Current issues with VRE outbreaks and experience with rapid detection using the Xpert™ VanA/VanB assay

Roland Leclercq, University Hospital of Caen, France National Reference Center for antimicrobial resistance (associated laboratory for enterococci)
University Hospital of Caen (Normandy, France), 1700 beds.

8th Century Abbey Mount Saint Michel
Enterococci at the hospital

- A major nosocomial pathogen in many countries
  - 3rd to 6th most prevalent genus in hospital-acquired infections

- *E. faecalis* (85-90%) and *E. faecium* (10%) infections. However, proportion of *E. faecium* is increasing (up to 35%).

Source: 2006 French PPS Raisin (http://www.invs.sante.fr/raisin/)
Multiple antibiotic resistant enterococci

Selective Pressure: β-lactams, Fluoroquinolones, anti-anaerobes, glycopeptides

- **E. faecalis**
  - Gentamicin HLR/β-lactamase +
  - **E. faecalis**

- **E. faecium**
  - Ampicillin-R
  - Vancomycin-R
  - **E. faecium**
  - Ampicillin-S vancomycin-R

- **Linezolid**
  - **E. faecium** van- linez-R

- **Gentamicin**
  - **E. faecalis**
  - Gentamicin HLR

Timeline:
- 1980
- 1990
- 2000
Particular enterococci

- MultiLocus Sequence Typing (MLST) of *E. faecium* isolates revealed the existence of host-specific genogroups, including a specific clonal complex designated CC17, associated with hospital-related isolates.

- CC17 isolates are
  - Resistant to ampicillin and quinolones.
  - Most contain particular genes: mobile elements, phage genes, genes encoding membrane proteins, regulatory genes, a putative pathogenicity island including the *esp* gene, and megaplasmids.

«Star wars: Attack of the clones»

Worldwide dissemination of VRE

- Initially VRE were reported in France and the United Kingdom in 1987, and then in the rest of Europe and in the USA.

- Since 1995, they are reported worldwide. *E. faecium* with the VanA-type (cross resistance vanco/teico) or the VanB-type (resistance to vancomycin only) are widely predominant.
Age-specific increase in hospitalizations due to VRE infections (USA 2000-2006)

Ramsey AM et al. ICHE. 2009: 30; 184-187
E. faecium in Europe: % VR E. faecium in blood cultures

(EARSS  http://www.earss.rivm.nl/)
Skin and soft tissue infections (Europe)

<table>
<thead>
<tr>
<th>Country</th>
<th>% MRSA (no. of <em>S. aureus</em> tested)</th>
<th>% VRE (no. of enterococci tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>48.4 (31)</td>
<td>0.0 (9)</td>
</tr>
<tr>
<td>France</td>
<td>25.0 (517)</td>
<td>0.0 (51)</td>
</tr>
<tr>
<td>Germany</td>
<td>13.7 (365)</td>
<td>2.7 (75)</td>
</tr>
<tr>
<td>Greece</td>
<td>42.5 (80)</td>
<td>35.3 (17)</td>
</tr>
<tr>
<td>Ireland</td>
<td>43.3 (134)</td>
<td>9.5 (21)</td>
</tr>
<tr>
<td>Israel</td>
<td>26.8 (87)</td>
<td>0.0 (13)</td>
</tr>
<tr>
<td>Italy</td>
<td>27.4 (197)</td>
<td>2.6 (38)</td>
</tr>
<tr>
<td>Poland</td>
<td>33.3 (72)</td>
<td>63.6 (11)</td>
</tr>
<tr>
<td>Russia</td>
<td>3.0 (34)</td>
<td>– (0)</td>
</tr>
<tr>
<td>Spain</td>
<td>21.6 (213)</td>
<td>0.0 (21)</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.4 (236)</td>
<td>0.0 (40)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>15.4 (91)</td>
<td>0.0 (14)</td>
</tr>
<tr>
<td>Turkey</td>
<td>11.7 (128)</td>
<td>15.8 (19)</td>
</tr>
<tr>
<td>UK</td>
<td>27.5 (356)</td>
<td>25.0 (4)</td>
</tr>
<tr>
<td>Overall</td>
<td>22.5 (2541)</td>
<td>5.1 (333)</td>
</tr>
</tbody>
</table>

Enterococci isolated in 9.3% of samples

### VRE 2007-08

<table>
<thead>
<tr>
<th>Enterococcus</th>
<th>% of resistance to vancomycin according to region (no of isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>APAC</td>
</tr>
<tr>
<td>faecium</td>
<td>14.1 (270)</td>
</tr>
<tr>
<td>faecalis</td>
<td>0.01 (440)</td>
</tr>
<tr>
<td>All</td>
<td>11.9 (710)</td>
</tr>
</tbody>
</table>

Enterococcus spp. were from blood (58.3%), urine (14.1%), and wounds (7.7%).

*E. faecium*: 2/3 from blood, 8% from urine.
VRE low prevalence, mostly \textit{vanA}
Zhanel \textit{et al.} et Ofner-Agostini \textit{et al.}, 2008

ST20, 17, 475 in 1992-94
Galloway-Peña \textit{et al.}, 2009

ST18, 16 et 17 in 1990-91
Galloway-Peña \textit{et al.}, 2009

ST114, 17, 281 et 50
Camargo \textit{et al.}, 2008

ST78, 132, 210 and 438 all \textit{vanA} and 97\% \textit{esp+}
Khan \textit{et al.}, 2009
E. faecium vanB outbreaks 2007-2008 
Söderblom et al., 2010

ST17, 18, 233, 6, 78, 65, 306
Abele-Horn et al., 2006
ST203, 282, 18, 17, 78, 192
Werner et al., 2008

ST8, 18, 64, 17, 16, 48, 185, 189, 6
Caplin et al., 2008

ST18, 17, 16, 63, 103, 4, 22, 71, 40, 74 all AREF
Coque et al., 2005

ST18, 203, 78, 192, 412, 17, 275, 306, 16, 65, 80 EFM and ST6 EFS
Lesteet al., 2009

ST78, 209 clonal
Stampone et al., 2005

ST65, 412, 203, 16, 17 EFM and ST28 EFS, Damani et al., 2009

ST18, 17, 16, 117, 324, 327, 330, 272 AmpR and ST326, 332, 334, 100, 52, 272, 296 AmpS
Top et al., 2008

ST78, 18, 16, 117, 324, 327, 330, 272 AmpR and ST326, 332, 334, 100, 52, 272, 296 AmpS
Top et al., 2008

ST18, 203, 78, 192, 412, 17, 275, 306, 16, 65, 80 EFM and ST6 EFS
Lesteet al., 2009

ST78, 209 clonal
Stampone et al., 2005

ST65, 412, 203, 16, 17 EFM and ST28 EFS, Damani et al., 2009

Europe
Australia and New-Zealand

First VRE 1994

_E. faecium vanB > vanA > E. faecalis vanB > vanA_
Bell et al., 1998, Christiansen et al., 2004 et 2007, Worth et al., 2008
First VRE isolated in 1996

ST78, 359, 343, 18, 444
Hsieh et al., 2009

EFM vanA
Yaslani et al., 2009

EFM vanA
De et al., 2009

EFM > EFS vanA
Koh et al., 2009

ST18, 25, 78, 203, 11, 280, 320, 321, 322, 323, 335
Zheng et al., 2007
ST78, 117, 203, 316, 362, 363, 364, 365
Zhu et al., 2009

ST78, 192, 203, 17, 204, 205, 206, 207
Soo Ko et al., 2005
A diversity of resistance genes
The seven van operons

vanC

vanE

vanG

vanL

vanA

vanB

vanD

D-Ala-D-Ser
Intrinsic
E. gallin./cass.

D-Ala-D-Ser
Acquired
E. faecalis

D-Ala-D-Lac
Acquired
E. faecium
and other E.

Two more in the *van* alphabet

Lebreton F et al. ESCMID, Vienna 2010
A huge reservoir

- Unsuspected carrier patients are a major reservoir
  - For one patient found positive in a clinical sample, between 2 and 10 contact patients are carriers

- Reservoir of vancomycin resistance genes not limited to enterococci and not limited to humans
The anaerobes as reservoir of van genes

- van genes (vanA, vanB) have been detected in other species than enterococci

- The vanB genes and Tn1549-like element have been detected in Clostridium sp., Eggerthella lenta, and Ruminococcus sp. Also, vanD and vanG in Ruminococcus

- Clostridium symbiosum MLG101 transferred its Tn1549-like element (vanB) to E. faecium and E. faecalis in the digestive tract of gnotobiotic mice

Stinear TP et al. The Lancet 2001; 357:855-6
The animal reservoir

- Ducks, chicken, pigs, horses, cows, goats, pets are carriers
- Urban and hospital wastewaters
- Various food products, meat, vegetables, cheese
- Contamination of meat by houseflies (generally $8 \times 10^4$ cfu of enterococci within 30 minutes) (Macovei et al. J Food Protect, 2008;71:435-9).

Heterogeneity of strains and frequent presence of Tn1546 (vanA) → Spread of genes rather than spread of strains
Into the wild

Badgers, wild boars, wild rabbits, woodmices, polar gulls

Who is afraid of VRE?

Multidrug resistance

Pathogenicity

Transfer of vancomycin resistance to MRSA
Multiple antibiotic resistance

TABLE 1. Proportion (%) of VRE clinical isolates resistant to antibiotics (other than glycopeptides) according to species and genotype.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Proportion (%) resistance</th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. faecium (n = 604)</td>
<td>E. faecalis (n = 30)</td>
<td>Other species(^a) (n = 15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VanA (n = 441)</td>
<td>VanB (n = 161)</td>
<td>VanD (n = 2)</td>
<td>VanA (n = 23)</td>
<td>VanB (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>93.7</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>51.5</td>
<td>77.4</td>
<td>.(^b)</td>
<td>53.8</td>
<td>57.1</td>
<td>13.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>78.5</td>
<td>99.4</td>
<td>100</td>
<td>69.6</td>
<td>85.7</td>
<td>33.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>21.8</td>
<td>23.6</td>
<td>50</td>
<td>60.9</td>
<td>57.1</td>
<td>13.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>2.5</td>
<td>1.2</td>
<td>0</td>
<td>30.4</td>
<td>28.6</td>
<td>20.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycyclin</td>
<td>63</td>
<td>3.7</td>
<td>100</td>
<td>87</td>
<td>85.7</td>
<td>73.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tigecyclin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>99.1</td>
<td>100</td>
<td>100</td>
<td>95.7</td>
<td>71.4</td>
<td>46.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lincomycin</td>
<td>95.5</td>
<td>95.7</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pristinamycin</td>
<td>0.7</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>71.4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>91.8</td>
<td>97.5</td>
<td>50</td>
<td>69.6</td>
<td>42.9</td>
<td>6.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMP-SMX(^c)</td>
<td>67.6</td>
<td>90.7</td>
<td>0</td>
<td>60.9</td>
<td>42.9</td>
<td>6.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>8.8</td>
<td>1.9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusidic Acid</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Daptomycin active in vitro: not licensed, rare resistant isolates, suboptimal dosages?
Quinupristin-dalfopristin: resistance
Outbreaks of linezolid-resistant enterococci

- Mostly G2576 mutation in clinical isolates
- Mutations of ribosomal proteins L3 and L4

Kainer et al., Emerg Infect Dis, 2007;13: 1024-1030
VRE: a feeble pathogen?

- VRE are considered feeble pathogens (Ratio infections/colonisations 5-10%)
- Increase in infections?

Enterococcal blood culture isolates from 11 Danish counties (2002 to 2006)

Vancomycin-R MRSA: Apocalypse now?

- Despite initial fears, only few *S. aureus* acquired *vanA* and did not spread
  - Nine isolates in the USA (7/9 in Michigan) and two other reports (Iran, India).
  - No spread although the US isolates belong to ST5 (includes USA100, USA800)

Lost in America?

- Plasmid-instability

- Low frequency of transfer (plasmid Inc18)

- Staphylococcal restriction enzymes are barriers for acquisition of vancomycin-resistance. Only few isolates are deficient in this system and easily acquire foreign genes

-Synergism between vancomycin and β-lactams (widely used in combination in ICUs)

Biological cost for *vanA* resistance in *S. aureus*, but not in enterococci

In enterococci and in the absence of induction by vancomycin, tight regulation of resistance expression (VanRBSB two component system) drastically reduces the biological cost associated with Vm resistance in enterococci, favoring their dissemination.

Foucault, M.-L. et al. PNAS in Press

Should we control VRE spread?

- Difficult to control (many unsuspected gut colonizations; huge gene reservoir)
- Few infections (<<10%)
- Other priorities...

• However
  - The number of infections will increase in the absence of control
  - Transfer of vancomycin resistance to staphylococci cannot be discarded
CONTROL OF VANCOMYCIN-RESISTANT ENTEROCOCCUS IN HEALTH CARE FACILITIES IN A REGION


**Table 3.** Prevalence of Colonization with Vancomycin-Resistant Enterococci among Patients or Residents of 30 Acute Care and Long-Term Care Facilities in the Siouxland Region in July and August 1997, October 1998, and October 1999.*

<table>
<thead>
<tr>
<th>Type of Facility</th>
<th>Colonization with VRE</th>
<th>1998 versus 1997</th>
<th>1999 versus 1998</th>
<th>1999 versus 1997†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1997</td>
<td>1998</td>
<td>1999</td>
<td>RELATIVE RISK (95% CI)</td>
</tr>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>40 (2.2)</td>
<td>26 (1.4)</td>
<td>9 (0.5)</td>
<td>0.6 (0.4–1.1)</td>
</tr>
<tr>
<td>Acute care</td>
<td>10 (6.6)</td>
<td>9 (5.5)</td>
<td>0</td>
<td>0.8 (0.4–2.0)</td>
</tr>
<tr>
<td>Long-term care</td>
<td>30 (1.7)</td>
<td>17 (1.0)</td>
<td>9 (0.5)</td>
<td>0.6 (0.3–1.0)</td>
</tr>
</tbody>
</table>

*Only data from the 30 facilities that participated in all three years of the study were included. VRE denotes vancomycin-resistant enterococci, and CI confidence interval.

†The results of the chi-square test for trend for the overall rates for 1997, 1998, and 1999 were also significant (P<0.001).
Glycopeptide-Resistant Enterococci, USA, 1989 – 2003

Vancomycin Resistance (%)


1st National Guidelines (CDC/HICPAC)
1st Assessment
3rd rank in MDR bacteria

Source: NNIS System, CDC
Failure of recommendations

- Failure of control in several countries, e.g., in the US
- However, such guidelines were disseminated only in 1995: more than 5 years after VRE emergence: too late?
- Not systematically applied in all healthcare facilities
- Other countries should benefit from the experience of countries which faced outbreaks earlier
Early Warning: The Detection of VRE Emergence in France, 2004 - 2005

National recommendations for GRE surveillance and control

GRE Expert meeting at InVS

Alert

3 large outbreaks in 3 teaching hospitals

Source: InVS/Raisin (http://www.invs.sante.fr/raisin/)

GRE notifications = GRE events
- a single case of colonisation or infection
- an outbreak
VRE outbreaks

GRE Notifications (N)
- 1
- 2 - 4
- 5 - 9
- 10 - 15
- 16 - 49

2004

2005

2006

2007

2008
GRE Notifications, France, 2009

GRE Notifications (N)

1
2 - 4
5 - 9
10 - 15
16 - 49
E. faecium in Europe: % VR E. faecium in blood cultures

(EARSS http://www.earss.rivm.nl/)
Strategy for controlling VRE

• After identification of the first clinical case, screening in stools (rectal swabbing) of contact patients

• Contact precaution for all patients in the unit and if more than one case, cohorting.
Detection of VRE carriers

• Requirements
  - Rapidity (detection of carriers as soon as possible)
  - Specificity, sensitivity of techniques
  - Cost (cost vs benefits)
Chromogenic media

Without enrichment: detection in 24h-48h

With enrichment: more sensitive (20-30% additional positives detected), but needs 48h-72h.
Real-time detection by real-time PCR: Cepheid Xpert™ VanA/VanB assay

• Fully automated system

• Cartridges Xpert ready-to-go
  - Technique does not require specialized technicians

• Detection of vanA, vanB genes
  - In 47 minutes:
    • Extraction
    • Purification
    • Amplification
    • Detection
Hospital outbreak

- January 2009: 40 cases of VRE in 3 medicine departments (4 infections)
- End of the outbreak: end of February
- Second outbreak episode in March (8 patients) related to readmission of a VRE carrier
- End of the second outbreak April 2009
- Screening campaign: all hospitalized patients in departments at risk for VRE
Screening campaign

- Chromogenic media (chromID™ VRE, bioMérieux) after enrichment in broth + vancomycin
- Xpert™ VanA/VanB assay
- 804 samples (prevalence study) (2-3 weeks)
Detection of VRE by Xpert™ VanA/VanB assay and from 804 rectal swabs

<table>
<thead>
<tr>
<th>Cepheid Xpert™ vanA/vanB assay</th>
<th>Culture pos</th>
<th>Culture neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>vanA or vanB (+)</td>
<td>11</td>
<td>116</td>
</tr>
<tr>
<td>vanA (+)</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>vanB (+)</td>
<td>3</td>
<td>112</td>
</tr>
<tr>
<td>vanA/vanB (-)</td>
<td>0</td>
<td>677</td>
</tr>
</tbody>
</table>

Bourdon et al., Diagnostic Microbiology and Infectious Diseases, 2010
### Sensitivity and specificity

<table>
<thead>
<tr>
<th>Result</th>
<th>Value (%) of Cepheid Xpert™ <em>vanA/vanB</em> assay (95% CI)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td></td>
</tr>
<tr>
<td><em>vanA</em> or <em>vanB</em> (+)</td>
<td>100 (70–100)</td>
<td>85.4 (82.7–87.7)</td>
<td>8.7 (4.8–15.0)</td>
</tr>
<tr>
<td><em>vanA</em> (+)</td>
<td>100 (62.8–100)</td>
<td>99.5 (98.7–99.9)</td>
<td>66.7 (38.8–86.5)</td>
</tr>
<tr>
<td><em>vanB</em> (+)</td>
<td>100 (38.2–100)</td>
<td>85.6 (82.9–87.8)</td>
<td>2.6 (0.6–7.7)</td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval calculated by the modified Wald method.
Management of VRE outbreak using Xpert™ VanA/VanB assay

• Outbreak of *vanB* E. *faecium*: October 2008 - April 2009

• Cohorting of patients into 3 zones: zone 1- carriers, 2- contacts, 3- admitted.

• Detection of carriers using chromogenic media

• 1,000 patients screened, there were 182 double screenings (PCR and culture)
## Cepheid GeneXpert vs culture

<table>
<thead>
<tr>
<th></th>
<th>Culture pos</th>
<th>Culture neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xpert vanA/vanB +</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>Xpert vanA/vanB -</td>
<td>1</td>
<td>121</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cepheid GeneXpert</td>
<td>95</td>
<td>76.1</td>
<td>33.3</td>
<td>99.1</td>
</tr>
</tbody>
</table>

*Cavalié et al., ECCMID, 2010*
**Poor specificity of vanA/B PCR (rectal swabs)**

<table>
<thead>
<tr>
<th>PCR technique</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD GeneOhm VanR</td>
<td>96.6</td>
<td>87</td>
</tr>
<tr>
<td>PCR1</td>
<td>92</td>
<td>49</td>
</tr>
<tr>
<td>PCR2</td>
<td>92</td>
<td>60</td>
</tr>
<tr>
<td>Cepheid GeneXpert</td>
<td>100</td>
<td>85.4</td>
</tr>
</tbody>
</table>

Role of PCR in VRE control

- High negative predictive value of Cepheid PCR for VRE screening

- In an outbreak situation: a negative result may be obtained in less than one hour, 24h/24h, and thereby limits the isolation of new admitted patients

- The higher diagnostic cost is balanced by the cost of isolation (rooms, material, staff)

- A positive PCR requires a culture to be carried out and keeping the patient in isolation until the result has been obtained.
Conclusion

• **Bad news**
  - Unlimited reservoir of VRE (strains and mobile genes)
  - *CC17* is happy with our hospitals.
  - Eradication does not seem possible, so far.
  - Capacity of *van* genes to disseminate in a variety of hosts (*staph?*)

• **Good news**
  - VRE can be controlled
    - Early detection and control is a key issue: the sooner, the better!
    - Easier in countries with low VRE prevalence
    - Fully automated PCR is an innovative and effective tool part of the global infection control strategy for VRE
Thank you

- French Institute for Public Health Surveillance (InVS) and Healthcare-Associated Infection Alert, Investigation and Surveillance Network (Raisin)
  - InVS: B. Coignard, JM. Thiolet, I. Poujol, D. Rahib, S. Maugat

- National Reference Centre for Antimicrobial Resistance, Enterococci Associate Laboratory
  - M. Fines-Guyon, M. Fines-Guyon

- And above all, Healthcare Professionals from Infection Control Units, Laboratories, Clinical Wards