



Vancomycin Resistant Enterococci:

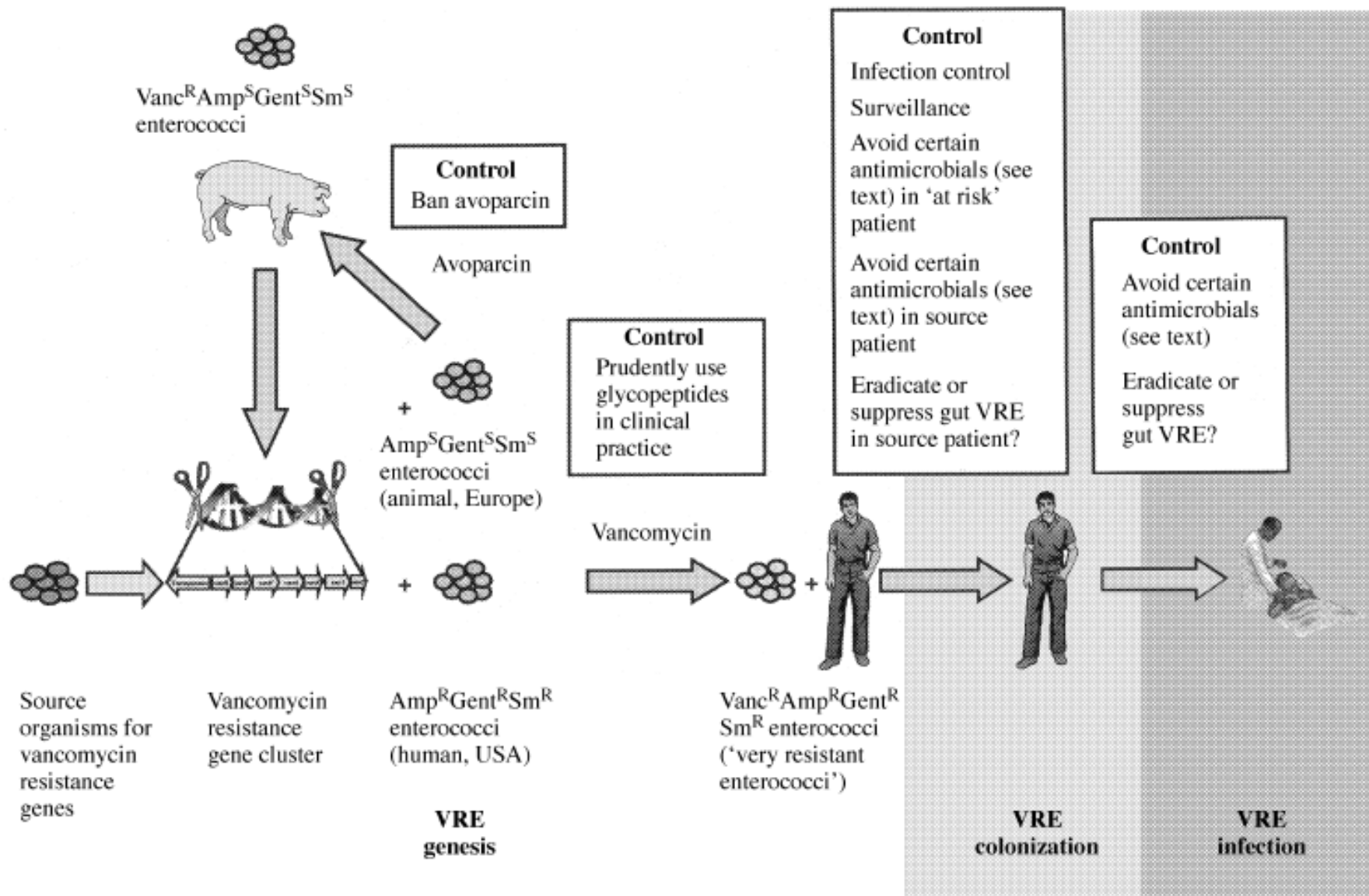
***Colonization**

***Detection**

***Prevention**

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Glycopeptide resistance types

	Acquired resistance								Intrinsic resistance
	high level		variable	moderate		low level			low level
	VanA	VanM	VanB	VanD	VanE	VanG	VanL	VanN	VanC1/C2/C3
Susceptibility									
Vancomycin	R	R	r-R	R	r	r	r	r	r
Teicoplanin	R	R	S	r-R	S	S	S	S	S
Transferability	+	+	+	-	-	+	-	+	-
Main enterococcal species	A/B ^a	A	A/B	A/B	B	B	B	A	G/D
Expression	I	?	I	C	I/C	I	I	C	C/I
Genetic location	Plasmid (Chr)	Plasmid (Chr)	Chr (plasmid)	Chr (plasmid)	Chr	Chr	?	Chr	Chr
Precursors end	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Lac	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser	D-Ala-D-Ser



VRE and the host

- Initial colonization followed by persistence rather than lethality
- Heavy stool colonization with numbers of enterococci exceeding 10^8 – 10^9 cfu/g of faeces precedes infection
- The reasons for this colonizing capacity are not fully understood
- Oxidative stress serves as an important host/environmental signal that triggers a wide range of responses in microorganisms like
 - Diminished susceptibility to penicillins, vancomycin and cationic antimicrobial peptides
 - Increased adhesion, biofilm formation and host colonization
 - A mutator phenotype and enhanced DNA transfer frequencies



VRE isolation sites

- Stool and perirectal swabs
- Groin
- Upper arms
- Oropharyngeal aspirate
- Duodenal aspirate
- Endotracheal aspirate



Risk factors for VRE colonization

- Immun suppression
- Severe underlying disease
- Hospitalization in ICUs
- Use of extended spectrum antibiotics
- Having an intraabdominal or cardiothoracic surgical procedure
- Having an indwelling catheter (urinary or central venous) or a nasogastric tube



Duration of VRE colonization

- The median duration of culture positivity of VRE is 6 weeks after discharge
- The median time to clearance after discharge is 9 weeks
- Prolonged colonization is related to:
 - Surgery
 - Antibiotic use during admission
 - Dialysis



VRE infection

- Develops in VRE-colonized patients, with the ratio of 8 to 11% depending on the patient population
- Portals of entry
 - the urinary tract,
 - intraabdominal or pelvic sources,
 - wounds and intravascular catheters.
- Isolation of VRE from the urine alone may be because of asymptomatic bacteriuria and therefore has limited clinical significance.
- Skin colonization may compromise the evaluation of blood cultures.
- Evaluation of risk factors are important for right interpretation



VRE epidemiology

- Infectious diseases caused by VRE have increased noticeably in recent years
- The proportion of VRE isolates continues to increase:
 - >1% in 1990
 - 15% in 1997
 - 28% in 2000
 - 87% in 2010
- Ability of enterococci to survive on inanimate surfaces increases the risk of transmission

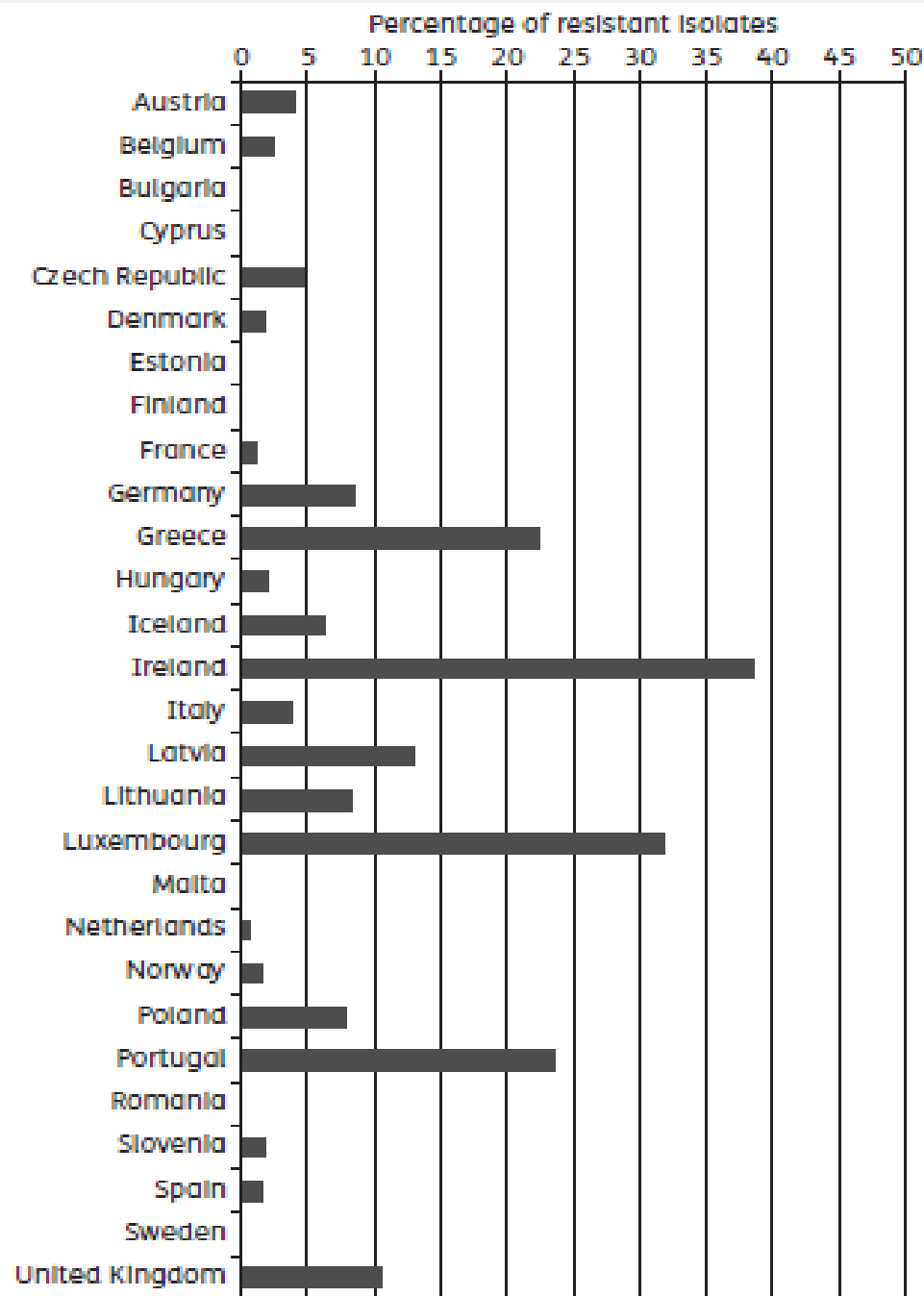
**NNIS, Am J Infect Control, 2003; 31: 481-498*

**Edelsberg J, et al. Diagn Microbiol Infect Dis, 2013.*



VRE epidemiology in Europe

- In 2005
- SENTRY antimicrobial surveillance program
- Boodstream isolates
 - France, Sweden and Switzerland: 0%
 - England: 66.7%
 - Ireland: 71.4 %
 - Turkey: 8.6 %



EARSS 2010

www.rivm.nl/earss/result/

Figure 2. Percentage of vancomycin resistance in *E. faecium* blood isolates from European countries in 2010.⁴

Extensive contact tracing and screening to control the spread of vancomycin-resistant *Enterococcus faecium* ST414 in Hong Kong

CHENG Vincent Chi-chung, TAI Josepha Wai-ming, NG Modissa Lai-ming, CHAN Jasper Fuk-woo, WONG Sally Cheuk-ying, LI Iris Wai-sum, CHUNG Hon-ping, LO Wai-kei, YUEN Kwok-yung and HO Pak-leung

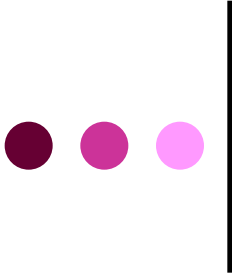
Keywords: vancomycin-resistant *Enterococcus faecium*; ST414; outbreak; contact tracing; screening

Background Proactive infection control management is crucial in preventing the introduction of multiple drug resistant organisms in the healthcare setting. In Hong Kong, where vancomycin-resistant enterococci (VRE) endemicity is not yet established, contact tracing and screening, together with other infection control measures are essential in limiting intra- and inter-hospital transmission. The objective of this study was to illustrate the control measures used to eradicate a VRE outbreak in a hospital network in Hong Kong.

Methods We described an outbreak of VRE in a healthcare region in Hong Kong, involving a University affiliated hospital and a convalescent hospital of 1600 and 550 beds respectively. Computer-assisted analysis was utilized to facilitate contact tracing, followed by VRE screening using chromogenic agar. Multi-locus sequence typing (MLST) was performed to assess the clonality of the VRE strains isolated. A case-control study was conducted to identify the risk factors for nosocomial acquisition of VRE.

Results Between November 26 and December 17, 2011, 11 patients (1 exogenous case and 10 secondary cases) in two hospitals with VRE colonization were detected during our outbreak investigation and screening for 361 contact patients, resulting in a clinical attack rate of 2.8% (10/361). There were 8 males and 3 females with a median age of 78 years (range, 40–87 years). MLST confirmed sequence type ST414 in all isolates. Case-control analysis demonstrated that VRE positive cases had a significantly longer cumulative length of stay ($P < 0.001$), a higher proportion with chronic cerebral and cardiopulmonary conditions ($P = 0.001$), underlying malignancies ($P < 0.001$), and presence of urinary catheter ($P < 0.001$), wound or ulcer ($P < 0.001$), and a greater proportion of these patients were receiving β -lactam/ β -lactamase inhibitors ($P = 0.009$), carbapenem group ($P < 0.001$), fluoroquinolones ($P = 0.003$), or vancomycin ($P = 0.001$) when compared with the controls.

Conclusion Extensive contact tracing and screening with a “search-and-confine” strategy was a successful tool for outbreak control in our healthcare region.



Extensive contact tracing and screening to control the spread of vancomycin-resistant *Enterococcus faecium* ST414 in Hong Kong

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- An outbreak in healthcare region in Hong Kong
- A case control study to identify the risk factors and nosocomial acquisition of VRE
- 11 patients colonized with VRE were detected in 20 days period
- 1 exogenous and 10 secondary cases
- Clinical attack rate: 2.8%
- Risk factors
 - Length of stay
 - Severe underlying diseases
 - Presence of urinary catheter
 - Wound ulcer
 - Use of BL-BLinh combinations, carbapenems, fluoroquinolones, and vancomycin



VRE epidemiology in Turkey ⁽¹⁾

- Pediatric oncology hospital in Gaziantep, Turkey
- Point prevalence study following an index case
- VRE colonization: 14.6 % (18/123)
- Point prevalence study has been repeated following training and infection control measures
- VRE colonization rate amongst the patients who were hospitalized more than 3 days, was 3.3 % (8/242)



Epidemiology in Turkey ⁽²⁾

- Erzurum, Atatürk University Hospital, 2008-10
- Colonization rate in burn patients
- Swabs were taken from rectal, umbilical region, throat and axilla
 - At the admission: 0
 - 7th and 14th days: 0.8 %
 - 28th day: 7 %
- VRE most frequently isolated from rectal swabs
- Correlation between colonization rate and infection with VRE in burn patients

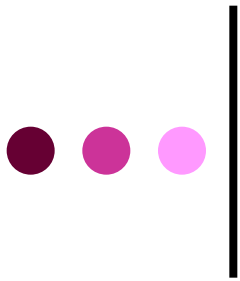
Management of Multidrug-Resistant Organisms In Healthcare Settings, 2006

- V.A.4.a. In microbiology laboratories, use standardized laboratory methods and follow published guidance for determining antimicrobial susceptibility of targeted and emerging MDROs. **Category IB**
- V.B.1.b. Continue to monitor the incidence of target MDRO infection and colonization after additional interventions are implemented. If rates do not decrease, implement more interventions as needed to reduce MDRO transmission. **Category IB**
- V.B.5.b.i. Obtain ASC from areas of skin breakdown and draining wounds. In addition, include the following sites according to target MDROs:
 - For VRE: Stool, rectal, or perirectal samples should be collected. **Category IB**



Screening methods

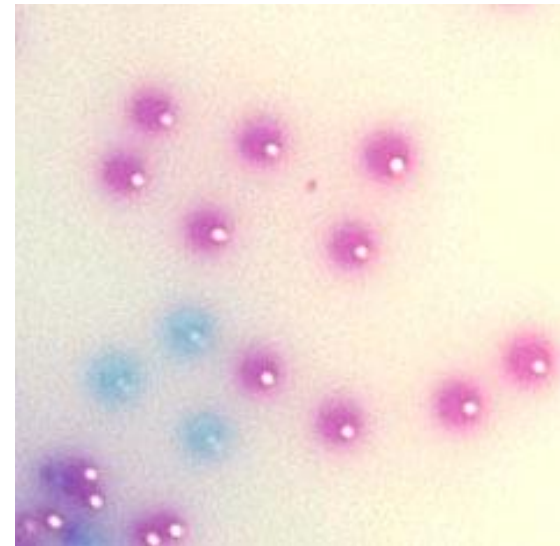
- 3-5 days is required for VRE culture
- Faster by using chromogenic agar media
- Isolation of the patient until the result of culture is cumbersome and expensive
- The risk for transmission of VRE is high in between
- PCR screening is faster but more expensive



Enterococcosel Agar



Chromogenic agars





Experience in Erciyes University Hospital, Kayseri, Turkey





1800 beds in total

- Burn unit
- 100 bed ICU
- Bone-marrow transplantation unit
- Hematology-oncology dept





Routine screening in Erciyes University Hospital : 2008-2009

- Screening at high-risk departments
 - Intensive care units
 - Hematology-Oncology dept
- Perirectal swab cultures were taken once in a month
- If positive, screening of all patients in the department was done once in a week
- In the absence of positive culture for 3 consecutive weeks, isolation measures which were taken for the patient were stopped
- In the absence of positive culture for 4 consecutive weeks in all patients in the department, screening was continued once in a month



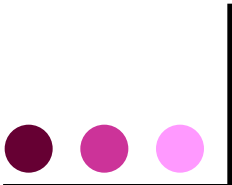
Extension of routine screening

- VRE screening in ERU Hospitals first started in ICUs in November 2008
- After isolation of clinical isolates of VRE in pediatric wards, screening was extended to the neonatal ICU
- As a result of the increasing number of patients colonized at each screening, it was decided to use molecular tests in March 2009

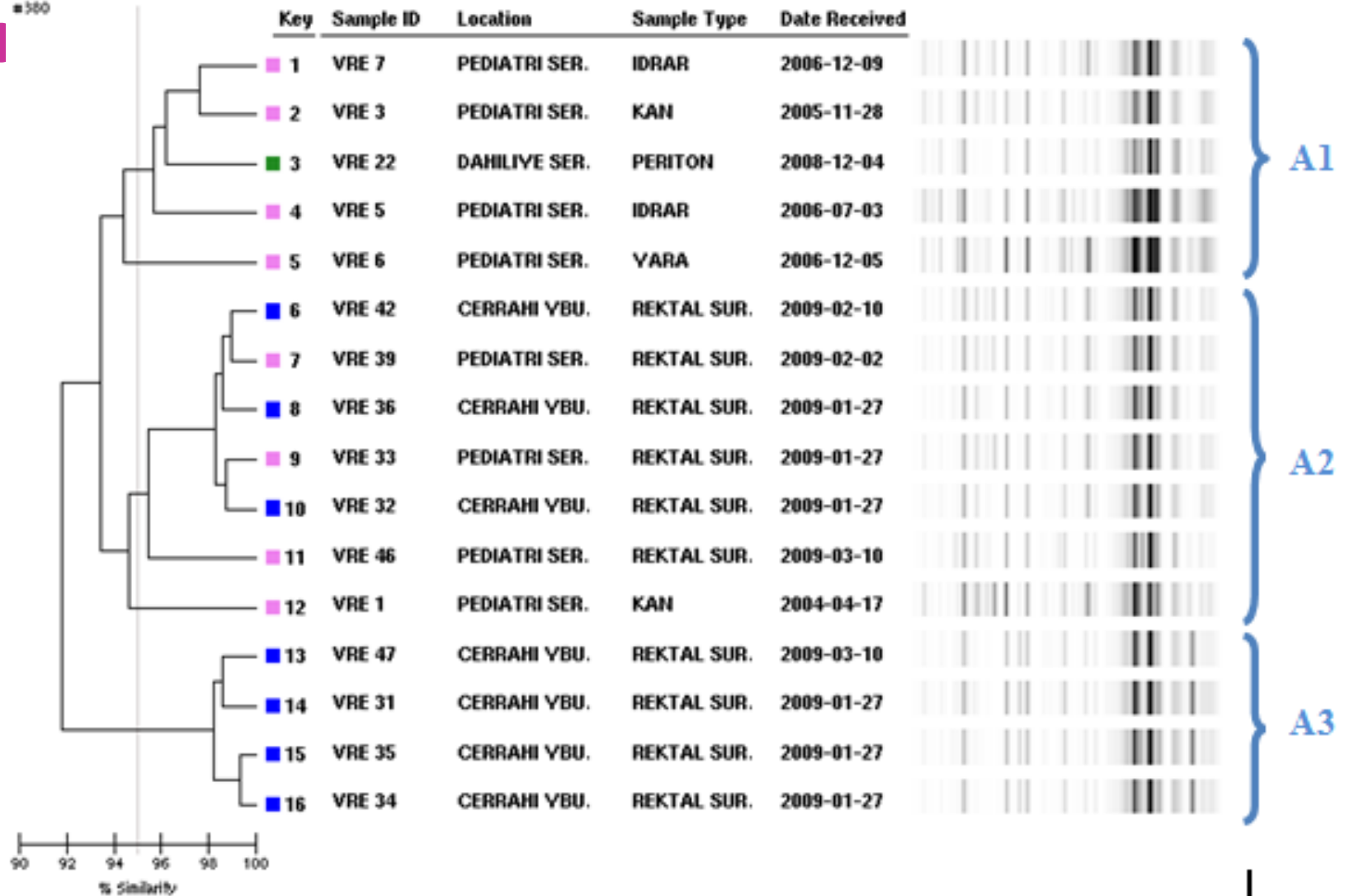


Molecular epidemiology of VRE in Erciyes University Hospital

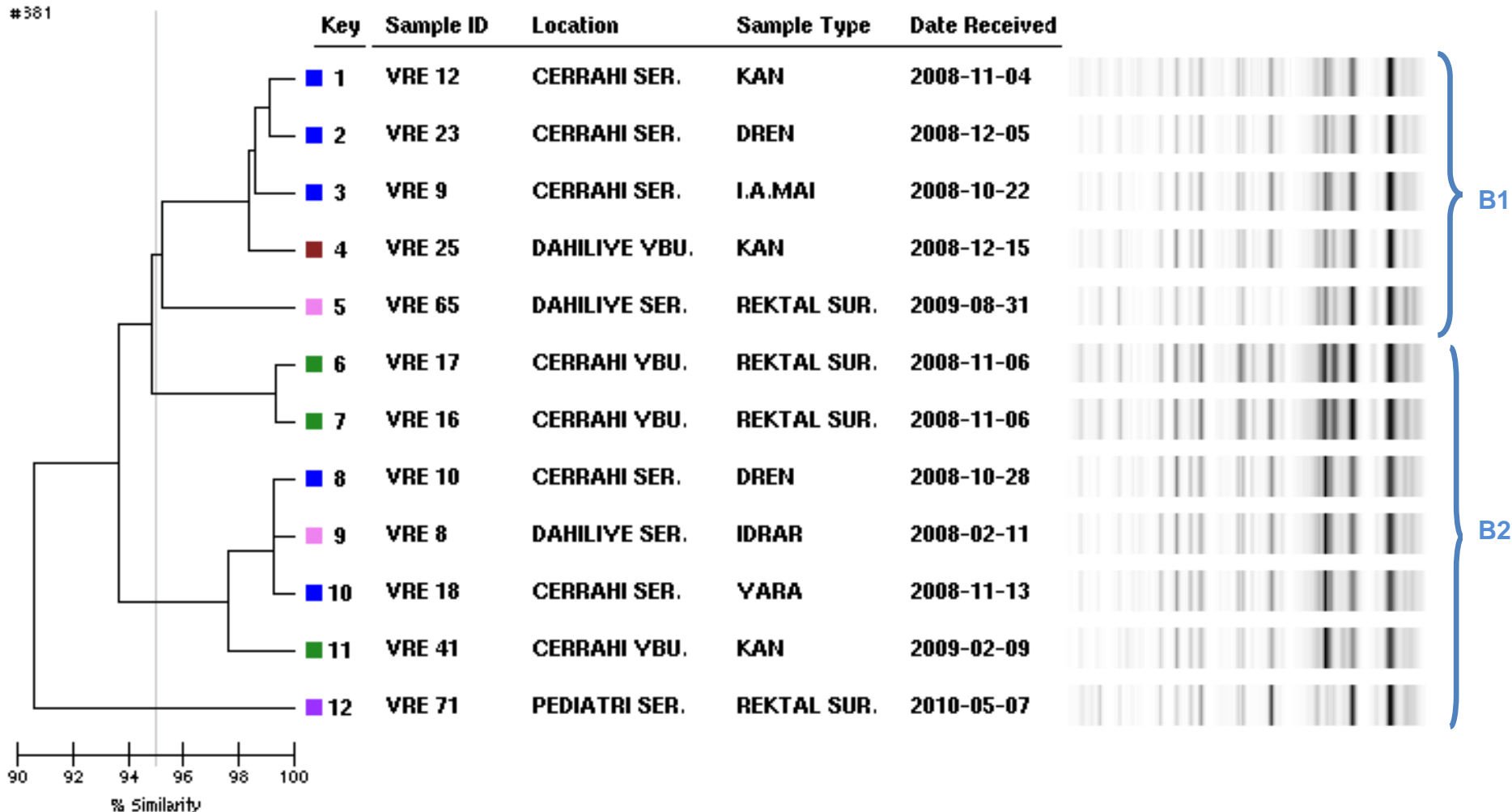
- 89 VRE isolates
- Diversilab rep-PCR
- 12 different clones were found and 7 of them were the main clones (A-G)
- The first strains of each of the clones were isolated from clinical specimens. Following that rapid colonization of hospitalized patients in the related clinics that have been observed



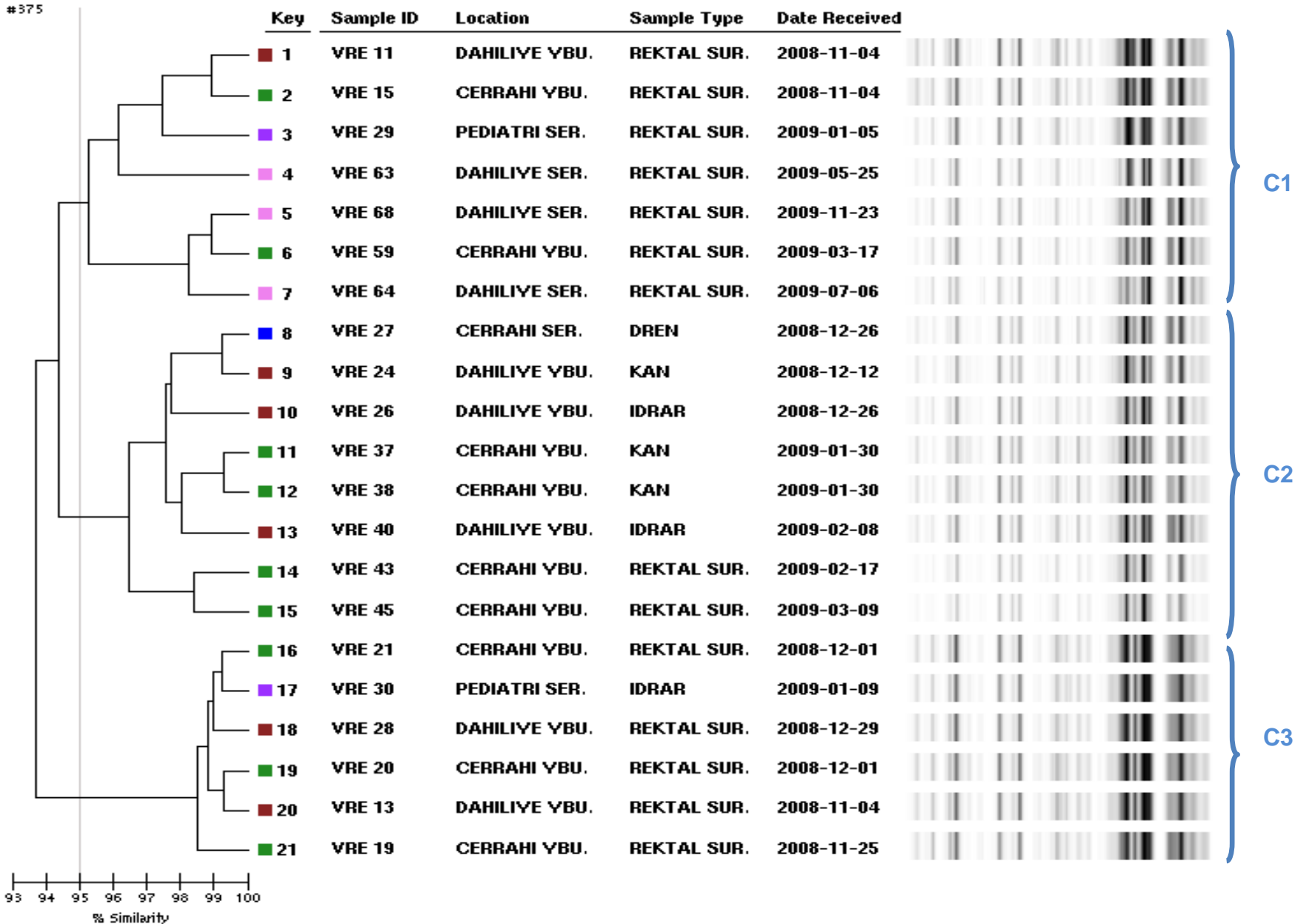
	Perirectal swab (%)	Blood (%)	Urine (%)	Wound (%)	Dren (%)	Peritoneal fluid (%)	Intra abdominal fluid (%)	In total
Pediatric	34 (56.7)	6 (46.2)	3 (37.5)	1 (33.3)				44
Surgical ICU	16 (26.7)	3 (23)	1 (12.5)					20
Internal Medicine	7 (11.6)	1 (7.7)	2 (25)			1 (100)		11
Surgery		1 (7.7)		2 (66.7)	3 (100)		1 (100)	7
Medical ICU	3 (5)	2 (15.4)	2 (25)					7
In total	60	13	8	3	3	1	1	89



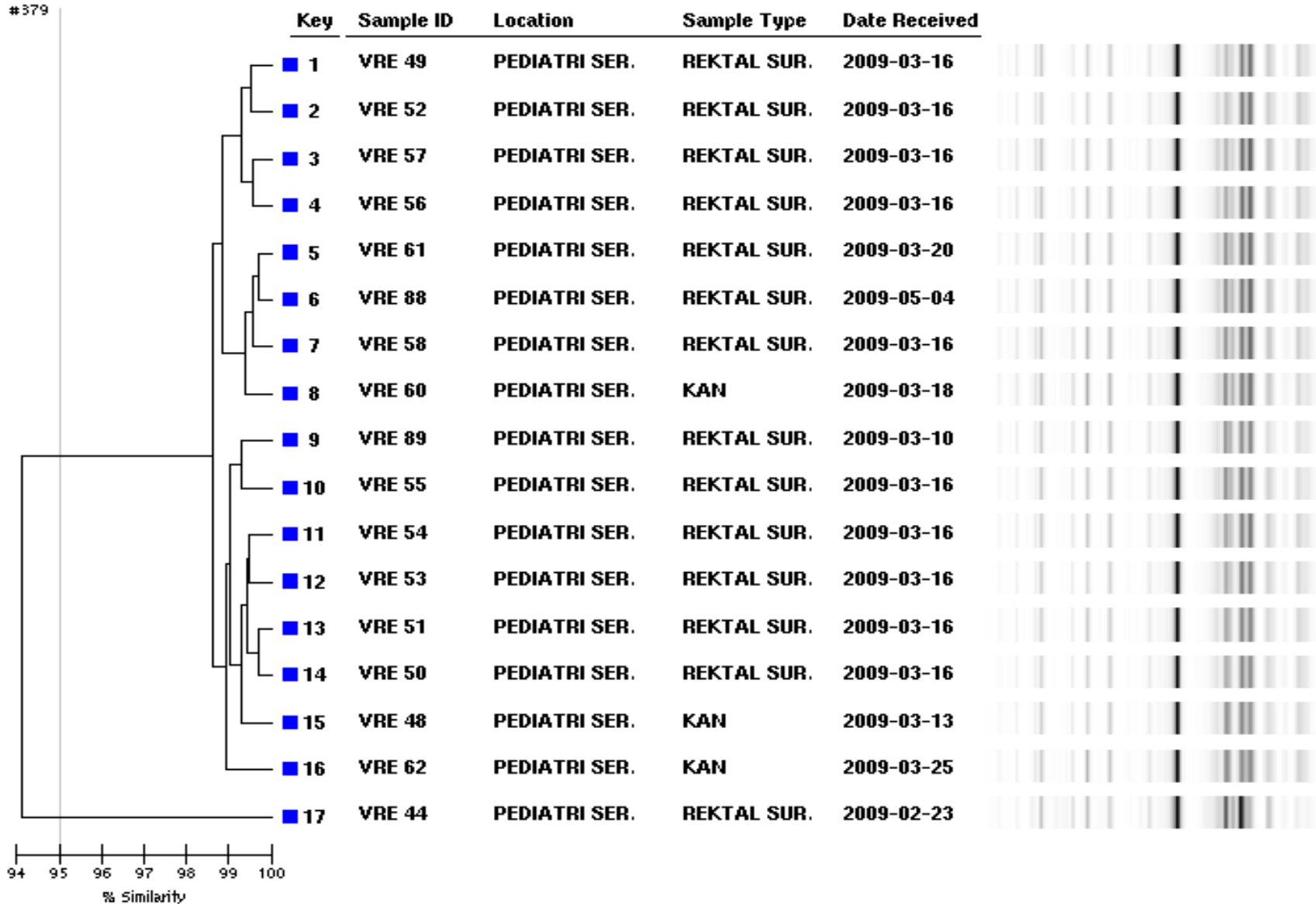
Dendrogram of Clone A



Dendrogram of Clone B

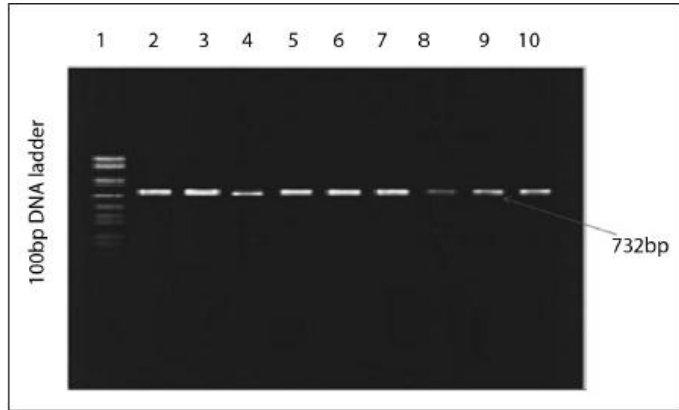


Dendrogram of Clone C



Dendrogram of Clone G

Decision making for a faster detection method



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Our selection criteria

- Fast
- Reliable
- Convenient to work directly from clinical samples
- Convenient to use in central labs working 24 hours
 - No need for specialist
 - No need for long preparations
 - No need for interpretation



Assigned weighted point values

- ICU readmission 1 point
- Chronic obst. lung disease 2 point
- Antibiotic treatment 3 point
- Vancomycin use 2 point

On the basis of risk scores ≥ 3 point

Sensitivity: 84.2 %

Specificity: 82.5 %

PPV: 15.2 %

NPV: 99.3 %

Reduction in the screening volume (by 80.1%)



Indications for PCR in Erciyes University Hospital

- Chemotherapy
- Admission from another hospital
- Antibiotic use at admission
- Intraabdominal surgery
- Severe predisposition
- Immunsuppression
- Hospitalization
- Chronic renal failure



First outbreak after PCR ⁽¹⁾

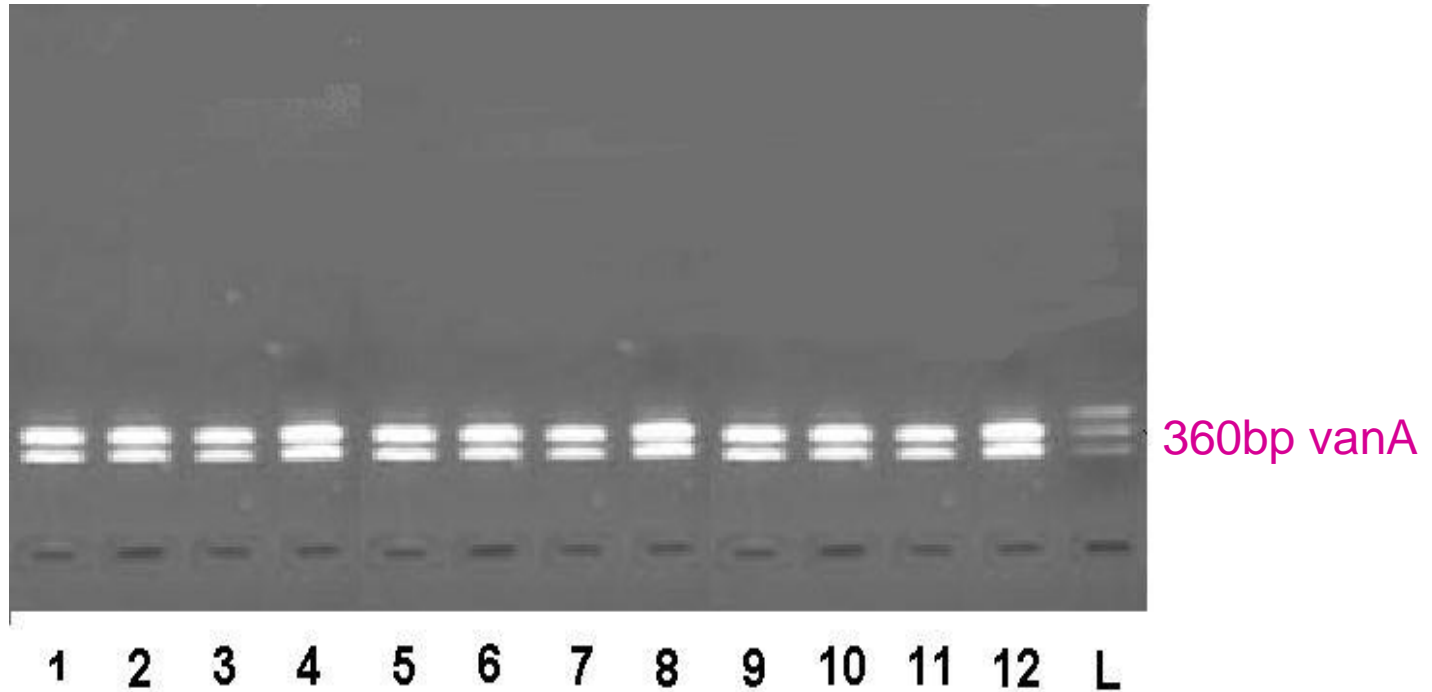
- VRE isolated from 12 patients hospitalized in neonatal ICU in May 2010
- The isolates identified by using API Rapid 32 Strep kit (Bio Merieux, Fransa)
- Susceptibilities of the isolates to vancomycin and teicoplanin were tested by using E-test (AB-Biodisk, Solna, İsveç)
- rep-PCR (DiversiLab, Biomerieux, Fransa) was used to investigate clonal relationship
- Vancomycin resistance genes were investigated by using Seeplex VRE ACE Detection multiplex PCR kit (Seegene, Kore)



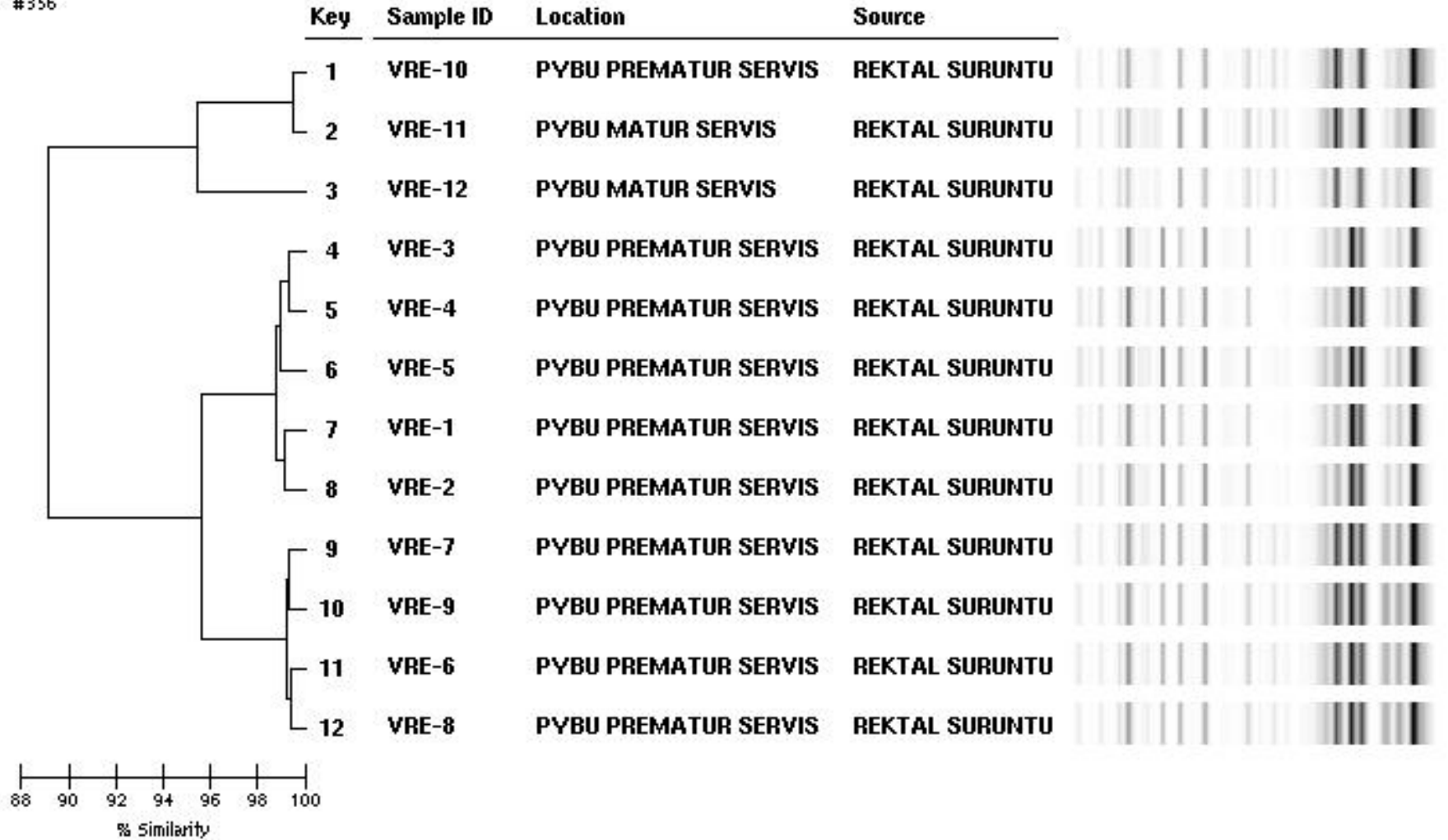
First outbreak ⁽²⁾

- All isolates were *vanA* positive *Enterococcus faecium* and resistant to vancomycin and teicoplanin
- 2 different clones were found with rep-PCR
 - 9 out of 12 belonged to clone A (75%),
 - 3 out of 12 belonged clone B (25%)
- Index case was a patient sent from another hospital 20 days ago
 - Never seen at our hospital before

● ● ● | All isolates were *vanA* positive
Enterococcus faecium



Diversilab v3.4
PC
#356





Second outbreak

- 2011
- A baby was sent from another city hospital for ophthalmologic examination
- Diagnosis of congenital heart disease
- The doctor on duty forgot to send perirectal swab for PCR at the admission
- One week later 15 babies at the same department colonized with same VRE



Third outbreak

- September 2012
- A patient sent by another hospital was admitted to haematology-oncology department
- Despite the indication, no order for PCR
- Result of routine screening for VRE following week
 - 20 patients were colonized with genetically the same VRE



An update at the wards

- Repetitive education courses
- Sanctions with the approval of head doctor
 - Official warning letters
 - Investigations
 - If necessary, punishment
- Audits from Infection Control Team
- Audit of admission from emergency department



Screening results in Erciyes University Hospital

Year	2009	2010	2011	2012
Rectal swabs (+)	5436 (167)	3909 (29)	8929 (192)	12422 (240)
PCR (+)	112 (29)	231 (31)	1052 (102)	1531 (191)
Colonization rate	3.1 %	0.7 %	2.1 %	1.9 %
Infection rate	0.2 %	0.1 %	0.1 %	0.2 %
Colonization/infection rate	7.1 %	13.7 %	4.6 %	11.3 %



Comparison of genexpert *vanA/vanB* real time-PCR with culture in VRE detection

- 2009-2011
- In total 1574 rectal swabs were evaluated
- Cepheid Genexpert *vanA/vanB* real time PCR (Cepheid, CA, USA)
- Chromogenic agar (bioMerieux, France)



1574 rectal swabs

		CULTURE	
		POSITIVE	NEGATIVE
PCR	POSITIVE 134 (133 vanA, 1 vanB)	118	51 (35*)
	NEGATIVE 1405	0	1405

Results of the comparison study

- *vanB* detected 25 of patients who had PCR-positive, culture-negative result
- Rectal swab cultures became positive in two weeks in 16 patients who were culture-negative, PCR-positive
- In 4 of 9 patients who were PCR-positive, culture-negative, weekly screening could not be done as they died
- 4 patients received antimicrobial therapy for VRE infection

Evaluation of the RT-PCR

	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)*	NPV (%)**
RT-PCR*	100	97	86.8	100

GeneXpert *vanA/vanB* Real Time PCR

Durmaz S, Erçal BD, Atalay A, Perçin D. 35. TMC Kongresi, 2012



Conclusions of the study ⁽¹⁾

- Genexpert vanA / vanB RT-PCR is a fast and sensitive method that can be used for early identification of VRE colonization
- It is remarkable that in one week PCR positive culture negative patients became positive
- Mismatch between culture and PCR in terms of vanB may be due to anaerobic bacteria in faecal flora carrying vanB resistance genes or inhibition of the strains with 6-8 mg/L vancomycin used in.



Conclusions of the study ⁽²⁾

- Possible reasons for PCR positive culture negative cases
 - DNA positivity may continue for a while due to dead bacteria
 - Due to growth of VRE in their blood cultures, two patients were receiving linezolid
- Isolation of patients positive by PCR is necessary to control the infection.
- Confirmation with culture is not necessary



Cost analysis (2012)

- 240 VRE positive in 12422 screening culture
 - Chromogenic agar – 1,5 \$
 - Additional tests – 1 \$
 - Identification and susceptibility – 10 \$
- **Total cost - 33.460 \$**

- If we have performed 12422 PCR
 - PCR-40 \$
- **Total cost – 496.880 \$**
- Cost for negative tests – 487.280 \$



Arch Intern Med. 2002 Oct 28;162(19):2223-8.

Health and economic outcomes of vancomycin-resistant enterococci.

Carmeli Y, Eliopoulos G, Mozaffari E, Samore M.

Division of Infectious Diseases, Tel Aviv Sourasky Medical Center, 6 Weizman St, Tel Aviv 62749, Israel. ycarmeli@caregroup.harvard.edu

Abstract

(1) case fatality rate, 17% vs 6% (RR, 2.13; $P = .04$);

cci (cases)

with those of control subjects matched for length of hospital stay until inclusion in the cohort, hospital location, and calendar date. The propensity to be a vancomycin-resistant enterococci case was modeled based on patient characteristics, and included in multivariable models to adjust for

(2) length of stay after inclusion in the cohort, 15.1 vs 8.5 days

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RESULTS: A total of 233 cases were compared with 647 controls. Groups were similar in age (mean, 62 years), sex (female, 47%), and length of stay before inclusion in the cohort (mean, 8.1 days), but differed in primary diagnosis and comorbidities, past infection or colonization with methicillin

transfer to an institution, 51% vs 35% (RR, 2.01; $P = .001$).

cluded in

follows: (1) case fatality rate, 17% vs 6% (RR, 2.13; $P = .04$); (2) length of stay after inclusion in the cohort, 15.1 vs 8.5 days (RR, 1.73; $P < .001$); (3) hospital costs, \$52 449 vs \$31 915 (RR, 1.40; $P < .001$); (4) surgery after inclusion in the cohort, 18% vs 10% (RR, 2.71; $P = .001$); (5) intensive care

hospital costs, \$52 449 vs \$31 915 (RR, 1.40; $P < .001$);

.01).

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adverse outcomes: increased mortality, morbidity, and costs.

SHORT REPORT

Open Access

Eradication of an outbreak of vancomycin-resistant *Enterococcus* (VRE): the cost of a failure in the systematic screening

Lélia Escaut^{1*}, Samir Bouam², Marie Frank-Soltysiak³, Eric Rudant⁴, Faouzi Saliba⁵, Najiby Kassis⁶, Paul Presiozi⁷ and Daniel Vittecoq¹

Abstract

Background: Vancomycin-resistant enterococci (VRE) are still a concern in hospital units tending to seriously ill patients. However, the cost-effectiveness of active surveillance program to identify asymptotically VRE colonized patient remains debatable. This work aims at evaluating the cost of a failure in the active surveillance of VRE that had resulted in an outbreak in a French University Hospital.

Findings: A VRE outbreak was triggered by a failure in the systematic VRE screening in a medico-surgical ward specialised in liver transplantation as a patient was not tested for VRE. This failure was likely caused by the reduction of healthcare resource. The outbreak involved 13 patients. Colonized patients were grouped in a dedicated part of the infectious diseases unit and tended by a dedicated staff. Transmission was halted within two months after discovery of the index case.

The direct cost of the outbreak was assessed as the cost of staffing, disposable materials, hygiene procedures, and surveillance cultures.

The loss of income from spare isolation beds was computed by difference with the same period in the preceding year. Payments were drawn from the hospital database. The direct cost of the outbreak (2008 Euros) was €60 524 and the loss of income reached €110 915.

Conclusions: Despite this failure, the rapid eradication of the VRE outbreak was a consequence of the rapid isolation of colonized patient. Yet, eradicating even a limited outbreak requires substantial efforts and resources. This underlines that special attention has to be paid to strictly adhere to active surveillance program.

Keywords: Active surveillance, Outbreak, Cost, Vancomycin-resistant *Enterococcus*



PCR according to indications

- 1531 PCR
- 191 positive result
- **Positivity rate: 12.5 %**
- Isolation procedures can start in 1 h
- Total cost: 61.240 \$
- **Cost for negative results – 53.600 \$**

SHEA Guideline for Preventing Nosocomial Transmission of Multidrug-Resistant Strains of *Staphylococcus aureus* and *Enterococcus*

Carlene A. Muto, MD, MS; John A. Jernigan, MD, MS; Belinda E. Ostrowsky, MD, MPH; Hervé M. Richet, MD; William R. Jarvis, MD; John M. Boyce, MD; Barry M. Farr, MD, MSc

ABSTRACT

BACKGROUND: Infection control programs were created three decades ago to control antibiotic-resistant healthcare-associated infections, but there has been little evidence of control in most facilities. After long, steady increases of MRSA and VRE infections in NNIS System hospitals, the Society for Healthcare Epidemiology of America (SHEA) Board of Directors made reducing antibiotic-resistant infections a strategic SHEA goal in January 2000. After 2 more years without improvement, a SHEA task force was appointed to draft this evidence-based guideline on preventing nosocomial transmission of such pathogens, focusing on the two considered most out of control: MRSA and VRE.

METHODS: Medline searches were conducted spanning 1966 to 2002. Pertinent abstracts of unpublished studies providing sufficient data were included.

RESULTS: Frequent antibiotic therapy in healthcare settings provides a selective advantage for resistant flora, but

patients with MRSA or VRE usually acquire it via spread. The CDC has long-recommended contact precautions for patients colonized or infected with such pathogens. Most facilities have required this as policy, but have not actively identified colonized patients with surveillance cultures, leaving most colonized patients undetected and unisolated. Many studies have shown control of endemic and/or epidemic MRSA and VRE infections using surveillance cultures and contact precautions, demonstrating consistency of evidence, high strength of association, reversibility, a dose gradient, and specificity for control with this approach. Adjunctive control measures are also discussed.

CONCLUSION: Active surveillance cultures are essential to identify the reservoir for spread of MRSA and VRE infections and make control possible using the CDC's long-recommended contact precautions (*Infect Control Hosp Epidemiol* 2003;24:362-386).



Preventing and controlling VRE transmission in all hospitals

- Active surveillance cultures to identify the reservoir for spread
- Hand hygiene
- Barrier precautions for patients known or suspected to be colonized or infected with VRE
- Antibiotic stewardship
- Educational programs for healthcare workers
- Good policy for cleaning and disinfection of surfaces
- Use of computer system to record long term isolation indicators for patients colonized with VRE, so that on return the computer will provide an alert regarding the need for isolation (Until 4 years in the absence of risk factors).
- Dedicated use of noncritical patient-care equipment to a single patient



Isolation precautions

- Place VRE-infected or colonized patients in private rooms or in the same room as other patients who have VRE
- Wear gloves
- Wear a gown
- Remove gloves and gown before leaving the patient's room and immediately disinfect your hands with alcohol based product
- Ensure that after glove and gown removal and hand disinfection, clothing and hands do not contact environmental surfaces in the patient's room that are potentially contaminated with VRE



Required elements of an effective active surveillance program

- Screening test
 - Must be timely, affordable, and reliable
- Clinical efficacy
 - Should reduce transmission rate to patients and health care workers
 - Should reduce infection rate by preventing acquisition
- Implementation
 - Hospital and administrative financial support
 - Systems and staff to screen patients
 - Systems and staff to monitor effectiveness and compliance
 - Education of patients, staff, and families
 - Adequate physical plant and supplies (eg, private rooms, gloves, gowns, and antimicrobial agents)
 - Plan to manage social isolation and safety of patients under contact precautions



Challenges for management of MDRO

- Magnitude of the reservoir
- Patient inconvenience
- Increased workload of healthcare workers
- Resistance of staff
- Half-hearted control measures
- Increased costs



In conclusion

- Clinical impact and burden of VRE should not be underestimated
- We may not relax even in the hospitals in which VRE rate is reported as low
- Remarkable survival abilities, genome plasticity and colonization capacity increase the impact of targeted prevention
- VRE screening is very important to prevent spreading in hospitals
- Although molecular methods are expensive compared to culture methods, when used in indications they are cost effective



Thank
You