# Rapid Detection of *Clostridium difficile* and Vancomycin-Resistant Enterococci: New Infection Control Imperatives

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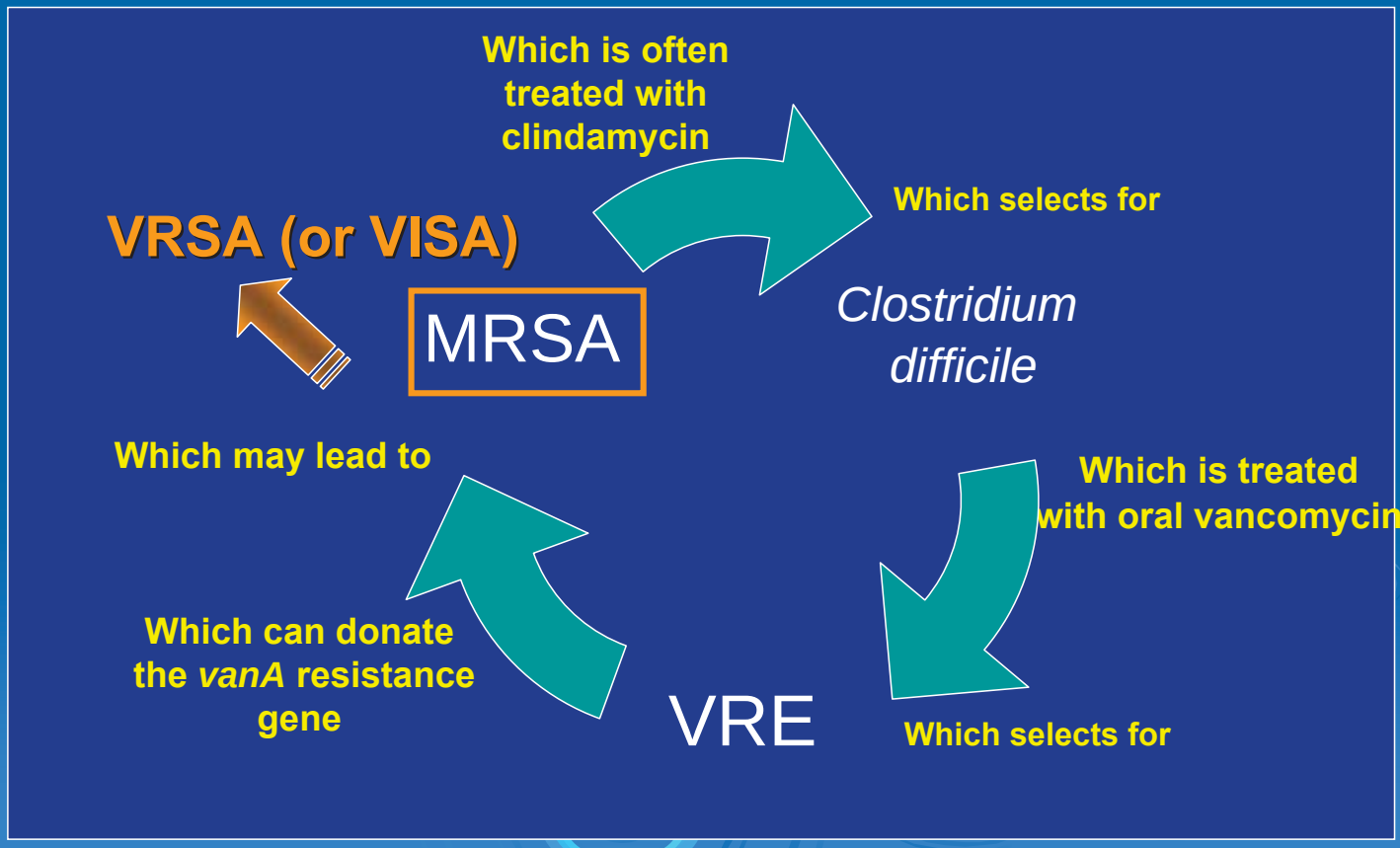
# The Issues

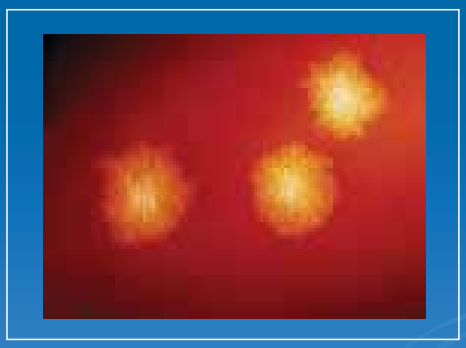
- New, more aggressive, and more virulent strains of *C. difficile* are emerging in healthcare and community settings
- Control of *C. difficile* in hospitals may require multiple interventions including changes in antimicrobial stewardship, environmental cleaning, and hand washing protocols
- Vancomycin-resistant enterococci are important healthcare associated infection especially in transplant patients
- Better laboratory methods are required to improve timely detection of both pathogens

# Inter-relatedness of Healthcare Associated Pathogens




# Outbreak Investigations Need to be Conducted by Highly Trained Individuals

# *Clostridium difficile* - the Organism

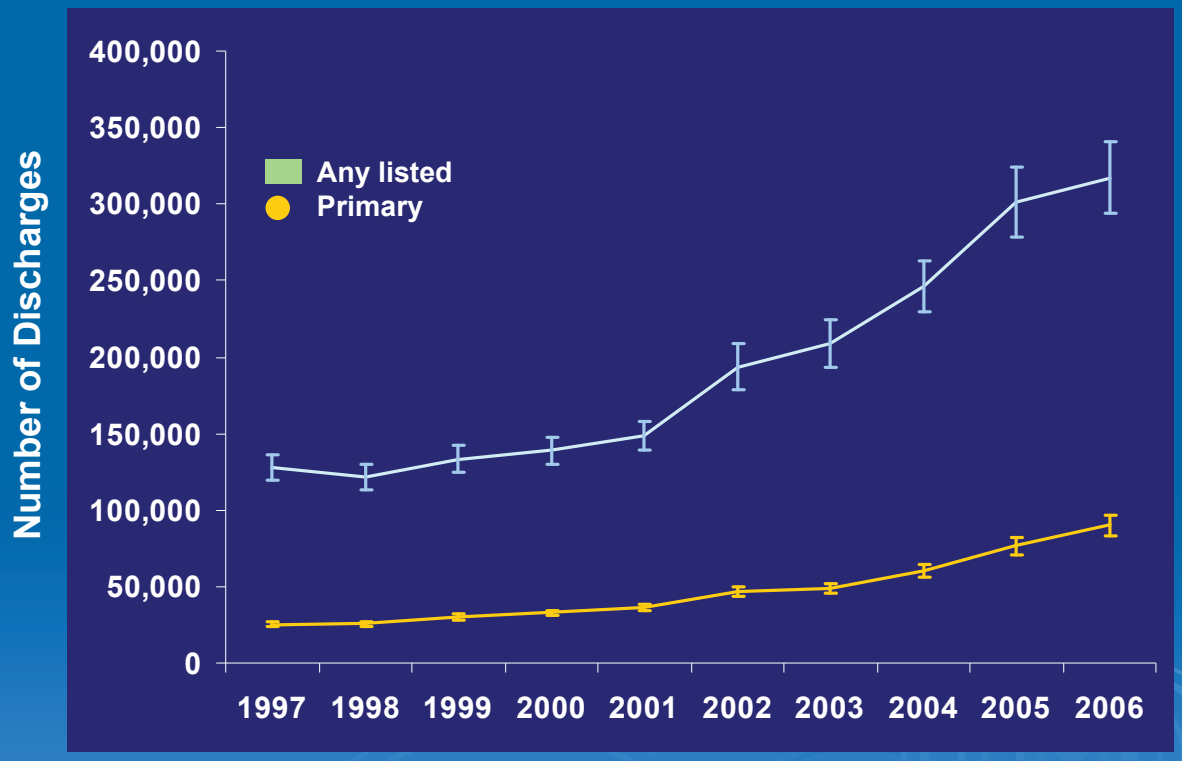


- *Clostridium difficile* is a Gram-positive, anaerobic, spore-forming bacillus.
- Spore formation is critical to its prolonged survival in the environment and ability to spread.
- Requires bleach for adequate disinfection
- Alcohol hand gels not effective, requires soap and water

# Changing Epidemiology of *Clostridium difficile* Infection

- **Increasing incidence and severity**
  - Up to 500,000 *C. difficile* in US annually with an associated mortality of 15,000 persons
- Recent outbreaks of severe disease caused by **epidemic strain** of *C. difficile* with increased virulence and fluoroquinolone resistance
- Although elderly are still most frequently affected, more disease reported in **"low-risk" persons**, including healthy persons in community and peripartum women
- *C. difficile* isolated from **retail meat** (beef, pork, turkey, and "ready to eat meats")

# National Estimates of Incidence based on Hospital Discharges with *C. difficile* as First-Listed or Any Diagnosis



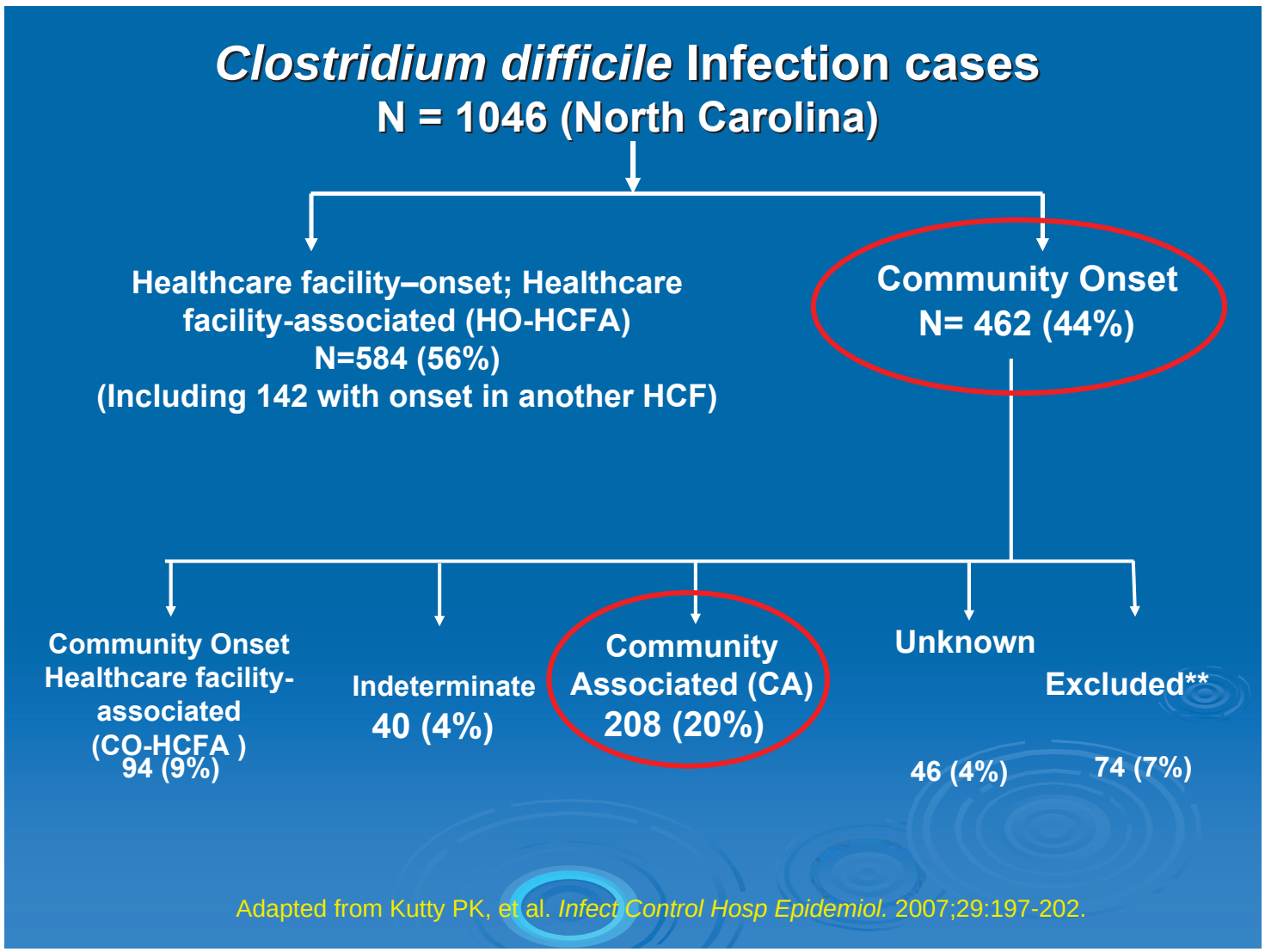



# New Epidemic Strain of *C. difficile*

- **Name:** BI/NAP1/027, toxinotype III
- Historically uncommon (particularly in U.S. strain collections), now epidemic
- Current strain more resistant to fluoroquinolones
- Carries extra toxin known as binary toxin
- Polymorphism in toxins A and B regulatory gene (*tcdC*) and increased toxin production *in vitro*
- Shows increased spore production

# Several Commonly Recognized Epidemic *C. difficile* Clones

- PCR- Ribotype/ PFGE/ REA type
- 001 / NAP2 / J
- 027 / NAP1 / BI (Binary positive)
- 078 / NAP7 / BK (Binary positive)
- 106 / NAP11 / DH
- Many other strains reported, some with binary toxin




Adapted from Kutty PK, et al. *Infect Control Hosp Epidemiol.* 2007;29:197-202.

# Laboratory Diagnosis of *C. difficile* Infection- Current Problems

**Laboratory manager**

- "We have rapid and sensitive tests for *C. difficile*
- Which one do you want?"
- Rapid
- Or sensitive

# Recent Comparison of Three Rapid Immunoassays (EIAs) for *C. difficile* in Spain

| Test name | Sensitivity/Specificity |
|---|---|
| • Wampole Toxins A & B | 55% / 95% |
| • ImmunoCard® Toxins A & B | 67% / 95% |
| • Xpect® C. *difficile* Toxin A/B | 49% / 96% |

- **Used toxigenic culture as the "gold standard"**

L Alcalá et al, JCM, 2008 Nov;46(11):3833-3835

# Recent Mayo Clinic Assessment of Multiple Tests

- Used toxigenic culture as the "gold standard", EIA Tests, which are widely used, DO NOT perform well

| Test name | Sensitivity/Specificity |
|---|---|
| • Premier™ Toxins A & B | 48% / 98% |
| • ImmunoCard® Toxins A & B | 48% / 99% |
| • Xpect® C. *difficile* Toxin A/B | 48% / 84% |
| • Triage C. *difficile* Panel (toxin A) | 33% / 100% |
| • Home-brew PCR (for *tcdC*) | 86% / 97% |

LM Sloan et al, JCM, 2008 Jun;46(6):1996-2001

# PCR Amplification Tests Improve Sensitivity Without Sacrificing Specificity

- Three commercial PCR tests for *C. difficile*
- BD-GeneOhm; FDA cleared, batch testing (1-4 hours depending on volume)
- Prodesse ProGastro™ Cd : FDA cleared, requires DNA isolation upfront (3 hours)
- Cepheid GeneXpert: FDA cleared, available as RUO product in U.S.; on demand testing results (45 minutes)

# GeneXpert *C. difficile* assay


## Product Profile (Europe)

- **Rapid detection of *C. difficile* in stool (45 minutes)**
- **Detection of three targets plus control will yield the following two results:**
  - Toxigenic *C. difficile* present
  - Presumptive epidemic strain 027:NAP1:BI



# Current Summary of U.S. Beta Trial Data (6 sites)

| | | Toxinogenic culture | | |
|---|---|---|---|---|
| | | Positive | Negative | Total |
| Xpert *C.difficile* | Positive | 119 | 29 | 148 |
| | Negative | 5 | 827 | 832 |
| Total | | 124 | 856 | 980 |

**Sensitivity = 95.9 %; Specificity = 96.6 %**

**PPV = 80.4%; NPV = 99.4%**

# Interventions to Control *C. difficile* in Hospitals

- Muto et al stressed the importance of using a comprehensive "Bundle" approach to control the 027/NAP1/BI strain in their hospital. 5 component intervention:
  - Education
  - Early case finding
  - Expanded infection control
  - Targeted antimicrobial management
  - Creation of a *C. difficile* management team

CID 2007; 45:1266-73

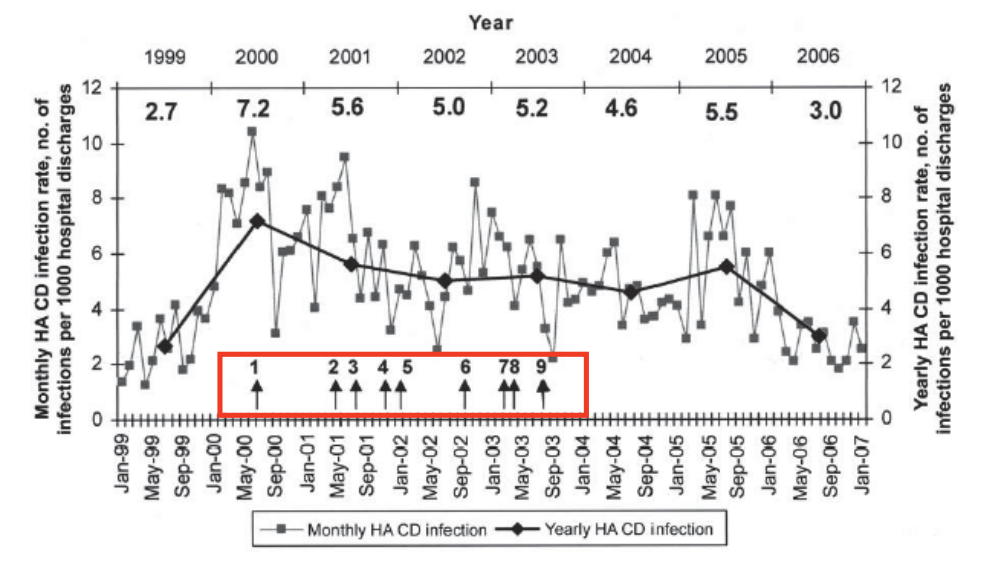
# Expanded infection Control Measures- Muto et al.

- Enhanced environmental cleaning
- Electronic flags and alerts on charts
  - Don't put infected and uninfected patients in the same room
- Hand hygiene with soap and water
- Prolonged duration of isolation
- Infection control audits
  - Monitoring hand hygiene

CID 2007; 45:1266-73

# Control of an Outbreak of Infection with the Hypervirulent *Clostridium difficile* BI Strain in a University Hospital Using a Comprehensive "Bundle" Approach

Carlene A. Muto,[1,7,8] Mary Kathleen Blank,[1] Jane W. Marsh,[7] Emanuel N. Vergis,[2] Mary M. O'Leary,[7] Kathleen A. Shutt,[7] Anthony W. Pasculle,[3] Marian Pokrywka,[1] Juliet G. Garcia,[1] Kathy Posey,[1] Terri L. Roberts,[1] Brian A. Potoski,[2,6,9] Gary E. Blank,[4] Richard L. Simmons,[5] Peter Veldkamp,[2] Lee H. Harrison,[7,8] and David L. Paterson[2,6]




CID 2007; 45:1266-73

# Interventions to Control *C. difficile* in Hospitals

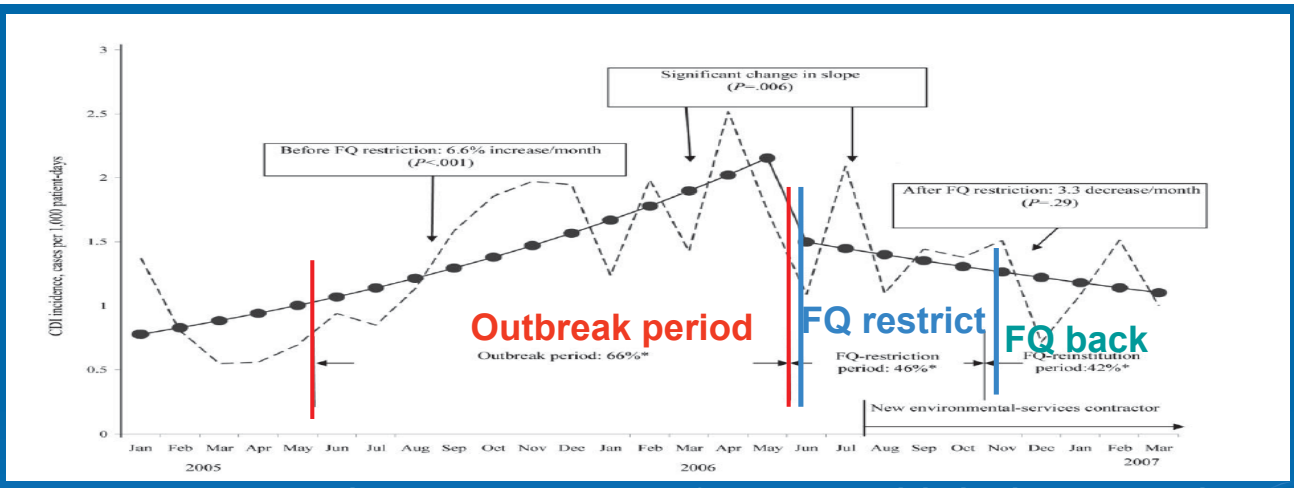
- Kallen et al reported that reduction of fluoroquinolone use was critical for interrupting the spread of NAP1/BI/027 strain of *C. difficile* in hospitals after multiple interventions had already failed to halt the spread of the organism

ICHE 2009; 30:264-272

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY MARCH 2009, VOL. 30, NO. 3

ORIGINAL ARTICLE

# Complete Restriction of Fluoroquinolone Use to Control an Outbreak of *Clostridium difficile* Infection at a Community Hospital




- Over 27 months, 319 cases of CDI, multiple interventions
- Try stewardship; 22% decrease in DDDs of antimicrobials
  - 66% decrease in use of FQs (complete restriction)
- Effect: 22% decrease in *C. difficile* infections
- Note: Environmental cleaning contractor also changed

# Environmental Control Issues

**What is on that keyboard? Detecting hidden environmental reservoirs of *Clostridium difficile* during an outbreak associated with North American pulsed-field gel electrophoresis type I strains (027/BI/NAP1)**

Donald M. Dumford III, MD,[a] Michelle M Nerandzic, BS,[b] Brittany C. Eckstein, BS,[b] and Curtis J. Donskey, MD[b,c]
Cleveland, Ohio

- 105 non-isolation rooms surveyed by culture
- 16% contaminated with toxin-producing *C. difficile*
- Outside of patients rooms:
  - 9 of 29 (31%) physician work areas positive
  - 1 of 10 (10%) nurse work areas
  - 9 of 43 (21%) piece of portable equipment
  - 50% of strains typed were the epidemic NAP1 strain

(Am J Infect Control 2009;37:15-9.)

# Vancomycin-Resistant Enterococci

- This organism gets little respect even though enterococci overall are the 3rd most common cause of healthcare associated infections in the 2006-2007 CDC (NHSN) data
- Enterococci are **2nd** most common cause of central-line associated blood stream infections, **3rd** most common cause of urinary tract infections, and **3rd** most common cause of surgical site infections

Hidron A, et al. (SHEA 2008) http://www.cdc.gov/ncidod/dhqp/SHEAabstract1.html



# Vancomycin-Resistant Enterococci

- The numbers of **VRE** device-associated infections are equal to the number of **MRSA** device-associated infections
- Most VR *E. faecium* were a concern in 1990s because they were untreatable; became treatable with approval of quinupristin-dalfopristin, linezolid, and daptomycin; but in 2008 VRE are again becoming resistant to each of these drugs

Hidron A, et al. (SHEA 2008) http://www.cdc.gov/ncidod/dhqp/SHEAabstract1.html

# *Enterococcus faecium* "Susceptibility" Test Report

**Outbreak strain from Tennessee**

| Drug | MIC (µg/ml) | Interpretation |
|---|---|---|
| Ampicillin | >128 | R |
| Penicillin | >128 | R |
| Vancomycin | >256 | R |
| Teicoplanin | >256 | R |
| Linezolid | >16 | R |
| Levofloxacin | >8 | R |
| High-level Gentamicin | >256 | R |
| High Level Streptomycin | >256 | R |
| Daptomycin | <1 | S |

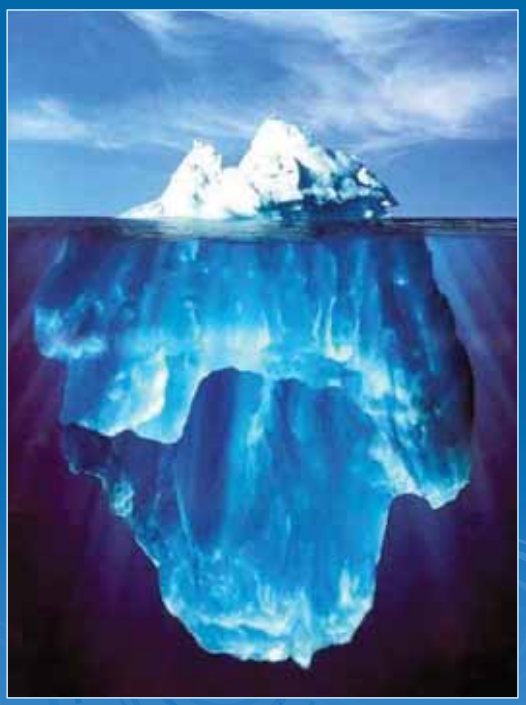


**Daptomycin resistance has emerged during therapy**

# Problem of Hidden Reservoir True for VRE as well as for MRSA (Huang et al. JID 2007:195:339-46)

**VRE identified** through routine cultures

**Asymptomatic carriers** identified through active surveillance cultures performed on admission or weekly thereafter. Increased detection of VRE colonized patients 2.2-17.0 fold, admission 3.3-15.4 fold, weekly



# Epidemiology of Vancomycin-Resistant Enterococci Among Patients on an Adult Stem Cell Transplant Unit: Observations From an Active Surveillance Program

Michael S. Calderwood, MD; Andreas Mauer, MD; Jocelyn Tolentino, MPH; Ernesto Flores, MT(ASCP), CIC; Koen van Besien, MD; Ken Pursell, MD; Stephen G. Weber, MD, MS

"Bone marrow and stem cell transplant patients are at high risk for colonization and infection with antimicrobial-resistant pathogens, and particularly with VRE …**30% of transplant patients who are colonized with VRE will go on to experience overt infection.**"

"Conclusion: Examination of epidemiological and microbiological data collected by an active surveillance program provides useful information about the epidemiology of VRE that can be applied to inform rational infection control strategies."

*Infect Control Hosp Epidemiol* 2008; 29:1019-1025

# The Burden of VRE not Limited to Adults

## Unrecognized Burden of Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant *Enterococcus* Carriage in the Pediatric Intensive Care Unit

Aaron M. Milstone, MD; Xiaoyan Song, PhD, MD, MSc; Claire Beers, RN, MSN; Ivor Berkowitz, MD; Karen C. Carroll, MD; Trish M. Perl, MD, MSc

The use of weekly surveillance cultures increased the number of detections of MRSA and VRE carriers in the PICU by 100% and 350%, respectively.

infection control and hospital epidemiology december 2008, vol. 29, no. 12

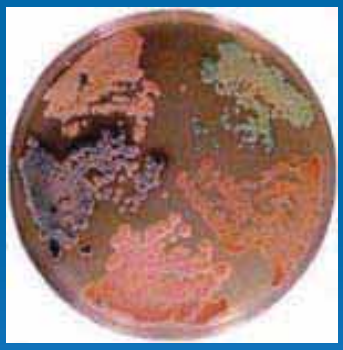
# Current Gold Standard

- Detection of VRE has traditionally relied upon culture
- Typical procedure includes growth in broth followed by inoculation on Bile Esculin Azide agar with vancomycin, gram staining and catalase + PYR-tests
- Direct methods such as Bile Esculin Agar plate is also used.
- Time to results **24 – 72 hours**

→ **Need for more rapid tests to identify VRE to minimize risk of spread within healthcare setting**

# Choosing A Surveillance Method

**Microbiology**
**Culture**
**2-3 days**



**Other Molecular Systems**
**"Real time" PCR**
**Average 1 day TAT**

**GeneXpert®**
**Real time PCR**
**Test results on demand**

# Searching for Vancomycin Resistance Genes in Fecal Samples

- Both BD and Cepheid have amplification tests that detect *vanA* and *vanB* vancomycin resistance genes, but don't specifically link the genes to an enterococcal host organism (unlike MRSA)
- Several studies show that detection of *vanA* is highly associated with recovery of a *vanA*-containing enterococci from stool



Launay A. et al. AAC 2006;50:1054-62

# Searching for Vancomycin Resistance Genes in Fecal Samples

**Current dilemma;** *vanB* genes are less common than *vanA* and found not only in enterococci but in several anaerobic species. So what is the value of a *vanB* assay?

- The *vanB* gene cluster from *Clostridium symbiosum* was transferred via a conjugal transposon to both *E. faecium* and *E. faecalis* isolates in the digestive tracts of gnotobiotic mice.
- Use *vanB* to track organisms with mobile resistance genes regardless of host



Launay A. et al. AAC 2006;50:1054-62

# GeneXpert *Vancomycin Resistance Gene Detection* Beta Study Results

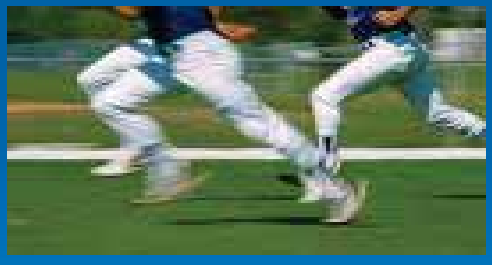
| | *vanA* | | *vanB* | |
|---|---|---|---|---|
| Specimen | Positive Agreement | Negative Agreement | Positive Agreement | Negative Agreement |
| | | | | |
| **Rectal Swab*** | **96.5% (83/86)** | **91.5% (725/792)** | **100% (13/13)** | **83.9%* (726/865)** |
| | | | | |

* More anaerobic organisms present?

Compared to direct culture results

# Infection Prevention Goals for the 21st Century

***When it comes to detecting Healthcare Associated Infections..***



**Rapid is routine**

**Key laboratory results are completed in <1 hour**

# SUMMARY

- MRSA, VRE, and *Clostridium difficile* are all inter-related infection control and infection prevention problems.
- *C. difficile* is emerging as a community-acquired infection, due in part to the emergence of a new epidemic clone, which produces binary toxin and is fluoroquinolone resistant
- VRE is an underappreciated threat to patient safety that should receive greater attention; control efforts would benefit from better surveillance
- Future molecular products will significantly reduced the time to recognize these pathogens, which will allow more timely infection control efforts (VRE and *C. difficile*) and decreased time to initiating effective therapy.