Journal of Hospital Infection 100 (2018) e216–e225

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Recommendations for the successful control of a large outbreak of vancomycin-resistant *Enterococcus faecium* in a non-endemic hospital setting

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ARTICLE INFO

Article history:
Received 23 November 2017
Accepted 14 February 2018
Available online 21 February 2018

Keywords:
VRE
ARE
Outbreak
Infection prevention

SUMMARY

Background: A large outbreak of three epidemic vancomycin-resistant *Enterococcus faecium* (VRE) clones affected the study hospital for almost two years.
Aim: To describe the strategy to successfully control this outbreak and eradicate VRE from the study hospital.
Methods: Infection control interventions started after detection of VRE in three patients. Hospital-wide surveillance was started after ongoing transmission despite isolation precautions, cleaning and contact tracing. Hygiene education and discipline were enhanced. Despite these interventions, additional measures were required to control the outbreak, such as ward disinfection with hydrogen peroxide vapour and the introduction of a VRE quarantine ward. Ultimately, ciprofloxacin prophylaxis for haematological patients on chemotherapy was abandoned.
Findings: Over a 22-month period, 242 VRE carriers were identified. Of these, 128 (53%) patients were detected by hospital-wide surveillance alone. Three epidemic clones were detected: ST494-*vanA* ($N = 160$), ST78-*vanA* ($N = 23$) and ST117-*vanB* ($N = 32$). In total, 5614 possible contacts were identified. VRE transmission occurred on 13 out of 23 wards. VRE was cultured from clinical specimens in 22 patients (seven with bacteraemia). Since January 2014, no further transmission of these VRE clones has been observed.
Conclusion: Infection control measures according to international guidelines were insufficient to expose the outbreak to its full extent and control it. Its full extent only became apparent after sustained hospital-wide screening. Successful control of this hospital-wide VRE outbreak was feasible, but required great effort. Final containment and eradication of the epidemic clones was achieved by environmental decontamination with hydrogen peroxide vapour, strict isolation precautions, a VRE quarantine ward and antimicrobial stewardship.

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https://doi.org/10.1016/j.jhin.2018.02.016
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Introduction

Vancomycin-resistant enterococci (VRE) are multi-drug-resistant micro-organisms that cause nosocomial infections. Compared with susceptible enterococci, VRE are associated with longer hospital stay and increased mortality [1,2]. Vancomycin resistance is usually caused by the *vanA* or *vanB* gene. Treatment options are limited. In many European countries, VRE is non-endemic, but the prevalence of VRE is rising globally [3]. Within hospitals, VRE spread through healthcare workers or the environment [4]. Current guidelines recommend active surveillance, screening and contact isolation precautions in VRE-positive patients in order to prevent further spread [5–7]. A previous study indicated that four rectal swabs, collected on separate days, were needed to detect >90% of carriers [8]. In most Dutch hospitals, there is no regular screening of patients for VRE. Over the past decades, colonization rates with hospital-associated ampicillin-resistant, vancomycin-susceptible *E. faecium* (ARE) increased in the Netherlands [9,10]. However, VRE were only detected sporadically in clinical cultures until 2012, without evidence for transmission [11].

In 2012, detection of identical VRE isolates in urine samples of three patients on two different wards appeared to be the start of a large hospital-wide outbreak with three different VRE sequence types (ST) which took over 18 months to control. This report consists of recommendations for the successful control of an outbreak in a non-endemic hospital setting by describing the epidemiology of the outbreak and the control measures taken.

Methods and interventions

Table I summarizes all aspects of the outbreak, including the definitions, outbreak characteristics, infection control measures, isolation and screening policies.

Design and setting

An outbreak in the 880-bed Dutch St Antonius hospital, between March 2012 and January 2014, is described retrospectively. This teaching hospital and tertiary referral centre specializes in heart/lung disease and cancer. Important departments are cardiothoracic surgery, haemato-oncology, haemodialysis and the intensive care unit (ICU). In September 2013, a newly built hospital site opened and two of the three original sites were closed.

Control measures

VRE screening policy

Based on the literature and the authors' experience, at least five negative rectal swab cultures from different days, after the end of potential exposure, are required to consider contact patients as VRE negative [8]. Over the first three months of the outbreak, five consecutive cultures were necessary to detect 95% of VRE-positive patients (data not shown). Initially, roommates of VRE-positive patients were screened for VRE. On wards with VRE transmission, all patients were screened. From May 2012, screening was extended to high-risk wards and patients from foreign hospitals. Hospital-wide surveillance was started in June 2012. In all patients found to be VRE positive during the first six months of the outbreak, VRE was only detected in rectal swabs obtained after the fourth day of admission. Therefore, from September 2012, weekly screening was limited to patients admitted for at least four days, unless a new VRE-positive patient had been detected on a ward. This reduced the number of patients to be screened weekly by over 60%.

Outbreak management team

The outbreak management team consisted of a clinical microbiologist, two infection control specialists, a member of the hospital management team, a representative from the medical staff, a communication expert, and the manager of housekeeping and logistics. This team was responsible for the policy concerning the outbreak, and internal and external communication.

Hygiene task force

Independent of the VRE outbreak management measures, a working group to improve compliance with standard hygiene measures, such as hand disinfection and daily change of uniform, was installed. Audits were performed.

Adjusted isolation precautions

Initially, all VRE-positive and VRE-suspected patients were cared for in contact isolation. From March 2013, strict isolation precautions were adopted for VRE-positive patients.

Cleaning policy and ward closure

Initially, all rooms were cleaned daily and disinfected when the patient was discharged. After VRE transmission between rooms, wards were closed, cleaned and disinfected. From June 2012, cleaning was intensified, and cleaners received further training. Transfer of materials between rooms was prohibited without cleaning and disinfection. Outdated hospital equipment and furniture were replaced. Important interventions were: identification of who was responsible for cleaning each of these materials, determination of the cleaning frequency (daily, weekly or monthly, depending on the frequency of use), and performance of audits. After intensive cleaning and disinfection of rooms and sanitary equipment of VRE-positive patients with chloride 250 ppm and alcohol 70%, some environmental cultures remained positive, occasionally triggering new episodes of VRE transmission. Therefore, from July 2012, hydrogen peroxide vapour (Alpheios, Heerlen, The Netherlands) was used for room disinfection on wards with VRE transmission. A glucoprotamine foam, which cleans and disinfects simultaneously, was introduced for cleaning [12].

Communication and education

Educational material was developed, and information sessions were organized. The marketing and communication department informed patients, hospital personnel and the public. Contact patients received an information letter and were invited to participate in VRE screening.

VRE outpatient clinic

The VRE outpatient clinic opened for follow-up of contact patients after discharge. Trained infection control nurses informed patients and sampled rectal swabs. Patients received swabs to perform the remaining cultures at home.

Table I
Implemented control measures during the outbreak: a detailed overview

Setting: 880-Bed Dutch teaching hospital and tertiary referral centre, three locations, 23 wards, including intensive care unit and haemodialysis.

Dates: 10th March 2012–January 2014.

Population characteristics: 45,000 medical admissions/year, 5614 patients screened for VRE, most admitted for more than four days. VRE epidemic of *vanA*-ST494 ($N = 160$), *vanA*-ST117 ($N = 32$) and one *vanB*-ST78 strain ($N = 23$).

Major infection control changes during the study

2012	March	Electronic labelling of VRE-positive patients. Contact isolation precautions. Screening and electronic labelling of direct contacts.
	April	Screening of the first hospital ward. Initiation of VRE outbreak management team.
	May	Screening of departments with high-risk patients. Actions to increase awareness of standard hygiene measures. Electronic labelling of ward contacts until five negative rectal cultures were obtained. Education of hospital personnel and auditing of the wards.
	June	Introduction of PCR-based screening. Weekly hospital-wide screening of all admitted patients.
	July	Closing wards with transmission between rooms. Disinfection of room with hydrogen peroxide vapour. New intensive care unit: all single rooms.
	July–October	VRE outpatient clinic. Hygiene task force.
	September	Weekly hospital-wide screening limited to patients admitted for at least four days. New haemato-oncology ward: all single rooms.
2013	January	Haemato-oncology ward: all patients in contact isolation.
	March	Haemato-oncology ward: termination of ciprofloxacin prophylaxis during neutropenia.
	March–October	Nursing VRE-positive patients on VRE quarantine ward.
	May	All VRE-positive patients nursed under strict isolation precautions.

Diagnosis: conventional culture, switched to culture-confirmed PCR (19th June 2012).

Antibiotic policy

Onset: routine hospital policy, including ciprofloxacin prophylaxis in haematologic cancer patients. Vancomycin-restrictive policy was already present.

March 2013: termination of ciprofloxacin prophylaxis in haematologic cancer patients.

Feedback: number of new anticipated (labelled) and unsuspected VRE-positive patients, number of transmissions on different wards, number of screened patients.

Contact isolation policy: all proven cases isolated in single rooms. If a single room was unavailable, cohort contact isolation of multiple VRE-suspected patients was established in a shared room. Aprons and gloves were worn before each contact with the patient or his/her surroundings. Personalized medical devices, cleaning and disinfection (70% alcohol) of medical and nursing materials before leaving the room. Rooms were cleaned daily. After patient discharge, the room and materials were cleaned and disinfected.

Strict isolation policy: similar to contact isolation precautions, but mask, hair cap and gown with long sleeves worn additionally. Patients nursed in isolation rooms with anteroom, with double-door separation and pressure control.

Vancomycin restrictive antibiotic policy details: the prevalence of meticillin-resistant *Staphylococcus aureus* is very low in the study hospital. The use of vancomycin was limited to severe infections with coagulase-negative staphylococci and *E. faecium*.

SDD ciprofloxacin prophylaxis in haematology patients was terminated: patients no longer received ciprofloxacin prophylaxis. Patients received piperacillin/tazobactam with/without gentamicin upon onset of neutropenic fever.

Isolation details (both phases): admission wards typically have two-person, four-person and single rooms and two isolation rooms. In July and September 2012, respectively, a new 30-bed intensive care unit and a new haemato-oncology ward were opened with single rooms only. In September 2013, a newly built hospital site opened and two of the three original sites were closed. Wall-mounted liquid soap and alcohol hand rub dispensers and sink present in each room. One alcohol handrub dispenser per bed (start date January 2013).

(*continued on next page*)

Table I (*continued*)

VRE screening policy
March 2012: screening of haemodialysis patients that had dialysed abroad, and screening of contacts of VRE-positive patients.
May 2012: screening high-risk wards.
June 2012: weekly hospital-wide screening.
September 2012: weekly hospital-wide screening of patients admitted for at least four days.
May 2014: in high-risk departments, weekly screening of patients admitted for at least four days. In other departments, monthly screening of patients admitted for at least four days. Once a VRE-positive patient is admitted to a ward, twice-weekly screening of patients on that ward.
October 2015: monthly hospital-wide screening of patients admitted for at least four days. In intensive care unit, weekly screening of patients admitted for at least four days. Once a VRE-positive patient is admitted to a ward, twice-weekly screening of patients on that ward.
Definitions (all phases)
ARE: ampicillin-resistant (MIC >4 mg/L), vancomycin-susceptible (MIC ≤4 mg/L) *E. faecium*.
VRE: Ampicillin- and vancomycin-resistant (MIC >4 mg/L) *E. faecium* carrying the *vanA* or *vanB* gene.
VRE-positive patient: patient with VRE cultured from clinical cultures or from a rectal swab for screening. All VRE-positive patients were labelled as such in the electronic patient records.
Contact (VRE-suspected) patient: patient who had been admitted to the same room as a VRE-positive patient or to a ward where transmission of VRE had occurred. Contact patients were labelled 'VRE-suspected' in the electronic patient record.
VRE transmission: two or more patients on same ward had AFLP-identical VRE-positive cultures.

VRE, vancomycin-resistant *Enterococcus faecium*; PCR, polymerase chain reaction; AFLP, amplified fragment length polymorphism; MIC, minimum inhibitory concentration; SDD, selective digestive decontamination.

Interventions on haemato-oncology ward

From January 2013, all patients, regardless of VRE status, were cared for in contact isolation. From March 2013, the use of ciprofloxacin prophylaxis during neutropenia was abandoned. Nowadays, empirical broad-spectrum antimicrobial therapy (i.e. piperacillin/tazobactam with/without gentamicin) is started during neutropenic fever.

VRE quarantine ward

From March to October 2013, all admitted VRE-positive patients were cared for on a separate ward manned by dedicated nurses.

Microbiology

Table II describes microbiological methods used for identification and molecular typing of VRE. At the study hospital, a *van*A/*van*B duplex polymerase chain reaction (PCR) was developed for high-throughput screening. Rectal swabs of three patients were pooled. Single enzyme amplified fragment length polymorphism (se-AFLP) typing was performed on all VRE isolates [13]. For comparison with circulating ARE isolates at the study hospital, se-AFLP was performed on 10 stored blood culture ARE isolates. From each separate AFLP type, a limited number of isolates was also typed by multi-locus sequence typing (MLST) at University Medical Centre Utrecht [14,15].

Results

Start of outbreak

In March 2012, VRE was detected in urine of three patients at two hospital locations. Screening cultures of contact patients were negative. The three VRE isolates appeared to have undistinguishable AFLP types, later identified as ST494-*vanA*. Subsequently, all patients admitted to the three wards were screened. Multiple patients tested positive. Some had been transferred to different locations in the meantime.

In April 2012, an outpatient management team was initiated. VRE surveillance was introduced in departments with patients at high risk for severe VRE infection (ICU, haemato-oncology and haemodialysis). A second VRE clone (discriminative AFLP pattern, MLST ST117-*vanB*) was detected in several patients.

Upon this finding, screening was extended to all hospital wards, using PCR screening of three patients at once. Positive PCR results without culture positivity only occurred for the *vanB* signal. During this hospital-wide screening, a third epidemic clone (ST78-*van*A) was found on two surgical wards and within haemodialysis patients.

Control of outbreak

Table III shows all recommended strategies to control a VRE outbreak in a non-endemic setting. VRE transmission occurred despite contact isolation precautions. Wards were closed, cleaned and disinfected. Initially, several wards experienced a resurgence of VRE transmission afterwards. Environmental cultures of surroundings, such as the bed, light cord and television remote control, were VRE positive. However, wards disinfected by hydrogen peroxide vapour remained free of VRE. The number of unexpected VRE-positive patients declined considerably after three months of weekly hospital-wide screening (August 2012).

Outbreak in the haemato-oncology department

In December 2012, after four months of minimal VRE transmission hospital-wide, an ST494-*vanA* outbreak occurred in the haemato-oncology department. Control was particularly difficult. Introduction of contact isolation precautions in all patients (January 2013), ward closure and disinfection did not prevent transmission. In March 2013, after comprehensive

Table II
Microbiological methods used for identification, susceptibility testing and molecular typing of vancomycin-resistant *Enterococcus faecium* (VRE)

Step	Action	Specifications
Period 1. VRE culture		
1	Overnight incubation of rectal swab in 5 mL enrichment broth	Brain–heart infusion broth with amoxicillin 0.016 mg/L, Mediaproducts BV, Groningen, Netherlands
2	Culture of broth aliquots on selective VRE media	Oxoid, Basingstoke, UK
3	MALDI-TOF identification	MALDI-TOF mass spectrometry, Bruker, Karlsruhe, Germany
4	Antimicrobial susceptibility testing	Vitek 2, bioMérieux, Marcy l'Etoile, France E-test, bioMérieux, Marcy l'Etoile, France
Period 2. Duplex vanA and vanB real-time PCR and culture		
1	Overnight incubation of rectal swab in 5 mL enrichment broth	Brain–heart infusion broth with amoxicillin 0.016 mg/L, Mediaproducts BV, Groningen, Netherlands
2	Aliquots (63 uL) of broth of three patients pooled in a single DNA isolation	DNA Isolation III kit, MagNA Pure LC system, Roche Diagnostics, Basel, Switzerland
3	*duplex vanA* and *vanB* real-time PCR on triplet	Fast Virus 1-Step Master Mix, ThermoFisher Scientific, Waltham, MA, USA; ABI Prism 7500SDS machine, Applied Biosystems, Waltham, MA, USA; standard PCR program van*A* gene PCR (cut-off positivity: Ct $\leq$ 33) Primers: van*A*For: 5′-GCC GGA AAA AGG CTC TGA A-3′ van*A*Rev: 5′-TCC TCG CTC CTC TGC TGA A-3′ TaqMan probe van*A:* FAM-ACG CAG TTA TAA CCG TTC CCG CAG ACC-TAMRA van*B* gene PCR (cut-off positivity: Ct $\leq$ 28.5) Primer van*B*For: 5′- CGC AGC TTG CAT GGA CAA-3′ van*B*Rev: 5′- GGC GAT GCC CGC ATT-3′ TaqMan probe van*B:* VIC- TCA CTG GCC TAC ATT C-MGB
4a.	PCR-positive triplet: incubation broth on selective VRE media	4b. PCR negative → three patients VRE negative
5	MALDI-TOF identification of suspected colonies	
6	*vanA*/*vanB* PCR on *E. faecium* isolates	6a. *vanA vanB* PCR positive → at least one of three patients VRE positive 6b. No growth *E. faecium* → three patients VRE negative. Negative cultures were only seen after positive *vanB* PCR
7	PCR positive: new cultures of each of the three patients for detection	Steps 4–6 repeated per patient → identification of VRE-positive patient
8	Antimicrobial susceptibility testing	Vitek 2, bioMérieux, Marcy l'Etoile, France E-test, bioMérieux, Marcy l'Etoile, France
9	se-AFLP [13]	Performed on all isolates. After restriction of isolated DNA, a primer-specific adapter was ligated. Amplified PCR products were separated on an agarose gel
10	MLST [14]	Performed on selected isolates.The alleles and sequence types were analysed and determined using the MLST database [15]

MLST, multi-locus sequence typing; PCR, polymerase chain reaction; se-AFLP, single enzyme amplified fragment length polymorphism; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight.

Table III
Recommended strategies regarding vancomycin-resistant *Enterococcus faecium* (VRE) in a non-endemic setting

Situation	Strategy	Strength of recommendation
0. No history of VRE outbreak	At least quarterly hospital-wide screening for VRE of patients admitted for at least four days	Strong
	Screening of patients who had been admitted to a hospital in a foreign country	Strong
1. Identification of single VRE-positive patient	Contact isolation precautions and electronic labelling of VRE-positive patients (and contacts)	Strong
	Screening of contact patients, e.g. by four to five separate cultures, last one at least seven days after (possible) exposure	Strong
	Inform patient and contacts	Strong
2. Suspected outbreak	Type VRE strains (in own hospital or reference centre)	Always
	Categorize patients: VRE-positive, contact/possible VRE-positive, VRE-negative. Cohort isolation	Always
	Actions to increase awareness of standard hygiene measures and improve compliance	Always
	(Audits of) Adherence to cleaning protocols	Always
3. Defined outbreak	Ward closure for new admissions	Consider
	Facilitate (large-volume) screening possibilities in laboratory, e.g. by polymerase chain reaction, pooling of patients	Always
	Optimize information and communication technology support	Always
	Inform hospital personnel (management, medical staff, nursing personnel, members of communication, safety, housekeeping and logistic departments) and mobilize for cooperation	Always
	Inform patients, surrounding hospitals, public health agency and the public	Always
	Give feedback on achievements during the outbreak	Always
	Increased surveillance, choose at least one strategy: - intensified screening of high-risk wards - intensified screening of patients admitted for at least four days - intensified hospital-wide screening of all patients	Always
	Initiation of outbreak management team	Always
	Screen all patients on hospital ward of VRE-positive patient, screen high-risk wards	Strong
	Risk of transmission to multiple persons or wards: hospital-wide screening for VRE of patients admitted for at least four days	Consider
	Notification to public health agency and/or healthcare inspectorate	Consider
	Environmental cultures	Consider
	Disinfection of rooms of VRE-positive patients with hydrogen peroxide vapour	Strong
	Disinfection of wards where VRE transmission occurs, e.g. with hydrogen peroxide vapour	Consider
	Evaluate sanitary conditions and cleaning of patient rooms and other vehicles of possible transmission	Always
	Restrictive antibiotic policy, e.g. vancomycin	Always
	VRE outpatient clinic for patient information and performing screening cultures	Consider
4. Ongoing transmission on ward, despite measures	More than contact isolation precautions alone, e.g. strict precautions, for increased awareness	Consider
	Contact precautions and electronic labelling in all (VRE-positive and VRE-negative) patients on specific ward	Consider
	Introduction of VRE quarantine ward	Consider
	Precautions specific for patient group of a particular ward	Consider
5. After recent control of VRE outbreak	Outbreak in one ward: periodical (e.g. monthly) ward screening for VRE of patients admitted for at least four days	Strong
	Outbreak in multiple wards: intensified periodical (e.g. monthly) hospital-wide screening for VRE of patients admitted for at least four days. Gradually decline frequency	Strong
	Screening of patients who had been admitted to a hospital in a foreign country	Strong

Always continue measures of previous situation.

deliberation, it was decided to discontinue ciprofloxacin prophylaxis during chemotherapy-induced neutropenia, and to transfer all known VRE-positive patients to a VRE quarantine ward under strict isolation precautions. Soon thereafter, the outbreak was controlled.

Definitive control of outbreak

After May 2013, transmission occurred incidentally. In October 2013, the quarantine ward was closed, although strict isolation precautions for VRE-positive patients were maintained throughout the hospital. Since January 2014, no further transmission of the three epidemic clones has been observed. Hospital-wide screening has been maintained, and gradually reduced to monthly intervals for wards without VRE-positive patients.

Outbreak overview

Figure 1 provides an overview of the incidence of VRE-positive patients between February 2012 and February 2014. In total, 242 VRE-positive patients were detected: 160 with ST494-*vanA*, 23 with ST78-*vanA*, 32 with ST117-*vanB* and 27 with other STs. A total of 5614 patients were labelled as contact patients. Of these contact patients, 491 died before five cultures were taken and 4370 (78%) had five consecutive negative cultures.

Weekly ward screenings took place on all ($N = 23$) clinical wards and in the haemodialysis department. Transmission occurred on 13 wards (57%). Eight wards were closed and disinfected, four of them more than once. VRE transmission occurred most frequently on the haemato-oncology ward ($N > 10$) despite intensive precautions. Of all VRE-positive patients ($N = 242$), 128 (53%) were detected by hospital-wide screening alone.

E. faecium epidemiology

se-AFLP typing revealed the presence of three outbreak clones, corresponding to the three MLST types. AFLP typing of 10 unselected ARE blood culture isolates from patients between 2010 and 2012 demonstrated the presence of one dominant ARE clone that was different from the outbreak clones. The se-AFLP pattern of one of three non-dominant ARE clones was indistinguishable from that of ST117-*vanB* (Figure 2).

Over the course of the epidemic, 27 patients had VRE with se-AFLP types distinct from the three epidemic STs; in these cases, prompt and intensified screening did not reveal transmission. Between January 2014 and January 2017, surveillance resulted in the detection of VRE in another 30 patients — all isolates with distinct se-AFLP types and without evidence of transmission.

Clinical impact

In 22 patients (9% of all VRE-positive patients), VRE was cultured from at least one clinical site (Table IV). The median time interval between first positivity in VRE-screen-positive patients and first clinical culture was 23.4 days (range 0–207 days). VRE bacteraemia was observed in seven patients (3% of all VRE-positive patients), all with severe comorbidity. Three of these patients died shortly after detection. For one of these patients (a patient with terminal pancreatic carcinoma), a direct causal role for VRE infection in death could not be excluded. Two of four surviving patients with VRE bacteraemia maintained positive faecal swabs up to four years after first detection of VRE.

Discussion

This description of a large outbreak of VRE that involved three different STs and took over a year to control shows that: (1) infection control according to international guidelines was insufficient to expose the outbreak to its full extent or control it; (2) successful control of a hospital-wide VRE outbreak is feasible, but requires great effort; and (3) the outbreak had limited clinical consequences [5,6,16,17].

This study demonstrated that relying on clinical cultures without regular surveillance will result in incomplete and considerably delayed detection of VRE, or no detection at all. Surveillance of high-risk patients, according to international guidelines, is insufficient if radical eradication is pursued [5,6,16,17]. Two STs were only detected during hospital-wide screening, in departments not associated with earlier known VRE transmission. Indeed, recent studies have demonstrated that a hospital-wide screening programme was required to

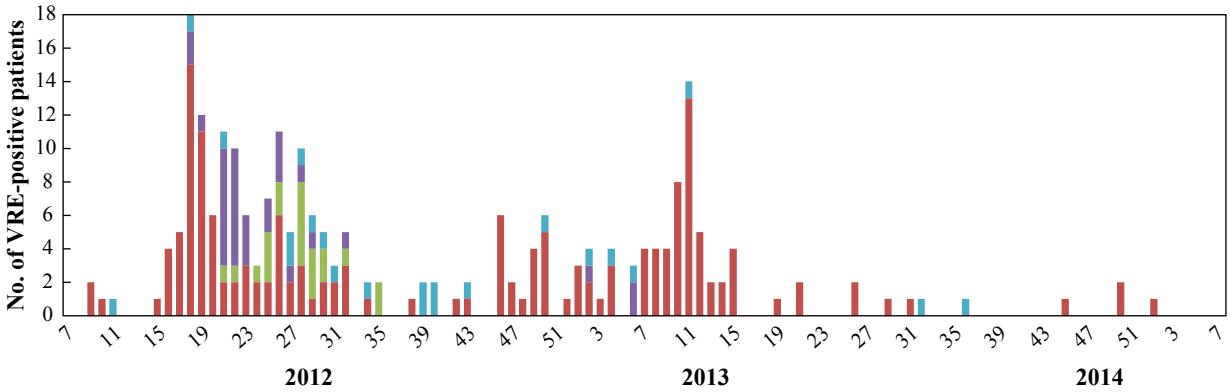

Figure 1. Epidemiological curve of new vancomycin-resistant enterococcus (VRE)-positive patients in time. ST494 was the dominant strain (red bars) that affected most patients ($N = 160$) and remained present for more than one year. After May 2013, all patients identified with outbreak strains were VRE-suspected patients. Two smaller outbreaks with ST78 (green bars, $N = 23$) and ST117 (purple bars, $N = 32$) were controlled more easily. Twenty-seven patients with different non-epidemic strains (blue bars) were detected.

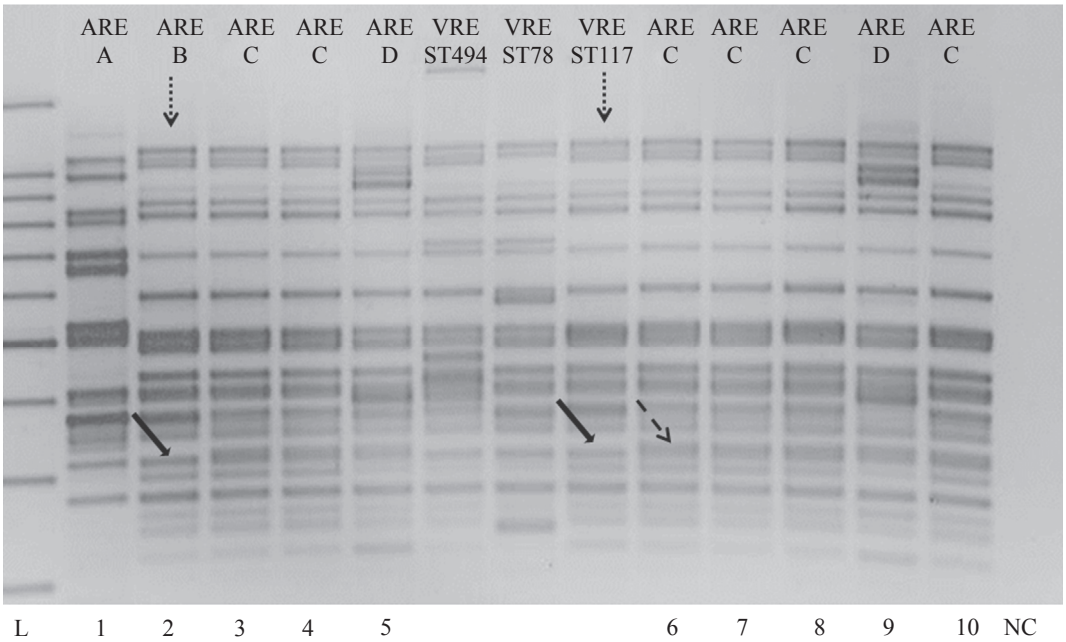

Figure 2. Amplified fragment length polymorphism (AFLP) typing patterns of the three epidemic vancomycin-resistant *Enterococcus faecium* (VRE) clones and ampicillin-resistant, vancomycin-susceptible *E. faecium* (ARE) clones of 10 different patients. Numbers 1–10 represent unselected ARE clones of blood cultures of 10 different patients over the period 2010–2012. One dominant ARE clone was seen (C), which did not correspond to one of the VRE outbreak clones. The AFLP type of ARE B was identical to that of the ST117 outbreak clone (dotted arrows). These clones have a single band (straight arrow) compared with a double band in ARE C (broken arrow). NC, negative control; L, 100-bp DNA ladder, with bands from 100 to 1500 bp.

identify all carriers, and that weekly screening helps to prevent nosocomial transmission of VRE [18,19]. The authors' experience confirmed that at least four to five rectal swabs for screening culture, collected on separate days, after the end of exposure are required [8]. The last culture should ideally be performed at least seven days after the last possible exposure [20]. The authors suggest limiting the screening to patients admitted for at least four days as transmission and subsequent rectal colonization takes time. This drastically reduces the number needed to be screened.

This study showed that successful control of a hospital-wide VRE outbreak requires active surveillance, effective and

Table IV
Characteristics of detection and clinical impact of vancomycin-resistant *Enterococcus faecium* (VRE)

	MLST 494 *vanA* *N* (%)	MLST 78 *vanA* *N* (%)	MLST 117 *vanB* *N* (%)	Other VRE *N* (%)	Total *N* (%)
Total no. of VRE-positive patients	160	23	32	27	242
Reason for culture with VRE:					
Labelled, contact screening[a]	74 (46)	7 (30)	13 (41)	4 (134)	98 (41)
Ward screening, not labelled	74 (46)	16 (70)	18 (59)	20 (65)	128 (53)
Clinical culture, not labelled	12 (8)	0 (0)	1 (0)	3 (11)	16 (3)
Patients with at least one positive clinical culture:	18 (11)	0	3 (9)	1 (0.5)	22 (9)
Blood	6 (4)	0	1 (3)	0	7 (3)
Intravascular catheter	3 (2)	0	0	0	3 (1)
Wound/pus	4 (3)	0	1 (3)	1 (0.5)	6 (2)
Urine	7 (4)	0	2 (6)	0	9 (4)
Other	1 (0)	0	1 (3)	0	2 (1)
Median (range) duration until first positive clinical culture (days)[b]	26.7 (0–207)	–	18.7 (3–69)	1 (1)	23.4 (0–207)

MLST, multi-locus sequence typing.
Overview of VRE-positive patients and their positive clinical cultures between March 2012 and January 2014.
[a] Patients that were electronically labelled because they were at risk for VRE carriage: contacts of VRE-positive patients, patients that dialysed abroad and family members of VRE carrier.
[b] Time from identification as a VRE carrier until positivity of the first clinical culture.

persistent infection control measures, and good communication between all stakeholders [19,21]. Recommended control strategies are summarized in Table III. Identification of VRE-positive patients, hand hygiene, education, contact precautions, active surveillance, environmental cleaning and antibiotic stewardship are known strategies in the prevention and control of VRE infections [5,8,19,22,23]. Initially, multiple transmission events occurred despite these precautions, probably because of survival of VRE in the environment, as demonstrated by environmental cultures [9]. The additional measures to control the outbreak effectively included: (1) hospital-wide screening using a PCR-based high-throughput screening method; (2) strict isolation precautions for VRE-positive patients; (3) contact tracing, labelling and screening of all patients on wards with VRE transmission; (4) closure and intensive cleaning of hospital wards with VRE transmission, with special attention to sanitary equipment, and hydrogen peroxide disinfection; (5) discontinuation of ciprofloxacin prophylaxis for haematology patients on chemotherapy; and (6) the introduction of a temporary VRE quarantine ward. Double-door separation, limited access of non-nursing personnel to these rooms and increased awareness may explain the added value of strict isolation precautions rather than the use of masks and caps [5]. Disinfection of rooms by hydrogen peroxide vapour was a novel approach, but has been shown to reduce the risk of VRE acquisition by 80% [24]. Increased awareness, dedicated nurses and physical separation were possible factors leading to the success of the VRE quarantine ward. Full support of the board of directors, the management team and the medical staff was crucial for the successful implementation of these measures and control of the epidemic.

The outbreak had a large impact on the entire hospital, including personnel and patients. The total costs for the hospital were estimated to be at least €2 million (40% laboratory, 30% nursing wards, 15% cleaning, 15% infection control). Hundreds of patients experienced disturbing isolation precautions, and even more were subjected to frequent rectal cultures. Once control had been achieved, surveillance had to be maintained, albeit at longer intervals. The work load of the department of medical microbiology and infection prevention increased significantly for months. It is the authors' belief that, in addition to routine VRE typing of *E. faecium* isolates from clinical samples, at least quarterly hospital-wide surveillance of patients admitted for at least four days should be strongly considered to prevent such large outbreaks. The enormous impact of unnoticed transmission justifies the financial expenses of active surveillance. After a recent outbreak, the surveillance frequency should be increased and then decreased gradually. As a result of all these efforts, the study hospital remained free of VRE transmission for the last three years. As a positive side effect of the VRE outbreak and all efforts to contain it, the awareness of healthcare workers regarding infection control in general has increased considerably at the study hospital.

The outbreak had limited clinical consequences; only 9% of VRE-positive patients had VRE in clinical cultures. Even fewer infections were observed, probably due to the low pathogenicity of VRE. Bacteraemia was observed in 3% of VRE-positive patients. As >80% of the entire hospital population was screened, this prevalence appears to be a reliable risk estimate for VRE-related disease. In contrast to previous studies, the present study did not observe VRE-related mortality, with one possible exception [1,2]. However, further studies to assess VRE-attributable risks are required to determine whether efforts to keep hospitals free of VRE are warranted in non-endemic countries.

The question remains how these three STs were first introduced to the study hospital. VRE had only been detected incidentally in Dutch citizens until 2011 [11]. This outbreak was one of the first outbreaks in the country for years. However, from 2012 to 2014, 26 new VRE outbreaks were reported and many more have been reported since [25]. The time needed to detect VRE in the study patients implies nosocomial acquisition. Both clonal lineages and plasmids influence the spread and persistence of vancomycin resistance among *E. faecium* [26,27]. Comparison with the endemic ARE clones in this study indicates that VRE ST117-*vanB* may have evolved from circulating ARE, possibly due to introduction of *vanB*-containing mobile genetic elements from gut anaerobes [28]. Nevertheless, some ST117-*vanB* patients had been transferred from one of more than 25 Dutch hospitals in which this ST was detected between 2012 and 2017, causing outbreaks in some of them. The AFLP patterns of ST494-*vanA* and ST78-*vanA* were clearly different from the endemic ARE isolates in this study; ST494 had not been reported in Dutch hospitals before this outbreak (Prof. R.J. Willems, personal communication). Most likely, therefore, they were introduced to the study hospital shortly before first detection. Acquisition of *vanA* genes has been described in ARE [29]. Hospital-wide surveillance for more than four years found no evidence for repeated introduction of these two epidemic STs into the hospital from the environment, but they were detected in other hospitals between 2012 and 2017.

In conclusion, successful control of a hospital-wide VRE outbreak is feasible in a non-endemic country, but requires great effort involving hospital-wide surveillance to expose its full extent. For effective control, more extended measures are needed than those formulated in current international guidelines [5,6,17]. Final containment and eradication of the epidemic STs was achieved by environmental decontamination with hydrogen peroxide vapour, strict isolation precautions, a VRE quarantine ward and antimicrobial stewardship. Whether the benefits outweigh these efforts should be debated at national and international level.

Acknowledgements

The authors wish to thank Prof. Rob Willems for data on Dutch VRE epidemiology and interpretation of the molecular typing data of VRE.

Conflict of interest statement
None declared.

Funding sources
None.

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