

UHN IPAC Education Day – November 14, 2008

I Need a Result...and Fast! -
Innovations in Diagnostic Testing

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Assistant Professor, U. of Toronto

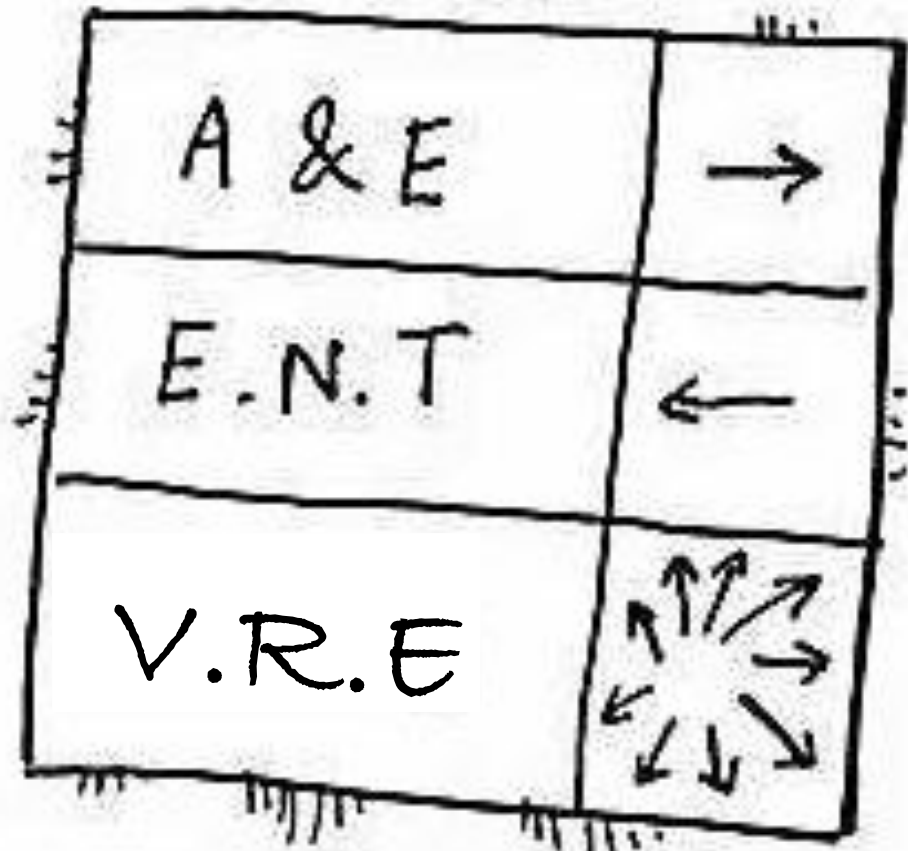
HOSPITAL



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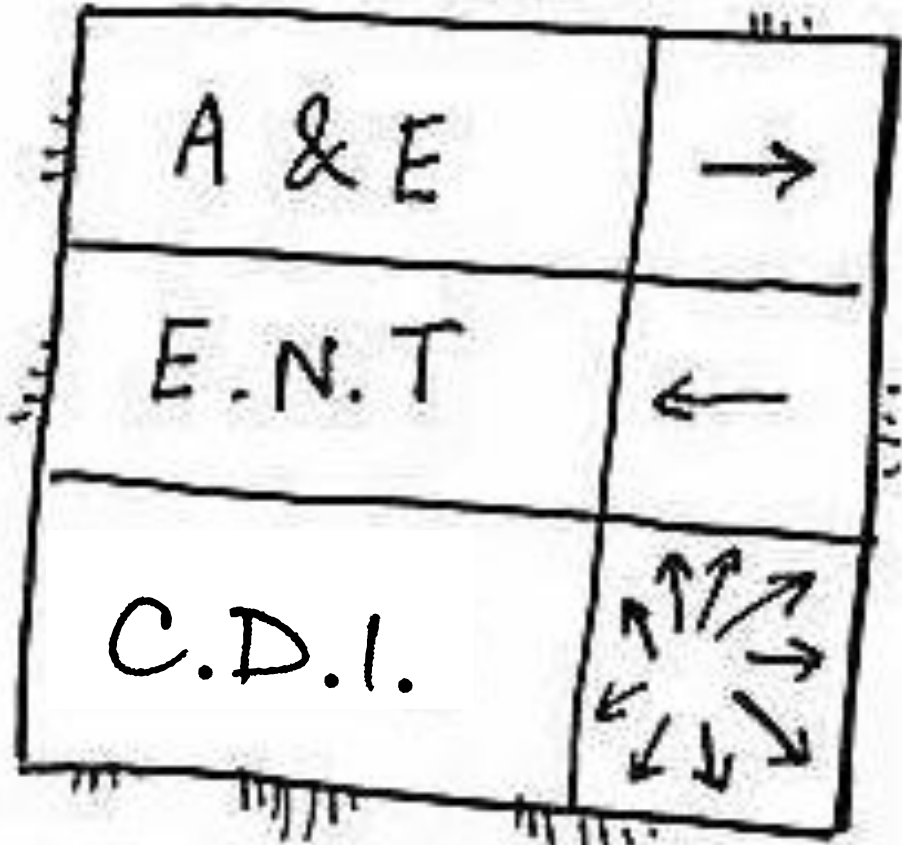
R9J

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R9J

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R9J

Objectives

Innovations in Diagnostic Testing

1. Methicillin-resistant *S. aureus* (MRSA)
2. Vancomycin-resistant enterococci (VRE)
3. *Clostridium difficile* (CDI)

 **GlobeLife**

Health

POSTED AT 4:58 AM EDT ON 10/09/07

Hospitals urged to post infection rates

LISA PRIEST

From Monday's Globe and Mail

GlobeLife

Health

globeandmail.com 

HOME NATIONAL WORLD REPORT ON BUSINESS SPORTS OPINIONS ARTS

POSTED ON 04/02/08

Ottawa targets hospital superbugs

LISA PRIEST

GlobeLife

Health

globeandmail.com



MRSA

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Health
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MRSA

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Health
VIRE

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HOME NATIONAL WORLD REPORT ON BUSINESS SPORTS OPINIONS ARTS

MRSA

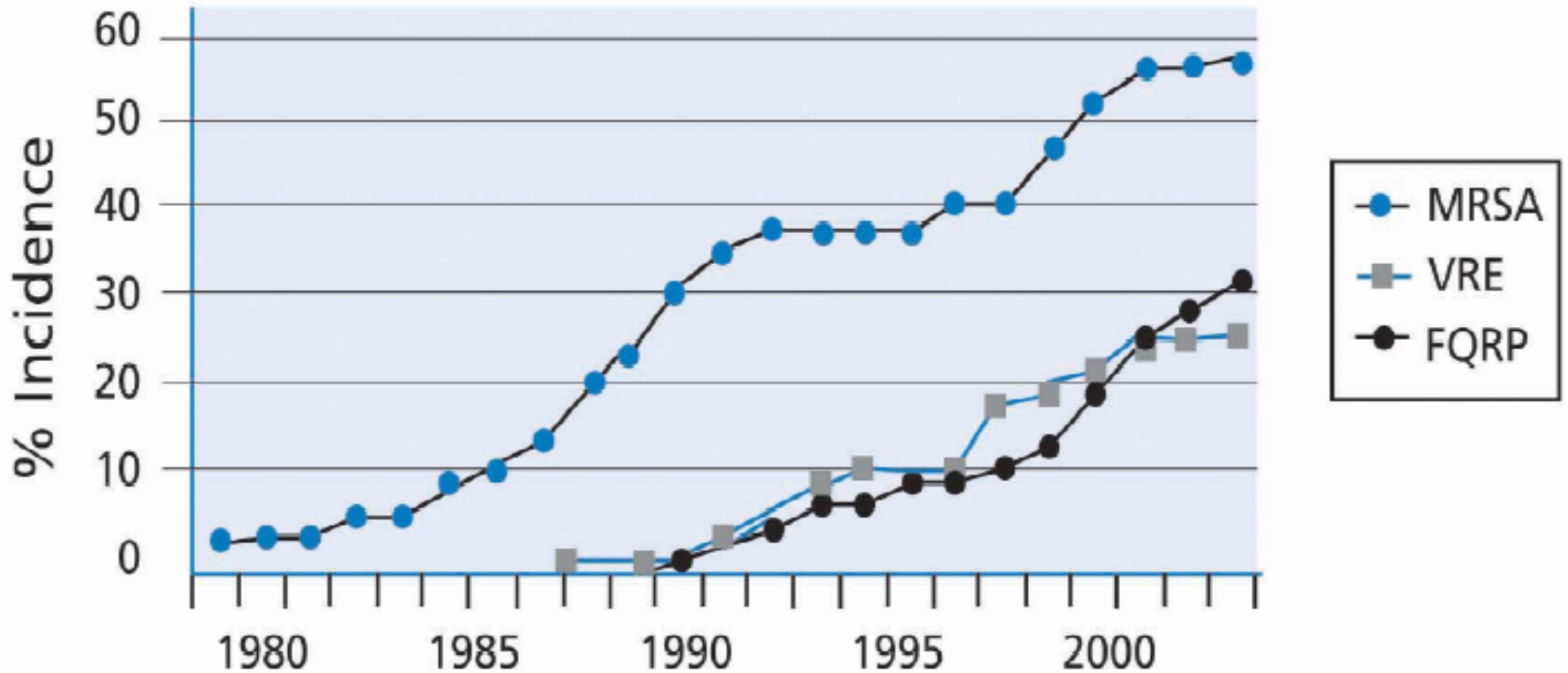
POSTED ON 04/02/08

Ottawa targets hospital superbugs

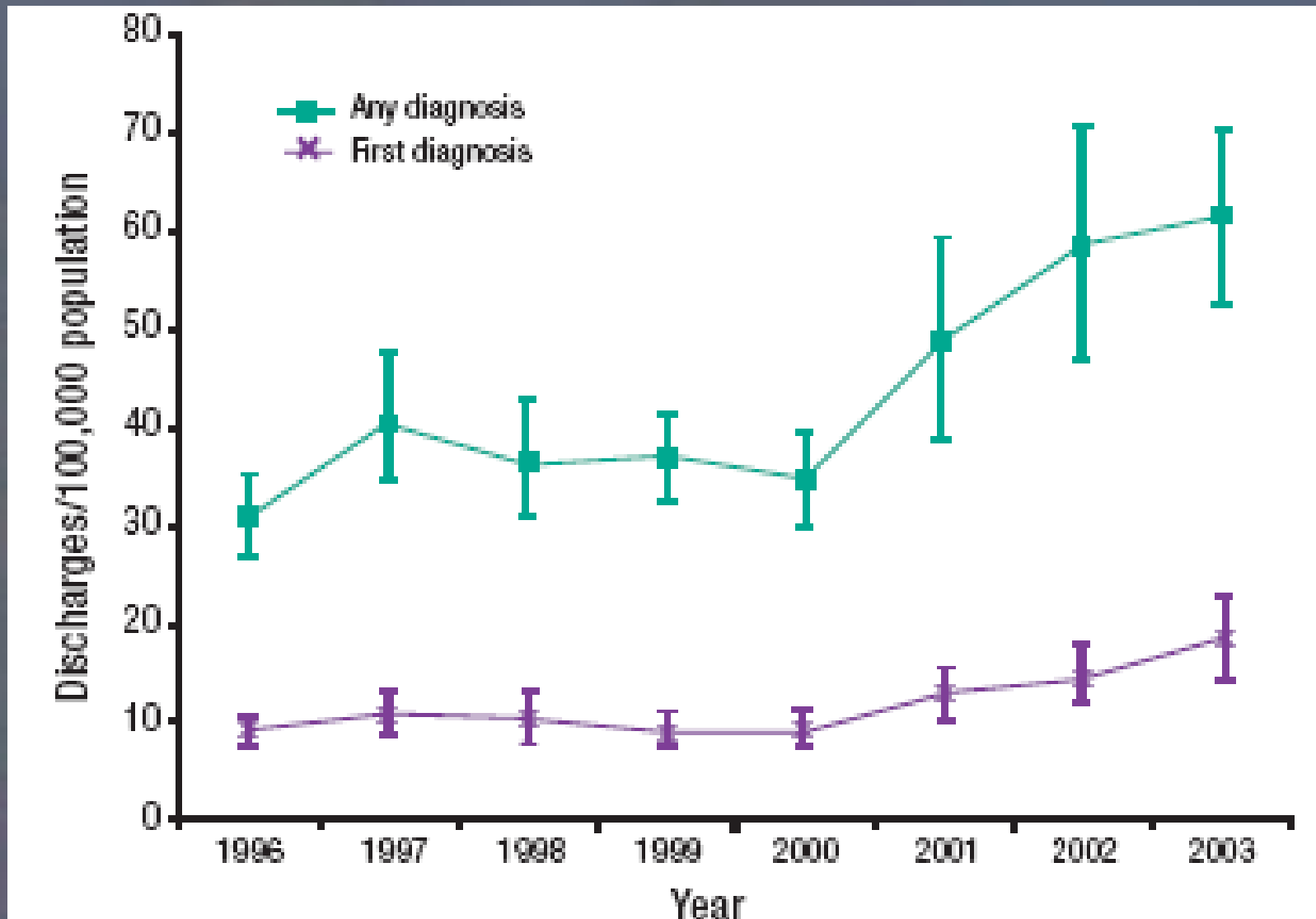
LISA PRIEST

C. difficile

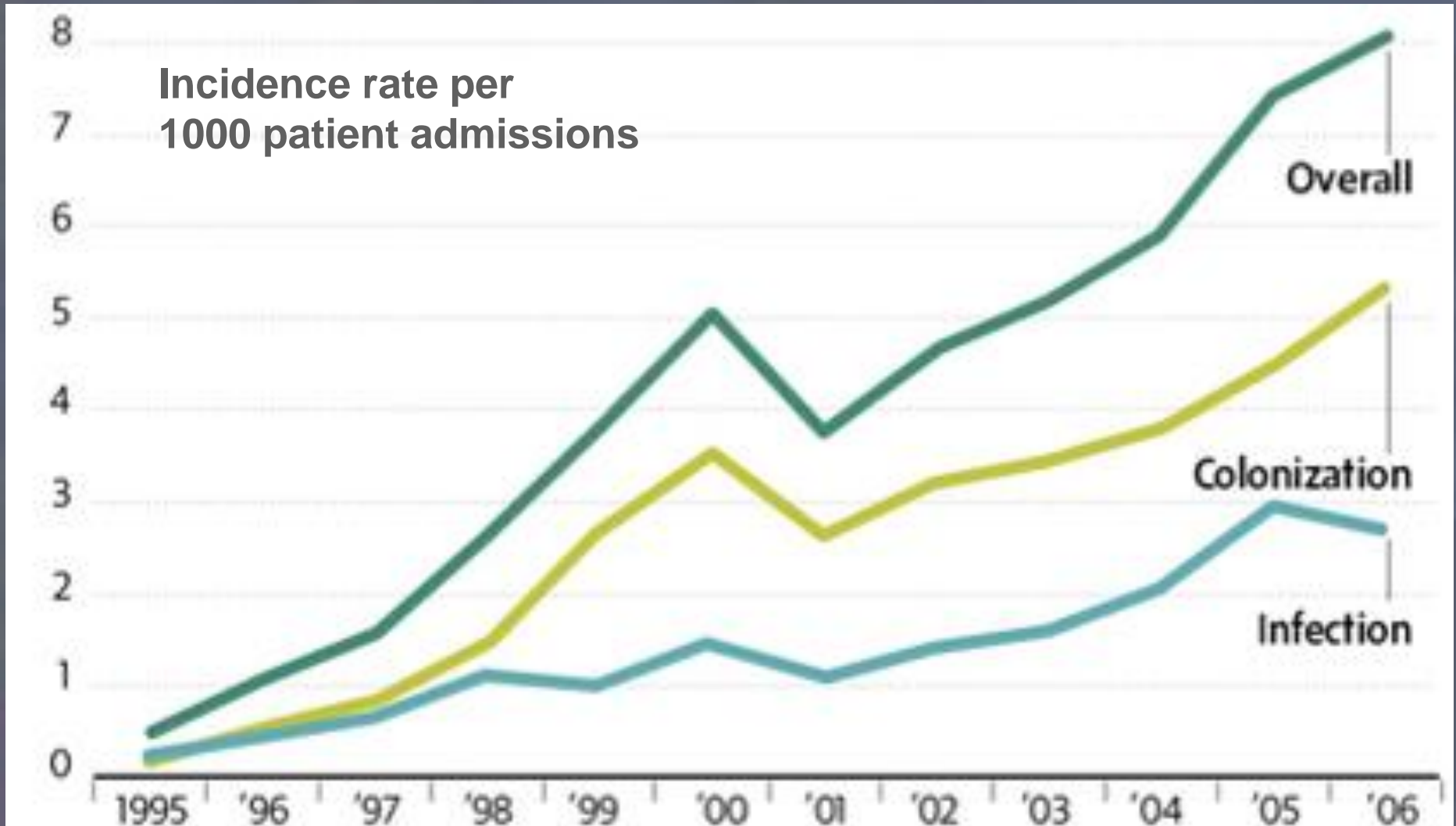
Superbugs in the US



CDI in the US



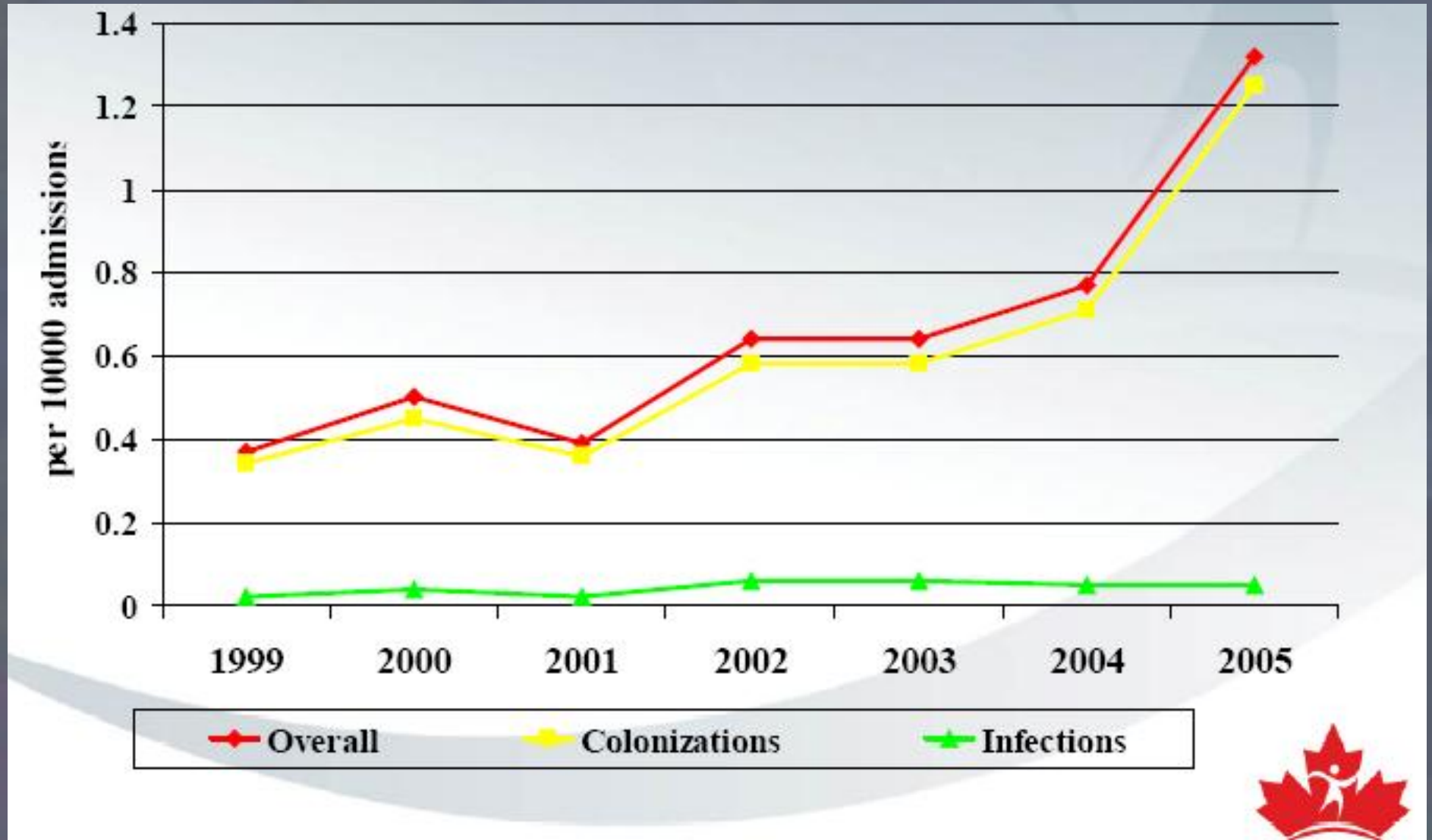
MRSA in Canada



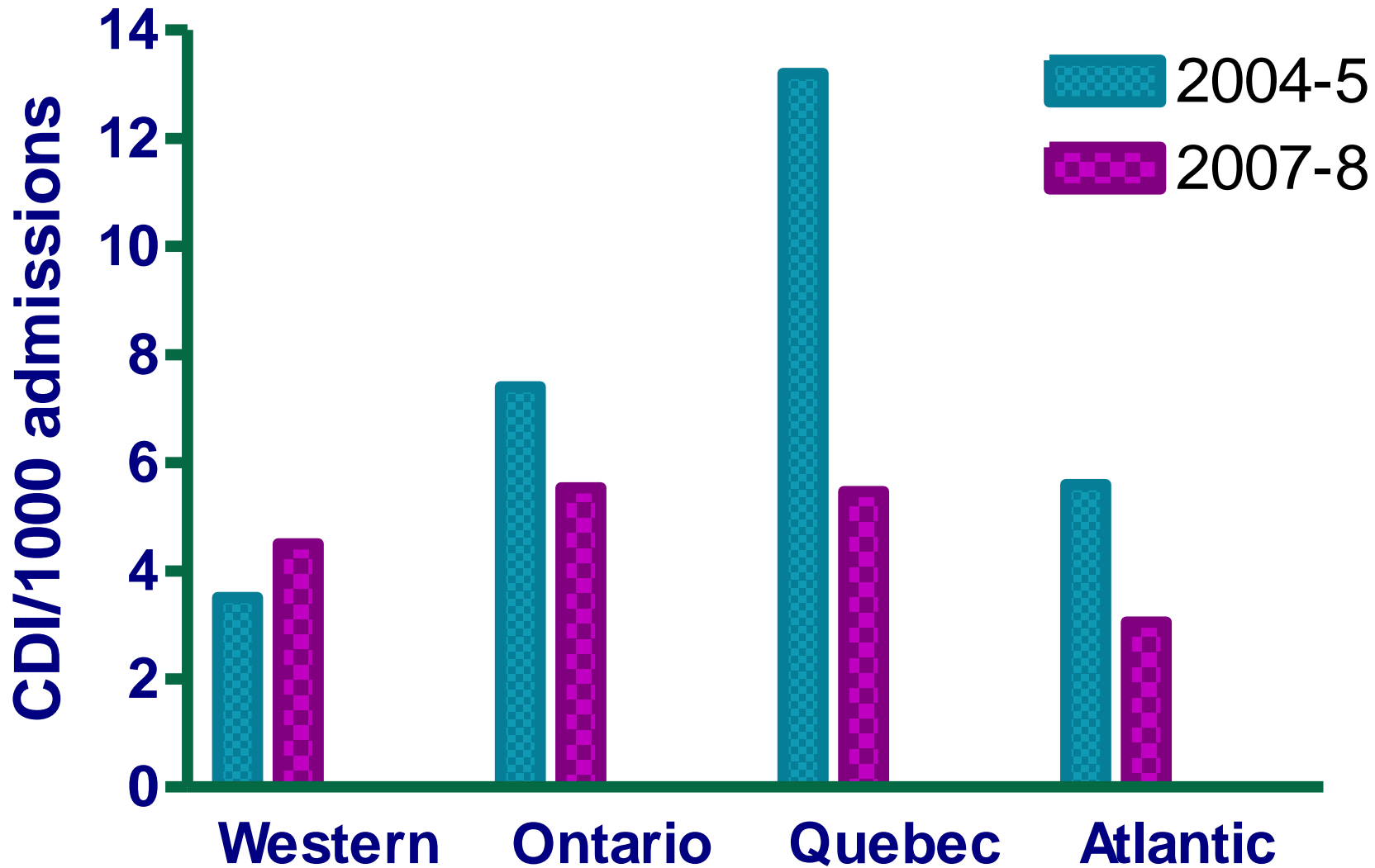
www.globeandmail.com (March 27, 2008)

www.phac-aspc.gc.ca/nois-sinp/survprog_e.html (CNISP site)

VRE in Canada



CDI in Canada



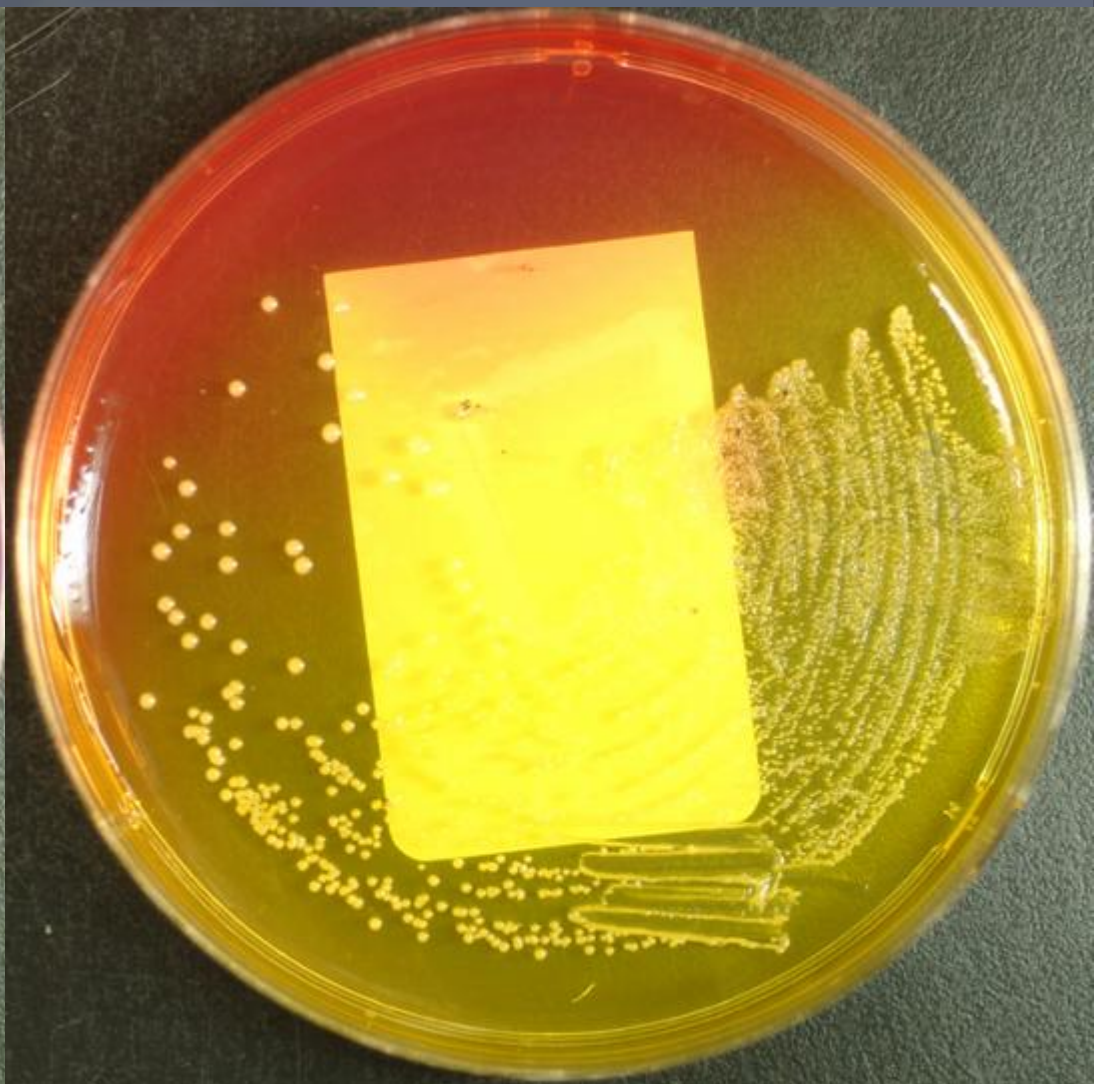
A microscopic image of MRSA (Methicillin-resistant Staphylococcus aureus) bacteria. The bacteria are arranged in several chains and clusters, appearing as small, spherical, purple-stained cells. The background is a light, slightly textured blue. A semi-transparent dark blue horizontal band is overlaid across the center of the image, containing the text 'MRSA' in white.

MRSA

Available Methods - MRSA

- Traditional Screening Agar +/- broth enrichment
 - Mannitol salt agar with oxacillin
 - Mannitol salt agar with cefoxitin
- Chromogenic Agar
 - Now the mainstay for most laboratories
 - Many brands
 - Biorad MRSA Select and Oxoid Denim Blue most popular given improved Sn/Sp and TAT compared with mannitol salt agar

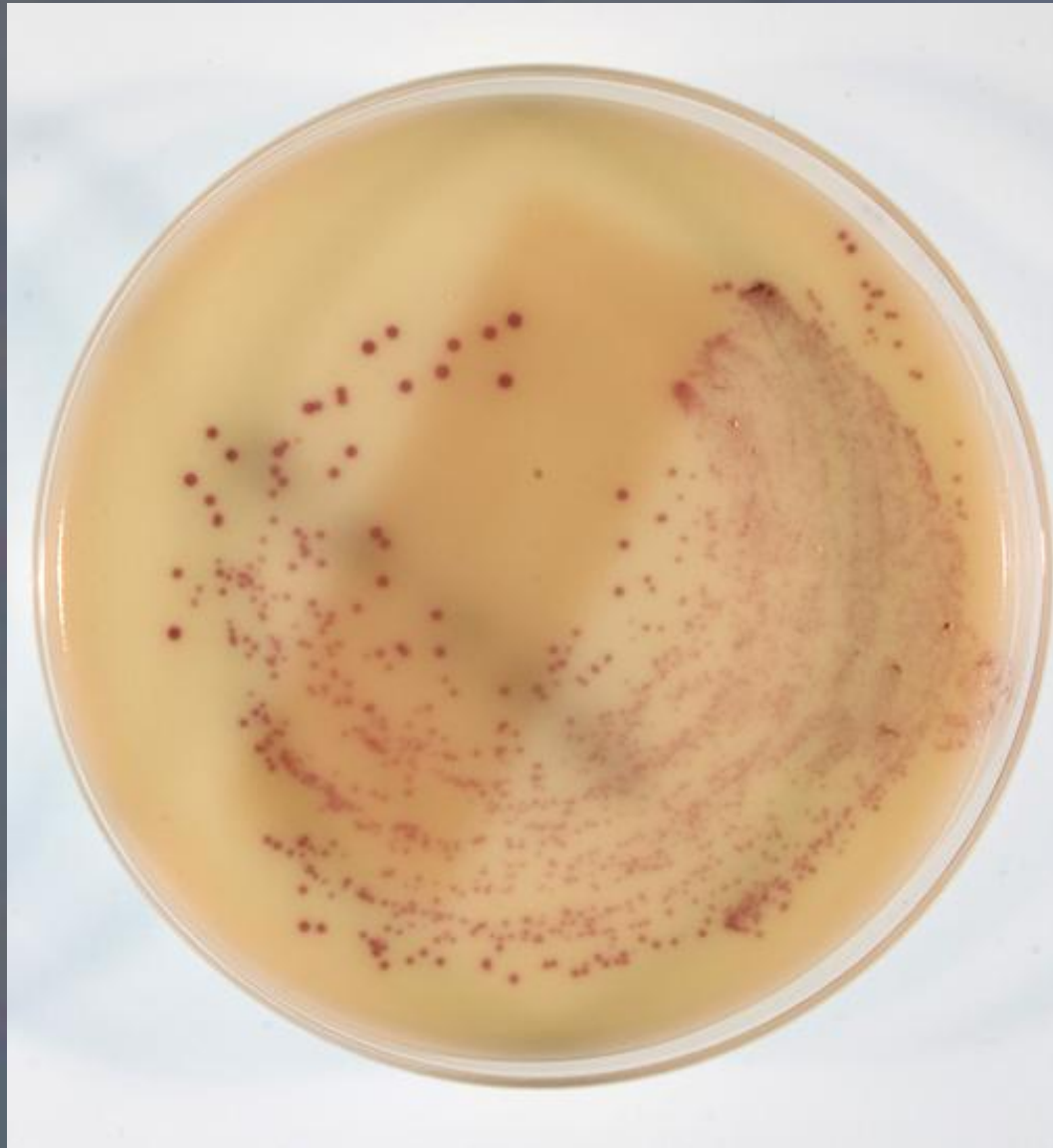
Mannitol-Salt Agar



Oxoid Denim Blue



Biorad MRSA Select



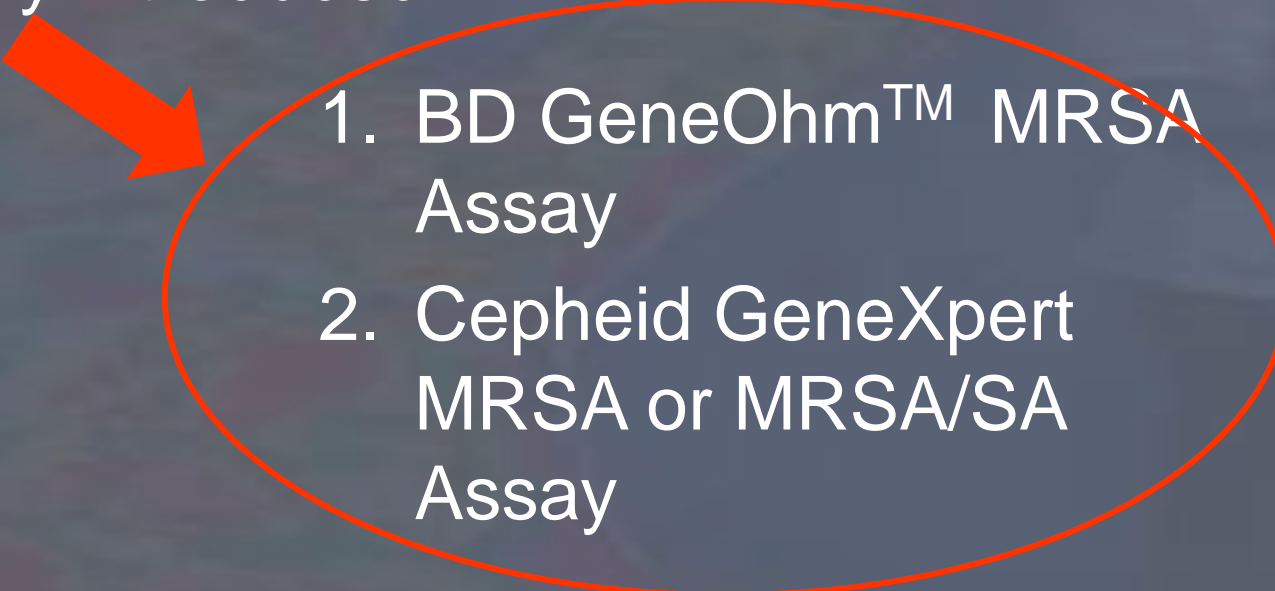
Available Methods - MRSA

- PCR
 - More recently introduced

Available Methods - MRSA

- PCR

- More recently introduced

- 
1. BD GeneOhm™ MRSA Assay
 2. Cepheid GeneXpert MRSA or MRSA/SA Assay

BD GenOhm™





BD GeneOhm™ MRSA

Knowing how and when
to treat a patient leads to
better medicine

Assay Performance¹

| | |
|--|-----|
| Sensitivity | 93% |
| Specificity | 96% |
| Negative Predictive Value (NPV) | 98% |
| Positive Predictive Value (PPV) ² | 85% |

¹ BD GeneOhm™ MRSA package insert, BD Diagnostics 2008

² Fourteen (14) of the 23 culture-negative specimens that were BD GeneOhm™ MRSA positive were found to be culture-positive upon further investigation. This resulted in a total of 140 culture-positive and BD GeneOhm™ MRSA positive specimens out of a total of 156 PCR positive specimens.

"Healthcare facilities must not accept ongoing multidrug-resistant organism (MDRO) infection outbreaks...as the status quo. With selection of infection control measures appropriate to their situation, all facilities can achieve the desired goal and reduce the MDRO burden substantially."

*- CDC/HICPAC, Management of MDROs
in Healthcare Settings, 2006*

In 2004, it was shown that 19% of patients colonized with MRSA at admission develop an infection, and for patients that acquire MRSA within the hospital, 25% go on to develop an infection.¹ Such infections pose up to a 23% mortality risk for those affected.²

Cepheid GeneXpert





Infinity workflow.

Near hands-free operation from a single workstation.

The entire Infinity workflow loop is managed from a single position: the operator workstation. Test cartridges enter the system by way of the integrated countertop conveyor. At the end of the Infinity workflow, they are deposited into a biohazard disposal bin located in the base of the workstation. This single-point approach reduces the need for operator movement around system components, delivering a more efficient testing workflow.

TOUCH-SCREEN DRIVEN XPERTISE™ SOFTWARE

CARTRIDGE CONVEYOR

BIOHAZARD DISPOSAL BIN

GeneXpert Infinity-48

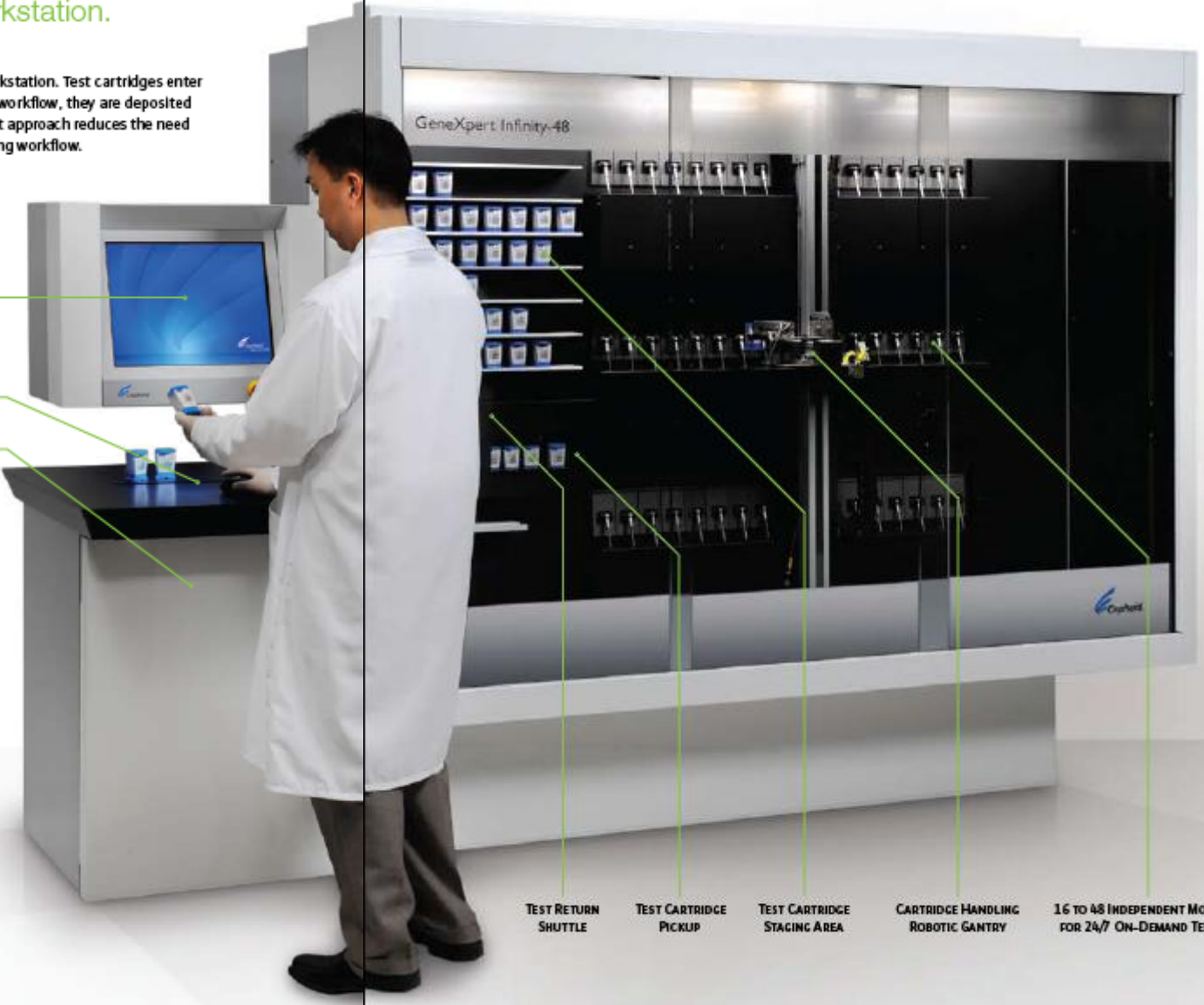
TEST RETURN SHUTTLE

TEST CARTRIDGE PICKUP

TEST CARTRIDGE STAGING AREA

CARTRIDGE HANDLING ROBOTIC GANTRY

16 TO 48 INDEPENDENT MODULES FOR 24/7 ON-DEMAND TESTING





 Cepheid.

Xpert™ MRSA

Xpert™ MRSA

Redefining Active MRSA Surveillance Testing.

Test Characteristics - MRSA

- Compared to confirmed positive by any method*:

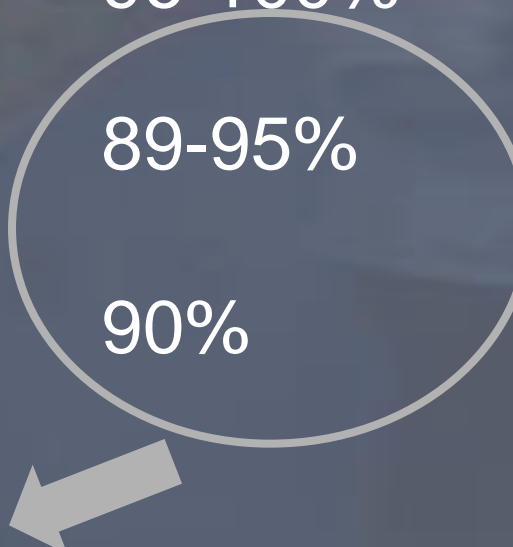
| Method | Sensitivity | Specificity |
|--------------------------------|--------------------|--------------------|
| Chromogenic agar | 90-99% | 96-100% |
| PCR (BD GeneOhm) | 93-100% | 89-95% |
| PCR (Cepheid GeneXpert) | 98% | 90% |

Test Characteristics - MRSA

- Compared to confirmed positive by any method*:

| Method | Sensitivity | Specificity |
|-------------------------|-------------|-------------|
| Chromogenic agar | 90-99% | 96-100% |
| PCR (BD GeneOhm) | 93-100% | 89-95% |
| PCR (Cepheid GeneXpert) | 93-100% | 90% |

*False positive due to *mec*-dropouts in cassettes



Summary of Methods - MRSA

| Method | Sn | Sp | TAT | Labour/skill intensive?* |
|-------------------------|----|-------|-------|--------------------------|
| Chromogenic agar | ↑ | ↑ | 24h | N |
| PCR (BD GeneOhm™) | ↑ | +/-↓ | 2-3h* | Y |
| PCR (Cepheid GeneXpert) | ↑ | +/-↓* | 75min | N |

*defined as either requiring a lot of labour or specialized skill sets

Summary of Methods - MRSA

| Method | Sn | Sp | TAT | Labour/skill intensive?* |
|-------------------------|----|-------|-------|--------------------------|
| Chromogenic agar | ↑ | ↑ | 24h | N |
| PCR (BD GeneOhm™) | ↑ | +/-↓ | 2-3h* | Y |
| PCR (Cepheid GeneXpert) | ↑ | +/-↓* | 75min | N |

*defined as either requiring a lot of labour or specialized skill sets

Summary of Methods - MRSA

| Method | Sn | Sp | TAT | Labour/skill intensive?* |
|-------------------------|----|-------|-------|--------------------------|
| Chromogenic agar | ↑ | ↑ | 24h | N |
| PCR (BD GeneOhm™) | ↑ | +/-↓ | 2-3h* | Y |
| PCR (Cepheid GeneXpert) | ↑ | +/-↓* | 75min | N |



*defined as either requiring a lot of labour or specialized skill sets



VRE

Available Methods - VRE

- Traditional Screening Agar +/- broth enrichment
 - Mainstay for most laboratories
 - Bile esculin azide agar with 6-8 mg/L vancomycin
 - mEnterococcus agar + 6mg/L vancomycin

Available Methods - VRE

- Traditional Screening Agar +/- broth enrichment
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 - Bile esculin azide agar with 6-8 mg/L vancomycin
 - mEnterococcus agar + 6mg/L vancomycin
- Chromogenic Screening Agar
 - Biomérieux ChromID VRE recently introduced

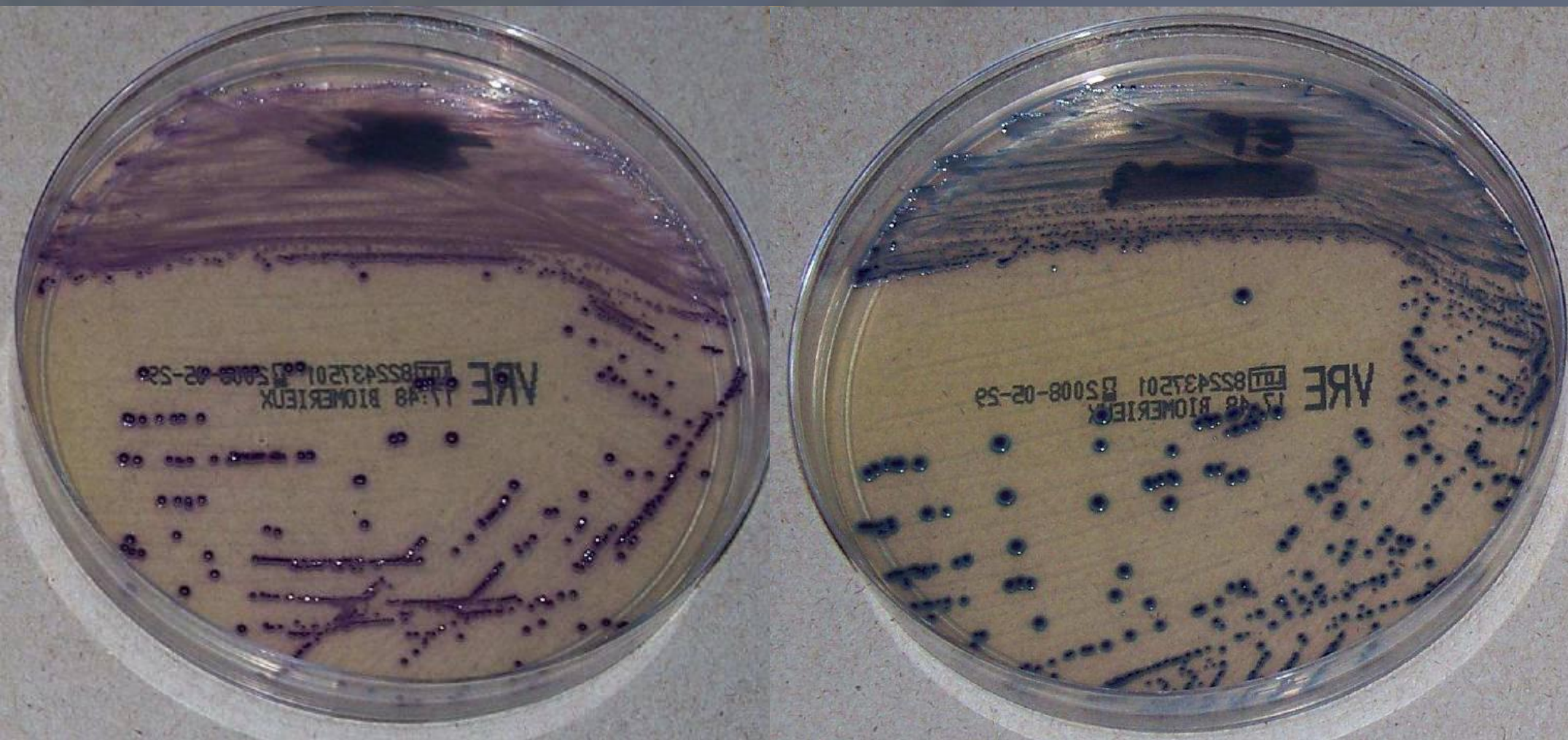
Available Methods - VRE

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- Chromogenic Screening Agar
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- PCR
 - More recently introduced

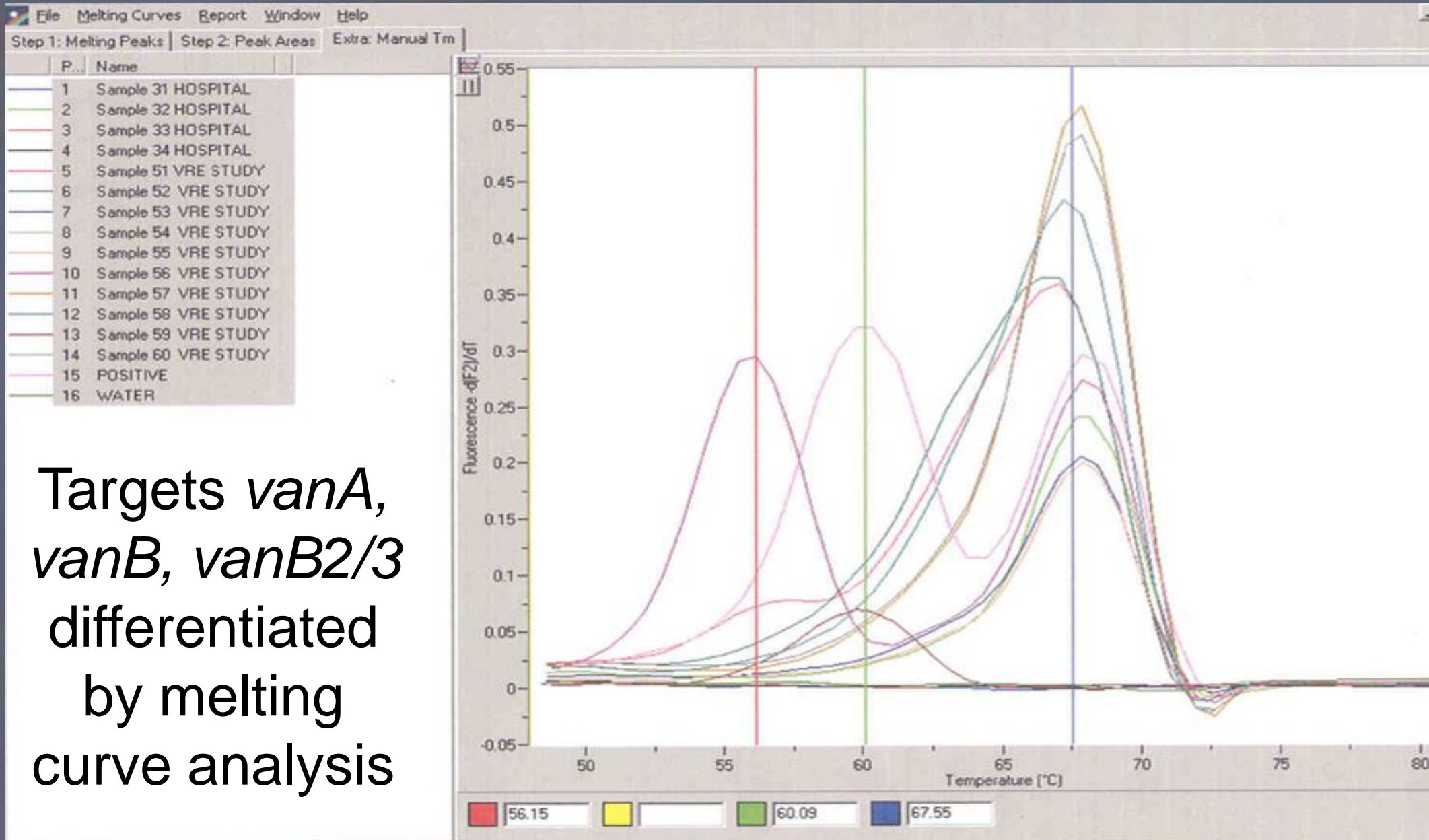
Available Methods - VRE

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- Chromogenic Screening Agar
 - Biomérieux ChromID VRE recently introduced
- PCR
 - More recently introduced
 1. Roche LC *vanA/vanB* assay
 2. BD GeneOhm™ VanR Assay

Biomérieux ChromID VRE



Roche LC *vanA/vanB* Assay



Targets *vanA*,
vanB, *vanB2/3*
differentiated
by melting
curve analysis

Test Characteristics - VRE

- Compared to confirmed positive by any method*:

| Method | Sensitivity | Specificity |
|-------------------------------|---------------------|----------------------|
| Traditional agar | 88-90% | 73-79% |
| Chromogenic agar | 86-96% (55-73%)* | 85-100% (74%) |
| PCR (Roche LC <i>vanA/B</i>) | 100% | 96-100%* (30-36%) |
| PCR (BD GeneOhm VanR) | 95-98% | 87-88%* |

Test Characteristics - VRE

- Compared to confirmed positive by any method*:

| Method | Sensitivity | Specificity |
|-----------------------|---------------------|----------------------|
| Traditional agar | 88-90% | 73-79% |
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| PCR (BD GeneOhm VanR) | 95-98% | 87-88%* |

*False negative
vanB E. faecalis

Test Characteristics - VRE

- Compared to confirmed positive by any method*:

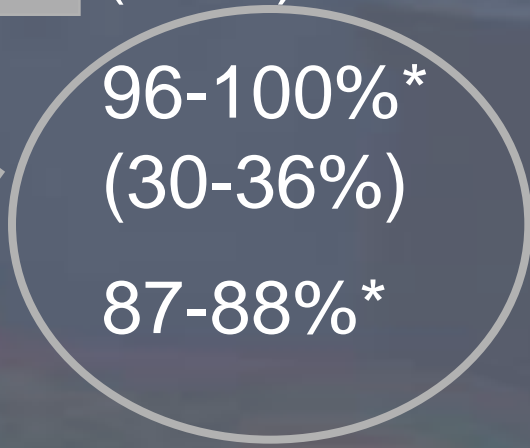
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Test Characteristics - VRE

- Compared to confirmed positive by any method*:

| Method | Sensitivity | Specificity |
|---|--------------------|----------------------|
| Traditional agar carrying this <i>van</i> determinant | 65-96% (55-73%) | 73-79% |
| Chromogenic agar | 85-98% (55-73%) | 85-100% (74%) |
| PCR (Roche LC <i>vanA/B</i>) | 100% | 96-100%* (30-36%) |
| PCR (BD GeneOhm VanR) | 95-98% | 87-88%* |

*False positive *vanB2/3* due to other organisms



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- |
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Timothy P Stinear PhD, Dianne C Olden PhD, Paul DR Johnson PhD, John K Davies PhD, Prof M Lindsay Grayson MD

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The Lancet, Volume 357, Issue 9259, Pages 855 - 856, 17 March 2001

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For more information

Summary of Methods - VRE

| Method | Sn | Sp | TAT | Labour/skill intensive? |
|----------------------------------|-------|----|--------------------------|-------------------------|
| Traditional agar | ↑ | ↓ | 84% 72-96h (up to 5d) | N |
| Chromogenic agar | +/-↓* | ↑ | 86% 24h (up to 96h) | N |
| PCR (Roche LC <i>vanA/B</i>) | ↑ | ↓* | <4h* | Y |
| PCR (BD GeneOhm™ VanR) | ↑ | ↓ | <4h* | Y |

Summary of Methods - VRE

| Method | Sn | Sp | TAT | Labour/skill intensive? |
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| PCR (BD GeneOhm™ VanR) | ↑ | ↓ | <4h* | Y |
| PCR (Cepheid GeneXpert) | (↑) | (↓) | <?h | N |

Summary of Methods - VRE

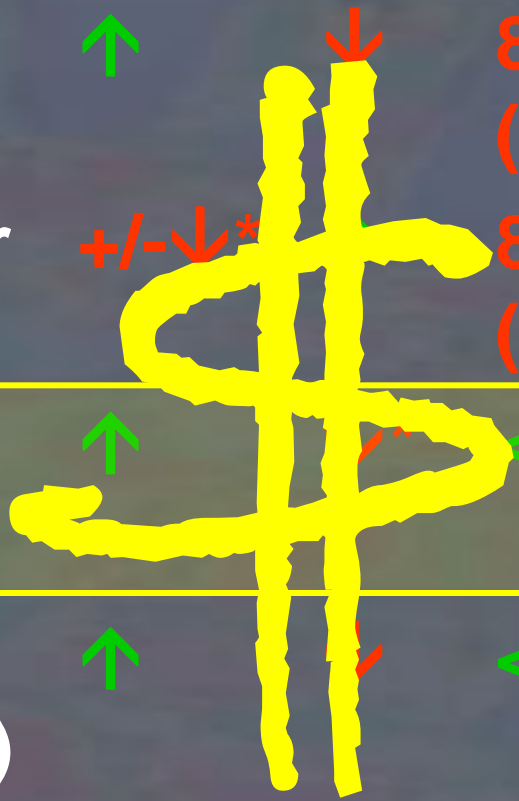
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| PCR (BD GeneOhm™ VanR) | ↑ | ↓ | <4h* | Y |
| PCR (Cepheid GeneXpert) | (↑) | (↓) | <?h | N |

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| Chromogenic agar | +/- ↓* | ↓ | 86% 24h (up to 96h) | N |
| PCR (Roche LC <i>vanA/B</i>) | ↑ | ↓* | <4h* | Y |
| PCR (BD GeneOhm™ VanR) | ↑ | ↓ | <4h* | Y |
| PCR (Cepheid GeneXpert) | (↑) | (↓) | <?h | N |



The background of the slide is a microscopic image of Clostridium difficile spores. The spores are rod-shaped and arranged in chains. They have a distinct, thick, multi-layered appearance, characteristic of their protective spore coat. The spores are set against a dark, blueish-grey background, which makes them stand out. The overall image is slightly blurred, giving it a soft, artistic feel.

Clostridium difficile

Available Methods – *C. difficile*

- Enzyme Immunoassay
 - Mainstay for most laboratories
- Cytotoxicity Assay
 - Excellent specificity

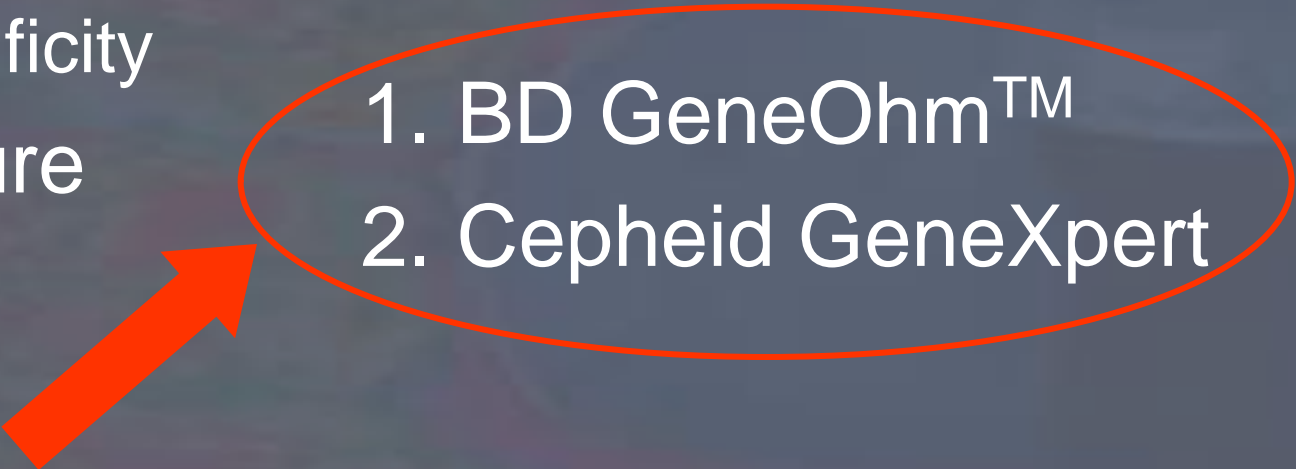
Available Methods – *C. difficile*

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- Toxigenic Culture
 - Gold standard

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 - PCR
 - Recently introduced
- 
1. BD GeneOhm™
 2. Cepheid GeneXpert

Test Characteristics – *C. difficile*

- Compared to toxigenic culture:

| Method | Sensitivity | Specificity |
|---------------------------|--------------------|--------------------|
| EIA | 57-64% | 99-100% |
| Cytotoxicity Assay | 64-76% | 99.6-100% |
| PCR (BD GeneOhm™) | 92-94% | 98% |

Test Characteristics – *C. difficile*

- Compared to toxigenic culture:

| Method | Sensitivity | Specificity |
|---------------------------|--------------------|--------------------|
| EIA | 57-64% | 99-100% |
| Cytotoxicity Assay | 64-76% | 99.6-100% |
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Summary of Methods – *C. difficile*

| Method | Sn | Sp | TAT | Labour/skill intensive? |
|--------------------|----|----|--------|-------------------------|
| EIA | ↓ | ↑ | <4h | N |
| Cytotoxicity Assay | ↓ | ↑ | 48-72h | Y |
| Toxigenic Culture | ↑ | ↑ | 72-96h | Y |
| PCR (BD GeneOhm™) | ↑ | ↑ | <2h* | Y |

Summary of Methods – *C. difficile*

| Method | Sn | Sp | TAT | Labour/skill intensive? |
|--------------------|-----|-----|--------|-------------------------|
| EIA | ↓ | ↑ | <4h | N |
| Cytotoxicity Assay | ↓ | ↑ | 48-72h | Y |
| Toxigenic Culture | ↑ | ↑ | 72-96h | Y |
| PCR (BD GeneOhm™) | ↑ | ↑ | <2h* | Y |
| PCR (GeneXpert) | (↑) | (↑) | <?h | N |

Summary of Methods – *C. difficile*

| Method | Sn | Sp | TAT | Labour/skill intensive? |
|--------------------|-----|-----|--------|-------------------------|
| EIA | ↓ | ↑ | <4h | N |
| Cytotoxicity Assay | ↓ | ↑ | 48-72h | Y |
| Toxigenic Culture | ↑ | ↑ | 72-96h | Y |
| PCR (BD GeneOhm™) | ↑ | ↑ | <2h* | Y |
| PCR (GeneXpert) | (↑) | (↑) | <?h | N |

Summary of Methods – *C. difficile*

| Method | Sn | Sp | TAT | Labour/skill intensive? |
|--------------------|-----|-----|--------|-------------------------|
| EIA | ↓ | ↑ | <4h | N |
| Cytotoxicity Assay | ↓ | ↑ | 48-72h | Y |
| Toxigenic Culture | ↑ | ↑ | 72-96h | Y |
| PCR (BD GeneOhm™) | ↑ | ↑ | <2h* | Y |
| PCR (GeneXpert) | (↑) | (↑) | <?h | N |







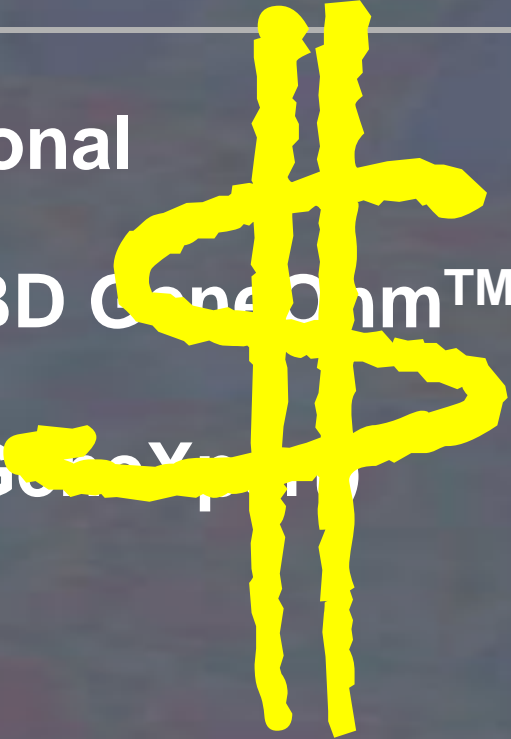
Cost-Effectiveness Analyses

Cost Comparison

| Method | Cost/test |
|-------------------|-----------|
| Traditional | <\$1 |
| PCR (BD GeneOhm™) | \$20-30 |
| PCR (GeneXpert) | \$40-50 |

Cost Comparison

| Method | Cost/test |
|-------------------|-----------|
| Traditional | <\$1 |
| PCR (BD GeneOhm™) | \$20-30 |
| PCR (GeneXpert) | \$40-50 |



Cost-effectiveness Analyses

- Increased Costs to Laboratory Budget
- Benefits
 - Increased sensitivity
 - Decreased TAT
 - Faster implementation and removal of precautions
 - Reduced transmission
 - Reduced colonization and infections



Savings to hospital in infection control and clinical care budget

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Upcoming Projects

CADTH Undertakes Four New Health Technology Assessments

Topics for health technology assessments (HTA) are selected twice a year by two of CADTH's Advisory Committees. Topics for evaluating medical devices and systems are selected by members of the Devices and Systems Advisory Committee (DSAC), and pharmaceutical topics are selected by members of the Advisory Committee on Pharmaceuticals (ACP). These committees met this spring in Ottawa from May 29 to 30 and June 5 to 6 respectively to select four new HTA topics (Table 1).

Table 1

New HTA Topics - Spring 2008

Devices and Systems

Rank

- 1 Rapid polymerase chain reaction (PCR) tests for methicillin-resistant staphylococcus aureus (MRSA) in hospitalized patients
- 2 Bariatric surgery for morbid obesity

Objectives

Innovations in Diagnostic Testing

1. Methicillin-resistant *S. aureus* (MRSA)
2. Vancomycin-resistant enterococci (VRE)
3. *Clostridium difficile* (CDI)

Acknowledgment

- Barbara Willey, A.R.T., Methods Development Technologist, UHN/MSH Department of Microbiology

Additional Reading

- Malhotra-Kumar S *et al.* Current trends in rapid diagnosis for methicillin-resistant *Staphylococcus aureus* and glycopeptide-resistant *Enterococcus* species. Journal of Clinical Microbiology 2008;46(5):1577-1587



Questions?