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Mycobacterium chimaera infections associated with heater-cooler units (HCU): closing another loophole in patient safety

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In 2011, invasive cardiovascular and disseminated infections by a slowly-growing non-tuberculous mycobacterium, *Mycobacterium chimaera,* were detected in patients who had undergone cardiothoracic surgery in Switzerland. *M. chimaera* was subsequently detected in the water tanks of heater-cooler units (HCUs) used to regulate the temperature of patients' blood in the cardiopulmonary bypass circuit, and in air samples from the operating room when the HCUs were running [1]. This report led investigators in other countries to look for similar cases among cardiothoracic surgery patients exposed to such devices. From 2014 onwards up to April 2015, cases of invasive cardiovascular infection by *M. chimaera* potentially linked to HCUs were consecutively detected in the Netherlands, Germany and the United Kingdom (UK) [2] and hereafter in the United States (US) [3]. An epidemiological link with use of a specific model of HCUs, the 3T device (LivaNova, UK; formerly Sorin, Germany), was confirmed by the detection of *M. chimaera* in these devices across affected cardiothoracic surgery centres [4]. Observational and experimental studies showed that exhaust air from contaminated HCUs can transmit aerosols with *M. chimaera* to the operating field under ultraclean laminar air flow ventilation [5,6].

Environmental testing at the manufacturing site identified contamination with *M. chimaera* of water tanks of LivaNova/Sorin 3T HCUs, as well as of water from the pump assembly area of the facility [4]. In April 2016, the preliminary results of an analysis of the whole genome sequence of outbreak-related *M. chimaera* isolates showed 'almost identical genome sequences' among clinical isolates from patients in three European countries and environmental isolates from 3T devices in the affected hospitals and at the device manufacturing site. These findings supported the hypothesis of a common-source, multi-country outbreak related to intrinsic contamination of 3T devices manufactured before September 2014 [4]. Recently, a study of whole-genome sequences of clinical isolates from *M. chimaera* infected open-heart surgery patients and from HCUs from hospitals in Pennsylvania and Iowa, US, reportedly showed few single nucleotide polymorphism (SNP) differences between outbreak-related isolates as compared with hundred-fold larger SNP differences between outbreak-related isolates and an epidemiologically unrelated isolate [7]. However, the full results of the analysis of whole-genome sequence data in relation to the epidemiological data from the outbreak investigations in Europe and the US have not been published to date*.

In this issue of *Eurosurveillance*, the first case of *M. chimaera* pleural infection in a lung transplant recipient from Australia is reported, together with results of environmental investigations that indicate frequent contamination with *M. chimaera* of HCU devices used in hospitals across Western Australia, suggesting that the outbreak extends beyond Europe and the US [8]. This report tests potential source hypotheses by whole-genome sequencing of clinical and environmental *M. chimaera* isolates. Of particular interest is the finding that the genomes of isolates from HCUs across four hospitals clustered in two groups, each composed of isolates differing by less than 17 SNPs. It remains to be seen whether these *M. chimaera* genotypes match those from HCUs in Europe and the US. Of note, a clinical isolate from the infected patient potentially exposed to one of the contaminated HCUs did not match environmental genotypes and showed over 600 SNPs differences from the isolates recovered from the devices. Although, in this case, the results were found sufficient to rule out the HCU as the source of infection, the authors recognise the limitation of their sampling method based on single colony genome analysis, which may have missed mixed-strain populations that were present in the tested samples. Furthermore, the whole-genome comparative analysis of a larger collection of *M. chimaera* isolates, including from sporadic

infections and environmental reservoirs worldwide, is awaited. It should reveal the genetic population structure of *M. chimaera* and ascertain the extent of common source contamination of HCUs as well as the fraction of HCU-associated infections attributable to the 3T device. Of note, the sharing before publication of genome sequence data on this emerging pathogen through public repositories, as advocated for improving public health investigations of international epidemics [9,10], has been recently implemented by several investigators [7]*.

In a second study in this issue, the occurrence of *M. chimaera* infection associated with treatment by extracorporeal membrane oxygenation (ECMO) devices was explored in a retrospective descriptive clinical study combined with prospective environmental sampling at a German supra-regional ECMO centre [11]. ECMO also uses thermoregulatory devices and is regarded as a potential further source for *M. chimaera* infections in a group of severely ill and often immunocompromised patients. However, in contrast to HCUs used in cardio-thoracic surgery, ECMOs are air-tight and closed systems, plausibly precluding the release of aerosols. Contamination with *M. chimaera* of water tanks from ECMO thermoregulatory devices from two manufacturers was documented, but no room air contamination was found. No patients with *M. chimaera* infection linked to ECMO devices were identified during the period of intensive care. A limitation of this single-centre study is the relatively short patient follow-up. Further prospective studies should elucidate the clinical relevance, if any, of *M. chimaera* contamination of ECMO devices.

Recognising the health hazard associated with mycobacterial contamination of HCUs used in cardio-thoracic surgery, national authorities in Europe and the US have issued health alerts to surgical facilities. They call for increased vigilance, active surveillance and implementation of risk mitigation measures such as removal of the HCU from the operating room to a side room as well as implementation of the updated decontamination and cleaning protocol as provided by the device manufacturer, or product recall [2,3,12,13]. The true extent of the 3T device-associated *M. chimaera* infections has not yet been determined and it is likely to remain underestimated. Jointly with experts from various European countries, the European Centre for Disease Prevention and Control (ECDC) developed a clinical and environmental investigation protocol based on available experience [14]. Still, both clinical and environmental surveillance face technical challenges as (i) symptoms of invasive *M. chimaera* infection can occur more than 5 years after surgery, (ii) the clinical presentation is non-specific and can be indolent, (iii) diagnosis of *M. chimaera* infections by mycobacterial culture is slow and of low sensitivity unless infected tissue is obtained by invasive sampling, and (iv) identification of mycobacteria at the species level requires specialised DNA sequence-based testing. Thus far, no direct nucleic-acid amplification or metagenomics assay has been proposed for the rapid detection of *M. chimaera* in clinical or environmental samples.

An improved understanding of the risk determinants associated with the use of HCUs and the extent of the *M. chimaera* outbreak are critical for appropriate communication to healthcare providers and patients and for raising their awareness. Risk assessments at hospital level and the timely diagnosis and treatment of *M. chimaera* infection among exposed patients, as well as close collaboration between device manufacturers and regulatory agencies to ensure safe use of the HCUs are essential to close this patient safety loophole [2,12,15]. Further to this incident of contamination of devices during manufacturing, growing evidence of contamination of HCUs with diverse non-tuberculous mycobacteria and other opportunistic pathogens suggests a wider aerosol-borne infectious hazard from water-containing devices used in surgery that will require further risk assessment before and after putting such devices into clinical use [4,16].

*Authors' correction

Upon the authors' request, the following corrections were made on 21 November 2016, after publication date:

The sentence 'However, whole-genome sequence data from the outbreak investigations in Europe and the US have not been published to date.' has been corrected to read 'However, the full results of the analysis of whole-genome sequence data in relation to the epidemiological data from the outbreak investigations in Europe and the US have not been published to date.'

The sentence 'To the best of our knowledge, the sharing before publication of preliminary genome sequence data on this emerging pathogen through public repositories, as advocated for improving public health investigations of international epidemics [9,10], has not yet been implemented.' has been corrected to read 'Of note, the sharing before publication of genome sequence data on this emerging pathogen through public repositories, as advocated for improving public health investigations of international epidemics [9,10], has been recently implemented by several investigators [7].'

Conflict of interest

None declared.

Authors' contributions

Both authors contributed to the drafting and reviewing of the manuscript.

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Outbreak of enterovirus D68 of the new B3 lineage in Stockholm, Sweden, August to September 2016

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We report an enterovirus D68 (EV-D68) outbreak in Stockholm Sweden in 2016. Between 22 August and 25 September EV-D68 was detected in 74/495 respiratory samples analysed at the Karolinska University Hospital. During the peak week, 30/91 (33%) samples were EV-D68 positive. Viral protein (VP)P4/VP2 sequencing revealed that cases were caused by B3 lineage strains. Forty-four (59%) EV-D68-positive patients were children aged ≤ 5 years. Ten patients had severe respiratory or neurological symptoms and one died.

We report an outbreak of enterovirus D68 (EV-D68) infections in Stockholm, Sweden in late August and September of 2016 caused by the newly described B3 lineage [1].

Patients, samples and routine diagnostics for respiratory viruses

The main study was based on respiratory samples analysed at the Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden, between 22 August and 25 September 2016 (n = 495; 183 nasopharyngeal aspirates, 232 nasopharyngeal swabs, 77 lower respiratory tract samples, 3 unspecified respiratory samples). The laboratory provides diagnostic services to six of seven major hospitals and approximately half of outpatient care in the Stockholm county (2.2 million inhabitants). Most samples (480 of 495) were from the catchment area and collected as part of routine diagnostics from inpatients and, to a lesser degree, outpatients. Fifteen samples were referred from other counties. For comparison, results from routine EV and rhinovirus diagnostics from the Karolinska University Hospital in 2014, 2015, and the remaining part of 2016 up to 13 November were also analysed.

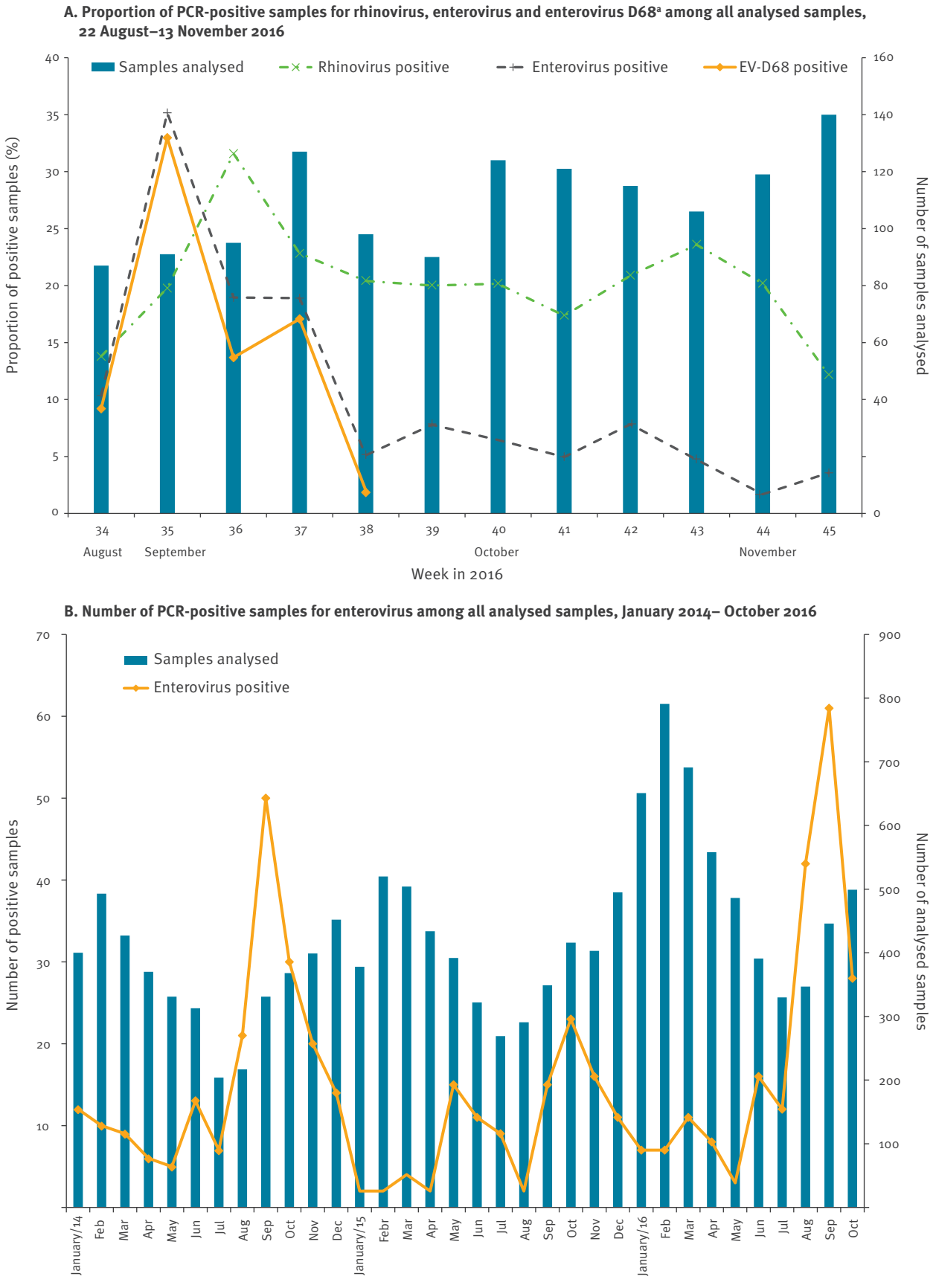
EV, rhinovirus and 10 other respiratory viruses were diagnosed using in-house real-time polymerase chain reactions (PCR)s [1]. The PCRs for EV and rhinovirus cross-react because the viruses are closely related. Based on results from extensive validation including sequencing, samples with dual reactivity for EV and rhinovirus were classified as rhinovirus if the PCR cycle threshold (Ct)-value for rhinovirus was›3 lower than the Ct-value for EV and otherwise as EV. Influenza A, influenza B and respiratory syncytial virus were diagnosed using the commercial Simplexa system [2]. The study was approved by Regional Ethical Review board in Stockholm, Sweden (registration number 2016/2004–32).

Enterovirus D68 polymerase chain reaction and sequencing

A real-time EV-D68 PCR was introduced in the late summer of 2016 and was based on the primers and probe of Piralla et al. [3] and used 5 µL of extracted RNA, 5 µL TaqPath 1-Step RT-qPCR Master Mix, CG (Thermo Fisher Scientific, Stockholm, Sweden), 100 nM of primers and probe in a total volume of 20 µL. An ABI7500 FAST Real Time PCR System (Applied Biosystems, Thermo Fisher Scientific, Stockholm, Sweden) was used with the following cycling profile: 2 min at 25 °C, 15 min at 50 °C, 2 min at 95 °C, and 45 cycles of denaturation for 10 s at 95 °C, annealing for 30 s at 60 °C.

Figure 1

Results of polymerase chain reaction (PCR) analysis of routine respiratory samples, Stockholm, Sweden, 2014–2016

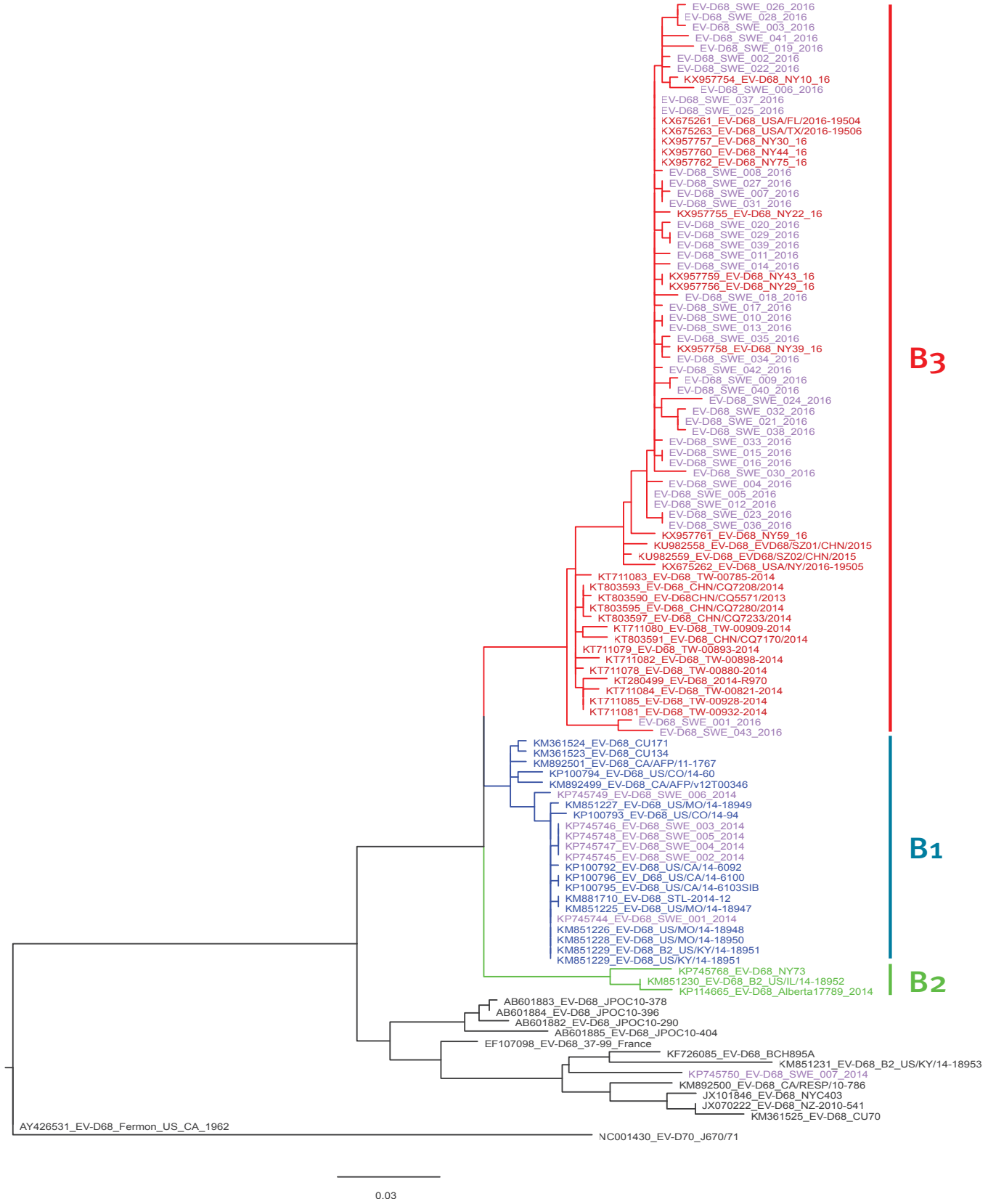


EVD-68: enterovirus D68.

[a] Enterovirus D68 data are not available from 25 September onwards, after which the test was only done on demand.

Figure 2

Maximum likelihood phylogenetic tree constructed using enterovirus D68 viral protein (VP)4/VP2 sequences (435 bp) from Stockholm, Sweden and relevant GenBank sequences



The B1, B2 and B3 lineages of EV-D68 are colour labelled and the new Swedish sequences from 2016 as well as published Swedish sequences from 2014 [4] are purple. The scale bar at the bottom indicates the number of nucleotide substitutions per site, according to the GTR+I+G model. The tree was rooted using the EV-D70 strain J670/71 (NC001430); the branch to the root has been shortened by a factor of ten.

Table

Characteristics of 10 enterovirus D68 infected patients with severe symptoms, Stockholm, Sweden, 22 August–25 September 2016

Patient code	Age group in years	Sex	Symptoms	Underlying disease	ICU days	Outcome
1	6–18	M	Acute flaccid myelitis Respiratory insufficiency Upper-lower respiratory infection	Previously healthy	17	Not yet fully recovered Still deglutition problem
2	6–18	M	Metabolic crisis Rhabdomyolysis Multiorgan failure	Congenital disorder of metabolism	3	Fatal
3	6–18	M	Respiratory failure	Previously healthy	3	Full recovery
4	1–5	M	Respiratory failure	Asthma	2	Full recovery
5	<1	M	Respiratory failure	Congenital muscle disease	11	Recovered to original state of health
6	<1	F	Respiratory failure	Tracheobroncheomalacia	2	Recovered to original state of health
7	<1	F	Respiratory failure	Congenital chromosomal abnormality	5	Recovered to original state of health
8	>18	F	Acute flaccid myelitis Bulbar symptoms Upper respiratory infection	Previously healthy	>6 weeks Ongoing ICU-care	Limited improvement Still paretic
9	>18	F	Septic Respiratory symptoms Skin rash	Previously healthy	0	Full recovery
10	6–18	M	Acute liver failure Exanthema	Previously healthy	0	Full recovery No other cause of the liver failure has been found Elevated levels of copper in urine in the acute phase to be followed up
11[a]	1–5	F	Acute flaccid myelitis Bulbar symptoms Respiratory insufficiency Upper-lower respiratory infection	Previously healthy	Ongoing ICU-care	Still complete tetraparesis

ICU: intensive care unit.

[a] Patient diagnosed in October, outside of the main study period from 22 August to 25 September.

Sequencing of the viral protein (VP)4/VP2 region of the EV/rhinovirus genome was performed with an in-house protocol and primers by Wisdom et al. [4,5]. EV-D68 sequences were deposited in GenBank under accession numbers KY215827–69*. The EV/rhinovirus species and type were determined by maximum likelihood phylogenetic trees constructed using Molecular Evolutionary Genetics Analysis (MEGA) 7.0.18 (GTR+I+G model), which included reference sequences available at www.picornaviridae.com and EV-D68 sequences that were downloaded from GenBank after a search using basic local alignment search tool (BLAST).

Description of the enterovirus D68 outbreak in Stockholm in the early autumn of 2016

Of the 495 respiratory samples obtained in the main study period between 22 August to 25 September, 72 were positive for rhinovirus alone while 122 (>25%) reacted as EV positive. Among these 122 samples, 21 tested positive for EV alone, and 101 were dually reactive for both rhinovirus and EV. Based on the analysis of Ct-values, 67 of the 101 dually reactive samples most likely contained EV alone, while 34 of these samples likely bore only rhinovirus. Thus a total of 88 samples were classified as EV positive and 106 samples were classified as rhinovirus positive (Figure 1A). The proportion of EV positive samples during the study period in 2016 (18%; 88/495) was significantly higher than the corresponding period in 2015 (2%; 9/366; p<0.001, Fisher exact test) and also higher than in 2014 (15%; 49/321) (Figure 1B).

A total of 149 respiratory samples from the study period were analysed with EV-D68 PCR. These included a subset of 34 samples that had tested positive for rhinovirus alone in earlier PCRs, and 115 samples with available material, among the 122 initially appearing as EV positive; 74 samples were positive for EV-D68. In the week of 29 August (week 35), 33% (30/91) of all respiratory samples were positive for EV-D68 (Figure 1A).

EV-D68-negative samples usually had an indication of rhinovirus based on the Ct-value for rhinovirus being›3 lower than the Ct-value for EV. In 20 of these samples rhinovirus was verified by VP4/VP2 sequencing. The 34 samples that had tested only positive for rhinovirus in prior PCRs were found negative by EV-D68 PCR.

In Figure 1A the two curves depicting the variations with time of the proportions of EV- and EV-D68-positive samples among all respiratory samples analysed during the study period, have almost identical trajectories. This justifies the classification EV and rhinovirus positive samples based on Ct-values. The Figure also indicates that almost all EV infections in the main study period were caused by EV-D68. After 25 September, specific EV-D68 diagnostics were only done on demand of physicians and the proportion of EV-positive samples remained at a lower level up to 13 November, suggesting that EV-D68 activity was likely low in October and early November.

The outbreak was caused by the new B3 lineage of enterovirus D68

VP4/VP2 sequencing was attempted on 80 samples from the study period (57 EV-D68 positive and 23 EV-D68 negative). Figure 2 shows that all successfully sequenced EV-D68 PCR positive samples from 2016 (n=43) belonged to the recently described B3 lineage of EV-D68 [6]. Within the B3 lineage, 41 of 43 Swedish sequences from 2016 formed a tight cluster together with unpublished Genbank sequences from the United States (US) collected in 2016.

Characteristics of patients with enterovirus D68 infection

EV-D68 positive patients (n = 74) were significantly older than EV-D68 negative patients (n = 75) (median 3.2 vs 1.1 years, p=0.039, Mann–Whitney U-test). The proportions of patients in the respective age groups‹1, 1–5, 6–18, and›18 years were 16% (12/74), 43% (32/74), 22% (16/74), and 19% (14/74), for EV-D68-positive patients, and 37% (28/75), 37% (28/75), 5% (4/75) and 20% (15/75), for EV-D68 negative patients. Female patients accounted for 56% (40/73; for one patient sex was unknown) and 48% (36/75) of the EV-D68 positive and negative samples, respectively. We are aware of ten patients with severe disease diagnosed during the main study period (Table).

Discussion

In 2014 EV-D68 emerged worldwide [7]. The emergence received high attention by public health authorities because of its magnitude and the clinical presentation of some patients who displayed severe respiratory and neurological symptoms, including acute flaccid paralysis [7-10].

There are indications that EV-D68 may be resurging in 2016 [11,12], but due to lack of systematic surveillance the true disease burden is unclear [7,11]. Here we report a recent large outbreak of EV-D68 infections in Stockholm, Sweden. Severe disease, including one death, was observed in ten of 74 (12%) patients with laboratory-confirmed EV-D68 infection during the study period and one additional patient diagnosed in October 2016. The outbreak peaked in early September and EV activity appears to have been considerably lower in October and early November. It is likely that verified EV-D68 cases represent the tip of an iceberg [7] because patients with milder symptoms are unlikely to have sought medical care or been sampled. Comparison of 2014, 2015, and 2016 indicated that we have documented a true outbreak of EV-D68 in 2016 and that infections also occurred in 2014. This agrees with limited EV-D68 retrospective PCR testing on EV-positive respiratory samples from 2014 (8 EV-D68 positive of 14 samples tested) and 2015 (none EV-D68 positive of 23 samples tested) as well as with published sequencing results on samples from 2014 [4]. It is unlikely that increased awareness and sampling have significantly influenced the findings as the total number of samples received per week was not dramatically different for 2014, 2015 and 2016 and reporting about the 2016 outbreak by the Swedish Public Health Institute and our laboratory to relevant health professionals (mainly paediatricians and infectious disease specialists) only occurred after the peak.

The outbreak was caused by closely related strains of the recently described B3 lineage [6]. Available data indicate that the B3 lineage arose recently in the evolution of EV-D68 and is actively spreading in parts of Europe [12] and the US during the 2016 season (unpublished GenBank sequences). It is unclear if the apparent epidemiological success of this lineage in 2016 is due antigenic drift or if the risk of severe disease differs from other EV-D68s, such as the B1 lineage that caused the worldwide outbreak in 2014.

In a recent rapid risk assessment the European Centre for Disease Prevention and Control (ECDC) stated that the increased numbers of EV-D68 (and EV-A71) detections reinforce the need for vigilance for EV infections, especially cases that present with more severe clinical syndromes [11]. This appears insightful in light of the recent outbreak in Stockholm.

Addendum

*The GenBank accession numbers were added on 23 November 2016.

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Conflict of interest

None declared.

Authors' contributions

RD, MG, BH, MRÖ, JA: conceived the study and analysed and interpreted the results. JE, KH, JL, PN, HR: collected and interpreted clinical data. RD and JA: drafted the manuscript, which was revised by all the authors.

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Severe paediatric conditions linked with EV-A71 and EV-D68, France, May to October 2016

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We report 59 cases of severe paediatric conditions linked with enterovirus (EV)-A71 and EV-D68 in France between May and October 2016. Fifty-two children had severe neurological symptoms. EV sequence-based typing for 42 cases revealed EV-A71 in 21 (18 sub-genotype C1, detected for the first time in France) and EV-D68 in eight. Clinicians should be encouraged to obtain stool and respiratory specimens from patients presenting with severe neurological disorders for EV detection and characterisation.

On 29 July 2016, via an Early Warning and Response System message, French health authorities informed public health authorities in European countries about a recent increase of severe acute neurological conditions reported by one of the main academic paediatric hospitals in Paris [1]. A first local retrospective survey showed that, since April 2016, 18 children presented with rhombencephalitis, encephalitis, cerebellitis or myelitis and additional four with facial nerve radiculitis. Enterovirus (EV) infection was confirmed in eight of the 22 cases. Case finding was rapidly implemented at a national level. All paediatric wards (including neurology, paediatric intensive care units, internal medicine and emergency wards) were invited to report any case with severe conditions e.g. neurological, cardiac, neonatal sepsis, with suspected association with EV infections, starting from 15 March 2016, onwards. For suspected cases, they were requested to collect clinical specimens including cerebrospinal fluid (CSF), nasopharyngeal aspirates, stools and/or blood specimens for EV testing, and typing if positive for EV genome detection. Simultaneously, the two EV National Reference Laboratories (NRLs) in Clermont-Ferrand and Lyon, notified all laboratories participating in the French EV surveillance network (RSE) [2], who were already aware of the EV-A71 outbreak in Catalonia, Spain, since June 2016 [3]. Although the focus was on paediatric cases, a message was also sent to neurologists, internists and intensivists treating adult patients and participating in a prospective cohort study on encephalitis in adults (ENCEIF survey) [4].

Here we briefly present the main findings after 6 months of this enhanced surveillance.

Description of cases

Seventy-five paediatric cases with severe conditions suspected to be potentially associated with EV infections were reported. Sixteen of them were excluded because of other aetiologies or lack of evidence of a possible EV infection and 59 were included in the analysis. Four cases in adults were also reported, however, here we only describe the 59 paediatric cases.

Patient characteristics and symptoms

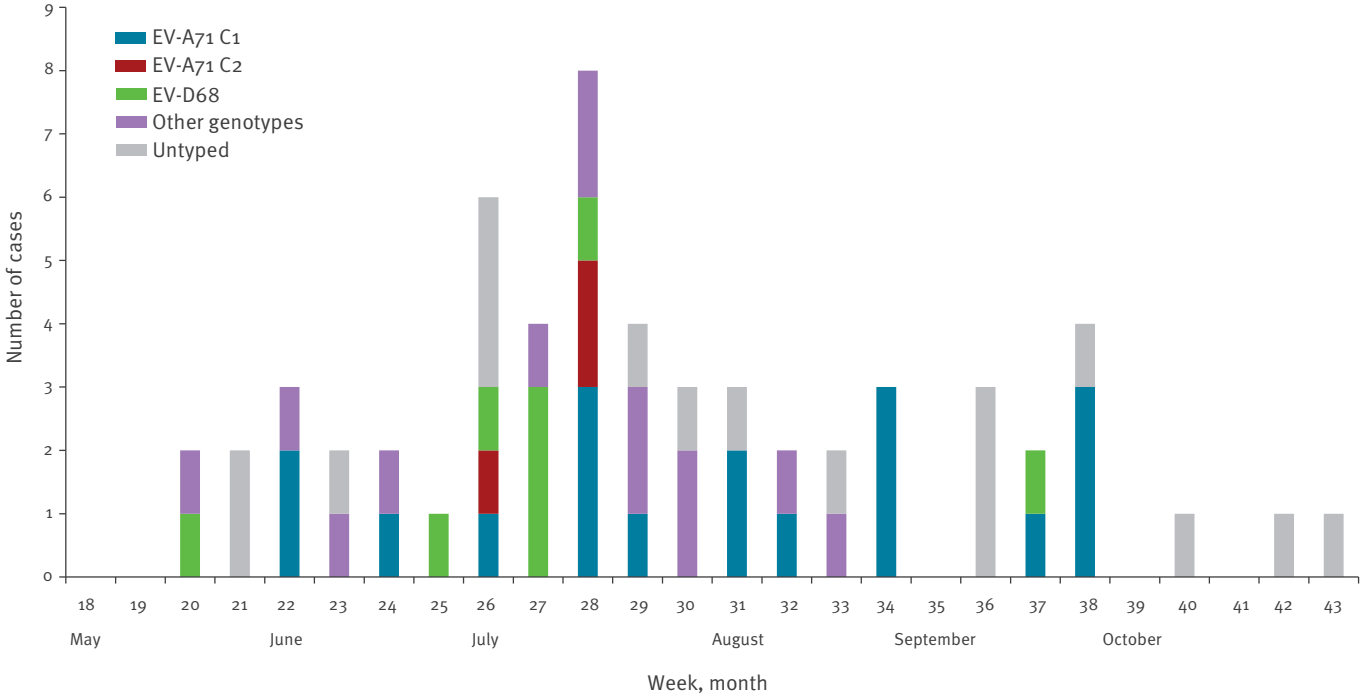
Median age at symptoms onset was 3 years, ranging from 1 month to 15 years, and the male to female sex ratio was 1.2 (32 male vs 27 female). Two thirds of the patients lived in the Paris area (Ile de France, n = 38) and 17% in Auvergne-Rhône-Alpes (n = 10), representing respectively 20% and 15% of the French metropolitan population, while further six of the 13 French metropolitan regions reported only 1 to 2 cases each.

The dates of symptoms onset ranged from 16 May to 30 October 2016 (week 20 to week 43), see Figure.

Fifty-two of 59 children (88%) presented with severe acute neurological symptoms such as

Figure

Distribution of severe paediatric cases linked with EV infections over time, by enterovirus genotype and week of symptoms onset, Metropolitan France, May–October 2016 (n=59)



EV: enterovirus.

rhomboencephalitis (n=15), encephalitis (n=11), cerebellitis (n=5), myelitis (n=4), cranial nerve radiculitis (n=2); 13 other cases had combined neurological disorders and two children had both severe rhomboencephalitis and myocarditis; three had severe neonatal sepsis and four presented with isolated cardiac symptoms i.e. myocarditis, pericarditis, acute cardiac failure.

One patient died and 21 patients needed prolonged hospital stay because their condition was severe and/or they had persistent myocardial or neurological deficits, such as polio-like persistent peripheral neuropathy, at hospital discharge. At least four children needed prolonged ventilator support (through a tracheostomy) and/or feeding support after being admitted in a rehabilitation center, because of persistent brain stem dysfunction.

Enterovirus detection and clinical picture associated with genotypes identified

In only eight of the 59 cases (13.5%), EV detection by real-time (RT)-PCR (5' untranslated region) on CSF samples was positive, while EV was detected in most peripheral samples, e.g. in stools of 43 (73%) and/or nasopharyngeal aspirates of 37 (62.7%) cases. In 42 cases, the EV could be typed (71%) by sequencing of the viral protein (VP)1 or the VP4-VP2 coding gene, performed by the NRLs.

EV-A71 was identified in 21 of 42 cases (50%); 18 EV-A71 belonging to the subgenotype C1, one associated with EV-D68, and three EV-A71 C2 among which one associated with an echovirus (E)3. All cases presented with rhomboencephalitis, encephalitis or encephalomyelitis, except one fatal case of acute cardiac failure. For the latter a brain stem failure cannot be excluded as brain MRI could not be performed before death. Two cases had presented with a hand, foot and mouth disease before developing neurological symptoms.

Excluding the EV-D68 case which was associated with EV-A71 C1 described above, EV-D68 was identified in eight of 42 cases. Four of them presented with neurological disorders i.e. rhomboencephalitis or myelitis, three with cardiac symptoms i.e. myocarditis, pericarditis, acute cardiac failure, and one with neonatal sepsis.

In the remaining 13 cases, various EV were identified: coxsackie (CV) A6 (n=2), CV-A16, CV-A10 and human rhinovirus (HRV) A56, CV-B3 (n=2), CV-B2, CV-B5, E-25 (n=2), E-13, E-6v, and E-30. All of the cases infected presented with neurological disorders.

Discussion

In France, routine EV surveillance and molecular typing involve the RSE network and focus mainly on EV-associated neurological symptoms in hospitalised patients, as one of the main aims of this surveillance

is to confirm the absence of circulation and to detect any possible importation of poliovirus, in a timely manner. Through this network, only a few sporadic cases of meningoencephalitis linked to EV-A71 [5-7] and one case of acute flaccid paralysis linked to EV-D68 [8] have been described in the country in the past 15 years. The impact of EV-A71 may have been previously underestimated because stool and respiratory specimens were not systematically collected from patients. Still, the enhanced surveillance set up in 2016 yielded an unusual number of reports of severe paediatric neurological cases associated with EV-A71. Moreover, whereas EV-A71 subgenogroup C2 viruses had been predominant in France since 2006 [5,9], in 2016, the EV-A71 subgenogroup C1 viruses were predominant. These EV-A71 C1 viruses had not previously been detected in France (data not shown) and were closely related to a new cluster of EV-A71 C1 viruses detected in 2015 in Germany [10,11]. Most of the cases were diagnosed in late July, concurrently with the usual peak of EV circulation in the country, but cases were still identified in September and October. Other EVs circulated scattered over the 6-month period of study, especially EV-D68, that circulated mainly in July, but one case was still detected in September.

Taking into account the severity of the initial and persisting symptoms and the fact that EV-A71 is the most neuropathogenic non-polio enterovirus in humans [5], it has been decided to prolong the enhanced surveillance at least until the end of 2016, as another peak in EV circulation may be observed during this autumn.

Ascertaining the diagnosis of EV infection was difficult during this outbreak, especially when investigating cases retrospectively. While EV detection in CSF samples was mostly negative, clinicians had to change their practise and, following the NRLs' recommendations, ask for EV detection in respiratory samples and rectal swabs or stool specimens. Such specimens, however, were not systematically available from severe neurological cases before surveillance was reinforced. Therefore, virological information was better for prospectively reported cases. The input of the RSE was an important complementary source of information, allowing rapid reporting of several cases that would have been missed otherwise. Nevertheless, case reporting was probably not exhaustive. Another remaining challenging question is the pathophysiology of such severe conditions in this paediatric population, in which asymptomatic or mild EV infections are very common, raising hypotheses concerning special strain virulence or peri-infectious inadequate immune response, as is often the case in paediatric non necrotising encephalitis.

Conclusion

Without control measures other than strengthening of personal hygiene for close contacts, and because of disease severity, accurate diagnosis of EV-associated severe conditions is a key issue. Clinicians should be encouraged to obtain stool and respiratory specimens from all patients presenting with symptoms suggestive of severe neurological disorders such as encephalitis, rhombencephalitis, cerebellitis, acute flaccid myelitis or acute flaccid paralysis, for EV detection and characterisation. Furthermore, the known epidemiological pattern and clinical picture of both EV-A71 and EV-D68 may be changing in Europe, as shown by the recent outbreak of EV-A71 in Spain, or the clusters of EV-D68 infections recently reported by Scotland and Sweden, making it necessary to reinforce the vigilance towards those infections.

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Conflict of interest

None declared.

Authors' contributions

Denise Antona, Clément Bassi, Daniel Lévy-Bruhl participated in the national investigation and analysis of cases.

Manoëlle Kossorotoff, Mélodie Aubart, Florence Moulin, Isabelle Desguerre were in charge of the medical care of the patients in Necker hospital; Manoëlle Kossorotoff and Isabelle Desguerre were the reference neurologists for clinicians following cases in other hospitals across the country.

Marianne Leruez-Ville analysed all patients' specimens in Necker hospital virology laboratory.

Isabelle Schuffenecker, Audrey Mirand, Cécile Henquell, Bruno Lina were in charge of the enterovirus sequencing in the 2 National reference laboratories, and were the reference virologists for all the laboratories of any hospital across the country.

Denise Antona, Manoëlle Kossorotoff, Isabelle Schuffenecker and Audrey Mirand contributed equally in drafting the paper; all the other authors revised the document.

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Mycobacterium chimaera colonisation of heater–cooler units (HCU) in Western Australia, 2015: investigation of possible iatrogenic infection using whole genome sequencing

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Following the reported link between heater–cooler unit (HCU) colonisation with *Mycobacterium chimaera* and endocarditis, mycobacterial sampling of all HCUs in use in Western Australia was initiated from August 2015, revealing *M. chimaera* colonisation in 10 of 15 HCUs. After *M. chimaera* was isolated from a pleural biopsy from a cardiothoracic patient who may have been exposed to a colonised HCU, a whole genome sequencing investigation was performed involving 65 specimens from 15 HCUs across five hospitals to assess if this infection was related to the HCU. Genetic relatedness was found between the 10 HCU *M. chimaera* isolates from four hospitals. However the *M. chimaera* isolate from the cardiothoracic patient was not genetically related to the HCU *M. chimaera* isolates from that hospital, nor to the other HCU isolates, indicating that the HCUs were not the source of the infection in this patient.

Introduction

Mycobacterium chimaera is a slow growing mycobacterium from the *Mycobacterium avium* complex. In 2004, *M. chimaera* was identified as a new species within the complex group [1] and has been associated with pulmonary infections, predominantly in immunosuppressed patients and in patients with pre-existing lung conditions such as chronic obstructive pulmonary disease and cystic fibrosis [2,3]. Since 2013, *M. chimaera* has been reported as a cause of prosthetic valve endocarditis, bloodstream and vascular graft infections in several countries in Europe and the United States (US) [4-10], linked to the colonisation of the heater–cooler units (HCUs) used during open heart surgery with postulated airborne transmission in the operating theatre [8,11].

In June 2015, an HCU manufacturer issued a warning, instructing hospitals to follow updated disinfection and maintenance procedures on HCUs and perform mycobacterial sampling. In response, private and public hospitals in Western Australia (WA) commenced mycobacterial sampling of their HCUs (all HCUs in WA have been purchased from the same manufacturer) in August 2015. In March 2016, a clinical isolate of *M. chimaera* was obtained from a cardiothoracic surgical patient in whom the surgery involved the use of one of the HCUs. This finding triggered an investigation to assess if this infection was related to the HCU.

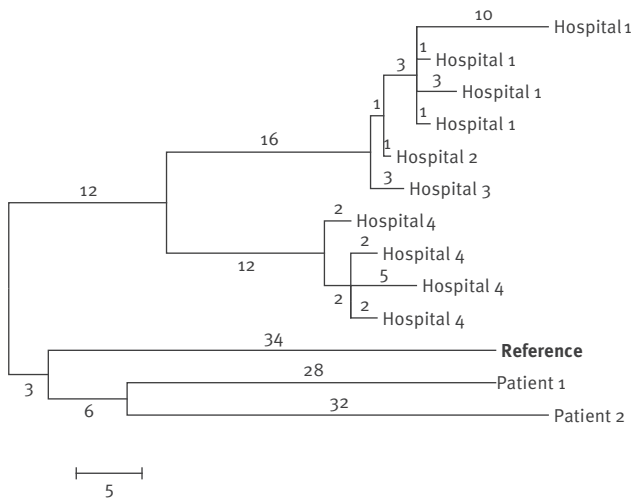
Case report and environmental sampling

A patient in their 50s underwent cardiothoracic surgery employing a HCU for cardiopulmonary bypass at Hospital 4 in December 2015. The surgery did not involve the implantation of prosthetic material. During this surgery, the HCU was placed as far as possible from the patient, with the exhaust towards the theatre exhaust vent and away from the patient.

Following the warning from the manufacturer, the water of all five HCUs at Hospital 4 was cultured and four of the five HCUs tested positive for *M. chimaera* in October 2015. All HCUs therefore underwent cleaning and disinfection following the manufacturer's instruction and were then deemed safe for use, the risk of

Figure

Genomic analysis of *Mycobacterium chimaera* strains grown from heater–cooler units from four hospitals, the cardiothoracic patient from Hospital 4 and a non-cardiothoracic patient, Western Australia, 2015–16 (n=12)



Patient 1: Hospital 4 cardiothoracic patient isolate, December 2015; patient 2: non-cardiothoracic patient isolate; reference: M chimaera strain MCIMRL6 (NCBI accession number: LJHN01000001).

Numbers indicate single nucleotide polymorphism differences.

postponing surgery while waiting for culture results being greater than the potential residual infective risk. As part of the monthly testing protocol, the HCUs were again sampled in November 2015 and *M. chimaera* was again cultured from one of the five HCUs after a 53-day incubation, i.e. after the patient's surgery. As the specific HCU used at the time of surgery was not recorded, it was not possible to conclude or exclude that the patient was exposed to a HCU colonised with *M. chimaera*. A process of recording the HCU used for each patient surgery has since been introduced.

Air sampling was also attempted from the operating theatres at Hospital 4, but the sampling plates were overgrown with other organisms such that interpretation of mycobacterial growth was not possible. Sampling from other hospital sources, such as potable water was not attempted.

One month after the operation, the patient developed bilateral pleural effusions and a pneumothorax with *Pseudomonas aeruginosa* isolated from the pleural fluid. During a 6-week course of piperacillin/tazobactam, the patient required four pleural drainage procedures, three for recurrent effusion and one for pneumothorax. One week after cessation of antibiotics, the patient redeveloped a pleural effusion and *P. aeruginosa* was again cultured. At this point the patient underwent decortication, and *M. chimaera* was cultured from a pleural biopsy. The patient was commenced on a combination of piperacillin/tazobactam, ciprofloxacin, azithromycin and ethambutol and slowly improved. Of note, the patient did not have signs and symptoms of disseminated *M. chimaera* infection. Mycobacterial blood cultures were not performed.

Methods

Mycobacterial culture from HCUs was performed at the Western Australian mycobacterial reference laboratory. Mycobacteriology culture methods for water samples based on the 2010 Gastroenterological Society of Australia guidelines [12] and comparable with subsequent British [13] and European [14] guidelines for *M. chimaera* isolation were followed. Aliquots of 50 mL were centrifuged at 3,000 g for 20 min, the supernatant discarded and the remaining 1–2 mL decontaminated using n-acetyl-l-cysteine-sodium hydroxide/sodium citrate. Two BBL MGIT tubes (Mycobacteria Growth Indicator Tube, Becton Dickinson, Sparks, US) and two Gerloff's egg slopes (with added nalidixic acid, vancomycin, amphotericin and polymyxin) were each inoculated with 0.5 mL of the processed sample and incubated for 8 weeks at 30 °C and 36 °C. Positive cultures were confirmed by acid fast staining, with subculturing on Middlebrook 7H11 plates for purity and identification. Single colony identification was performed by 16S rRNA gene sequencing.

The pleural biopsy was similarly cultured but without NaOH processing, with the clinical isolate initially identified on solid media at 30 °C after 21 days.

Whole genome sequencing (WGS), using aMiSeq platform (Illumina, San Diego, US), was performed on all HCU *M. chimaera* isolates, the patient isolate and a *M. chimaera* isolate from a non-cardiothoracic patient. *M. chimaera* strain MCIMRL6 (NCBI accession number: LJHN01000001), a clinical respiratory isolate, was used as the reference sequence [15]. The Illumina paired-end sequencing data, with an average of 70 × coverage depth, were analysed for genetic relatedness using the Nullarbor bioinformatic pipeline software [16] to identify single nucleotide polymorphisms (SNPs) in the core genome by comparison with the reference sequence. SNPs in recombination events were removed based on the method described by Feng et al. A maximum parsimony phylogenetic tree was constructed using MEGA (v7.0) [17].

Results

Sixty-five specimens from 15 HCUs used in five WA hospitals were cultured for mycobacteria over a 12-month period from August 2015 to July 2016. The sampling pattern initially varied between hospitals but became more regular for all hospitals with HCUs over time as standardised testing intervals were established. Single mycobacterial isolates from 10 different HCUs from four hospitals, as well as the patient isolate and the second clinical isolate from a non-cardiothoracic patient were confirmed as *M. chimaera* by WGS. In addition, *M. intracellulare* and *M. gordonae* were also isolated from HCUs. The *M. chimaera* HCU isolates clustered into two groups, one from Hospital 4 and one from Hospitals

1–3. The two groups differed by 28 SNPs, with 2–17 SNP differences between isolates within a group. The isolate from the patient in Hospital 4 did not cluster with the Hospital 4 HCU isolates; it differed from them by at least 63 SNPs (Figure). Likewise, the non-cardiothoracic patient isolate did not cluster with the HCU isolates.

Discussion

An association of HCU colonisation with *M. chimaera* and subsequent deep tissue infections in cardio-pulmonary bypass patients has been reported in Europe and the US [5-7,11] but published molecular epidemiological information is scarce [8]. Our WGS investigation revealed frequent *M. chimaera* colonisation of HCUs across several hospitals in WA. The WGS results show that the HCU *M. chimaera* isolates in WA were genetically related as they all shared common SNPs, which is consistent with contamination from a common source. There was no transfer of HCUs between hospitals in WA to implicate a single hospital contamination event. The hospital tap water supply cannot be excluded as a source, but only sterile packaged water or filtered tap water is used in the filling and cleaning of HCUs in WA. Given that all the HCUs in WA were produced at the same manufacturing site, one hypothesis is the HCUs were contaminated during production at this site, as recently suggested by Haller et al. [6]. In their study they showed that isolates from cardiothoracic patients, HCUs and the manufacturing site were almost identical; however, their typing results have not been published. To examine this hypothesis further, systematic WGS of isolates collected from HCUs in multiple geographical locations is required. Notably, the two HCUs from the WA hospital that did not yield any positive cultures for *M. chimaera* were significantly older (more than 10 years) than the HCUs in Hospitals 1–4 and thus may have been manufactured before a possible contamination event at the manufacturing site.

The *M. chimaera* isolate from the cardiothoracic patient was not genetically related to the HCU *M. chimaera* isolates from that hospital, nor to the other HCU isolates, indicating that the HCUs were not the source of the infection in this patient. Although this finding is reassuring, the presence of multiple different strains in an individual specimen may not have been detected by our sampling method as only one colony was selected from the culture media for WGS. Furthermore, *M. chimaera* cases have been diagnosed up to five years after cardiovascular surgery [6] and therefore we may detect linked clinical cases into the future.

Interestingly, both patient isolates and the reference strain were from respiratory specimens but were not closely related to each other or to the HCU isolates. This would suggest heterogeneity in the environmental *M. chimaera* populations able to infect the respiratory tract of these patients and the HCUs. Due to the probability of contamination with *M. chimaera* at the overseas manufacturing site it is possible that the observed genetic differences between the patient and HCU isolates may simply reflect different *M. chimaera* populations in water sources in the two countries. It is currently unknown if different *M. chimaera* strains have different pathogenicity to cause infections of either prosthetic heart valves or the respiratory tract.

Conclusion

Our study has demonstrated the usefulness of WGS in the analysis of a potential iatrogenic *M. chimaera* infection and shown that some HCUs used in WA are colonised with *M. chimaera*, as observed in countries on the northern hemisphere. As yet, no HCU-related infections have been identified in patients undergoing cardiopulmonary bypass procedures in WA. We must maintain a high level of suspicion in the population at risk while continuing regular disinfection and mycobacterial monitoring of our HCUs.

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Conflict of interest

None declared.

Authors' contributions

James Owen Robinson: initiated the research, analysed the data and wrote the manuscript.

Stanley Pang: generated the whole-genome sequencing data, analysed the data, produced the figure and reviewed the manuscript.

David John Speers, Terillee Keehner, Anthony David Keil, Victoria D'Abrera, Peter Boan, Geoffrey Wallace Coombs: analysed the data and reviewed the manuscript.

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Research article

Clinical implications of *Mycobacterium chimaera* detection in thermoregulatory devices used for extracorporeal membrane oxygenation (ECMO), Germany, 2015 to 2016

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Mycobacterium chimaera, a non-tuberculous mycobacterium, was recently identified as causative agent of deep-seated infections in patients who had previously undergone open-chest cardiac surgery. Outbreak investigations suggested an aerosol-borne pathogen transmission originating from water contained in heater-cooler units (HCUs) used during cardiac surgery. Similar thermoregulatory devices are used for extracorporeal membrane oxygenation (ECMO) and *M. chimaera* might also be detectable in ECMO treatment settings. We performed a prospective microbiological study investigating the occurrence of *M. chimaera* in water from ECMO systems and in environmental samples, and a retrospective clinical review of possible ECMO-related mycobacterial infections among patients in a pneumological intensive care unit. We detected *M. chimaera* in 9 of 18 water samples from 10 different thermoregulatory ECMO devices; no mycobacteria were found in the nine room air samples and other environmental samples. Among 118 ECMO patients, 76 had bronchial specimens analysed for mycobacteria and *M. chimaera* was found in three individuals without signs of mycobacterial infection at the time of sampling. We conclude that *M. chimaera* can be detected in water samples from ECMO-associated thermoregulatory devices and might potentially pose patients at risk of infection. Further research is warranted to elucidate the clinical significance of *M. chimaera* in ECMO treatment settings.

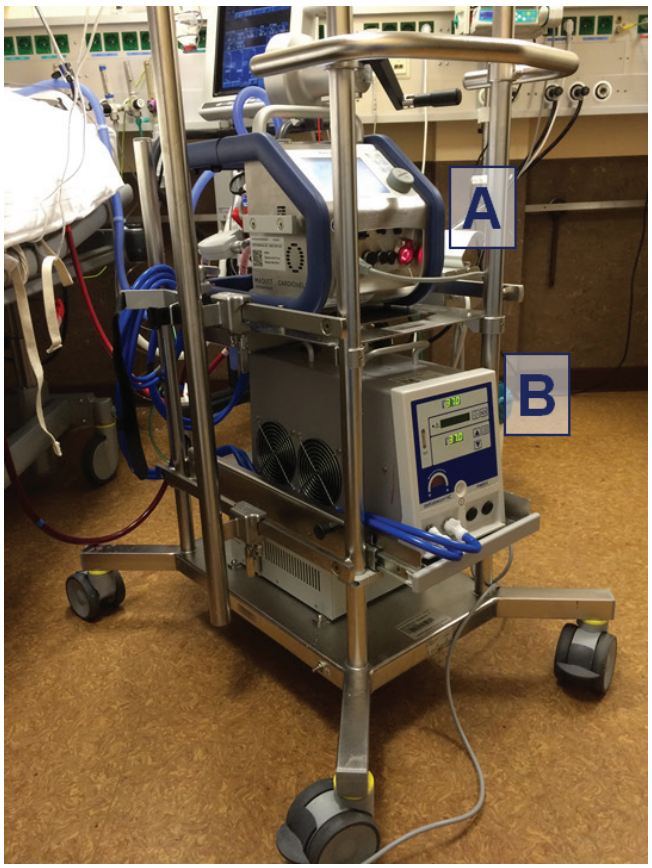
Introduction

Mycobacterium chimaera is a slowly growing atypical mycobacterium that is closely related to the more commonly encountered species *M. avium* and *M. intracellulare* [1]. The potential of *M. chimaera* to cause clinical disease was previously considered to be low [2,3], however, a multi-country outbreak of severe infections due to *M. chimaera* was recently described in patients who had undergone open-chest cardiac surgery [4]. Indeed, *M. chimaera* was identified as the causative agent of deep-seated infections such as endocarditis and vertebral osteomyelitis in patients from different European countries (e.g. Germany, the Netherlands, Switzerland) [5,6] and from North America [7]. Interestingly, these infections occurred up to 5 years after the patients had been exposed to cardiothoracic surgical procedures, during which heater-cooler units (HCUs) were used.

Atypical mycobacteria can be detected in household water [8] and water-containing medical devices [9-11], and it had thus been suggested that the HCUs, which use water for thermoregulation during cardioplegia, might constitute the common source of the recent outbreak [12]. Indeed, an air-borne transmission of M. *chimaera*

Figure 1

The functional set-up of an ECMO treatment unit, consisting of (A) an ECMO system; and (B) a thermoregulatory device at a medical intensive care unit, Homburg/Saar, Germany



ECMO: extracorporeal membrane oxygenation.

in the operating room was confirmed [13] and a report by Haller et al. provided evidence that at least some of the HCUs might already have been contaminated at the manufacturing site [14]. Preventive measures to reduce the risk of transmission during cardiac surgery are now being implemented worldwide. Meanwhile, it remains to be elucidated whether other water-containing medical devices might also pose patients at risk of acquiring infections due to *M. chimaera*.

Veno-venous extracorporeal membrane oxygenation (ECMO) is an established treatment for patients with severe acute respiratory distress syndrome (ARDS) [15,16]. Additionally, veno-arterial circuit configurations offer a prolonged circulatory support, which is comparable to the short-term support provided by cardiopulmonary bypass (CPB) during cardiac surgery [17-20]. All extracorporeal circuits (ECC) consist of a tubing system, which is connected to a roller or centrifugal pump to maintain the active blood transport and guides the flow through the membrane oxygenator. Control units are used to adjust the blood flow between 2 and 7 L per minute. Thermoregulatory devices, heater units (HUs) or HCUs are engaged to adjust the blood temperature within the ECC [21]. All commercially available thermoregulatory systems run in analogy to those used in the operating room with circulating water. Hence, it may be hypothesised that ECMO treatment might also constitute a risk for transmission of water-borne pathogens. While patients treated with ECMO for respiratory failure have smaller potential entry sites for pathogens than those undergoing open-chest heart surgery, they are nevertheless critically ill and highly immunocompromised, and are thus susceptible to opportunistic infections. Additionally, as patients may be subjected to ECMO treatment for a prolonged duration of up to several months [22,23], there is a need to assess their potential exposure to water-borne pathogens such as *M. chimaera* in thermoregulatory devices used for ECMO.

Here, we present an in-depth assessment on the occurrence of *M. chimaera* in an ECMO centre in Germany, with a particular focus on potential mycobacterial transmission pathways and the clinical significance arising from our findings. Our investigation comprises two specific parts, i.e. (i) a prospective microbiological sampling of water from ECMO devices and from the environment for *M. chimaera* (August 2015–August 2016); and (ii) a retrospective patient chart analysis to identify potentially exposed individuals with positive *M. chimaera* culture results and previous ECMO treatment (April 2010–June 2016).

Methods

Study site and study procedures

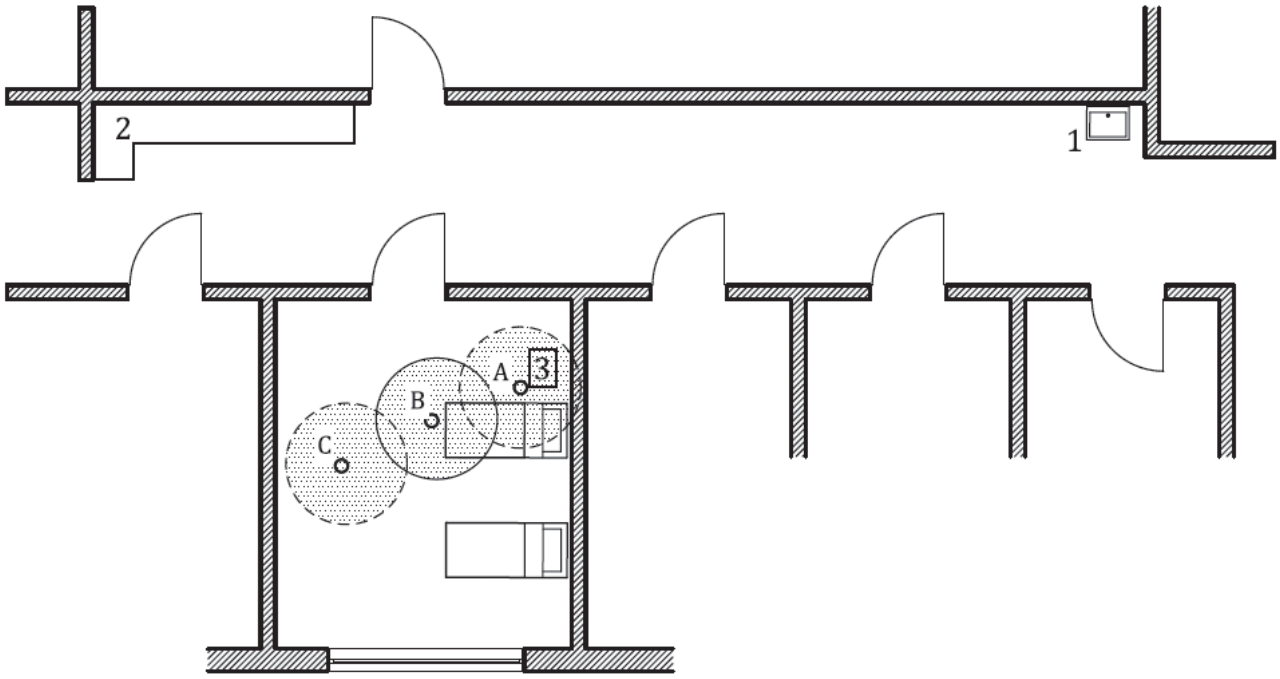
The current study was carried out at the pneumological intensive care unit (ICU) at Saarland University Medical Center in Homburg, southwest Germany. This medical centre is a supra-regional ECMO centre and provides approximately 20 lung transplantations per year. Microbiological investigations pertaining to the presence of atypical mycobacteria in HCUs used during cardiac surgery were initiated in March 2015, and the prospective sampling of water from devices used for ECMO treatment was subsequently started in August 2015. Prompted by these microbiological investigations, a retrospective patient chart review of individuals treated with ECMO at our centre in the preceding 6 years was initiated in mid-2016 to further assess the significance of *M. chimaera* in this specific setting.

Characteristics of extracorporeal circuits and thermoregulatory devices

During the study period, veno-venous ECMO cannulation was performed using the femoral (draining) and jugular (return) veins as main cannula entry sites. As a standard, we used 23 F draining cannulae at a length of 38 or 55 cm, as appropriate, and 19 F returning cannulae (Maquet Holding B.V. and Co. KG, Rastatt, Germany) with a heparin coating. Some patients underwent single stage cannulation using a bicaval double-lumen cannula (27 F or 31 F Avalon Elite, Avalon Laboratories; Rancho Dominguez, United States of

Figure 2

Ground plan of the intensive care unit, Homburg/Saar, Germany



ECMO: extracorporeal membrane oxygenation.

The figure schematically shows the floor with the individual patient rooms where sampling took place. Water for thermoregulatory devices was taken from a sink (1) on the ward. The sink is equipped with a Pall Aquasafe filter to avoid microbial contamination. The filter is changed every 30 days, as recommended by the manufacturer. ECMO units are primed with sterile saline solution in the priming area (2). The ECMO machine and the thermoregulatory device are installed at the bedside (3) of the patient. Water samples were taken from the tap (1) and from the thermoregulatory devices. Air sampling took place (A) next to the ECMO device; (B) next to the patient; and (C) at 2–3 m distance from the patient and the ECMO device, but in the same room.

America). Standard oxygenators were 7.0L-HLS or Quadrox-I with a ROTAFLOW Centrifugal Pump RF 32 primed with physiological saline solution used on the Maquet CardioHelp or ROTAFLOW platform. Different thermoregulatory devices were used according to individual requirements; heater units such as 'Heater Unit HU 35' (Maquet) or HCUs such as 'Deltastream HC' (Medos Medizintechnik AG; Stolberg, Germany) and 'NovaTherm' (Novalung GmbH; Heilbronn, Germany). The functional set-up of an ECMO system with a heater unit is shown in Figure 1.

All thermoregulatory devices were temporarily leased from the manufacturers and filled with filtered tap water (Aquasafe filter AQ31F1S, PALL Corporation; Dreieich, Germany; filter width: 0.2 µm). The priming of all circuits and corresponding thermoregulatory devices was performed within a central priming area and the devices were then placed bedside while being used. A schematic diagram of these operational areas is shown in Figure 2.

Processing and microbiological analysis of water from ECMO devices, tap water and environmental samples

For investigation of atypical mycobacteria, 100–250 mL of water were collected from the water tanks of thermoregulatory devices used for ECMO treatment, and were processed according to a protocol issued by the European Centre for Disease Prevention and Control (ECDC) [24]. In brief, water samples were concentrated by centrifugation and subsequently decontaminated using N-acetyl-L-cysteine sodium hydroxide (NALC-NaOH). Additional examinations were carried out on filtered tap water (filter width 0.2 µm) that was used to fill the tanks of the ECMO devices. Of note, the tap water used is also regularly checked for compliance with the German drinking water directive [25]. Microscopy using auramine staining was carried out on all samples, and water samples were plated on two different media, i.e. (i) 7H11 Middlebrook agar; and (ii) Löwenstein-Jensen agar. Additionally, cultures in liquid media were also performed and water samples were inoculated into the MGIT 960 system. All culture media were obtained

Table 1

Mycobacterial testing characteristics of water samples from thermoregulatory devices used for ECMO treatment at a pneumological intensive care unit, Germany, 2015–2016

Patient (n = 18)	Thermoregulatory device (n = 10)	Device model (Manufacturer)	Sampling date	Microscopy	Culture	Species identification
1	1	Deltastream HC (Medos)	August 2015	**Positive (+ + +)**	**Positive**	*M. chimaera*
2	2	Deltastream HC (Medos)	August 2015	Negative	**Positive**	*M. chimaera*
3	3	HU35 (Maquet)	December 2015	Negative	Negative	–
4	4	Deltastream HC (Medos)	January 2016	Negative	Negative	–
5	5	Deltastream HC (Medos)	January 2016	**Positive (+)**	**Positive**	*M. chimaera*
6	4	Deltastream HC (Medos)	January 2016	Negative	**Positive**	*M. chimaera*
7	6	Deltastream HC (Medos)	January 2016	Negative	Negative	–
8	7	HU35 (Maquet)	January 2016	Negative	Negative	–
9	4	Deltastream HC (Medos)	March 2016	**Positive (+)**	**Positive**	*M. chimaera* and *M. gordonae*
10	8	NovaTherm (NovaLung)	March 2016	Negative	Negative	–
11	9	Deltastream HC (Medos)	March 2016	Negative	Negative	–
12	4	Deltastream HC (Medos)	March 2016	**Positive (+ + +)**	**Positive**	*M. chimaera*
13	6	Deltastream HC (Medos)	March 2016	Negative	Negative	–
14	9	Deltastream HC (Medos)	April 2016	Negative	Negative	–
15	6	Deltastream HC (Medos)	April 2016	Negative	**Positive**	*M. chimaera*
16	8	NovaTherm (Novalung)	April 2016	Negative	**Positive**	*M. chimaera*
17	9	Deltastream HC (Medos)	August 2016	**Positive (+ +)**	**Positive**	*M. chimaera*
18	10	Deltastream HC (Medos)	August 2016	Negative	Negative	–

ECMO: extracorporeal membrane oxygenation; M: *Mycobacterium*.

For microscopy of auramine-stained slides, the following semi-quantitative grading scheme was adopted: (i) negative (no mycobacteria seen on the microscope slide); (ii) + (up to 50 mycobacteria seen per 100 observation fields); (iii) ++ (5-50 mycobacteria seen per 10 observation fields); and (iv) +++ (≥5 mycobacteria seen per observation field).

from Becton Dickinson (Heidelberg, Germany) and were incubated for up to 8 weeks.

Environmental room air sampling was carried out in patient rooms during ECMO treatment while thermoregulatory devices, which had previously tested positive for *M. chimaera*, were running. For each sampling, 100–200 L of room air was collected using the MBASS 30 microbiological air sampling system (Umweltanalytik Holbach GmbH; Holbach, Germany) and conducted over selective 7H10 Middlebrook agar plates during one minute. During each sampling, air specimens were taken at three different locations, i.e. (i) next to the ECMO device; (ii) next to the patient; and (iii) in 2–3 m distance from the patient and the ECMO device, but in the same room. Additionally, swabs (eSwab, Copan Diagnostics; Brescia, Italy) were taken once from the surface and connecting tubes of selected ECMO thermoregulatory devices, and were subsequently analysed for the presence of mycobacteria. All agar plates were examined twice weekly during eight weeks for signs of mycobacterial growth. Suspicious colonies were identified to the species level using a commercially available molecular typing system (GenoType NTM-DR, Hain Lifescience; Nehren, Germany). Additionally, a subsample of positive specimens was sent to a reference centre for molecular diagnostics at the University Hospital Regensburg, Germany, where the species identification of *M. chimaera* was confirmed by partial sequencing of the 16S, ITS and *rpoB* gene sequences.

Retrospective patient analysis and microbiological work-up of patient samples

Using an electronic database, we retrospectively identified all patients undergoing ECMO treatment (excluding extracorporeal CO2 removal; ECCO2R) at the pneumological ICU at Saarland University Medical Center between April 2010 and June 2016.

Respiratory samples were taken if clinical signs and symptoms of respiratory infection were present and/or whenever a potential infection was clinically suspected. Bronchial specimens obtained during or after ECMO treatment were reviewed both clinically and microbiologically for findings suggestive of mycobacterial infection.

Due to the retrospective nature of the analysis, no specific protocol was implemented before the start of the study for the microbiological work-up of patient samples. Standard diagnostic procedures were followed and bronchial aspirates and bronchoalveolar lavage specimens of patients undergoing ECMO treatment were immediately sent to the microbiology laboratory using a pneumatic transport system. Upon receipt at the laboratory, samples were decontaminated using

Table 2

Characteristics and clinical course of patients diagnosed with *Mycobacterium chimaera* in respiratory specimens while treated with ECMO at a pneumological intensive care unit, Germany, 2010–2016 (n=3)

Patient number	Sex	Age (years)	Underlying disease and operative intervention	Indication for ECMO	Time of ECMO treatment (days)	Risk factor for *M. chimaera*	Days from ECMO treatment onset to sampling for *M. chimaera*	Clinical course
1	Male	Mid 70s	CTEPH, PEA and CABG	ARDS	48	Previous open-chest cardiac surgery	5	Died on ECMO (cardiogenic shock)
2	Male	End 20s	AML, allogenic SCT	GVHD	113	None	6	Died on ECMO (septic shock)
3	Female	Early 30s	CF, LTx, CLAD	ARDS	40	Previous open-chest cardiac surgery	205	Survived (re-LTx)

AML: acute myeloid leukaemia; ARDS: acute respiratory distress syndrome; CABG: coronary artery bypass grafting; CF: cystic fibrosis; CLAD: chronic lung allograft dysfunction; CTEPH: chronic thromboembolic pulmonary hypertension; ECMO: extracorporeal membrane oxygenation; GVHD: graft vs. host disease; LTx: lung transplantation; PEA: pulmonary endarterectomy; re-LTx: lung retransplantation; SCT: stem cell transplantation.

NALC-NaOH and mycobacterial examinations were carried out as follows: (i) microscopy using Kinyoun or auramine staining; (ii) MGIT 960 liquid media culture; and (iii) culture on solid agar media (Löwenstein-Jensen agar; Stonebrink agar). All patient samples were incubated for up to 8 weeks and mycobacteria were identified as described above.

Species identification of *M. chimaera* had not uniformly been performed between 2010 and 2015, thus all isolates that had previously been identified as either *M. intracellulare* or *M. avium* were re-cultured from a biobank and subjected to molecular genetic testing for unambiguous species identification.

Results

Detection of *Mycobacterium chimaera* in water and air samples

Between August 2015 and August 2016, a total of 18 water samples originating from 10 different thermoregulatory devices used for ECMO treatment were subjected to microbiological analyses. *M. chimaera* was detected in nine specimens i.e. half of all examined water samples. Of the ten analysed thermoregulatory devices, water obtained from seven tested positive in at least one sample. In five water samples, mycobacteria were visible by microscopy, which suggests presence of a relatively high number of mycobacteria. The liquid medium culture (MGIT) was earliest to give positive results in all cases, after approximately 2 weeks of incubation (10–16 days). In one water sample which tested positive for *M. chimaera*, a co-colonisation with *M. gordonae* was observed. Details on the microbiological test results are given in Table 1.

Filtered tap water, which was commonly used to fill the thermoregulatory devices for ECMO treatment, was subjected to microbiological examinations at three different time points (several weeks apart), but neither bacterial nor mycobacterial pathogens were detected.

When analysing nine room air samples from the pneumological ICU, no atypical mycobacteria and no non-fermentative Gram-negative rods were detected during 8 weeks of incubation. Of note, some specimens contained low quantities of environmental Gram-positive (e.g. *Arthrobacter* spp., *Bacillus subtilis*, *Corynebacterium amycolatum* and *Micrococcus luteus*) and Gram-negative bacteria (e.g. *Moraxella osloensis*). Environmental moulds (e.g. *Penicillium citrinum*) were also found.

A series of 12 swabs taken from different surfaces and connecting tubes of two running ECMO thermoregulatory devices remained uniformly negative for *M. chimaera*.

Occurrence of *Mycobacterium chimaera* in patients treated with ECMO

We reviewed the electronic charts of all 118 patients who had received ECMO support between April 2010 and June 2016. Bronchial specimens (bronchial aspirates and/or bronchoalveolar lavage samples) from 79 patients (67.0%) were analysed for the presence of mycobacteria during or after ECMO therapy. All patients received respiratory ECMO support either due to severe ARDS or as a temporary ‘bridging procedure’ to planned lung transplantation. A total of 32 of 79 (40.5%) patients were male and the mean age was 46.8 years (standard deviation (SD): 16.7 years). The mean duration of ECMO treatment was 20.2 days (SD: 46.6 days), and 58.3% of the analysed patients survived to discharge.

Mycobacteria were observed upon microscopy (auramine staining) in bronchial specimens from one individual among the 79 patients. In three cases, mycobacterial cultures were bacterially contaminated and could not be analysed, thus leading to a final cohort of 76 patients with mycobacterial culture results after the onset of ECMO treatment. Cultures for mycobacteria were positive in four patients and the mycobacterial species were identified as *M. chimaera* in three and *M. malmoense* in one of them. The three cases of *M. chimaera* were critically reviewed to investigate the possible clinical significance of this finding. Brief descriptions on the patient characteristics are given below and in Table 2.

Patient 1

In 2010, a man in his mid-70s developed severe acute respiratory distress syndrome (ARDS) and received ECMO therapy after pulmonary endarterectomy and coronary artery bypass grafting had been performed as treatment for chronic thromboembolic pulmonary hypertension and coronary heart disease. Eight days before ECMO initiation, the patient was screened for mycobacteria and was negative. On day 5 with ECMO support, a bronchial specimen was obtained that yielded *M. chimaera*. The patient died in cardiogenic shock after 48 days of ECMO treatment.

Patient 2

In 2013, a man in his late 20s underwent allogenic stem cell transplantation for acute myeloid leukaemia, which he developed after treatment of Hodgkin's lymphoma with thymic infiltration. The patient developed graft vs. host disease with pulmonary involvement. Due to progressive respiratory failure, he was treated with ECMO with the intention to bridge the time to lung transplantation. After 6 days with ECMO, a bronchial aspirate was sent to the laboratory and *M. chimaera* was found once, but not in follow-up examinations 2 and 4 weeks later. Some weeks later, the patient was temporarily treated with clarithromycin, rifampicin, ethambutol and moxifloxacin for a clinically suspected mycobacterial infection. The patient died 113 days after initiation of ECMO therapy in septic shock with bacteraemia due to *Enterococcus faecium*.

Patient 3

A woman in her 30s with cystic fibrosis developed a restrictive chronic allograft dysfunction with consecutive lung failure after previous lung transplantation. Hence, she was treated with ECMO in October 2014 and re-transplanted after 40 days with extracorporeal support. She had multiple bronchial aspirates being sampled for the presence of mycobacteria before ECMO (last sampling 11 days earlier) that were always negative. Two hundred five days after ECMO initiation, *M. chimaera* was detected in a bronchial aspirate. The patient is still alive (›650 days) and her clinical condition is good.

Discussion

In the present single-centre study, *M. chimaera* was detected in a considerable amount of water samples taken from different thermoregulatory devices of two different providers during ECMO treatment. Indeed, half of all analysed specimens grew *M. chimaera*, whereas no mycobacteria were found in room air samples and swabs from ECMO system surfaces. *M. chimaera* was also detected in three ECMO patients in a retrospective analysis over 6 years, but the transmission pathways as well as the clinical relevance of the findings remain uncertain.

M. chimaera was recently described as the causative agent in a multi-country outbreak of severe invasive infections, and pathogen transmission likely occurred through contaminated HCUs used during cardiac surgery [4,5,7,14]. By acknowledging the aetiological role of *M. chimaera* in this outbreak, its clinical relevance had to be reconsidered because previous studies had described *M. chimaera* to be of rather low pathogenicity [26]. Indeed, an analysis of 97 culture isolates from German patients detected a clinical relevance in merely 3.3% of all samples [2], and there is only a limited number of case reports providing evidence of infections due to *M. chimaera* in immunocompromised patients, such as those with severe anorexia nervosa [27], chronic obstructive pulmonary disease [28] and cystic fibrosis [29]. The patients on ECMO treatment described in our report were also immunocompromised and might thus have been at risk of clinical *M. chimaera* infection.

M. chimaera is able to form biofilms and may persist in water samples [8], which may partially explain its long-lasting occurrence in water-containing HCUs used for open-chest cardiac surgery [4,6]. While device contamination during the production process [14] and a subsequent air-borne transmission [13,30,31] have been proposed as transmission pathways for this recent outbreak, the clinical significance of our findings in ECMO devices and the potential risks for patients remain to be elucidated. However, several characteristics seen in our study differ from those observed in connection with cardiac surgery. First, *M. chimaera* was detected in water from two different providers of thermoregulatory devices, thus rendering contamination during the production process of a single, specific device relatively unlikely. Second, an air-borne transmission of *M. chimaera* from the ECMO device to the patient could not be demonstrated. The ECMO-related thermoregulatory devices are, in contrast to HCUs used during cardiac surgery, air-tight and closed systems. In line with this, we did not find any evidence of detectable mycobacteria upon air sampling in patient rooms during ECMO treatment.

It is important to note that the mere diagnosis of an atypical mycobacterium in a bronchial specimen is not necessarily linked to an ongoing infection [32]. Indeed, following careful retrospective patient chart assessment in our study, we consider the detection of

M. chimaera in bronchial aspirates from three patients during or after ECMO treatment not to be evidently associated with the *M. chimaera* contamination of the thermoregulatory devices. Patient 2 of the aforementioned patients, who was highly immunocompromised, suffered from pulmonary graft vs. host disease after allogenic SCT and had not been tested for atypical mycobacteria before ECMO therapy. Thus, it cannot be excluded that he might have already been colonised with atypical mycobacteria before ECMO treatment. In contrast, Patients 1 and 3 had been negative in mycobacterial sputum analyses before ECMO initiation. However, both patients had also been exposed to HCUs during open-chest surgery. Further molecular diagnostics could have helped to further characterise the origin of the *M. chimaera* strains found in these patients, e.g. through molecular analyses comparing their genetic characteristics to those of *M. chimaera* strains detected in water from ECMO devices and HCUs used in cardiac surgery.

ECMO is a life-saving technology, in particular for patients with severe respiratory failure despite maximal medical treatment [16,33,34]. Such patients suffer from comorbidities, are frequently immunocompromised and thus a highly vulnerable population. We therefore recommend that specific investigations for *M. chimaera* should be carried out in more ECMO centres to identify whether this pathogen constitutes a potentially relevant infectious agent in ECMO treatment settings. In our study, we were unable to identify a distinct source of the *M. chimaera* contamination. No mycobacteria were found in the tap water used to fill the thermoregulatory devices, thus rendering a contamination with environmental mycobacteria unlikely. A contamination during the manufacturing process of the thermoregulatory devices cannot be excluded, but seems rather unlikely because devices of different manufacturers were affected. Additionally, cross-contamination from cardiac HCUs used in the operating theatre might also have occurred, e.g. when surgery was performed on ECMO patients and the same oxygenator was used on different thermoregulatory devices.

Our study has several limitations. First, it is a single-centre study with a limited sample size. Yet, our report is the first systematic assessment of *M. chimaera* beyond the setting of cardiac surgery, and therefore provides important additional evidence. Second, our clinical patient analysis is retrospective, mainly due to the fact that we initiated the current study only after the publication of the first outbreak reports related to HCU devices used during cardiac surgery. The retrospective design of our patient chart review might have biased some of our results, specifically pertaining to repeated sampling procedures for *M. chimaera*. Future research on this topic should thus preferably employ a prospective study design. Third, repeated sampling of water from thermoregulatory devices might have further improved the detection rate and more sophisticated microbiological analyses e.g. whole-genome sequencing and comparison of *M. chimaera* isolates obtained from water and patient samples could have elucidated the genetic relatedness of the mycobacterial strains. Fourth, additional microbiological investigations of all water samples pertaining to e.g. *Legionella* spp. and *Pseudomonas* spp. might have helped to better assess the water quality and to better quantify the contamination of the thermoregulatory devices.

Conclusions

Patients receiving ECMO treatment are often highly immunocompromised and prone to opportunistic infections, including those caused by atypical mycobacteria. The detection of *M. chimaera* in a considerable amount of water samples from thermoregulatory ECMO devices in our centre should encourage further research in other hospital centres to elucidate the origin of such contamination. Additionally, the hitherto unclear clinical relevance of *M. chimaera* in the setting of ECMO treatment needs to be assessed. Strict adherence to disinfection protocols published by the manufacturers of thermoregulatory devices as well as continued microbiological surveillance for *M. chimaera* are recommended to minimise the risk of infection.

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Conflict of interest

None declared.

Authors' contributions

Specimen sampling: FCT, US, AK, KH, PML, SLB. Microbiological diagnostics: US, UR, BG, MH, SLB. Clinical patient chart review: FCT, PML. Patient treatment: FCT, AK, HW, RB, PML. Wrote the manuscript: FCT, PML, SLB. All authors have read and approved the final version of the manuscript.

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Prevention of hospital-acquired bloodstream infections through chlorhexidine gluconate-impregnated washcloth bathing in intensive care units: a systematic review and meta-analysis of randomised crossover trials

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We assessed the impact of 2% daily patient bathing with chlorhexidine gluconate (CHG) washcloths on the incidence of hospital-acquired (HA) and central line-associated (CLA) bloodstream infections (BSI) in intensive care units (ICUs). We searched randomised studies in Medline, EMBASE, Cochrane Library (CENTRAL) and Web of Science databases up to April 2015. Primary outcomes were total HABSI, central line, and non-central line-associated BSI rates per patient-days. Secondary outcomes included Gram-negative and Gram-positive BSI rates and adverse events. Four randomised crossover trials involved 25 ICUs and 22,850 patients. Meta-analysis identified a total HABSI rate reduction (odds ratio (OR): 0.74; 95% confidence interval (CI): 0.60–0.90; p = 0.002) with moderate heterogeneity (I^2 = 36%). Subgroup analysis identified significantly stronger rate reductions (p = 0.01) for CLABSI (OR: 0.50; 95% CI: 0.35–0.71; p < 0.001) than other HABSI (OR: 0.82; 95% CI: 0.70–0.97; p = 0.02) with low heterogeneity (I^2 = 0%). This effect was evident in the Gram-positive subgroup (OR: 0.55; 95% CI: 0.31–0.99; p = 0.05), but became non-significant after removal of a high-risk-of-bias study. Sensitivity analysis revealed that the intervention effect remained significant for total and central line-associated HABSI. We suggest that use of CHG washcloths prevents HABSI and CLABSI in ICUs, possibly due to the reduction in Gram-positive skin commensals.

Introduction

Hospital-acquired bloodstream infections (HABSI) and the subgroup of central line-associated bloodstream infections (CLABSI) are associated with substantial morbidity, mortality, and healthcare costs in adults and children [1-5], with higher infection rates among hospitalised children [6]. Data from the EPIC II study have shown that of all nosocomial infections in the intensive care unit (ICU), 15% were bloodstream infections (BSI), with CLABSI accounting for 4.7% [7,8]. Due to the substantial impact on patient outcomes and their preventable nature, reduction of HABSI is the emphasis of several patient safety initiatives [9-11].

CLABSI results from catheter tip contamination by commensal skin flora at time of device insertion and later from microorganisms migrating from skin to the catheter tip or lumen [12]. The risk of CLABSI can be reduced by antiseptic skin preparation immediately before catheter insertion and by maintaining asepsis at insertion site and catheter access points [13]. As a substantial proportion of primary BSI originate from vascular access devices, these infections also decrease following preventive interventions targeting CLABSI [14].

Chlorhexidine gluconate (CHG) has broad antimicrobial action, prolonged residual effect, and is the agent of choice for skin disinfection before catheter insertion [13,15,16]. CHG can also be used in basic hygienic care as a liquid bathing agent or as pre-packaged CHG-impregnated washcloths [17].

A substantial number of studies investigated the value of CHG washcloth patient bathing. Three recent systematic reviews summarised the available evidence concerning colonisation and infection rates [18-20]. Low-quality, non-randomised studies demonstrated mixed effects for prevention of BSI. The effect of CHG-impregnated washcloths on hard outcomes such

Box 1

Systematic Review Protocol

Inclusion criteria
• Randomised controlled trials
• Adult ICU population
• Paediatric ICU population
• Neonatal ICU population
• Intervention arm including patient bathing with CHG washcloths
• Control arm including other standard bathing procedures (not with CHG or other antiseptic)
• Records investigating impact of intervention in HABSI and CLABSI
• Full text available
Exclusion criteria
• Descriptive studies
• Before-and-after design
• Evidence of confounders such as other interventions implemented at the same time as CHG washcloth bathing (i.e. care bundles)
• Comparative studies
• Reviews, systematic reviews and meta-analysis
• Studies that did not use CHG in the form of washcloths

CHG: chlorhexidine gluconate; CLABSI: central line-associated bloodstream infection; HABSI: hospital-acquired bloodstream infection; ICU: intensive care unit.

as rates of HABSI and CLABSI in both adult and paediatric ICU patients remains unclear. We performed a systematic review and meta-analysis of randomised-controlled trials to assess the impact of daily care with CHG washcloths on rates of total HABSI and CLABSI in adult and paediatric ICU patients. Subgroup analysis identified the impact on Gram-positive and Gram-negative microorganisms.

Methods

Search strategy

The Medline, EMBASE, Cochrane Library and Web of Science databases were systematically searched using combinations of the key terms 'chlorhexidine', 'chlorhexidine impregnated washcloths', 'neonatal', 'paediatric' 'intensive care unit', 'bloodstream infection', 'catheter related infection' and 'randomised controlled trial' (Box 1-2, Figure 1). The search strategy included publications until end of April 2015. No predefined review protocol was registered.

Study selection

Eligible studies included randomised trials done in adult, paediatric and neonatal ICUs that compared the impact of daily bathing with CHG washcloths with that of non-antiseptic impregnated washcloths or other standard bathing procedures on HABSI rates. Languages were restricted to English, French, Dutch and Portuguese. The primary outcome measure was number of HABSIs per patient-days. One reviewer performed study selection and consensus was achieved between two reviewers. Search results were screened by title and abstract. Selected papers underwent a full-text assessment and eligibility issues were resolved between reviewers (EA, KB, SB).

Data extraction and quality assessment

Extracted data included study setting, design and sample size, implemented interventions, definitions and primary outcome data on rates of CLABSI and HABSI per patient-days in the treatment and control groups from the intention-to-treat populations. Data were manually calculated when necessary. Secondary outcome measures included Gram-positive and Gram-negative aetiology, study-related adverse events and number of catheter-days and patients. When available, the protocols were examined for discrepancies between original study objectives and the published data. Two independent reviewers performed data extraction and independently assessed the methodological quality of included studies using the Cochrane risk-of-bias assessment tool (EA, KB) [21].

Statistical analysis

A random-effects meta-analysis using the inverse variance method obtained odds ratios (OR) and 95% confidence intervals (CI) for total HABSI rates per 1,000 patient-days. A random-effects model was chosen to encompass clinical heterogeneity in baseline standards of care between ICUs. Heterogeneity was predefined and assessed through the I2 test ($I2 \leq 25\%$ for low, $25\% < I2 < 50\%$ for moderate and $I2 \geq 50\%$ for high). Predefined subgroup analysis and meta-regression were performed on HABSI subtype (CLABSI and non-central line HABSI) and pathogen subtype (Gram-negative and Gram-positive). Sensitivity analysis assessed the impact of varying incidence rate denominator data (number of catheter-days and patients) and the removal of studies with a high risk of bias. Assessment of publication bias by funnel plot was planned when considered meaningful (i.e. at least 10 studies included). Review Manager version 5.2.0 was used for meta-analysis models and Comprehensive Meta Analysis version 2.0 was used to perform meta-regression. A p value ≤ 0.05 was considered statistically significant.

Results

The search strategy yielded 291 records. Following title, abstract and full-text assessment, four papers were included for meta-analysis (Figure 2) [22-25], and one study was excluded because it had an inappropriate

Box 2

Search terms used for study selection

1. MEDLINE search (181 titles found, 7 without accessible full text, 159 excluded, 18 duplicates, 4 eligible studies)

- Chlorhexidine impregnated washcloths AND catheter related bloodstream infection
- Chlorhexidine impregnated washcloths AND bloodstream infection
- Chlorhexidine[MeSH Terms] AND infection transmission[MeSH Terms] AND care units, intensive[MeSH Terms]
- Chlorhexidine[MeSH Terms] AND bath[MeSH Terms] AND pediatric intensive care units[MeSH Terms]
- Chlorhexidine[MeSH Terms] AND bath[MeSH Terms] AND intensive care unit[MeSH Terms]
- Chlorhexidine[MeSH Terms] AND care, neonatal intensive[MeSH Terms]
- Chlorhexidine[MeSH Terms] AND care unit, intensive[MeSH Terms] AND catheter related infection[MeSH Terms]
- Chlorhexidine wash[MeSH Terms] AND BSI
- Chlorhexidine impregnated AND CLABSI
- Chlorhexidine impregnated AND BSI
- Chlorhexidine impregnated AND Pediatric
- Chlorhexidine impregnated AND Neonatal
- Randomized controlled trial[Publication Type]) AND ICU AND Chlorhexidine
- Randomized controlled trial[Publication Type] AND intensive care unit) AND chlorhexidine impregnated
- Chlorhexidine[MeSH Major Topic] AND randomized controlled trial[Publication Type] AND ICU

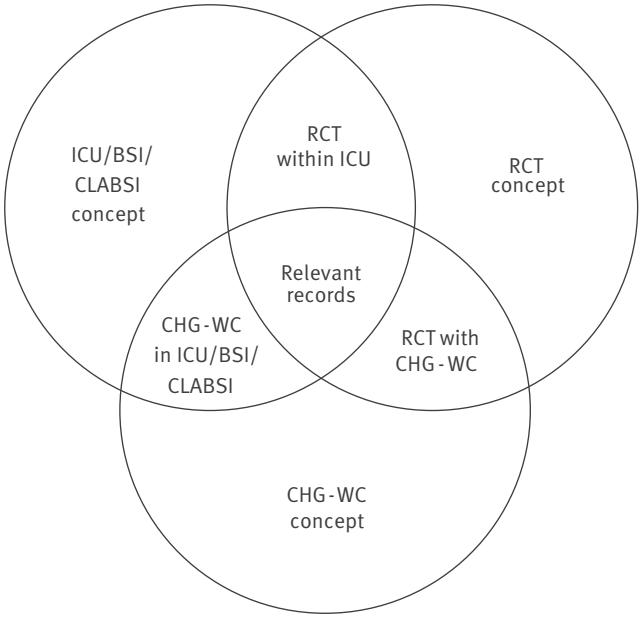
2. EMBASE search (14 titles found, 12 excluded, 2 duplicates)

- Bath/ and *chlorhexidine gluconate/ and intensive care unit/
- Chlorhexidine washcloths and intensive care unit).af
- Chlorhexidine washcloths and neonatal).af
- Randomized controlled trial.pt. and chlorhexidine washcloths.af
- 3 Web of Science search (81 studies found, 78 excluded, 3 duplicates)
- TS=(chlorhexidine AND wash*) AND TS=(intensive care unit)
- TS=(chlorhexidine AND wash*) AND TS=(pediatric)
- TS=(chlorhexidine AND wash*) AND TS=(neonatal intensive care)
- TS=(chlorhexidine AND wash*) AND TS=(BSI)
- TS=(chlorhexidine AND wash*) AND TS=(CLABSI)
- 4. Cochrane Library search (15 titles found, 7 excluded, 8 duplicates)
- 'Randomized* in Publication Type AND chlorhexidine wash* AND "intensive care unit" NOT "oral"NOT "hand" in Trials'
- 'Randomized* in Publication Type and chlorhexidine bath* and Intensive Care Unit in Trials'
- 'Randomized* in Publication Type and chlorhexidine bath* and "intensive care unit" and "neonatal" in Trials'
- 'Randomized* in Publication Type and chlorhexidine bath* and "intensive care unit" and "BSI" in Trials'
- 'Randomized* in Publication Type and chlorhexidine washcloth and "intensive care unit" in Trials'

BSI: bloodstream infection; CLABSI: central line-associated bloodstream infection; HABSI: hospital-acquired bloodstream infection; ICU: intensive care unit.

Figure 1

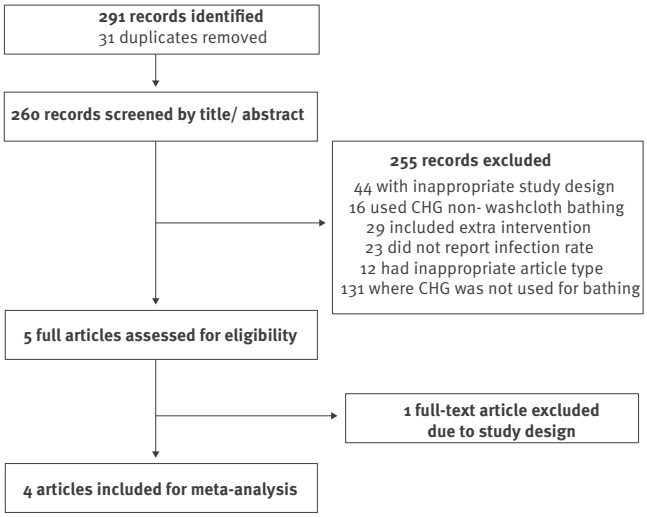
Study selection according to online databases



BSI: bloodstream infection; CHG-WC: chlorhexidine gluconate washcloth; CLABSI: central line-associated bloodstream infection; ICU: intensive care unit; RCT: randomised controlled trial.

Figure 2

Summary of literature search and study selection (n = 291)



CHG: chlorhexidine gluconate.

non-randomised study design. The included studies were non-blinded cluster-randomised crossover trials involving, together, 22,850 patients from 15 adult and 10 paediatric ICUs (Table 1). The treatment group included daily patient bathing with 2% CHG washcloths. Control groups applied daily bathing with non-antiseptic impregnated washcloths or other non-medicated standard bathing procedures in ICUs with comparable baseline infection rates.

The four included studies compared daily 2% CHG washcloth patient bathing with a control arm applying washcloths not impregnated with CHG: non-medicated washcloths [22,23], soap and water [24] or not further specified non-medicated standard bathing procedures [25]. Climo et al. performed their study in nine medical adult ICUs and bone marrow transplantation units [22] and Bleasdale et al. performed a single-centre study in a medical ICU [24]. Milstone et al. studied the intervention impact in 10 paediatric ICUs [25]. Noto et al. selected five adult ICUs in the same institution (cardiac, trauma, neurological, medical and surgical) [23]. Total HABSI rates in the control arm were comparable between the three multicenter studies (5.5–6.6 HABSI per 1,000 patient-days) [22,23,25], with one study reporting twice larger infection rates (12.2 HABSI per 1,000 patient days) in a single ICU [24]. The rates of CLABSI in the control arm varied per study between 0.19 [23], 1.7 [22,25] and 9.9 CLABSI per 1,000 patient days [24].

All 25 units were randomly assigned to either a treatment or a control group. Duration of study period was 10 weeks [23], 6 months [22,25], and 6 or 7 months in both control and treatment groups [24]. Three of the four studies applied washout phases between control and treatment study periods, lasting two [23,24] or six weeks [25]. The study by Climo et al. did not include a washout phase between intervention and control study periods [22]. Three of the studies reported that nurses received training on how to perform bathing and how to identify adverse events related or unrelated to the treatment [22,24,25]. All four trials were non-blinded to patients, caregivers and staff.

Climo et al., Bleasdale et al. and Noto et al. included all admitted adult patients in the ICUs who agreed to participate except those with adverse skin conditions [22-24]. Eight patients refused to participate in the study by Climo et al. and were not included in the final analysis [22]. Bleasdale et al. excluded three patients who lacked skin integrity, declined participation or developed a skin rash. However, these patients were included in the final intention-to-treat analysis [24]. Milstone et al. used an intention-to-treat approach when selecting paediatric patients for analysis. All children admitted in the paediatric ICU were eligible for this study except those younger than two months, those with a present epidural or lumbar drain, skin disease, burns or CHG allergy or those without parental consent. The intention-to-treat population included all children older than two months with an informed consent to participate, whereas the per-protocol population included all the children who received treatment and were not excluded because of adverse reactions [25]. Finally, Noto et al. stated that all admitted patients were randomised and patients admitted during the washout periods were excluded [23].

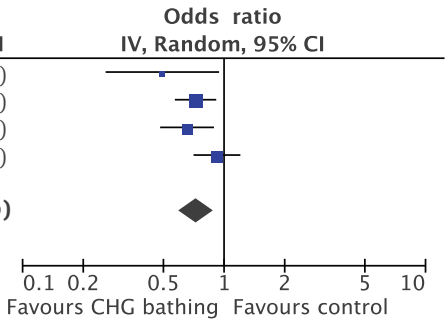
Figure 3

Meta-analysis of the impact of chlorhexidine gluconate washcloth bathing on total rate of hospital-acquired bloodstream infections per patient-days (n = 4 studies)

Study or subgroup	CHG bathing Events	Total	Control Events	Total	Weight	Odds ratio IV, Random, 95% CI
Bleasdale 2007	14	2,210	27	2,119	8.2%	0.49 (0.26 – 0.94)
Climo 2013	119	24,931	165	25,000	35.0%	0.72 (0.57 – 0.91)
Milstone 2013	66	15,057	107	16,024	26.0%	0.65 (0.48 – 0.89)
Noto 2015	100	19,202	117	20,721	30.7%	0.92 (0.71 – 1.20)
Total		**61,400**		**63,864**	**100.0%**	**0.74 (0.60–0.90)**
Total events	299		416			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.72$, df = 3 (p = 0.19); $I^2 = 36\%$

Test for overall effect: Z = 3.04 (p = 0.002)



CHG bathing: chlorhexidine-impregnated washcloth bathing; CI: confidence interval; control: bathing with non-impregnated washcloths.

Figure 4

Subgroup analysis of rates of central line-associated bloodstream infection and non-central line-associated hospital-acquired bloodstream infection per patient days (n = 4 studies)

Study or subgroup	CHG bathing Events	Total	Control Events	Total	Weight	Odds ratio IV, Random, 95% CI
1.7.1 CLABSI						
Bleasdale 2007	9	2,210	21	2,119	20.1%	0.41 (0.19 – 0.89)
Climo 2013	21	24,931	43	25,000	45.1%	0.49 (0.29 – 0.82)
Milstone 2013	13	15,057	28	16,024	28.4%	0.49 (0.26 – 0.95)
Noto 2015	4	19,202	4	20,721	6.4%	1.08 (0.27 – 4.32)
Subtotal		**61,400**		**63,864**	**100.0%**	**0.50 (0.35 – 0.71)**
Total events	47		96			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.45$, df = 3 (p = 0.69); $I^2 = 0\%$

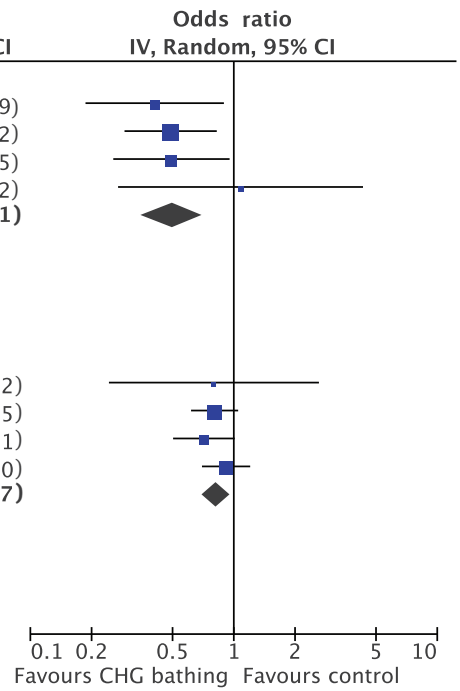
Test for overall effect: Z = 3.90 (p < 0.0001)

1.7.2 Non-central line BSI						
Bleasdale 2007	5	2,210	6	2,119	1.9%	0.80 (0.24 – 2.62)
Climo 2013	98	24,931	122	25,000	38.6%	0.80 (0.62 – 1.05)
Milstone 2013	53	15,057	79	16,024	22.6%	0.71 (0.50 – 1.01)
Noto 2015	96	19,202	113	20,721	36.9%	0.92 (0.70 – 1.20)
Subtotal		**61,400**		**63,864**	**100.0%**	**0.82 (0.70 – 0.97)**
Total events	252		320			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.28$, df = 3 (p = 0.73); $I^2 = 0\%$

Test for overall effect: Z = 2.33 (p = 0.02)

Test for subgroup differences: $Chi^2 = 6.41$, df = 1 (p = 0.01), $I^2 = 84.4\%$

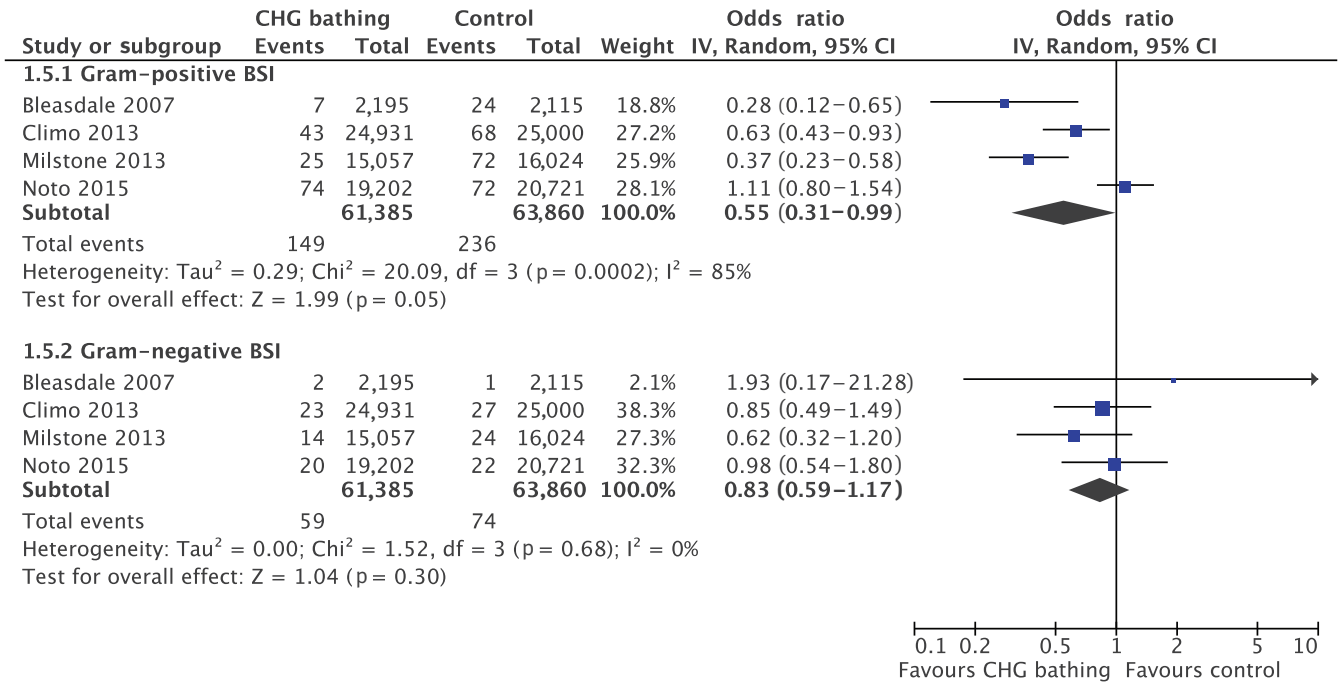


BSI: bloodstream infection; CHG bathing: chlorhexidine-impregnated washcloth bathing; CI: confidence interval; CLABSI: central line-associated bloodstream infection; control: bathing with non-impregnated washcloths.

Climo et al. and Noto et al. defined primary HABSI as a BSI detected at least 48 hours after admission without an attributable secondary source of infection. Bleasdale et al. used the 1988 definitions from the United States Centers for Disease Control and Prevention (CDC) for nosocomial infections for HABSI and CLABSI [26]. These criteria require catheter cultures to define central line bloodstream infections, as opposed to more recent CLABSI definitions of a HABSI occurring in in a patient with a central line (within 48 hours) with no other clear infectious source. Climo et al. and Noto et al. applied the CDC and National Healthcare Safety Network (NHSN) definitions for CLABSI and HABSI [27]. Noto et al. reported combined primary and secondary HABSI rates. Milstone et al. likewise applied CDC/NHSN definitions, however they defined their bloodstream infections by any single positive blood culture, including for commensal skin microorganisms [25]. The authors justified the adjusted definition criteria by stating that morbidity from bacteraemia is significant

Figure 5

Subgroup analysis of rates of hospital-acquired Gram-positive and Gram-negative bloodstream infections per patient days (n = 4 studies)



BSI: bloodstream infection; CHG bathing: chlorhexidine-impregnated washcloth bathing; CI: confidence interval; control: bathing with non-impregnated washcloths.

Noto et al. reported microorganism data on combined primary and secondary hospital-acquired bloodstream infection [23].

in critically ill children. Microorganisms identified as Gram-positive or Gram-negative were isolated from combined primary BSI and CLABSI [22,24,25] or from total HABSI [23].

Three studies evaluated study-related adverse events associated with the use of CHG washcloths [22,24,25], but none reported serious adverse events. Milstone et al. specified the occurrence of skin reactions in 69 (2%) patient admissions, with a greater percentage occurring in the treatment group than in the control group (n = 43 (3%) vs n = 26 (1%); p<0.0001). Only 28% (12/43) of these reactions were considered to be due to CHG washcloths. Crude incidence of CHG-related adverse events was 1.12 per 1,000 patient-days (95% CI: 0.06–2.02) [25]. One study found a higher overall incidence of skin reactions in the control group (n=130 (3.4%)) rather than the intervention arm (n=78 (2%)), with all reactions considered not related to the CHG washcloth bathing intervention [22]. Bleasdale et al. reported three cases of skin reaction in the intervention group, which were likewise not attributed to CHG washcloth use [24]. The study by Noto et al. did not report any adverse events [23]. Only the study by Bleasdale et al. studied the minimum inhibitory concentration (MIC) for chlorhexidine resistance of microorganisms in the control and intervention arms, however neither the data nor significance values were reported.

Risk of bias assessment was performed using the Cochrane Collaboration tool for risk of bias assessment (Table 2) [21]. Besides the inability to blind the intervention to patients and staff and the lack of compliance measurements for interventions or baseline hygienic practices in all studies, the main confounder that introduced a high risk of bias was the simplified definition applied by Milstone et al. for their paediatric population. In that study, only one positive blood culture was required to diagnose a bloodstream infection, including commensal skin microorganisms. In the same vein, none of the included articles reported diagnostic methods of catheter or blood culturing. Other sources of bias included lack of a washout phase and no mention of outcome assessment blinding in the Climo et al. study. Issues that confounded generalisability include higher HABSI rates in the Bleasdale et al. trial and lower HABSI rates and shorter mean length of stay in the Noto trial.

Meta-analysis was performed on the randomised crossover trials to assess the impact of CHG washcloth bathing. A reduction in the rate of total HABSI was associated with CHG washcloth bathing (OR: 0.74; 95% CI: 0.60–0.90; p=0.002, Figure 3) with moderate statistical heterogeneity (I2=36%). One study did not demonstrate a rate reduction of total HABSI [23].

Table 1

Summary of included studies (n = 4)

Study	Setting	Sample size	Intervention group	Control group	Primary outcome	Secondary outcome	Results
Climo (2013) [22]	9 ICU and bone marrow transplant units	7,727 patients	CHG-WC daily bathing	Daily bath with non-medicated washcloths	Primary, secondary, and central line-associated BSI	Primary HABSI and CLABSI microorganisms	Control: 88 primary HABSI, 43 CLABSI, 34 secondary HABSI for 25,000 patient-days. Intervention: 69 primary HABSI, 21 CLABSI, 29 secondary HABSI for 24,931 patient days.
Noto (2015) [23]	5 adult ICUs (neurological, trauma, surgical, medical, cardiovascular)	9,340 patients	CHG-WC daily bathing	Non-medicated washcloths	Combined primary and secondary HABSI, and CLABSI	Combined primary, secondary HABSI, and CLABSI microorganisms	Control: 113 primary and secondary HABSI, 4 CLABSI for 20,721 patient-days. Intervention: 96 primary and secondary HABSI, 4 CLABSI for 19,202 patient days.
Bleasdale (2007) [24]	1 medical ICU	836 patients	CHG-WC daily bathing	Soap and water bathing	Combined primary HABSI and CLABSI, and secondary HABSI	Combined primary HABSI and CLABSI microorganisms	Control: 21 CLABSI, 1 primary HABSI, 5 secondary HABSI for 2,119 patient days. Intervention: 9 CLABSI, 0 primary HABSI, 5 secondary HABSI for 2,210 patient days.
Milstone (2013) [25]	10 paediatric ICUs	4,947 patients	CHG-WC daily bathing	Either soap and water or non-medicated washcloths	Combined primary and secondary HABSI, and CLABSI	Combined primary HABSI and CLABSI microorganisms	Control: 79 primary and secondary HABSI, 28 CLABSI for 16,024 patient days. Intervention: 53 primary and secondary HABSI, 13 CLABSI for 15,057 patient days.

ICU: intensive care unit; BSI: bloodstream infection; CHG-WC: 2% chlorhexidine gluconate washcloth; CLABSI: central line-associated bloodstream infection; HABSI: hospital-acquired bloodstream infection.

In Climo et al.'s study, CLABSI rate was 53% lower in the CHG washcloth group than in the control group [22]. Bleasdale et al. described a lower CLABSI risk in the CHG washcloth group than in the control group [24]. Milstone et al.'s study on paediatric patients found a decreased incidence of BSI in patients with a central line ($p = 0.03$). However, CHG washcloth bathing was not associated with a significantly decreased incidence of CLABSI ($p = 0.08$) [25]. Noto et al. did not report a significant impact of using CHG washcloths on the rates of CLABSI [23].

Subgroup analysis found a significant reduction in CLABSI (OR = 0.50; 95% CI: 0.35–0.71; $p \leq 0.001$, Figure 4) and non-central line-associated HABSI rates per 1,000 patient days (OR = 0.82; 95% CI: 0.70–0.97; $p = 0.02$). Both subgroups displayed lower heterogeneity compared with the total HABSI rate reduction ($I2 = 0\%$), demonstrating that heterogeneity between studies is partially explained by which infectious outcome is being studied. The effect of CHG washcloth bathing was more pronounced for CLABSI prevention and the difference in impact was significant ($p = 0.01$). Three of the four studies reported the cultured microorganisms for combined primary and central line-associated HABSI, while the Noto study reported data on combined primary and secondary HABSI [25]. Subgroup analysis found a significant decrease in Gram-positive (OR = 0.55; 95% CI: 0.31–0.99; $p = 0.05$) but not Gram-negative HABSI (OR = 0.83; 95% CI: 0.59–1.17; $p = 0.68$) (Figure 5). Meta-regression did not identify a significant difference between Gram-positive and Gram-negative subgroups.

A funnel plot was not created due to the small number of included studies. Sensitivity analysis compared meta-analysis results for varying denominators per HABSI. The intervention effect per number of patients was comparable for total HABSI (OR = 0.73; 95% CI: 0.58–0.91; $p = 0.006$), CLABSI (OR = 0.50; 95% CI: 0.35–0.71; $p = 0.0001$) and non-central line HABSI (OR = 0.82; 95% CI: 0.68–0.97; $p = 0.02$). Three trials demonstrated that the overall effect on CLABSI per catheter-days was similar (OR = 0.52; 95% CI: 0.36–0.74; $p = 0.0003$) with one study demonstrating a non-significant decrease [25]. The definitions of HABSI in the paediatric population of Milstone et al. required only one blood culture, even in the case of skin commensals. After exclusion of this high-risk-of-bias study, meta-analysis identified a reduction of the total HABSI (OR = 0.76; 95% CI: 0.59–0.99; $p = 0.04$) and CLABSI rate per patient days (OR = 0.50; 95% CI: 0.33–0.76; $p = 0.02$), and the rate reduction for non-central line HABSI, Gram-positive and Gram-negative HABSI became non-significant. The difference between CLABSI and non-central line HABSI remained significant after removal of this high-risk-of-bias trial ($p = 0.02$).

Table 2

Cochrane risk-of-bias assessment of included studies (n = 4)

	Climo (2013) [22]	Noto (2015) [23]	Bleasdale (2007) [24]	Milstone (2013) [25]
Random sequence generation and allocation concealment	Investigators were unblinded to intervention assignment. No mention of blinding of outcome assessments.	Infection control personnel responsible for adjudicating infection outcomes were blinded to the treatment assignments.	One of three reviewers was blinded to intervention assignment. To avoid bias, infection rates were calculated with a computer algorithm on a data warehouse.	Investigators were unblinded to intervention assignment. Outcome assessors were masked to random allocations.
Selection bias	Medium risk	Low risk	Low risk	Low risk
Blinding of participants and personnel	Due to the nature of the study, none of the studies could blind intervention to staff or patients.			
Blinding of outcome assessment	Investigators were unblinded to intervention assignment. No mention of blinding of outcome assessments.	Infection control personnel responsible for adjudicating infection outcomes were blinded to the treatment assignments.	Two reviewers were unblinded to intervention assignment; a third reviewer was blinded. To avoid bias, infection rates were electronically calculated using a computer algorithm on a data warehouse.	Investigators were unblinded to intervention assignment. Outcome assessors were masked to random allocations.
Performance bias	Medium risk	Low risk	Low risk	Low risk
Incomplete outcome data	Reported cost-effectiveness outcomes did not coincide with the protocol. Adverse events reported. Chlorhexidine susceptibility testing was reported. No compliance reporting.	Reported primary and secondary outcomes coincided with the protocol. No data on chlorhexidine resistance. No compliance reporting.	Reported primary and secondary outcomes coincided with the protocol. Adverse events reported. Chlorhexidine susceptibility testing was reported. No compliance reporting.	Reported primary and secondary outcomes coincided with the protocol. Adverse events reported. No data on chlorhexidine resistance. No compliance reporting.
Detection bias	Low risk	Low risk	Low risk	Low risk
Selective reporting	Cost-effectiveness data not mentioned in the study report but mentioned in the study protocol. Only intention-to-treat group reported.	Intention-to-treat and as-treated group analysis provided. Adverse events not reported.	Only an intention-to-treat analysis was performed. Three patients excluded from the CHG bathing procedure were considered part of the intervention arm.	Per protocol and intention-to-treat group analysis provided.
Attrition bias	Low risk	Low risk	Low risk	Low risk
Other sources of bias	Sage Products supplied the washcloths, technical and educational support, but was not involved in the study design, analysis or manuscript preparation.	Single-centre study with lower baseline HABSI rates and length of stay compared with other included studies.	Single-centre study with higher baseline CLABSI rates compared with other studies.	Different institutions' ethics committees decided how to obtain informed consent. BSI criteria required only one blood culture for commensal microorganisms.
Other bias	Low risk	High risk	Medium risk	High risk

BSI: bloodstream infection; CHG: chlorhexidine gluconate; CLABSI: central line-associated bloodstream infection; HABSI: hospital-acquired bloodstream infection.

Discussion

This meta-analysis of four trials, involving 25 ICUs and 22,850 patients, provides evidence that daily patient bathing with CHG washcloths can reduce the incidence of HABSI. This effect appears mainly to be due to a reduction in CLABSI, possibly based on eradication of Gram-positive skin commensals. After removal of a high-risk-of-bias study, the intervention impact in the Gram-positive and non-central line-associated HABSI subgroups became non-significant. No significant adverse skin events were reported as related to CHG washcloth bathing. One study planned a cost-effectiveness analysis per protocol, but did not report this in the final publication [22]. Among the four studies, significant reductions in individual infection rate were demonstrated for total HABSI (n = 3) and for the subgroups of Gram-positive HABSI (n = 3) and CLABSI (n = 3). The subgroup analysis of non-central line HABSI demonstrated rate reductions, however no single study could independently demonstrate significance. Only Noto et al consistently reported non-significant results: in contrast to the other included studies, their CLABSI rate did not change, with broad CIs [23]. A possible explanation could be the infection rate in the control group (0.19 CLABSI per 1,000 patient-days), which was at least 10 times lower compared with other trials [22,25], and the mean length of stay of 2.5 days, approximately half that of the other included studies [22,24,25].

Two previous systematic reviews had found evidence of the preventive effect of CHG washcloth bathing for CLABSI [18] and HABSI [20]. Another could not conclude that CHG washcloth bathing could reduce BSI rates [19]. However, the majority of included studies were low-quality non-randomised before–after studies, did not focus solely on ICU patients, and applied different CHG bathing interventions. In contrast, this review focused on non-rinse CHG washcloth bathing to prevent HABSI in ICUs, including pediatric ICUs.

Strengths of this meta-analysis comprise the comprehensive search strategy, inclusion of high-quality randomised crossover trials, risk-of-bias assessment, random-effects meta-analysis with subgroup analysis of HABSI and pathogen subtypes, low statistical heterogeneity in the HABSI types subgroup analysis and sensitivity analysis of high-risk-of-bias studies and denominator data. Limitations include non-blinding to the intervention, partially compensated by the crossover design, lack of compliance measurements and lack of reporting of baseline hygienic practices. Since all four included trials were carried out in critically ill patients with a high level of dependency on staff, patient self-reporting of compliance and tolerance was not performed. One trial did not report blinding of outcome assessment and lacked a washout period [22] and another was single-centre, even though it included two geographically distinct units that permitted a randomised crossover design [24].

Clinical and methodological heterogeneity stemmed from differing infection rates, varying methods of reporting HABSI types and definition criteria of HABSI in the paediatric study. Different baseline standards of care leave more or less room for improvement and HABSI prevention, which can influence the perceived effect of the CHG washcloth intervention. The Bleasdale study had higher rates of HABSI in the control arm and the Climo study higher rates of CLABSI, compared with other hospital settings. This could have produced interpretation and applicability bias in that a situation with more room for improvement in healthcare quality may predispose the infection rate reduction to be stronger [24]. Nevertheless, in the subgroup analysis of central line and non-central line HABSI, the heterogeneity between studies decreased ($I2 = 0\%$), indicating that the intervention effect was related to a proportional decrease in HABSI of central line or non-central line origin. An important source of methodological heterogeneity was the Milstone study due to their definition of bacteraemia as one, instead of two, positive blood culture of commensal skin organisms [25]. According to the current evidence, commensal Gram-positive bacteria cause a large proportion of BSI in children; however, they frequently contaminate blood cultures [28,29]. This change in HABSI definition means that the observed intervention effect may represent a false reduction in the yield of contaminated blood cultures that was due to a decrease in commensal skin flora and not to a reduction in bloodstream infections. After removal of this high-risk-of-bias study, a significant reduction was still maintained for total HABSI rates and particularly for the CLABSI subgroup.

The main purpose of patient safety strategies should be to improve quality of care by reducing the clinical and economic burden of healthcare-associated infections. Studies performed in the pre-surgical context have proven the cost-effectiveness of CHG washcloths for preventing surgical site infection [30]; it is unknown if this could be replicated in the ICU context. Studies have hypothesised that CHG washcloth bathing is potentially cost-effective through prevention of CLABSI and that nurses preferred this method over non-washcloth bathing [31-33].

An important concern raised regarding application of antiseptics is the potential selection of antiseptic-resistant pathogens, which should be monitored when introducing universal decolonisation strategies [34]. Only one study measured CHG MIC values between treatment arms, but reflected that the overall increase in resistance in the chlorhexidine group could represent a reduction in isolates that are inhibited by very low CHG concentrations [23].

Conclusion

This meta-analysis provides evidence that the use of CHG washcloths prevents HABSI in ICUs. The impact of CHG washcloth bathing appeared to be primarily due to its prevention of CLABSI. This effect was beneficial and comparable for CLABSI in all four studies. The reduction was possibly due to the reduction of commensal Gram-positive skin microorganisms. However, since the rate reduction was primarily due to Gram-positive bacteria, the possibility still remains that the intervention effect is partially explained by a reduction in blood culture contamination. Hospitals with high baseline hygienic standards of care and lower CLABSI rates may benefit less from CHG washcloth bathing; rather, the intervention can work as a 'safety net' when basic hygienic preventive measures are breached. Further research should apply separate classifications of primary, secondary and central line-associated HABSI types, should report catheter cultures to diagnose bloodstream infections to increase certainty and lower the risk of bias due to improper attribution of blood culture contaminants, should report baseline hygienic standard of care practices and should attempt to measure compliance with the daily CHG washcloth bathing intervention. A cost-effectiveness analysis can assess the added benefit of CHG washcloth bathing, taking into account differing standards of care.

Conflict of interest

None declared. SB holds a research mandate of the Special Research Fund at Ghent University.

Authors' contributions

EA and KB conceived of and designed the study, performed the search of published work, literature search, data acquisition, interpretation and synthesis, independently performed the quality assessment and wrote the paper. In case of doubt regarding inclusion criteria, all investigators had access to the full article. KB performed the statistical analyses. SB conceived of and designed the study, contributed substantially to the search of published work, data interpretation and synthesis and critically revised the final manuscript.

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Eurosurveillance 5th scientific seminar on 30 November at ESCAIDE - 20 years of communicating facts and figures in a changing world

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On the occasion of our 20-year anniversary, the 5th*Eurosurveillance* Scientific Seminar will have '20 years of communicating facts and figures in a changing world' as its topic.

Featuring speakers Professor David Heymann, Head of the Centre on Global Health Security at Chatham House, London, and Chairman of Public Health England, UK, and Professor Lawrence Madoff, Director, Division Of Epidemiology And Immunization, Massachusetts Department of Public Health and Editor of ProMED-mail (the programme for Monitoring Emerging Diseases), and moderated by Professor Panayotis Tassios, Associate editor of *Eurosurveillance*, the seminar is held at the same venue as ESCAIDE to ensure that as many participants as possible can use the opportunity to listen to the speakers.

For the full programme, please go to the *Eurosurveillance* homepage.

ECDC publishes 2015 surveillance data on antimicrobial resistance and antimicrobial consumption in Europe

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On the occasion of the European Antibiotic Awareness Day on 18 November 2016, the European Centre for Disease Prevention and Control will release 2015 data on antimicrobial resistance [1] and antimicrobial consumption [2] from 30 European Union (EU) and European Economic Area (EEA) countries. The data are accompanied by summaries highlighting the latest trends [3,4].

The latest data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) show high and increasing resistance percentages for Gram-negative bacteria in many parts of Europe. This is reflected by the increase in combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides resistance at EU/EEA level between 2012 and 2015 for both *Escherichia coli* and *Klebsiella pneumoniae*. Although carbapenem resistance percentages remained low for most countries in 2015, resistance to carbapenems increased significantly for *K. pneumoniae* at EU/EEA level over the last four years. Data on polymyxin resistance in EARS-Net are sparse, but some countries, especially those with high percentages of carbapenem resistance, report presence of isolates with polymyxin resistance.

The latest data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) showed that overall consumption of antibiotics in the community remained unchanged from 2011 to 2015. However, when measuring the antibiotic consumption as a number of packages per 1,000 inhabitants and per day (used by ESAC-Net as the best available surrogate for prescriptions), six countries experienced a significant decrease during the period the same period.

In the hospital sector, the overall consumption of antibiotics remained stable in the EU/EEA. At the national level, antibiotic consumption of carbapenems and polymyxins used to treat patients with serious multidrug-resistant bacteria is still at a low level compared to the overall consumption of antibiotics for systemic use in the hospital sector. However, significant increasing trends in the consumption of carbapenems (six countries) and polymyxins (eight countries) were reported for the period 2011–2015.

In countries with high levels of multidrug resistance, including resistance to carbapenems, only a few therapeutic options are available; among these are polymyxins (e.g. colistin). The presence of isolates with resistance to polymyxins and increasing trends in polymyxin consumption in several countries is an important warning that options for the treatment of infected patients are becoming even more limited.

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