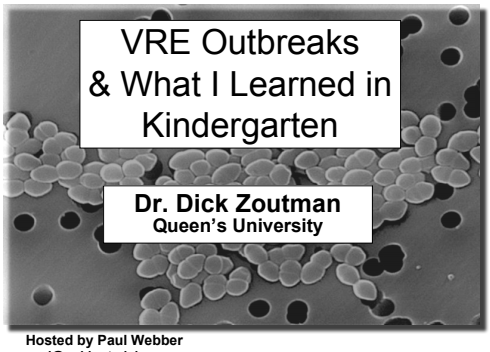
VRE Outbreaks & What I Learned in Kindergarten

Dr. Dick Zoutman, Queen's University, Kingston
A Webber Training Teleclass



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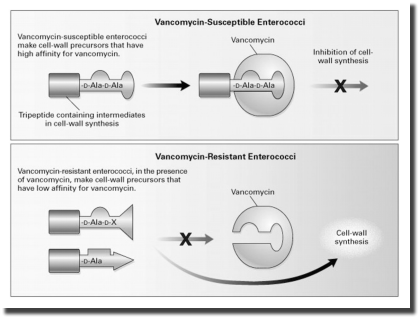
Mechanism of VanA Resistance



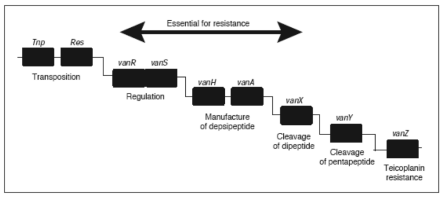
Glycopeptide-resistant Enterococcal Phenotypes

- VanA, VanB, VanC, VanD, VanE, and VanG have been described
- They can usually be distinguished on the basis of the level, inducibility, and transferability of resistance to vancomycin and teicoplanin.
- vanA and vanB are the most clinically relevant

vanA Resistance

- VanA-type glycopeptide resistance is characterized by acquired inducible resistance to both vancomycin and teicoplanin
- Mediated by transposon Tn1546
- Tn1546 contains the vanA gene cluster that encodes 8 polypeptides
- This transposon may be located on plasmids or on the chromosome
- The transfer of vanA vancomycin resistance from *E faecalis* to *S aureus* via Tn1546 was described recently

The Van A Operon



vanB Resistance

- VanB-type glycopeptide resistance is similar to vanA but teicoplanin still active
- The vanB gene cluster has homology to the vanA gene cluster
- The vanB sequence varies among different enterococcal isolates

General Epidemiology of VRE

- Colonization, which does not result in symptoms, may last for long periods and may serve as a reservoir for the transmission of VRE to other patients
- Within hospitals, widespread colonization with VRE may occur with a comparatively small number of documented infections
- Therefore, tracking colonization with VRE through active surveillance in high-risk units is an important component of preventing further transmission

General Epidemiology of VRE (2)

- Colonization is contingent on exposure to VRE and on being a "susceptible" host
- With regard to exposure to VRE, the most important considerations are proximity to and duration of exposure to those already colonized with VRE.
- When the proportion of patients colonized with VRE on a particular ward (the so-called colonization pressure) is high (>50%), other risk factors for colonization (described subsequently) become less important

General Epidemiology of VRE (3)

- "Susceptible hosts" are at high risk for VRE colonization.
- These include patients who are severely ill and those receiving multiple and prolonged courses of antimicrobial agents.
- Colonization in these hosts often occurs in long-term care facilities and urban referral hospitals.
- Solid (especially abdominal) organ transplant recipients and hematology patients are at particularly increased risk for colonization with VRE.
- Health care workers and their household members are also at risk for VRE colonization

Clonal Complex 17

- Insights into the population structure of *E. faecium* were obtained from molecular-typing data
- Pointed towards host specificity of *E. faecium* and the existence of a distinct subpopulation, designated CC17 based on multilocus sequence typing (MLST)

Global Spread of CC17

- CC17 has been found to be globally dispersed
- CC17 nosocomial *E. faecium* subpopulations in Brazil, Germany, Italy, Korea, The Netherlands, Singapore, US and Sweden
- And Canada

Adaptive Diversification of VRE

- Epidemiological and population biological studies show the existence of distinct enterococcal subpopulations
- Eg. *E. faecium* CC17 that is specifically adapted to the hospital environment
- Example of adaptive diversification splitting enterococcal lineages into derived groups due to frequency-dependent ecological interactions (selective pressure)

CC17 a New Subspecies?

- Studies of Enterococcal genomics reveal genetic diversity and genome plasticity of *E. faecalis* and *E. faecium*
- Significant difference in gene contents between CC17 isolates and other *E. faecium* isolates
- Some suggest that CC17 is in fact a distinct *E. faecium* subspecies

Emergence of CC17 *E. faecium*

- CC17 is distinct from animal-associated *E. faecium*
- has acquired glycopeptide resistance through horizontal gene transfer
- The emergence of CC17 *E. faecium* coincided with an increase in the number of *E. faecium* nosocomial infections relative to infections caused by *E. faecalis*
  - Treitman AN, Yarnold PR, Warren J, Noskin GA. Emerging incidence of *Enterococcus faecium* among hospital isolates (1993 to 2002). J Clin Microbiol 2005; 43:462–463.
  - Top J, Willems R, Blok H, et al. Ecological replacement of Enterococcus faecalis by multiresistant clonal complex 17 Enterococcus faecium. Clin Microbiol Infect 2007; 13:316–319.

CC17 Ecological Success

- The ecological success of CC17 in the hospital environment is partly related to increased antibiotic resistance
- Eg. ampicillin and quinolone resistance are specifically associated with this clonal complex
- BUT, not the whole story…
- the enterococcal surface protein gene, esp
  - a virulence gene contained on a pathogenicity island
  - was found to be specifically linked to CC17

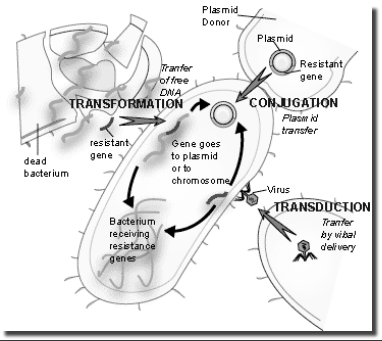
A Hospital VRE Clade

- A recent comprehensive comparative genomic analysis of 97 *E. faecium* isolates from different ecological and evolutionary backgrounds
- CC17 and non-CC17 using a mixed whole-genome microarray based on the total genomes of nine *E. faecium* isolates
- hospital associated CC17 isolates were genetically highly related & grouped together in a "hospital clade" distinct from non-CC17 human community and animal isolates
  - Leavis HL, Willems RJ, Van Wamel WJ, et al. Insertion sequence-driven diversification creates a globally dispersed emerging multiresistant subspecies of E. faecium. PLoS Pathog 2007; 3:75–96.

Evolution of a Hospital "Species"

- Micro-array data confirms distinct clustering of hospital associated clinical and outbreak isolates
- also identified more than 100 genes that were specifically enriched among CC17 isolates
- These CC17 specific genes include only antibiotic-resistance genes, but also putative virulence genes, genes encoding metabolic pathways, phage genes, integrated plasmids and insertion sequence elements

Horizontal Gene Transfer Mechanisms



Multi-Step Wise Gene Acquisition

- The set of more than 100 CC17-enriched genes are not clustered on one genomic region
- Acquisition of these genes most probably has occurred multistep-wise and has been pivotal in the progression of *E. faecium* from an enteric commensal towards a hospital adaptation organism
  - Baquero F, Coque TM, Canton R. Antibiotics, complexity, and evolution. ASM News 2003; 69:547–552.
  - Leavis HL, Bonten MJ, Willems RJ. Identification of high-risk enterococcal clonal complexes: global dispersion and antibiotic resistance. Curr Opin Microbiol 2006; 9:454–460.

The Advantage of Genetic Plasticity

- MLST and microarray data of *E. faecium* and *E. faecalis* clearly demonstrate enormous genome plasticity and diversity
- This plasticity facilitates survival and persistence of these microorganisms in environments that require continuous adaptation to changing conditions
- ie. hospitals

Horizontal Gene transfer

- Transmission of vancomycin resistance occurs through clonal spread as well as HGT
- HGT of vancomycin resistance most likely occurs in the gastrointestinal tract, which implies co-colonization of a VRE donor and a vancomycin-susceptible acceptor strain

Transfer of vanA and vanB

- In-vivo transfer of vanA and vanB genes has been documented in the intestine of mice and in the intestines of human volunteers
- Dahl et al demonstrated that horizontal gene transfer of vancomycin-resistance genes occurs without selective pressure & is linked to plasmid maintenance systems and occurs at high frequencies
  - Dahl KH, Mater DD, Flores MJ, et al. J Antimicrob Chemother 2007; 59:478–486.

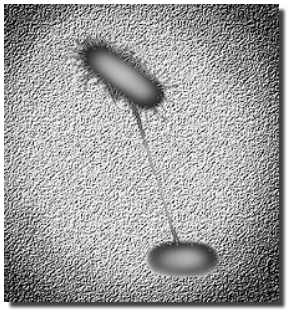
Selective Pressure vs Selective Persistence

- VRE are able to persist in the absence of glycopeptide antibiotics
- vanA elements on mobile genetic elements lined to post-segregational killing 'plasmid addiction' systems
- These plasmids encode a bacteriocidal toxin and a specific anti-toxin that neutralizes the toxin
- If the plasmid is lost, the antitoxin (unstable) is degraded & results in toxin mediated killing of plasmid-free daughter cells

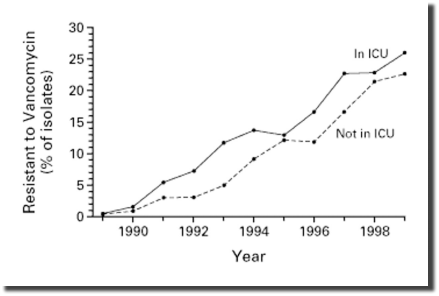
Selective Pressure vs Selective Persistence (2)

- creates a replication advantage for plasmid containing (i.e. VRE) bacteria.
- found ubiquitously and often physically linked to vanA elements
- Eg. found in VRE recovered from poultry in Norway, 3–8 years after ban on avoparcin, and resides on the same plasmid as the vanA element
  - Sletvold H, Johnsen PJ, Simonsen GS, et al. Comparative DNA analysis of two vanA plasmids of Enterococcus faecium isolated from poultry and a poultry farmer in Norway. Antimicrob Agents Chemother 2007; 51:736–739

Bacterial Conjugation



CDC VRE Data



Epidemiology of VRE in US

- In the United States, hemodialysis patients have a 10% prevalence rate of colonization with VRE.
- A recent multicenter epidemiological study showed that 28% of enterococci cultured from 25 North American intensive care units (ICUs) were resistant to vancomycin
  - Streit JM, Jones RN, Sader HS, Fritsche TR. Int J Antimicrob Agents. 2004;24:111-118.

European Prevalence of VRE Bacteremia (EARRS)

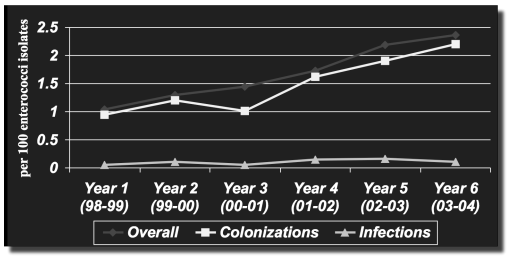
- In 2007 above 5% in 10 countries
  - of which three countries exhibited prevalence rates above 10% and five countries even above 25%
- Since 2002, the emergence of VRE in european hospitals has followed that of the US, but with a 10- to 15-year delay

VRE Rates in Europe

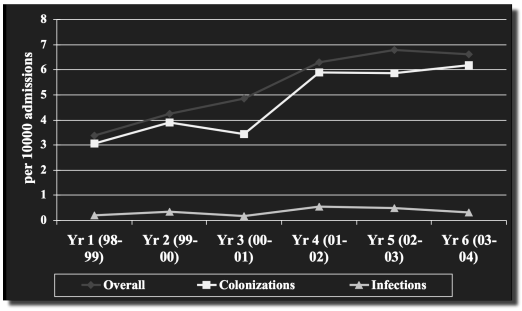
Canadian VRE Surveillance Results

- From 1998 to 2004
- a total of 2125 new cases of VRE
- 92.7% vanA *E. faecium*
- Clinical Infection rate = 7.6% (n=161)

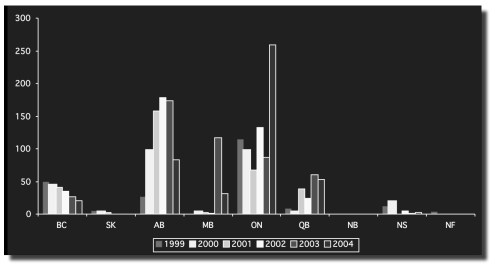
VRE Incidence Rates per 100 enterococci isolates



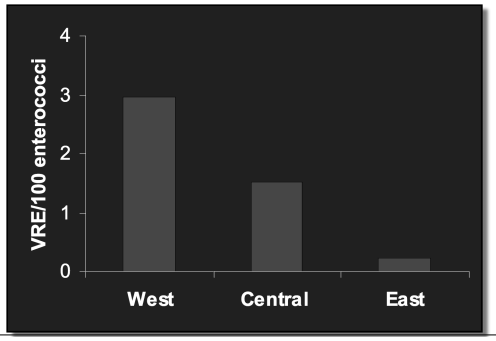
VRE Incidence Rate per 10,000 patient admissions



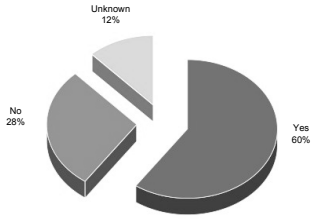
Number of VRE Cases by Province and Year



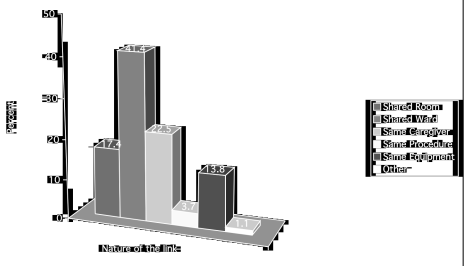
VRE per 100 enterococci by Region



Is this patient Epi-linked to others within your facility?



If Epi-linked, what was the nature of the link?



*Categories not mutually exclusive

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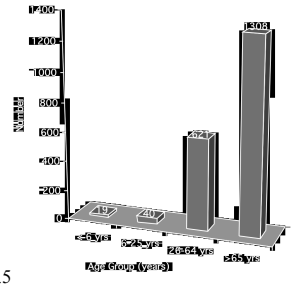
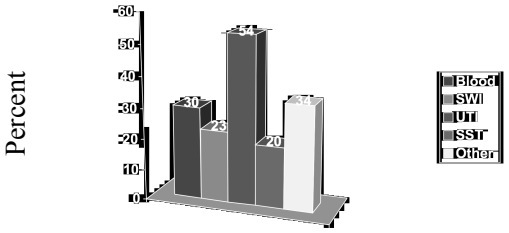
VRE Cases by age group



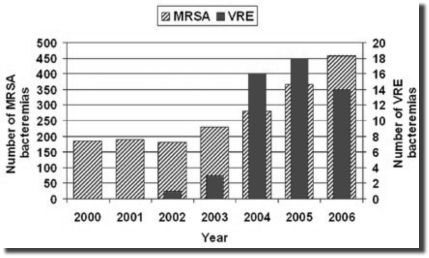
Mean age = 67.5
Range= 1 month - 98.9 yrs

VRE Infections

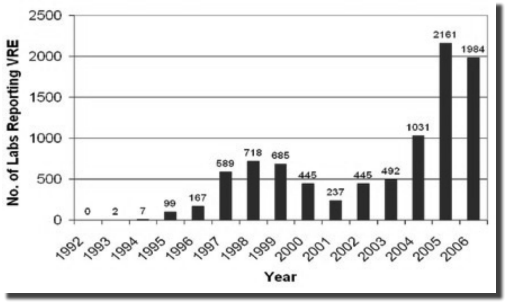
(n=161)



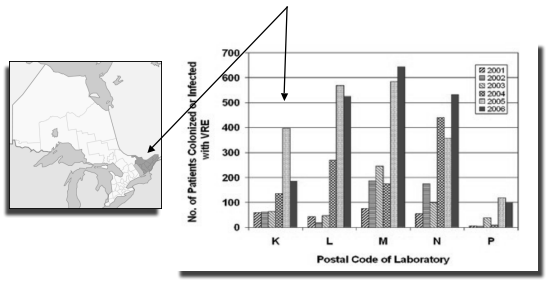
Ontario MRSA & VRE Bacteremias 2000-2006



Ontario VRE Vases 1992-2006



VRE By Ontario Postal Code Regions



Incidence of VRE Infections

- Infection with VRE usually develops in patients colonized with the bacteria
- with the ratio of infected-to-colonized patients dependent on the specific patient population.
- It is highest in hematology patients and organ transplant recipients

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Mortality of VRE Infections (Bacteremia)

- Mortality rates for patients with VRE bacteremia vary depending on the population at risk
- autologous peripheral blood stem cell transplants ~10% mortality
- Patients with endocarditis caused by VRE 30%
- solid tumors ≥50%
- critically ill and liver transplant patients ≥70% mortality

VRE impact on LOS and costs

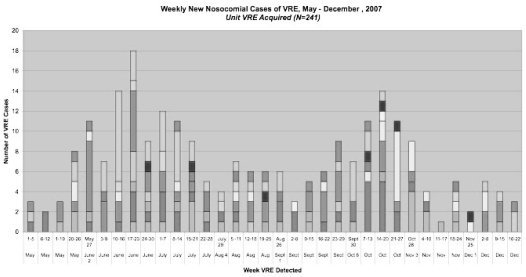
- *Enterococcus faecalis/Enterococcus faecium* (bacteraemia): a retrospective analysis of patients[a] with bacteraemia from January 1992 to December 1995

Pathogen	n	LOS (days)	Hospital cost ($)
VRE	21	35[b]	83 897[c]
VSE	32	17[b]	56 707[c]

VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci
[a]n=53. [b]p=0.004. [c]p=0.04

Stosor et al. Arch Intern Med. 1998;158:522–527

VRE Outbreak Epi Curve



KGH VRE by In Patient Unit

Total	**241**
Med	50
Med	48
ICU	40
Surg	25
ECU	23
Med	10
Med	9
Surg	9
Surg	8
LTC	7
Gyn	7
Med	3
CCU	2

May-Dec 2007

Infection Control Interventions

- Universal gloving for all patient contact
- Contact precautions for all known Positive VRE patients
- Contact precautions for all Potential VRE patients
- Isolation Unit created on June 28, 2007.
- The Isolation Unit was moved on October 3, 2007

Hygiene Interventions

- Disposable bedpans, urinals, graduated measuring containers will be used
- Single use bedpans in use for all other patients on isolation disposed in Sanibags®
- Sanibags® in use for all commodes

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Hand Hygiene Interventions

- Tables are located at each of the entrances with signage, alcohol hand sanitizer and fact sheets. The tables are re-stocked daily
- Alcohol sanitizer bottles in all patient rooms
- Perform hand hygiene audits
- Results of hand hygiene audit disseminated

Environmental Services

- Increased Environmental Services staff to two staff during days and one on evenings per inpatient unit.
- Enhanced deep cleaning of all adult inpatient units
- Twice daily cleaning of the isolation unit is ongoing. This includes patient rooms, sunroom, kitchenette and nurses station.
- Twice daily cleaning of the ECU and ICU

Bacterial Persistence on Hospital Surfaces

Type of bacterium	Duration of persistence (range)
Acinetobacter spp.	3 days to 5 months
Bordetella pertussis	3 – 5 days
Campylobacter jejuni	up to 6 days
Clostridium difficile (spores)	5 months
Chlamydia pneumoniae, C. trachomatis	≤ 30 hours
Chlamydia psittaci	15 days
Corynebacterium diphtheriae	7 days – 6 months
Corynebacterium pseudotuberculosis	1–8 days
Escherichia coli	1.5 hours – 16 months
Enterococcus spp. including VRE and VSE	5 days – 4 months
Haemophilus influenzae	12 days
Helicobacter pylori	≤ 90 minutes
Klebsiella spp.	2 hours to > 30 months
Listeria spp.	1 day – months
Mycobacterium bovis	> 2 months
Mycobacterium tuberculosis	1 day – 4 months
Neisseria gonorrhoeae	1 – 3 days
Proteus vulgaris	1 – 2 days
Pseudomonas aeruginosa	6 hours – 16 months; on dry floor: 5 weeks
Salmonella typhi	6 hours – 4 weeks
Salmonella typhimurium	10 days – 4.2 years
Salmonella spp.	1 day
Serratia marcescens	3 days – 2 months; on dry floor: 5 weeks
Shigella spp.	2 days – 5 months
Staphylococcus aureus, including MRSA	7 days – 7 months
Streptococcus pneumoniae	1 – 20 days
Streptococcus pyogenes	3 days – 6.5 months
Vibrio cholerae	1 – 7 days

Kramer et al. BMC Infectious Diseases 2006, 6:130

More Environmental Interventions

- Procedure for Cleaning Patient Rooms:
  - 1 Toilet brush per patient room – single use, discard after use
  - Clean surfaces with Percept;
    - Use clean rags, no double dipping
    - Rags are placed in laundry bag after each use
  - 1 mop head for each isolation room
    - No re-dipping mop heads in germicidal solution
    - Mop heads are placed in laundry bag after each use
  - Isolation cleaning
    - Include walls, replace curtains

Education

- VRE Fast Facts education package
- Room Cleaning Procedures & VRE Interventions education package was distributed.
- 10-15 minute education sessions on VRE were provided.
- A 15 minute video webcast
- Education session provided at the request of Portering Services.
- Lunch and Learn session on VRE
- A poster display for VRE education and Hand Hygiene
- Numerous Infomemos
- ID Rounds on VRE

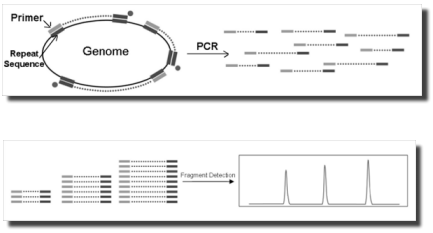
Information Campaign

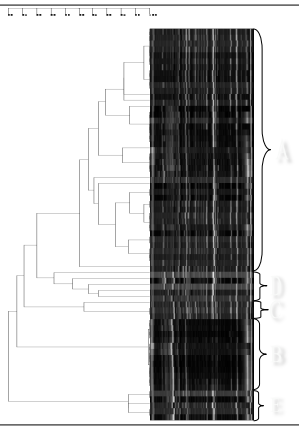
- Signage for the five main entrances to hospital and to all adult inpatient units are posted to educate the public and staff about the visitor restrictions and to encourage hand hygiene.
- Tent cards were developed with hand hygiene messaging and placed in the cafeteria and café.
- Three signs have been developed for use to education of staff and visitors on hand hygiene and isolation procedures. They are "It's OK to Ask, Stop Clean Your Hands, and Remove Gloves and Gowns". A four sign on hand hygiene is being developed for use across the institution.
- Infomemos distributed at regular intervals to update staff, physicians and volunteers. An article on VRE was published in the October Hospital New paper.
- Daily distribution of 'Operation Vanquish VRE Interventions' to Directors and Managers.
- Presentation at "Sign-In" Rounds
- Weekly Distribution of epidemic curve of new nosocomial cases of VRE and point prevalence survey compliance rates to Directors and Managers.
- Daily distribution of number of VRE Positive and Potential patients in-house.
- 60+ VRE Outbreak Committee meetings

Microbial Surveillance for VRE

- Weekly VRE Point Prevalence Surveys were conducted
- IC and Nursing has developed a Medical Directive for VRE
- Microbiology initiated new media to identify VRE faster and reduce turn around time of VRE testing by up to 2 days
- Development and validation of in house PCR method
- Molecular typing of VRE isolates

rep-PCR



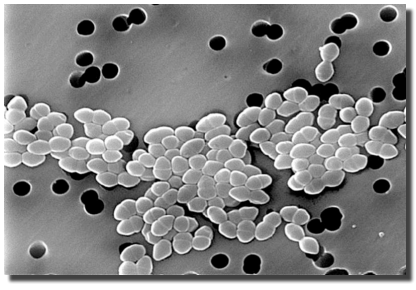


Rep-PCR Typing of VRE Isolates

Compliance Monitoring

- Compliance Audit of universal gloving and contact precautions on inpatient units by direct observation were conducted August 2007.
- Hand Hygiene Audit as per MOHLTC protocol on inpatient units by direct observation is ongoing.

SEM of *E. faecalis*



Active Surveillance Cultures (ASC)

- A recent University of Maryland mathematical model showed that active surveillance in the ICU reduced VRE transmission by a projected 39%
  - Perencevich EN, Fisman DN, Lipsitch M, Harris AD, Morris JG Jr, Smith DL. Clin Infect Dis. 2004;38:1108-1115.

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Does Active Microbial Surveillance Help Control MRSA & VRE?

- Using an interrupted time series design, Huang et al retrospectively evaluated four sequential interventions in eight ICUs in one institution over a 9-year period:
  - use of maximum sterile barriers during placement of central lines
  - introduction of an alcohol based hand rub for hand hygiene
  - a hand hygiene promotion campaign
  - culture-based active surveillance for MRSA

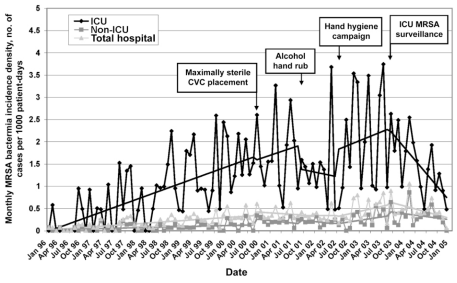
Huang et al Results

- Demonstrated a 75% decrease in the incidence of hospital-associated MRSA bacteremia in ICU patients
- But only during the period when active surveillance for MRSA was implemented
- No sustained effect during periods when any of the other three interventions were implemented
- There was a concurrent 40% decrease in the incidence of hospital-associated MRSA bacteremia in non-ICU patients

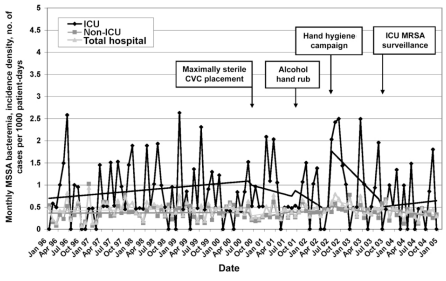
Huang et al (2)

- Overall, these effects resulted in a 67% decrease in MRSA bacteremia hospital-wide
- The incidence of hospital-associated MSSA bacteremia did not change during the four intervention periods
- The incidence of new cases of MRSA and VRE colonization also decreased during the period when active surveillance was practiced
  - Huang SS, Yokoe DS, Hinrichsen VL, et al. Impact of routine intensive care unit surveillance cultures and resultant barrier precautions on hospital-wide methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis 2006; 43:971–978

BWH Impact on MRSA

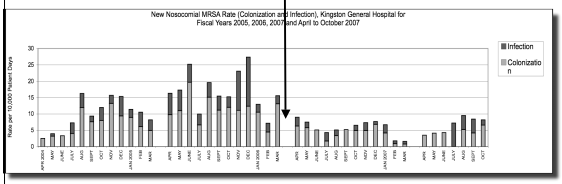


BWH Impact on MSSA



MRSA at KGH 2004-2007

MRSA PCR & Medical Directive Introduced



Seek & Destroy: MRSA & VRE

- Nosocomial spread of MRSA & VRE can be controlled by means of active detection and isolation of all colonized patients
- Longstanding successful control achieved by multiple northern European countries and the state of Western Australia
- failure of other European nations and other Australian states that do not routinely use this approach

Seek & Destroy: MRSA & VRE (2)

- This approach has worked to control MRSA & VRE infection when tried in other countries that have generally failed to control them in the past also corroborates these findings
  - Muto CA, Giannetta ET, Durbin LJ, Simonton BM, Farr BM. Cost effectiveness of perirectal surveillance cultures for controlling vancomycin- resistant Enterococcus. Infect Control Hosp Epidemiol 2002; 23:429-435.
  - Ostrowsky BE, Trick WE, Sohn AH, et al. Control of vancomycin resistant enterococcus in health care facilities in a region. N Engl J Med 2001; 344:1427-1433.
  - Mascini EM, Troelstra A, Beitsma M, et al. Genotyping and preemptive isolation to control an outbreak of vancomycin-resistant Enterococcus faecium. Clin Infect Dis 2006; 42:739-746.

Siouxland Regional Study

- Healthcare facilities in the three-state Siouxland region (Iowa, Nebraska, and South Dakota)
- Formation of a coalition and development of an effective region-wide infection control intervention
- Reduced rates of VRE transmission by ASC and isolation of infected patients
- The overall prevalence rate of VRE in the 30 participating facilities decreased from 2.2% in 1997 to 0.5% in 1999
  - Ostrowsky, B. E., Trick, W. E., Sohn, A. H., Quirk, S. B., Holt, S., Carson, L. A., Hill, B. C., Arduino, M. J., Kuehnert, M. J., & Jarvis, W. R. (2001) N Engl J Med 344, 1427-1433.

In Western Europe

- Reduced rates of MRSA transmission in The Netherlands, Belgium, Denmark, and Scandinavian countries after the implementation of aggressive and sustained infection control interventions
- ASC, preemptive use of Contact Precautions, and, in some instances, closure of units to new admissions
- MRSA accounts for a very small proportion of S. aureus clinical isolates in these countries
  - Verhoef, J., Beaujean, D., Blok, H., Baars, A., Meyler, A., van der Werken, C., & Weersink, A. (1999) Eur J Clin Microbiol Infect Dis 18, 461-466.
  - Salmenlinna, S., Lyytikainen, O., Kotilainen, P., Scotford, R., Siren, E., & Vuopio-Varkila, J. (2000) Eur J Clin Microbiol Infect Dis 19, 101-107.

Mathematical Modeling

- A mathematical model characterizing MRSA transmission dynamics predicted that,
- in comparison to conventional culture methods, the use of rapid detection tests decrease isolation needs in settings of low-endemicity and result in more rapid reduction in prevalence in highly-endemic settings
  - Bootsma, M. C., Diekmann, O., & Bonten, M. J. (2006) Proc Natl Acad Sci U S A 103, 5620-5625.

Hospital Environmental Cleaning

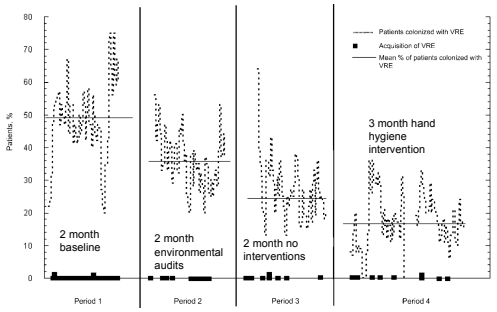
- A quasi-experimental study of an intervention to improve environmental cleaning
- Found that the intervention was associated with a two-fold increase in the number of environmental sites that were cleaned appropriately
- and a reduced risk of acquisition of VRE
  - Hayden MK, Bonten MJ, Blom DW, et al. Reduction in acquisition of vancomycin- resistant Enterococcus after enforcement of routine environmental cleaning measures. Clin Infect Dis 2006; 42:1552–1560.

VRE Outbreaks & What I Learned in Kindergarten

Dr. Dick Zoutman, Queen's University, Kingston

A Webber Training Teleclass

Hayden et al Results



Is A Private Room Safer?

- Admissions 2001-2005
- 37,418 patients had 294,242 roommates for a mean of 1.93 roommates per day
- Manual stepwise regression using Cox Proportional Hazards model

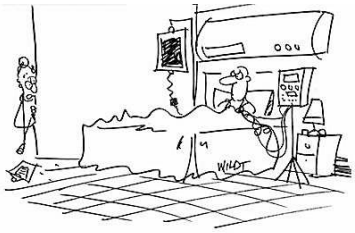
Variable	HR for MRSA Acquisition	P value
Daily Roommates	1.06	0.001

The Inanimate Environment Can Facilitate Transmission

~ Contaminated surfaces increase cross-transmission ~

Abstract: The Risk of Hand and Glove Contamination after Contact with a VRE (+) Patient Environment. Hayden M, ICAAC, 2001, Chicago, IL.

But I Did Not Touch Anything!



"You'll find my bedside manner improves greatly when you're no longer contagious."

My Hands are OK!

Clean My Hands

VRE Outbreaks & What I Learned in Kindergarten
Dr. Dick Zoutman, Queen's University, Kingston
A Webber Training Teleclass

Pooh Is Yucky

Keep It Clean

Teleclass Education . . . May & June

May 1	***Infection Control in Personal Services Settings***	Dr. Bonnie Henry, BC Centre for Disease Control
May 8	***Selecting Microbial Chemicals: Buyer Beware***	Dr. Syed Sattar, University of Ottawa
May 15	***Adverse Events in Dialysis***	Dr. Matthew Arduino, CDC
May 22	***Bedpan Decontamination - Manual vs. Mechanical***	Gertie van Knippenberg Gordebeke, The Netherlands
June 19	***Environmental Sampling - Methods and Strategies***	Dr. Lynne Sehulster, CDC
June 25	***Perhipheral Line Sepsis***	Dr. Steven McBride, Auckland, New Zealand
June 26	***The CIC Examination Process: Computer-Based Testing***	CBIC Board Members & Guests