera* was detected in an invasive sample (e.g. blood, tissue biopsy or implanted prosthetic material). A probable case was defined as a confirmed case, but without detection of *M. chimaera* in an invasive sample.

An HCU was considered as contaminated, when cardiac surgery centres found NTM and/or other bacteria from environmental samples from the HCU and sent a report to the Federal Institute for Drugs and Medical Devices (BfArM) in Germany.

Prospective case finding and identification of contaminated HCUs

Prospective case finding was conducted from April 2015 onwards and results until end February 2016 are presented here. The mandatory surveillance of healthcare-associated outbreaks in Germany was applied for reporting clinical cases and this surveillance is described in detail elsewhere [11].

The public health authorities and healthcare professionals in Germany were informed about the ongoing outbreak and requested to notify cases fulfilling the case definition [12]. Specifically, the German National public health institute (Robert Koch Institute (RKI)), the German Society of Thoracic and Cardiovascular Surgery and the German Society of Infection informed federal states' authorities and societies' members, respectively, about case definitions and notification according to the article 6 of the 'Protection against Infection Act' (Infektionsschutzgesetz, IfSG) [12-15].

The mandatory notification system for incident reports of medical devices was used to detect contaminated HCUs in Germany. Incident reports were collected and analysed by BfArM in accordance with the corresponding legal framework 'The Act on Medical Devices' (Medizinproduktegesetz) and 'The Medical Device Safety Plan' (Medizinprodukte Sicherheitsplanverordnung).

HCU users were requested to submit any incident report associated with HCUs to BfArM [16]. On 10 July 2015, the BfArM recommended to place HCUs outside of the operation theatre and monitoring of contamination in HCUs [17].

At the European level, the European Centre for Disease Prevention and Control (ECDC) assessed the risk of invasive cardiovascular infection by *M. chimaera* potentially associated with heater-cooler units used during cardiac surgery in Europe also, in April 2015 [10]. The risk assessment was forwarded to regional German public health authorities. From April 2015 onwards, ECDC also provided a platform for exchange of information and a protocol for case detection and environmental testing [18]. The protocol was shared with all European Union/European Economic Area (EU/EEA) countries with the purpose to obtain information in a harmonised way, to further investigate the association between invasive infection by *M. chimaera* and HCUs, and to allow assessing the burden of these infections. The protocol was shared with the German heart surgery centres that detected clinical cases.

Table 2

Mycobacterium chimaera-positive samples from environmental investigations at the manufacturing site of new HCUs and of used HCUs from at the manufacturer's service centre, July 2014 to June 2015

Date	Type of sample	Source of sample
16 Jul 2014	Water (100 mL)	Used HCU from Switzerland
29 Jul 2014	Water (100 mL)	New HCU from manufacturing site
5 Aug 2014	Water (100 mL)	New HCU from manufacturing site
11 Aug 2014	Water (100 mL)	New HCU from manufacturing site
19 Feb 2015	Water (100 mL)	Used HCU from the Netherlands
10 Jun 2015	Water (volume not specified)	Sample taken in pump assembly area at the manufacturing site

HCU: heater-cooler unit.
The environmental investigations were performed by the manufacturer.

Investigation at the HCU manufacturing site and at the manufacturers' service centre

In July 2015, the Bavarian Health and Food Safety Authority (LGL), assisted the Bavarian regulatory authorities with on-site investigations and took environmental samples at the manufacturing site and in the service centre of the implicated manufacturer. Samples were taken from the production line, on-site tap water and from a used and disassembled HCU from this manufacturer in the service centre. All samples were sent to the National Reference Centre (NRC) for Mycobacteria Borstel, Germany.

On its own initiative, the HCU manufacturer conducted environmental sampling for NTM at the manufacturing site where the HCUs are assembled and in the service centre where used HCUs are disassembled for decontamination from July 2014 onwards. Environmental samples were sent to a local microbiological laboratory and NTM isolates were submitted to the NRC in Borstel for further analysis.

Culturing and typing

Mycobacteria were cultured in different laboratories. The development of standard protocols for microbiological *M. chimaera* diagnostic was coordinated by ECDC in collaboration with laboratories such as the NRC Borstel in Europe; these protocols were published by ECDC in August 2015 [18].

Next generation sequencing (NGS) of isolates is still ongoing.

Ethics

A formal ethical review process and approval was not required for this outbreak investigation in accordance with article 25, section 1 of the IfSG.

Results

At the beginning of our investigation, in April 2015, we were informed by cardiac surgery centre A in Germany about a confirmed case that became symptomatic before 2015 [3]. During April 2015 to February 2016, the mandatory surveillance of healthcare-associated outbreaks identified four additional confirmed cases of *M. chimaera* infection who had been exposed to an HCU in two different cardiac surgery centres (B and C) in Germany (Table 1). These cases developed a symptomatic *M. chimaera* infection five months to five years after exposure to a HCU. All five confirmed cases were male and aged above 50 years (range 53–80) when diagnosed with *M. chimaera* infection, four had aortic valve replacement and two underwent coronary artery bypass grafting, one died. All had been exposed to HCUs from one single manufacturer during open chest surgery. No cases with NTM infections other than *M. chimaera* were notified. Our investigations did not reveal epidemiological links between cases of the different sites.

Between January 2015 and February 2016, the BfArM received 26 incident reports of contaminated HCUs from 16 of the total of 78 German cardiac surgery centres from different German regions. Three of the 16 centres reported contamination of HCUs of another manufacturer but *M. chimaera* detection from these HCUs was not reported. Overall, the contaminations of the HCUs included *M. chimaera* and other bacteria such as *Pseudomonas aeruginosa, Legionella pneumophila* and *Stenotrophomonas maltophilia* and fungi. All three centres in which German cases were exposed sent incident reports about contamination of HCUs from the same German manufacturer. Two of these centres reported *M. chimaera* detection in HCU water samples including one reporting also detection of *M. chimaera* in air samples. The third centre reported NTM in HCU water samples, results of further specification were not reported.

During the environmental investigations performed by the Bavarian regulatory authorities on 2 July 2015, six of 20 samples obtained were *M. chimaera*-positive. All positive samples were from one disassembled HCU that had been used in cardiac surgery centre D in Germany and was disassembled for decontamination in the service centre of the manufacturer. The disassembled HCU was produced before modifications in the post-production process that were implemented

by the manufacturer in response to the findings of *M. chimaera* contamination. The samples included in the investigations were water (ca 100 mL), swab and biofilm and were collected from different sources: residual water, filler neck, patient bridge, biofilm from patient recirculation and patient bath.

In December 2015, the HCU manufacturer provided the RKI with information about six *M. chimaera*-positive samples from environmental investigations conducted between July 2014 and June 2015, including two contaminated HCUs from Switzerland and the Netherlands, respectively (Table 2).

On 22 December 2015, public health authorities in the EU/EEA and worldwide were notified by Germany about the suspected common source of *M. chimaera* via the EU Early Warning and Response System (EWRS) and via an International Health Regulation (IHR) notification.

Discussion

We present data that show that *M. chimaera* was isolated in clinical samples from (i) infected patients in Germany who had undergone open chest surgery, (ii) in samples from used HCUs from three different countries and (iii) in samples from new HCUs and the environment at the manufacturing site of one manufacturer. This suggests that at least some of the five German cases with *M. chimaera* infection may have occurred due to contamination of the HCUs by *M. chimaera* at the manufacturing site.

Preliminary typing results indicate that the *M. chimaera* isolates detected by the authorities and the isolates from the manufacturer appear to be almost identical (unpublished data). The *M. chimaera*-positive environmental samples at the manufacturing site prompted the manufacturer to modify the manufacturing process, which now includes ethanol disinfection and an active drying of the HCU water circuit before shipment. When the Bavarian regulatory authorities conducted onsite visits, no *M. chimaera*-positive sample was recovered except from a used HCU which had been disassembled for decontamination. The returned unit had been manufactured before August 2014. According to the information provided by the manufacturer, HCUs manufactured before mid-August 2014 may have had environmental mycobacteria presence in the unit at the time of delivery. Our investigations could not elucidate if and until when contaminated HCUs may have been delivered to customers from this manufacturer.

As of end of March 2016, two additional notifications of patients with *M. chimaera*-positive clinical specimens are under investigation in Germany. Until now we could not obtain data on all surgical interventions prior the *M. chimaera* diagnosis of these patients.

A limitation of our study is that we did not conduct active case finding. It is likely that the passive surveillance has led to an underestimation of the actual number of cases of *M. chimaera* infections in Germany. Furthermore, the true number of cases is probably underestimated since there is no typical clinical picture for infections with *M. chimaera*. Patients present with nonspecific symptoms, a variety of infection sites and a culture for mycobacteria is usually not part of a routine diagnostic work-up in patients presenting with signs of infection.

M. chimaera was not the only bacterial species isolated from HCUs. Contamination of HCUs with other bacteria was reported from various cardiac surgery centres in Germany. Furthermore, bacteria were also isolated from HCUs produced by other manufacturers. It is possible that some of the cases were infected due to contamination of HCUs at the cardiac surgery centres. It is also possible that some of the cases occurred due to exposure to HCUs produced by other manufacturers.

Infections by *M. chimaera* are rare and their occurrence, when detected, is considered unusual [19]. The reported *M. chimaera* infections might therefore be regarded as an indicator of a potential microbial hazard caused by the water-bearing HCUs in the healthcare environment.

Further investigations are needed to differentiate between the risk of *M. chimaera* infection from HCUs contaminated at the manufacturing site, the risk of infection from HCUs contaminated during use and the risk of infection from other medical devices that include an HCU such as extracorporeal membrane oxygenators [20]. In two recent publications, Götting et al. and Sommerstein et al. gave interesting insights into possible mechanisms of airborne transmission by HCUs [4,6]. In the cases described here, NGS should help determine the fraction that may be due to contamination at the manufacturing site or during use at the cardiac surgery centres.

To allow for targeted public health action, it is important that manufacturers of medical products share the findings of their own investigations into bacterial contamination, as demonstrated in this outbreak investigation. Sharing the results by the manufacturer, as well as information on the implemented corrective measures, allowed us to better understand the risks involved in HCU use. Regulatory authorities in Germany are continuing their information exchange with the manufacturers that produce HCUs to provide a sustainable solution for minimising the risks of infection in patients exposed to HCUs.

Conclusions

We present evidence on *M. chimaera* detection in clinical samples from infected German patients having been exposed to HCUs produced by the same manufacturer, in three cardiac surgery centres, in samples from used HCUs from three different countries and in samples from new HCUs and the environment at the manufacturing site of one manufacturer. In summary,

this suggests a point source for the reported *M. chimaera* infections and for *M. chimaera*-positive samples from HCUs and the environment. Notifications of contaminated HCUs of different manufacturers and with various bacteria, indicate a general problem with water-bearing systems in the healthcare environment.

We recommend that until sustainable measures for a safe use of HCUs in operation theatres are implemented, users continue to adhere to the instructions for use of the HCU and the Field Safety Notices issued by the manufacturer, implement a local monitoring for bacterial contamination of the HCUs and continuously check the websites of relevant national and European authorities for current recommendations for the safe operation of HCUs.

Acknowledgements

We would like to thank the HCU manufacturer for sharing their investigation results with the German authorities. The authors would like to thank colleagues of the NRC Borstel for the microbiological analysis. Furthermore, we would like to thank health personnel as well as local and regional public health authorities who notified clinical cases and contaminated HCUs. Finally we would like to thank HP Blank who supported surveillance and data management at RKI.

Conflict of interest

The authors have shared the manuscript with the manufacturer before publication. This has not led to changes of the content. The authors have declared that they have no competing interests.

Authors' contributions

SH, MAS, OH and TE were part of the outbreak team at RKI and conducted the epidemiological outbreak investigations. SH, TE and DP designed the investigation. SH, TE, DP, AJ, DLM and CH drafted the manuscript. All authors critically revised the manuscript and approved the final version. TE is corresponding author and guarantor.

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Annexe 3

Information de sécurité 2015 LivaNova

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AT THE HEART OF MEDICAL TECHNOLOGY

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«Name1»
«Name2»
«Name3»
«Address»
«Address»

FIELD SAFETY NOTICE

Cardiac Surgery Mycobacterium Risks
Disinfection and Cleaning of Sorin Heater Cooler Devices

Affected Devices:	Sorin Group perfusion system – Heater Cooler 1T and Heater Cooler 3T devices (refer to Attachment 1 for affected catalog and serial numbers)
Date:	03. June 2015
Reference No:	9611109-06/03/15-002-C
Attention:	Hygiene Specialists, Cardiac Surgery Operating Room Responsible, Risk/ Safety Managers, Distributors, Clinicians, Perfusionist and other users of these devices
Reason:	Sorin has become aware that the actual disinfection practices and the water maintenance that some users have been performing are not always conducted according to our Instructions for Use. Without vigilant performance of the disinfection and maintenance procedures per the Instructions for Use, organisms can multiply in a heater cooler device and potentially form biofilm. The biofilm provides an opportunity for bacteria, including Mycobacteria, to colonize within the device. Once colonized, there is a possibility that bacteria can become aerosolized when the heater cooler device is operated and serve as a source for contamination. Although water from the heater cooler device is not intended to contact the patient directly, fluid leakage from the device or aerosolization generated by a contaminated water circuit during device operation may create conditions in which the organisms could potentially contact the patient and subsequently contaminate the surgical site. Sorin Group is providing this notification to: (1) remind you of the importance of following the company's disinfection and maintenance procedures; (2) inform you that there is a possibility that bacteria can become aerosolized when the heater cooler device is operated and serve as a source for contamination; and (3) provide you with updated Instructions for Use regarding disinfection and maintenance procedures.

Dear Valued Customer:

The purpose of this letter is to advise you that Sorin Group Deutschland GmbH ("Sorin") is executing a voluntary field safety correction for the Heater Cooler 1T and the Heater Cooler 3T devices ("heater cooler devices"). This field safety notice describes below, immediate action to be taken by you.

- If your heater cooler device has been strictly maintained according to the Instructions for Use, please strictly adhere to the new Instructions for Use provided in **Attachment 1** of this letter.
- If your heater cooler device has **not** been strictly maintained according to the Instructions for Use, please perform the steps included in the *Immediate Customer Action* section of this letter.

Description of Issue

Sorin has become aware of cases of non-tuberculous mycobacteria endocarditis or deep infection following cardiac surgery during which the heater cooler device was used. There is a risk that surgical patients may experience invasive cardiovascular infection, including endocarditis, or other deep-surgical-site infections due to non-tuberculous mycobacteria, such as Mycobacterium chimaera. Because the symptoms may be slow to manifest, it is possible that many months may pass after completion of the surgical procedure before a surgical patient presents with an infection. In some cases, it is possible that infection could lead to death. Sorin's investigation into these cases is ongoing. To date, the investigation has not determined a causal connection between the heater cooler device and these cases. In some instances there has been a suggestion of such a link; however, infection following cardiac surgical procedures can be caused by numerous, other sources.

The heater cooler device which is provided non-sterile may develop highly contaminated water due to the failure to follow the Instructions for Use for water maintenance and water circuit disinfection. If contaminated water is used in the device **and** the user performs inadequate maintenance and/or fails to strictly adhere to the user instructions for cleaning of the heater cooler device, the device could become a source for contaminating the surgical environment. This condition can occur where there has been a build-up of biofilm within the water circuit of the device. Although water from the heater cooler device is not intended to contact the patient directly, fluid leakage from the device or aerosolization generated by a contaminated water circuit during device operation may create conditions in which the organisms could potentially contact the patient and subsequently contaminate the surgical site.

Contamination of heater cooler units with other waterborne pathogens, like *Mycobacterium abscessus* and non-fermenting gram-negative bacteria, has also been detected in the water of certain heater cooler units. However, no cases of patient infection have been determined to be caused by heater cooler devices. Further, Sorin's investigations into the potential association of heater cooler units with infections by *Mycobacterium chimaera* and other pathogens are ongoing.

If there is a need for further communication based on the investigation results, we will provide you the information.

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Immediate Customer Action

- ✓ Sorin reminds its customers using heater cooler devices about the importance of adhering to correct maintenance of the device at all times and, in particular, to assure that the cleanliness of the water is maintained. **Attachment 1** of this notification includes the new Instructions for Use for the cleaning and disinfection of the Sorin heater cooler devices. Please discard the existing IFU and follow this new IFU which includes updated cleaning and disinfection instructions.
    - o Assure that your team understands Mycobacteria and the potential contamination risks for cardiac surgical procedures, for example, that Mycobacterium is widely distributed in the ecosystem including chlorinated drinking water from the tap, it is inherently resistant to chemical disinfectants and antibiotics, and under the right conditions, it has a propensity to form biofilm and it can also be aerosolized.

- ✓ Healthcare providers involved in the care of patients who have undergone open heart surgery should be vigilant for cases of endocarditis or other cardiovascular infection of unidentified origin with specific testing for slow-growing non-tuberculous Mycobacteria such as *Mycobacterium chimaera* performed as indicated.

- ✓ Verify that this letter has reached your local team and that the recommended monitoring has been considered for your cardiac surgery operating rooms and area. This includes the monitoring of the area water not only for typical microorganisms, but also for slow growing non-tuberculosis Mycobacteria that requires special monitoring practices.

Actions to be taken by the user on the device

- ✓ Review your inventory and identify any heater cooler devices per the attached list, **Attachment 2**.

- ✓ For each unit, determine if the device has been maintained according to the Instructions for Use. If yes, strictly adhere to the new Instructions for Use provided in **Attachment 1** of this notification.

  Note: It is recommended to implement a microbiological monitoring of the water quality (by heterotrophic plate count (HPC) measurement), including monitoring for non-tuberculous Mycobacteria on a monthly basis (Coliform bacteria, P. aeruginosa and non-tuberculous mycobacteria should not be detectable in 100ml). The water in the device should meet microbiological drinking-water quality according to national drinking-water standards.

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- ✓ If the device has not been maintained according to the Instructions for Use, follow instructions in the table below:
  Note: Please consult your Infection Control Manager for executing the following steps.

Step 1 / Submission of Test Sample
✓ Take two 100ml or greater water samples from one of the drain valves at the back of the device **prior to** the disinfection step: (1) for heterotrophic plate count measurement; and (2) for non-tuberculous mycobacteria analysis. ✓ Submit samples (1 & 2) to a microbiological lab for heterotrophic plate count measurement of the water and to determine if non-tuberculous mycobacteria are detectable. ✓ Perform disinfection of the water circuit of the heater cooler device(s) according to the new instructions for use provided in **Attachment 1** of this notification. ✓ Replace any accessories and products that are used in conjunction with the heater cooler device which may be potentially contaminated (e.g. tubing and connectors, graduated beaker, warming blanket) by new or re-processed parts. ✓ While awaiting test results from the microbiological lab, operate the heater cooler device outside of the operating room, if structurally possible, and proceed to **Step 2.** Note: For technical support regarding the installation outside the OR (max. distance, routing) please contact your local service representative. ✓ If it is not possible to move the heater cooler device outside the operating room, take the device out of service or proceed to **Step 3**.
Step 2 / Interim Process (If heater cooler device can be operated outside the operating room)
✓ Perform the water maintenance and disinfection of the water circuit of the device(s) according to the new instructions for use provided in **Attachment 1** of this notification. ✓ Implement a bi-weekly microbiological monitoring of the water quality (by heterotrophic plate count (HPC) measurement), including monitoring for non-tuberculous mycobacteria. The samples shall be taken prior disinfection. ✓ When you receive the results from the lab go to **Step 4**

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Step 3 / Heater Cooler operated in operating room
✓ Place the heater cooler in a way that the flow conditions of the surgical side are not disturbed by the heater cooler device fans. o Maintain maximum distance from surgical field; o Position heater cooler such that the fan exhausts of the device are directed away from the surgical field; o Position heater cooler fan exhausts close to the suction exhaust (outtake) of the operating room. ✓ The water in the tank must be changed **every day**. ✓ In order to prevent microbial growth and to avoid biofilm build-up, add medical grade 3% hydrogen peroxide solution to the tank contents (follow instructions provided in the new IFU, which direct 150 ml for the heater cooler 3T or 50 ml for the heater cooler 1T). ✓ Perform a **weekly** disinfection as described in the new IFU to kill the waterborne pathogens such as non-tuberculous mycobacteria. ✓ Implement a bi-weekly microbiological monitoring of the water quality (by heterotrophic plate count (HPC) measurement), including monitoring for non-tuberculous mycobacteria. The samples shall be taken prior to disinfection. ✓ Take microbiological air samples for non-tuberculous mycobacteria in the operating room when the heater cooler is running on a bi-weekly basis. ✓ When you receive the results from the lab go to **Step 4**
Step 4 / Review of Lab Analysis and Action
✓ If the microbial counts are within the specified limits (meet microbiological drinking-water quality and Coliform bacteria, P. aeruginosa and non-tuberculous mycobacteria are not detected in 100ml), the device can be placed back into the operating room. Continue to use and maintain the device according to the new IFU, **Attachment 1** ✓ Implement a microbiological monitoring of the water quality, including monitoring for non-tuberculous Mycobacteria on a monthly basis. ✓ If you find microbial counts in the water are greater than the limits specified above, contact your infection control manager to determine appropriate actions and immediately contact your service representative for support. ✓ If non-tuberculous mycobacteria are found in the air of the operating room, when the heater cooler is operated, remove the heater cooler from service and immediately contact your service representative for support. o For emergency surgeries please consult your infection control manager to determine appropriate actions.

For technical support please contact your local service representative.

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Please complete and return the attached Confirmation Form (see **Attachment 3**) by fax to «Number» or by email to «E-mail Address».

Transmission of this Field Safety Notice

Please assure within your organization that this notice is communicated to all personnel who need to be aware of this Field Safety Notice. In case you have transferred products to a third party please communicate this information to them and also inform the below mentioned contact person.

Please maintain awareness on this notice and resulting action for an appropriate period to ensure effectiveness of the corrective action.

Contact reference person

For questions regarding this Field Safety Notice, please contact Christian Peis, Director QA, Sorin Group Deutschland GmbH at +49 89 323 01 152, via fax at +49 89 323 01 333 or via e-mail at SGD.fsca@sorin.com

A copy of this Field Safety Notice has been provided to the appropriate Regulatory Agencies who are aware of these actions.

Thank you for your cooperation in this matter. Sorin Group is committed to provide quality products and service to its customers and we apologize for any inconvenience this situation may have caused.

Sincerely,

i.V. Christian Peis
Director Quality Assurance

Enclosures:

Attachment 1: New Instructions for Use

Attachment 2: Affected Product List

Attachment 3: Customer Response Form

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Attachment 2
Affected Product List

FIELD SAFETY NOTICE

Cardiac Surgery Mycobacterium Risks
Disinfection and Cleaning of Sorin Heater Cooler Devices

Reference # 9611109-06/03/15-002-C

Product Code	Product description	Affected Serial Number range
16-02-50	Heater-cooler 1T, 230V	16S00808 - 16S02268
16-02-80	Heater-cooler 3T, 230V	16S10027 - 16S15641
16-02-81	Heater-cooler 3T, 240V	16S10743 - 16S11708
16-02-82	Heater-cooler 3T, 208V	16S10772 - 16S15523
16-02-83	Heater-cooler 3T, 127V	16S11455 - 16S15190
16-02-85	Heater-cooler 3T, 120V	16S10958 - 16S15634
16-02-95	Heater-cooler 3T, 200V	16S12004 - 16S15385

Please refer to Attachment 3 for affected Systems at your site.

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Annexe 4

Formulaire de réponse client

INFORMATION DE SECURITE - **MISE A JOUR**

Risques de mycobactérie en chirurgie Cardiaque
Désinfection et nettoyage des Générateurs thermiques Sorin
Référence # 9611109-11/11/16-008-C

Merci de compléter et retourner ce formulaire sous 2 jours

1. Nous AVONS lu et compris le contenu de l'Information de sécurité ci-jointe □ oui □ non
2. Nous N'AVONS PAS compris l'Information de sécurité ci-jointe et demandons un complément d'information □ oui □ non

Listez les numéros de série des Générateurs Thermiques Sorin utilisés dans votre établissement :

Code produit	Description du produit	Numéro de série concerné

Etablissement (Nom):	<<Print Your Company name here>>
Pays :	<<Print Your Country here>>
Contact (Nom):	<<Print Your Contact Name here>>
E-mail:	<<Print Your E-mail address here>>
Numéro de fax:	<<Print Your Fax No. here>>
Numéro de téléphone:	<<Print Your Phone No. here>>

Envoyé par	**SIGNATURE**	**DATE**
:……..	……..	……../……../……..…

Pour renvoyer ce formulaire ou pour toute question concernant cette Information de sécurité ou le service désinfection profonde, veuillez nous contacter :

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Fax Number:	+44 – 2080806540 (international)
Phone Number:	0800-914510 (France)

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