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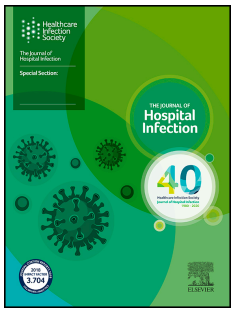

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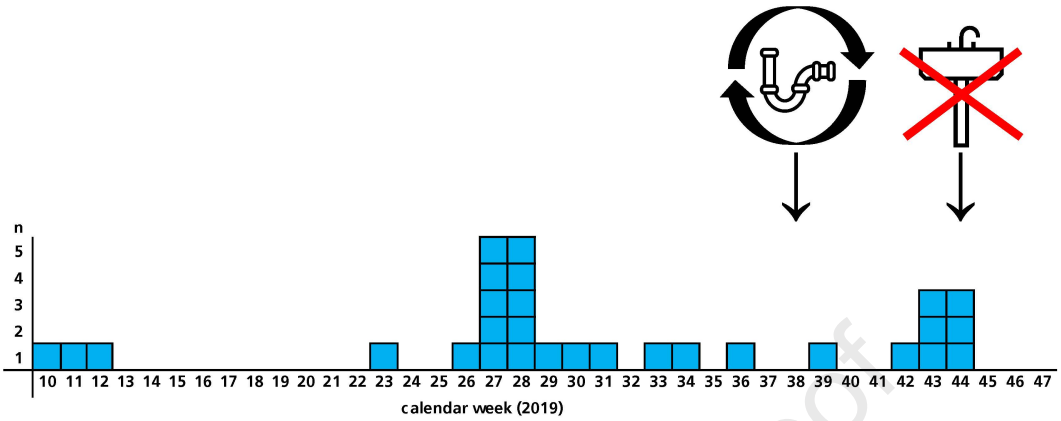

Graphical abstract: Epicurve of a multidrug-resistant *Pseudomonas aeruginosa* outbreak at a tertiary care hospital in Switzerland affecting 29 patients. Siphon replacement on 3 intensive care subunits failed to terminate the outbreak. The outbreak ceased after sink removal.

An intensive care unit outbreak with multidrug-resistant *Pseudomonas aeruginosa* – spot on sinks

Verena Schärer[1], Marie-Theres Meier[1], Reto A. Schuepbach[2], Annelies S. Zinkernagel[1], Mathilde Boumasmoud[1], Bhavya Chakrakodi[1], Silvio D. Brugger[1], Martin R. Fröhlich[2, 3], Aline Wolfensberger[1], Hugo Sax[1,4], Stefan P. Kuster[1], Peter W. Schreiber[1]

[1] Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, and University of Zurich, Zurich, Switzerland

[2] Institute for Intensive Care Medicine, University Hospital Zurich, and University of Zurich, Zurich, Switzerland

[3] Department of Perioperative Medicine, Kantonsspital Aarau, Aarau, Switzerland

[4] Department of Infectious Diseases, Bern University Hospital and University of Bern, Bern, Switzerland

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Corresponding author:

Peter W. Schreiber, MD

Department of Infectious Diseases and Hospital Epidemiology

University Hospital Zurich

Rämistrasse 100

8091 Zurich, Switzerland

Tel: +41 43 253 9842

E-mail: peterwerner.schreiber@usz.ch

Summary

Background

Pseudomonas aeruginosa and other Gram-negative bacteria have the ability to persist in moist environments in healthcare settings, but their spread from these areas can result in outbreaks of healthcare-associated infections.

Methods

We report the investigation and containment of a multidrug-resistant *P. aeruginosa* outbreak in 3 intensive care units of a Swiss university hospital. A total of 255 patients and 276 environmental samples were screened for the multidrug-resistant *P. aeruginosa* outbreak strain. We describe the environmental sampling and molecular characterization of patient and environmental strains, control strategies implemented, including waterless patient care.

Results

Between March and November 2019, the outbreak affected 29 patients. Environmental sampling detected the outbreak strain in nine samples of sink siphons of three different intensive care units sharing an identical water sewage system and on one gastroscope. Three weeks after sink siphon replacement, the outbreak strain grew again in siphon-derived samples and newly-affected patients were identified. The outbreak ceased after removal of all sinks in the proximity of patients and in medication preparation areas and minimization of tap water use. Multilocus sequence typing indicated clonality (sequence type 316) in 28/29 patient isolates and all 10 environmental samples.

Conclusions

Sink removal combined with the introduction of waterless patient care terminated the multidrug-resistant *P. aeruginosa* outbreak. Sinks in intensive care units might pose a risk for point source outbreaks with *P. aeruginosa* and other bacteria persisting in moist environments.

Introduction

Intensive care unit (ICU) patients are severely affected by healthcare-associated infections (HAI) for many reasons [1]. The ICU population comprises very sick patients frequently featuring risk factors for infections such as immunosuppression, cancer, or chronic obstructive pulmonary disease [2]. Several invasive measures are routinely conducted in these patients, thus resulting in the disintegrity of natural barriers. HAIs also contribute to morbidity and mortality. For example, central line-associated bloodstream infections have been reported to represent a 2.27-fold increased mortality risk [3]. In addition, the use of antibiotics, especially broad-spectrum antimicrobials, prompts a selection pressure for multidrug-resistant (MDR) pathogens [4]. In a recent national point prevalence study in Switzerland, Gram-negative pathogens contributed to 43% of all HAIs [1]. Among pathogens causing HAIs, *Pseudomonas aeruginosa* is of major relevance as antibiotic resistance is common and the frequency of multidrug resistance is increasing [5-7]. *P. aeruginosa* has the capability to persist in moist environments in healthcare settings [8-13] and spread from these areas can lead to promoting outbreaks through the contamination of medical devices, medical products, and the hands of healthcare workers. We describe an outbreak of a MDR *P. aeruginosa* in several ICUs that was first detected in March 2019 and attributed to contaminated sink siphons.

Methods

Following the ORION recommendations, we provide a detailed description of the outbreak, its source, and containment measures implemented [14].

Setting

The University Hospital Zurich is a 941-bed tertiary care hospital located in Zurich, Switzerland, with approximately 40,000 admissions per year. The Institute for Intensive Care Medicine comprises six specialized ICUs with a total of 64 beds. The ICU for cardiac and vascular surgery (ICU 1; 12-bed capacity), visceral/thoracic/transplantation surgery (ICU 2; 12-bed capacity), and internal medicine (ICU 3; 12-bed capacity) share a similar architectural layout and are located in the same building (one below the other) and connected to a common sewage system (Figure 1). All taps in these three ICUs were equipped with terminal all-bacteria filters (Pall-Aquasafe Water Filter AQ14F1S; Pall, Portsmouth, UK).

In March 2019, an outbreak with a multidrug-resistant *P. aeruginosa* was identified in ICU 1. The detection of a MDR *P. aeruginosa* featuring an identical resistance pattern in three patients within three subsequent weeks triggered an outbreak investigation. The susceptibility pattern of the outbreak strain showed resistance to all routinely tested antibiotics (i.e., piperacillin/tazobactam, ceftazidime, cefepime, imipenem, meropenem, gentamicin, tobramycin, ciprofloxacin and levofloxacin), except for a variable susceptibility for amikacin. Susceptibilities for ceftolozane-tazobactam, aztreonam and colistin were variable, while all isolates were susceptible to ceftazidime-avibactam.

Case definition

All patients with at least one clinical or screening specimen that detected *P. aeruginosa* featuring the antibiotic resistance pattern of the outbreak strain and either linked to the outbreak epidemiologically and/or by molecular characterization methods were considered to be part of the outbreak. Patients already known to be colonized with MDR *P. aeruginosa* were not considered to be outbreak-related.

Patient data collection

Collected data included age, sex and reason for hospitalization, survival, and information on whether an individual was infected or colonized with the outbreak strain. For individuals suffering from an infection, information on the site of infection was collected. All colonized or infected patients were followed up at least until hospital discharge. Patients that died during follow-up were assessed for the potential contribution of the outbreak strain to death. This assessment included a clinical case review by two physicians (VS and PWS). Classification as contributing to death required the presence of an infection with the outbreak strain in a temporal relationship to subsequent death and the absence of other evident causes of death. Microbiological results of patient samples were retrieved from different microbiology databases (Institute of Medical Microbiology, University of Zurich, Laboratory of the Department of Hospital Epidemiology, University Hospital Zurich, and the laboratories of referring hospitals).

Patient screening

From May to December 2019, patient screenings were scheduled on outbreak-related wards. Each screening included a respiratory specimen (tracheobronchial secretions, sputum or nasal and pharyngeal swab), groin swab, urine culture in catheterized patients, and wound swabs in patients with wounds. Outbreak-related wards encompassed ICU 1, ICU 2, ICU 3 and normal wards with the transfer of affected patients. From 1 July to 30 November 2019, repeated point prevalence screenings were performed. All patients hospitalized on an outbreak-related ward were tested on one day of the week. Weekly screening continued until three repeated ward screenings did not identify any incident cases. Screenings encompassed several wards affected by the outbreak, but most took place in ICU 1. During November and December 2019, all patients on ICU 1 were screened at the time of admission and discharge.

Environmental sampling

Environmental samples were taken from numerous medical devices and surfaces including sink siphons, which were considered to be potentially linked to the outbreak. Swabs (eSwab; Copan, Brescia, Italy) were used for environmental sampling from surfaces, and placed into Amies medium after sampling. After identification of the outbreak strain in sink siphons, air samples were collected at a distance of 30-50 cm from the affected sinks while the tap was turned on (MAS-100 NT, MBV, Staefa, Switzerland; running for 5 min at a rate of 100 L/min., Columbia agar with 5% sheep blood). Laboratory analyses were performed at two different microbiology laboratories (Laboratory of the Department of Hospital Epidemiology, University Hospital Zurich, and Bioexam Lucerne). *P. aeruginosa* grown from collected specimens were tested for antimicrobial susceptibilities according to standard protocols.

Molecular characterization

The initial determination as to whether an MDR *P. aeruginosa* isolate belonged to the outbreak was based on phenotypic resistance testing. To investigate clonality, a subset of 34 patient-derived isolates was analyzed by multilocus sequence typing (MLST) and 11 isolates were characterized by pulsed-field gel electrophoresis [15-17]. All environmental isolates featuring the susceptibility pattern of the outbreak strain were characterized by MLST.

Containment measures

Containment measures included the use of contact precautions (wearing of gowns by healthcare workers, isolation in a single room or optical measures to increase awareness of the patient zone) for all colonized or infected cases, staff education, increased availability of alcohol-based handrub dispensers, enhanced environmental cleaning, screening of patients for the presence of the outbreak strain, a transient reduction in the number of beds, and removal of curtains between ICU beds. After identification of the outbreak strain in sink siphons, waterless patient care was introduced in October and November 2019. All sinks in patient and medication preparation areas were removed and almost all patient care activities that formerly involved tap water were replaced by waterless alternatives as described in Table I. Prior to the implementation of waterless patient care, sinks in patient areas were used for body washing, oral care, hair washing, shaving of patients, and washing of visibly soiled hands of health care workers; sinks in the medication preparation area were used for dissolving oral medication.

Ethics approval

The Zurich Cantonal Ethics Commission (Req-2020-00108) waived the necessity for a formal ethical evaluation based on the Swiss law on research on humans.

Results

Patient characteristics

From March to December 2019, 29 patients were identified with the MDR *P. aeruginosa* outbreak strain (Table II). Median age was 64 years (interquartile range, 57-69), 24 (82.8%) were male and 24 (82.8%) suffered from an underlying cardiac or vascular disease. Infection with the outbreak strain was present in 17 (58.6%) patients, whilst 12 (41.3%) patients were colonized. The outbreak strain contributed to death in nine (31.0%) patients.

Patient screening

From May to December 2019, a total of 255 patients were screened. In 10 patients, the outbreak strain was identified by outbreak-related screenings (34.5% of the 29 affected patients), whereas in 19/29 (65.5%) patients, the outbreak strain was isolated in clinical samples or screening specimens

collected for other reasons. Most (n=16 [55.2%]) MDR *P. aeruginosa* isolates were detected in airway samples (13 tracheal secretions, three sputa). The temporal course of newly identified cases is shown in Figure 2.

Environmental testing

A total of 276 environmental samples were analyzed for the presence of the outbreak strain (Supplementary Table 1). MDR *P. aeruginosa* isolates with the resistance pattern of the outbreak strain were identified in 10/134 (7.5%) samples gathered from sinks (each including siphons, partly combined with sink surfaces) and on 1/8 (12.5%) gastroscopes used in at least two patients colonized with the corresponding MDR *P. aeruginosa*, suggestive of a transmission by this medical device. None of the 17 air samples from ICU 1 and ICU 2 tested positive for the outbreak strain.

Molecular characterization

P. aeruginosa isolates from 28/29 (96.6%) outbreak-related patients were analyzed by MLST (samples from one outbreak-related patient failed to re-grow). Overall, MLST was applied to 34 patient-derived samples that encompassed the previously mentioned 28 outbreak-related isolates and six MDR *P. aeruginosa* isolates with a slightly different phenotypic resistance pattern. All outbreak-related patient samples corresponded to sequence type (ST) 316, thus indicating clonality. In addition, 11 MDR *P. aeruginosa* isolates from outbreak-related patients were analyzed by pulsed-field gel electrophoresis with all showing similar patterns and further supporting clonality. Among the remaining six patient-derived samples, different sequence types were reported and relatedness to the outbreak was considered unlikely. Eleven environmental samples with growth of the MDR *P. aeruginosa* were investigated by MLST. Nine samples gathered from sinks and one from a gastroscope corresponded to ST 316, confirming their relatedness to the outbreak. One isolate from a sink siphon that showed an identical resistance pattern as the outbreak strain resulted in a different sequence type.

Course of the outbreak

At the end of August 2019, the outbreak strain was reported for the first time in environmental samples. Two different samples derived from sinks in ICU 2 tested positive for the corresponding

MDR *P. aeruginosa*. The affected sinks were immediately closed, disinfected with an aldehyde-based disinfectant and the siphons were replaced by factory-new siphons. This finding prompted testing of all sink siphons in the three ICUs of the corresponding common building sewage tract. Overall, the outbreak strain was detected in five samples, including samples from ICU 1, ICU 2 and ICU 3. Subsequently, all sinks were temporally closed, disinfected and siphons replaced. Approximately three weeks after re-opening, sinks that had previously tested positive for the outbreak strain were re-tested and the outbreak strain was found again in two samples. Recurrence of the outbreak strain in refurbished sinks prompted the implementation of waterless patient care in the ICUs. An interdisciplinary and interprofessional team consisting of ICU physicians, ICU nurses, plumbing technicians, and infection prevention and control team members was established. Measures included removal of all sinks in patient areas and in areas used to prepare medication (Figure 1), use of bottled spring water (Eptinger AG, Eptingen, Switzerland) for the dissolving of oral medication and oral care, and body care with disposable washing cloths (Table I). After implementation of these measures, the outbreak ceased immediately.

Discussion

We report here the successful control of an outbreak with MDR *P. aeruginosa* affecting 29 patients over a period of 9 months in a tertiary care hospital in Switzerland. In total, 17 patients (58.6%) developed invasive infections and nine patients (31%) died. In all fatal cases, the outbreak strain caused or at least contributed to this outcome. The outbreak could be traced to contaminated sink siphons and ceased only after sink removal in patient areas and areas used for the preparation of medication.

The outbreak was initially detected on ICU 1 and most affected patients had a stay on this specific ICU. However, environmental samples from ICU 2 and ICU 3 also grew the outbreak strain. All these ICUs share a similar architectural layout and use a common water sewage system and this finding suggests that contamination was not just limited to the sink siphons of ICU 1, but also present the sewage system of the three ICUs. In outbreaks originating from a common source, such as contaminated sinks, periods over weeks to months without detection of clinical samples have been described. Fraenkel *et al* and Gatho *et al* reported months without the detection of outbreak-related *P. aeruginosa* isolates [18, 19]. Similarly, we did not detect any additional cases between calendar

weeks 13 and 22 of 2019. The relevance of sink contamination as a source of pathogen transmission is likely underestimated as surveillance usually focuses on ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa* and *Enterobacter* spp.) pathogens, resulting in a relevant bias for outbreak identification.

The disruption and dispersion of established biofilms in different parts of sinks, especially in siphons, can result in the transmission of pathogens to patients. Opening the tap can generate splashes and even aerosols containing the pathogen, which can contaminate healthcare workers' hands or the surfaces next to the sink [9, 20, 21]. Our outbreak investigation also included air sampling in proximity to contaminated sinks while the water was running, but results did not yield any growth of the outbreak strain. By contrast, Hopman *et al* reported detection of a genetically identical carbapenemase-producing *P. aeruginosa* isolate in shower drains, corresponding air samples and an exposed patient, suggestive of airborne transmission [22].

Different approaches to control sink-related transmissions and outbreaks have been described. Improvement of design features were reported to be successful, e.g,. installation of tap spouts that do not flow directly into the drain to prevent splashing or increasing the depth of the basin to prevent cross-contamination of hands and splashing [9, 23]. However, the sinks in the three ICUs affected by our outbreak were already well-designed regarding tap positioning and basin depth. Disinfection with different products or cleaning of sinks cannot decontaminate the sinks completely and has only a temporary effect [24, 25]. Complete or partial sink replacement has been applied successfully in controlling outbreaks, but has also been shown to result only in a temporary effect as frequently a reservoir in the wastewater system leads to a retrograde re-contamination of sinks [26].

Our initial intervention regarding the contaminated sinks was the replacement of all siphons combined with disinfection of the sinks on the three affected ICUs. Fraenkel *et al* described a Swedish outbreak due to VIM-2 producing *P. aeruginosa*. The authors reported elimination of the outbreak strain from contaminated sinks with replacement of one colonized sink and disinfection of another colonized one [19]. However, the timespan between any intervention and the re-testing might be crucial as too early testing might be negative due to a low bacteria load below the detection limit. Notably, in our outbreak, the sink siphons were again contaminated with the outbreak strain a few weeks after these measures, while a new cluster of colonized and infected patients was detected at the same time. These findings supported the hypothesis of a reservoir in the sewage system,

prompting the elimination of all sinks in patient and medication preparation areas and the implementation of waterless patient care. After initial skepticism, acceptance of waterless patient care by healthcare workers was finally high, despite many changes in the workflow. Of note, a recent international guideline for ICU design recommends sinks in patient rooms [27] and some national societies of intensive care medicine require sinks in patient rooms as a prerequisite for certification as an ICU [28, 29]. Our findings strongly support revision of this guidance. Further recent studies also support the removal of sinks in patient rooms to prevent healthcare-associated infections/colonization of ICU patients with MDR *P. aeruginosa* [18, 26]. Interestingly, although Gatho *et al* had already established risk mitigation strategies for water use with a focus on the dedicated training of healthcare workers and modification of behaviours, they did not prevent a later outbreak with a VIM-producing *P. aeruginosa* [18]. In our outbreak investigation, there was also one contaminated gastroscope that could have transmitted the outbreak strain between two outbreak-related patients. This finding prompted an investigation of the endoscope reprocessing process. In addition, further spread of the outbreak strain occurred between consecutive patients, most likely via hands and surfaces.

Our study has limitations. As common in outbreak investigations, screening strategies evolved over time and focused on outbreak-related wards, which might have missed a few colonized patients. Patient and environmental samples were analyzed in different laboratories, but all were certified for the samples they analyzed.

Conclusions

Water systems in ICUs represent a risk for outbreaks with biofilm-associated bacteria, especially in stagnant water, such as sink siphons. Siphon replacement showed only a temporary effect. The definitive removal of sinks and introduction of waterless patient care proved successful for containment of the outbreak. The use of sinks in ICUs needs to be reconsidered and guidelines and policies should be revised accordingly.

Author contributions

VS: investigation, data curation, formal analysis, writing - original draft

MTM: investigation, data curation, formal analysis, implementation of waterless patient care, writing - review & editing

RAS: implementation of waterless patient care, writing - review & editing

ASZ: investigation, writing - review & editing

MB: investigation, writing - review & editing

BC: investigation, writing - review & editing

SDB: investigation, writing - review & editing

MRF: implementation of waterless patient care, writing - review & editing

AW: investigation, writing - review & editing

HS: investigation, formal analysis, writing - review & editing

SPK: investigation, formal analysis, writing - review & editing

PWS: investigation, data curation, formal analysis, supervision, writing - original draft

Conflict of interest statement

PWS received travel grants from Pfizer and Gilead, honoraria as speaker and advisory board member from Pfizer, honoraria from Gilead as an advisory board member outside of the submitted work. All other authors declare no competing interests.

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Figure captions

Figure 1. Schematic floor map and localization of sinks in ICUs 1 to 3.

Figure 2. Epicurve of the multidrug-resistant *Pseudomonas aeruginosa* outbreak.

1 indicates replacement of all sink siphons on the three intensive care units sharing a similar architectural layout and a common sewage system.
2 indicates removal of all sink siphons and the introduction of waterless patient care.

426 # Tables

427 **Table I. Components of waterless patient care**

Procedure	New standard with waterless patient care
Handwashing of visible soiled hands	Use of a designated 'contaminated' sink outside of patient and medication preparation areas, followed by alcohol-based hand disinfection
Dissolving of oral medication	Dissolving of oral medication with bottled spring water (Eptinger AG, Eptingen, Switzerland)
Drinking water for patients	Bottled spring water (Eptinger AG)
Body washing	Disposable washing gloves either with (once daily, Sinaqua dermal glove, chlorhexidine 2%, Welcare, Orvieto, Italy) or without chlorhexidine (Sinaqua dermal glove, Welcare). For heavy contamination, filtered water can be used
Oral care	Bottled spring water (Eptinger AG)
Hair washing	Disposable cap internally coated with a pre-moistened cloth (Sinaqua shampoo cap, Welcare)
Shaving	Use of filtered water
Intermittent haemodialysis	Use of modified pre-existing connections in patient areas*
Disposal of waste water	Use of designated 'contaminated' sink outside of patient and medication preparation areas
Use of gowns and gloves	No change in pre-existing indications

428 * Flushing of water pipes scheduled twice weekly.

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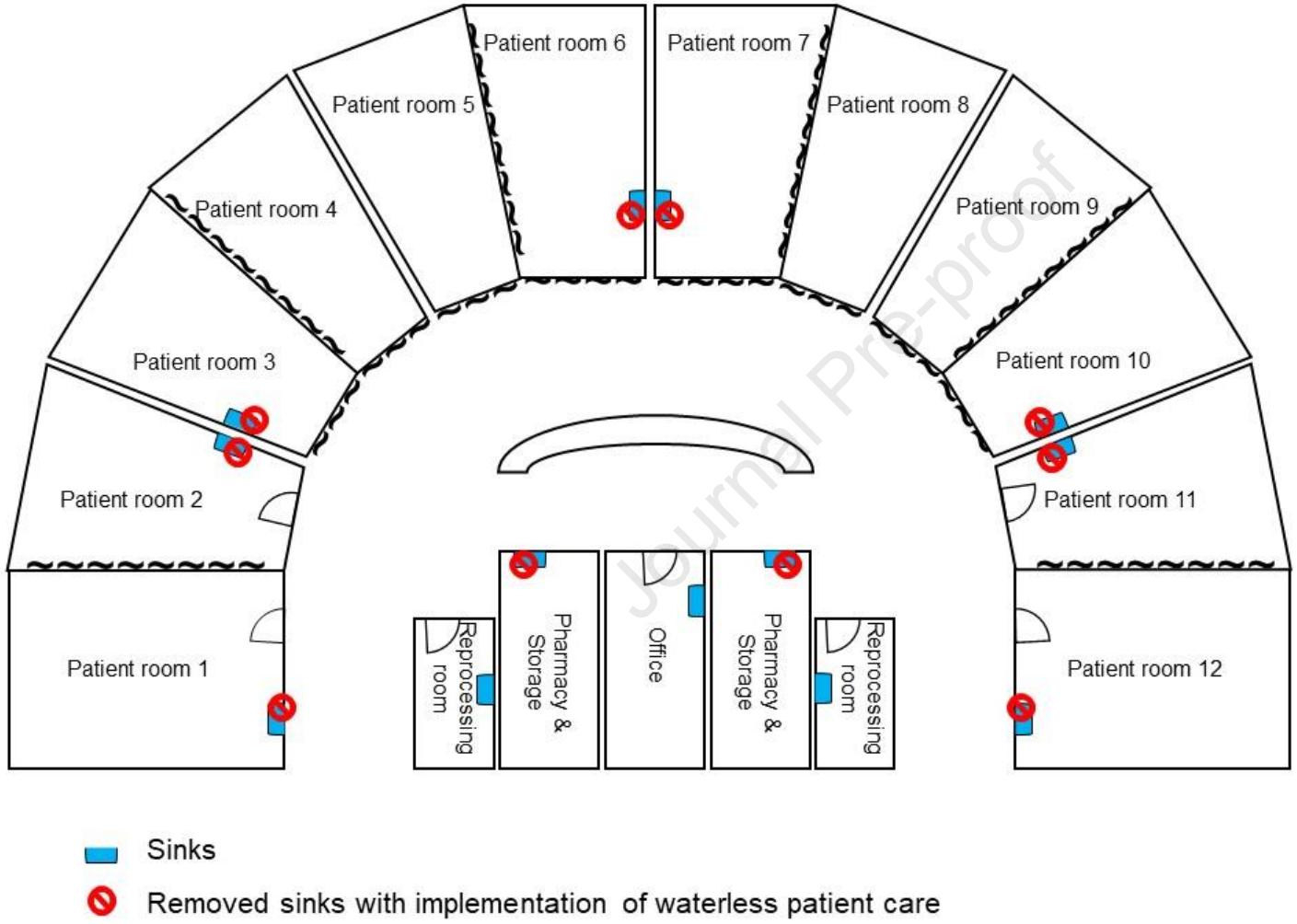
Table II. Patient characteristics

Variable	Value [#]
Age, years (median, interquartile range)	64 (57-69)
Male	24 (82.8%)
Reason for hospitalization (%)	
Cardiovascular disease • coronary heart disease • heart transplantation • aortic dissection type A • endocarditis • other	24 (82.8) • 7 (24.1) • 3 (10.3) • 3 (10.3) • 3 (10.3) • 8 (27.6)
Malignoma (%)	3 (10.3)
Other (%)	2 (6.9)
Location of patient at time of detection of infection or colonization with the outbreak pathogen (%)	
ICU for cardiac and vascular surgery	12 (41.4)
ICU for visceral, thoracic and transplantation surgery [##]	4 (13.8)
Other wards of the University Hospital Zurich [###]	6 (20.7)
Other hospitals (referring hospitals) [####]	7 (24.1)
Specimen with first detection of the outbreak pathogen* (%)	
Airway specimen	17 (58.6)
Screening pool **	7 (24.1)
Groin swab	3 (10.3)
Urethral swab	2 (6.9)
Wound swab	2 (6.9)
Urine culture	1 (3.4)
Ascites	1 (3.4)
Stool	1 (3.4)
Effect of pathogen on patient [¶]	
Colonization (%)	12 (41.4)
Infection (%) [¶¶] • respiratory tract infection • bacteraemia • foreign body-associated infection • other location[¶¶¶]	17 (58.6) • 13 (44.8) • 3 (10.3) • 2 (6.9) • 3 (10.3)

[#] Data are reported as number (%) of patients, unless otherwise indicated.
[##] 2/4 (50%) patients were formerly located on the ICU for cardiac and vascular surgery.
[###] 4/6 (66.7%) patients were formerly located on the ICU for cardiac and vascular surgery.
[####] 7/7 patients (100%) were formerly located on the ICU for cardiac and vascular surgery.
* More than one category is possible per patient if sampling took place on the same day.
** Two or more of the following samples were analyzed as a pooled sample: groin swab, nasal/pharyngeal swab, wound swab and rectal swab.
[¶] Until end of follow-up (patients were followed at least until discharge from the University Hospital Zurich or an external hospital).
[¶¶] Multiple sites per patient are possible.
[¶¶¶] One gingivitis, one infection of a tracheostomy wound, and one peritonitis.

444 **Figure 1**



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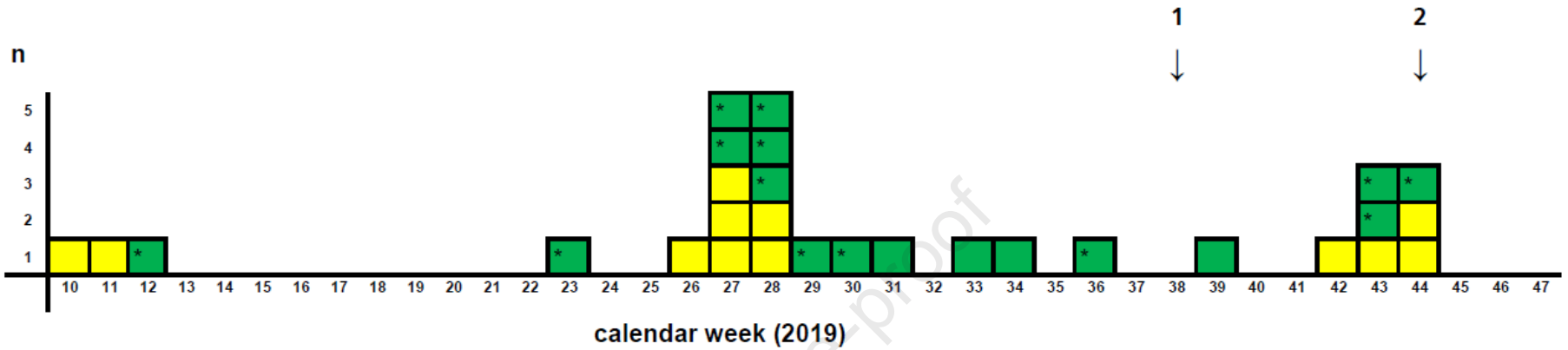
447 **Figure 2**



Location of patient at collection of first positive specimen:
Intensive care unit for cardiac and vascular surgery
Other (University Hospital Zurich or referring hospital)
* Patient formerly located on intensive care unit for cardiac and vascular surgery

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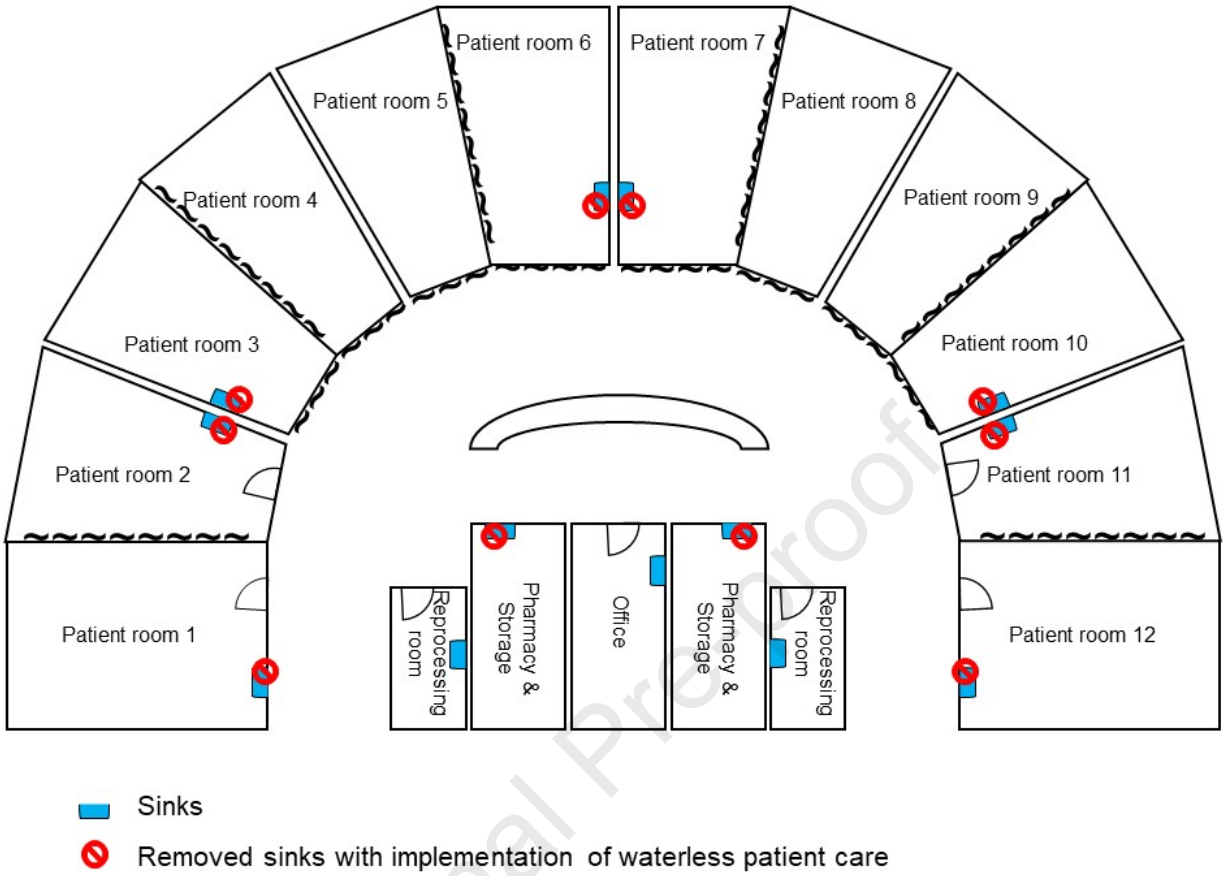

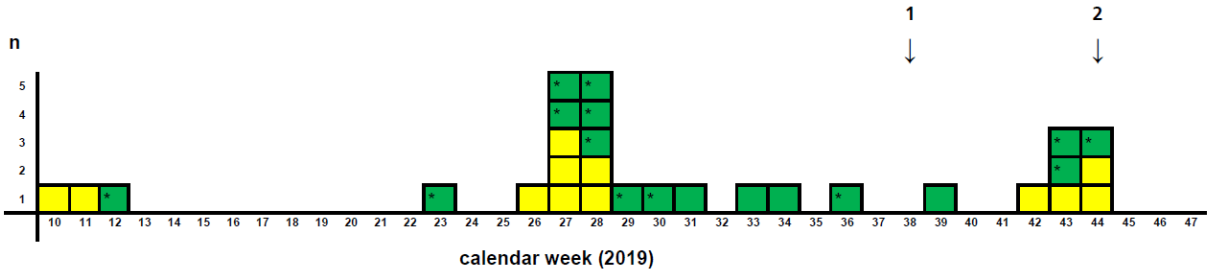

Location of patient at collection of first positive specimen:

Intensive care unit for cardiac and vascular surgery

Other (University Hospital Zurich or referring hospital)

* Patient formerly located on intensive care unit for cardiac and vascular surgery