# Report of the Breakpoint Working Group

- Members present
  - George M. Eliopoulos, Co-Chairholder, Jim Lewis Co-Chairholder,
  - Karen Bush, Recording Secretary
  - Amy Mathers, David Nicolau, Mair Powell, Maichael Satlin, Paul Schreckenberger, Audrey Schuetz, Simone Shurland, Melvin Weinstein, Matthew Wikler, Barbara Zimmer

# Oritavancin (ORI) Breakpoint Presentation
(See Briefing documents 6.1.0, 6.1.1, 6.1.2, 6.1.3)

- ORI by FDA 8/2014 for acute bacterial skin and skin structure infections (ABSSSI) due to designated Gram-positive bacteria.
- Ad Hoc Working Group (members: Jim Lewis, chairholder; Mary Jane Ferraro, Robin Patel, Jim Jorgensen and Mike Satlin)
- Dr. Moek covered the microbiological properties of the drug and the pharmacological characteristics supporting a single dose of 1200 mg.
- Dr. Wikler reviewed the clinical studies conducted with oritavancin.

# FDA Approved Breakpoints

| | MIC (mg/ml) | | |
|---|---|---|---|
| **Microorganism** | S | I | R |
| **Staphylococcus aureus (including methicillin-resistant isolates)** | ≤0.12 | - | - |
| **Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus intermedius** | ≤0.25 | - | - |
| **Enterococcus faecalis (vancomycin-susceptible isolates only)** | ≤0.12 | - | - |

# Oritavancin exhibits potent in vitro activity against ABSSSI pathogens

*2010-2012 surveillance study in US and Europe*

| | Cumulative % inhibited at oritavancin MIC (µg/mL) | | | | | | |
|---|---|---|---|---|---|---|---|
| **Organism (n)** | **≤0.008** | **0.015** | **0.03** | **0.06** | **0.12** | **0.25** | **0.5** |
| *S. aureus* (13,336) | 2.6 | 26.5 | 67.3 | 91.3 | 98.5 | 100 | -- |
| MSSA (7,800) | 2.9 | 26.7 | 67.7 | 91.6 | 98.5 | 100 | -- |
| MRSA (5,536) | 2.2 | 26.2 | 66.6 | 90.8 | 98.5 | 100 | -- |
| *E. faecalis** (2,088) | 20.6 | 62.5 | 87.8 | 96.8 | 99.5 | >99.9 | 100 |
| *S. pyogenes* (960) | 11 | 31.7 | 57.5 | 78.8 | 92.8 | 99.4 | 100 |
| *S. agalactiae* (920) | 3.5 | 22 | 47.5 | 73.4 | 90.1 | 98.5 | 100 |
| *S. dysgalactiae* (34) | 5.9 | 11.8 | 23.5 | 58.8 | 88.2 | 100 | |
| *S. anginosus* group** (163) | 87.1 | 94.5 | 97.5 | 99.4 | 100 | -- | |

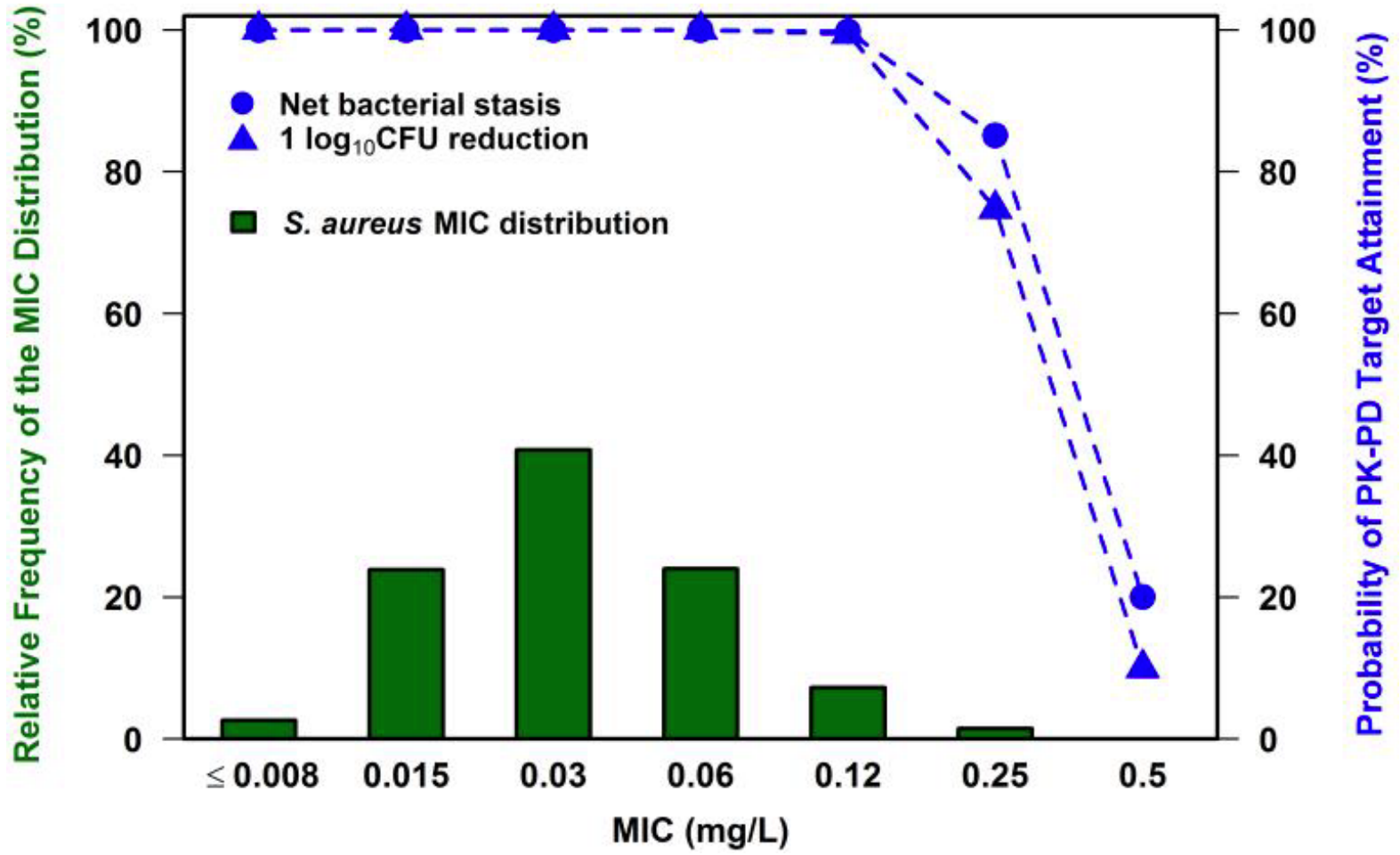
* Vancomycin-susceptible isolates only

** Includes *S. anginosus*, *S. constellatus* and *S. intermedius*

Source: 12-TMC-02 (JMI SENTRY surveillance of clinical isolates collected between 2010-2012 from the US and Europe)

Vertical black line within table for each organism or group represents FDA breakpoint

# Probabilities of PK-PD target attainment by MIC for *S. aureus*




Source of oritavancin MIC distribution:12-TMC-02 (JMI SENTRY surveillance of clinical isolates collected between 2010-2012 from the US and Europe)

Pharmaniaga 2014 ICAAC A-1309

# The sponsor requested that CLSI accept the FDA-approved breakpoints.

- **Ad-hoc WG unanimously agreed**
- **Discussion**
  - No disagreements were voiced concerning the proposal.
- **Motion:** A motion was made and seconded to accept the FDA breakpoints.
- The motion passed with a vote of Yes= 10; No = 0; Abstain = 2.
- Suggested Table 1 placement – Staph - Group B, Strep – Group C, Enterococus – Group B

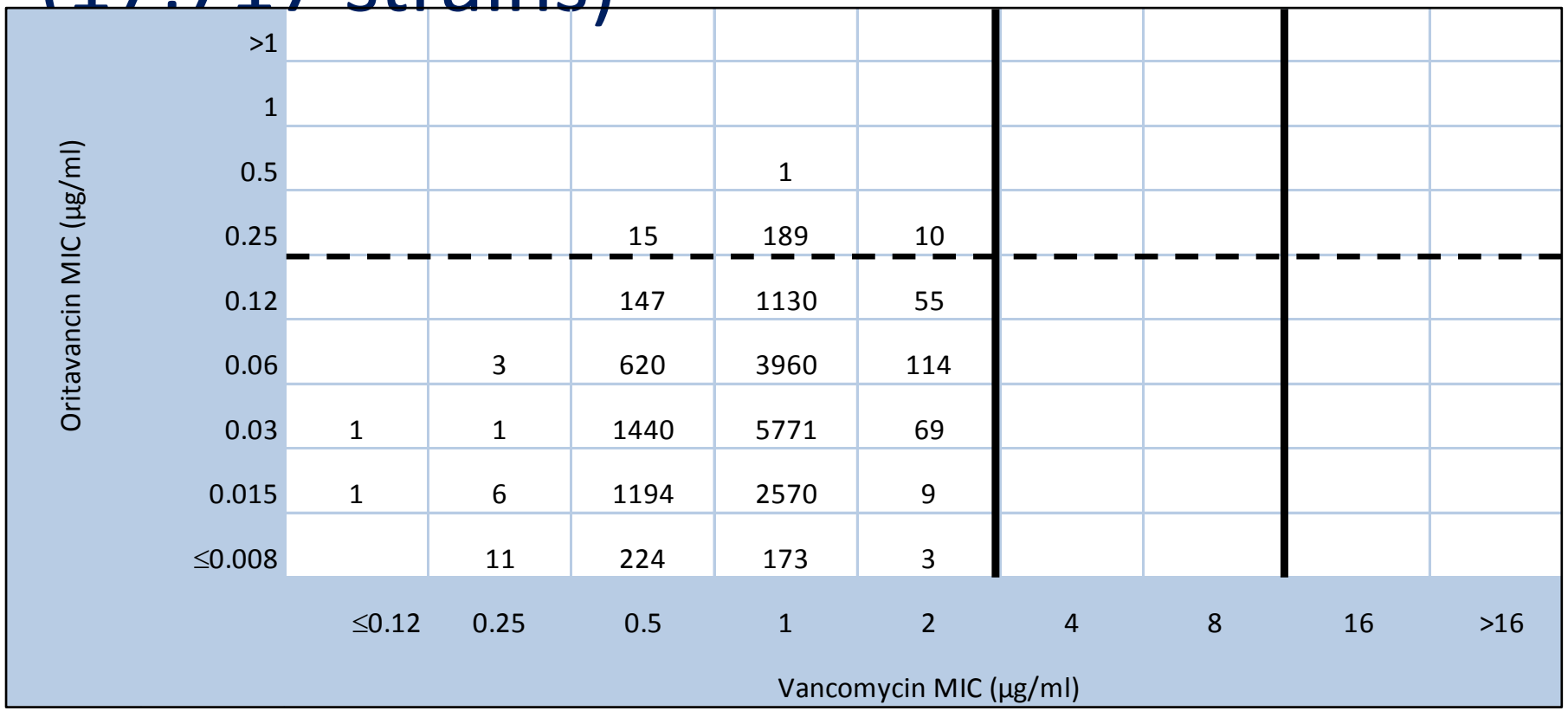
# Surrogate testing with vancomycin (VAN) be to predict ORI susceptibility requested by the sponsor

- For use prior to the FDA approval of automated testing
- Ad-hoc WG unanimously agreed to the following comment:
  - “Isolates of designated organisms that are susceptible to vancomycin can be considered and reported to be susceptible to oritavancin. Susceptibility to oritavancin should be tested directly in vancomycin non-susceptible isolates.”
- A lively discussion ensued
  - All ORI-NS *S. aureus* isolates tested as VAN-S (approx. 2% of the total of 17,717 strains).
  - However, all but one of these strains had ORI MICs one dilution higher than the breakpoint (0.25 mg/ml), within the error of the test.

# More lively discussion…

- How did the surrogate work for VISA and hVISA?
  - many hVISA test ORI-S.
  - All hVISA from clinical trials (n=21) were ORI-S, but some hVISA in a larger dataset had elevated MICs for both ORI and VAN.
- Different mechanisms of action for ORI were possible, VAN-S isolates may not include ORI resistant strains?
- Some clinical microbiologists are hesitant to call VAN-S isolates ORI-S. Wording was suggested that perhaps a footnote could indicate that all VAN-S isolates are likely ORI-S.
- It was clarified by MJ Ferraro that the intention of the Ad Hoc WG was to provide guidance for the use of oritavancin but not to call isolates ORI-S based on VAN testing.

# Scattergram of oritavancin and vancomycin MICs against *S. aureus* (17,717 strains)[a]




1.2% false susceptible

a. Strains isolated in 2011-2013 from US and Europe; broken horizontal line is FDA breakpoint for oritavancin; vertical black lines are S and R breakpoints for vancomycin

# Motion

- The following motion was made and seconded that a comment should be added to the CLSI documents stating:
  - Isolates of designated organisms that are susceptible to vancomycin can be considered to be susceptible to oritavancin. Susceptibility to oritavancin should be tested directly in vancomycin non-susceptible isolates.
- The vote was Yes = 8; No = 2; Abstain = 2
- Objections from the two WG members who voted NO:
  - Too many isolates that are ORI-NS may be called S.
  - In the future, we probably will see ORI-R/VAN-S isolates, and we will have to change the wording in the CLSI books.

# Action requested for Table 1

- Table 1A: *Staphylococcus* spp.
  - Group B: *Oritavancin[XX]
    - *MIC testing only; disk diffusion test unreliable
    - [XX] *Isolates of Staphylococcus aureus that are susceptible to vancomycin can be considered susceptible to oritavancin. Susceptibility to oritavancin should be tested directly in vancomycin non-susceptible isolates*

# Action requested for Table 1

- Table 1A: *Enterococcus* spp.
  - Group B: *Oritavancin[YY]
    - *MIC testing only; disk diffusion test unreliable
    - [YY] *Isolates of Enterococcus faecalis that are susceptible to vancomycin can be considered susceptible to oritavancin. Susceptibility to oritavancin should be tested directly in vancomycin non-susceptible isolates*

# Action requested for Table 1

- Table 1B: *Streptococcus* spp., β-Hemolytic Group
  - Group C: *Oritavancin[ZZ]
- Table 1B: *Streptococcus* spp., Viridans Group
  - Group C: *Oritavancin[ZZ]
    - *MIC testing only; disk diffusion test unreliable
    - [ZZ] *Isolates of Streptococcus pyogenes, S. agalactiae, S. dysgalactiae, S. angiosus, S. constellatus, and S. intermedius that are susceptible to vancomycin can be considered susceptible to oritavancin. Susceptibility to oritavancin should be tested directly in vancomycin non-susceptible isolates*

# Telavancin
# (See Briefing Documents 6.3.0 and 6.3.1)

- BPs originally approved by CLSI in 2011.
- Changes in methodology - DMSO and solution preparation in 0.002% P-80 have resulted in lower telavancin MICs.
- CLSI QC ranges have been revised
- Breakpoint revisions are now requested based on
  - Normal MIC distributions based on new testing methodology
  - PK/PD target attainment using new MICs
  - Clinical outcome data correlations with MICs tested with new methodology
- The sponsor requests approval of recently updated FDA BPs. EMA/EUCAST BPs are identical.

# FDA Approved Breakpoints

| Organism | Interpretation | MIC (mg/ml) | Zone diameter (mm) |
|---|---|---|---|
| **Staphylococcus aureus** | Susceptible | ≤0.12 | ≥15 |
| | Intermediate | - | - |
| | Resistant | - | - |
| **Enterococcus faecalis (vancomycin-susceptible isolates only)** | Susceptible | ≤0.25 | ≥15 |
| | Intermediate | - | - |
| | Resistant | - | - |
| **Streptococcus pyogenes Streptococcus agalactiae** | Susceptible | ≤0.12 | ≥15 |
| | Intermediate | - | - |
| | Resistant | - | - |
| **Streptococcus anginosus Group** | Susceptible | ≤0.06 | ≥15 |
| | Intermediate | - | - |
| | Resistant | - | - |

# SENTRY 2011 Surveillance Results: Revised Methodology

| Organism (number tested) | MIC (µg/mL) | | Number (cumulative %) of isolates inhibited at each telavancin MIC (µg/mL) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 50% | 90% | ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 |
| *Staphylococcus aureus* - MSSA (3386) | 0.03 | 0.06 | 119 (3.5) | 1780 (56.1) | 1473 (99.6) | 13 (100.0) | 1 (100.0) | |
| *Staphylococcus aureus* - MRSA (2357) | 0.03 | 0.06 | 51 (2.2) | 1137 (50.4) | 1160 (99.6) | 9 (100.0) | -- | |
| *Enterococcus faecalis* van-susceptible only (754) | 0.12 | 0.12 | 7 (0.9) | 15 (2.9) | 217 (31.7) | 495 (97.3) | 19 (99.9) | 1 (100) |
| *Streptococcus pyogenes* (436) | ≤0.015 | 0.06 | 232 (53.2) | 134 (83.9) | 69 (99.8) | 1 (100) | | |
| *Streptococcus agalactiae* (343) | 0.06 | 0.12 | 7 (2.0) | 62 (20.1) | 225 (85.7) | 49 (100) | | |
| *Streptococcus anginosus* group (94) | ≤0.015 | 0.03 | 48 (51.1) | 39 (97.6) | 7 (100) | | | |

*shaded boxes indicate FDA-approved breakpoints

JMI study 10-AST-01: TLV International Surveillance Report, 2011

# Phase 3 Clinical Data Supporting Revised Breakpoints

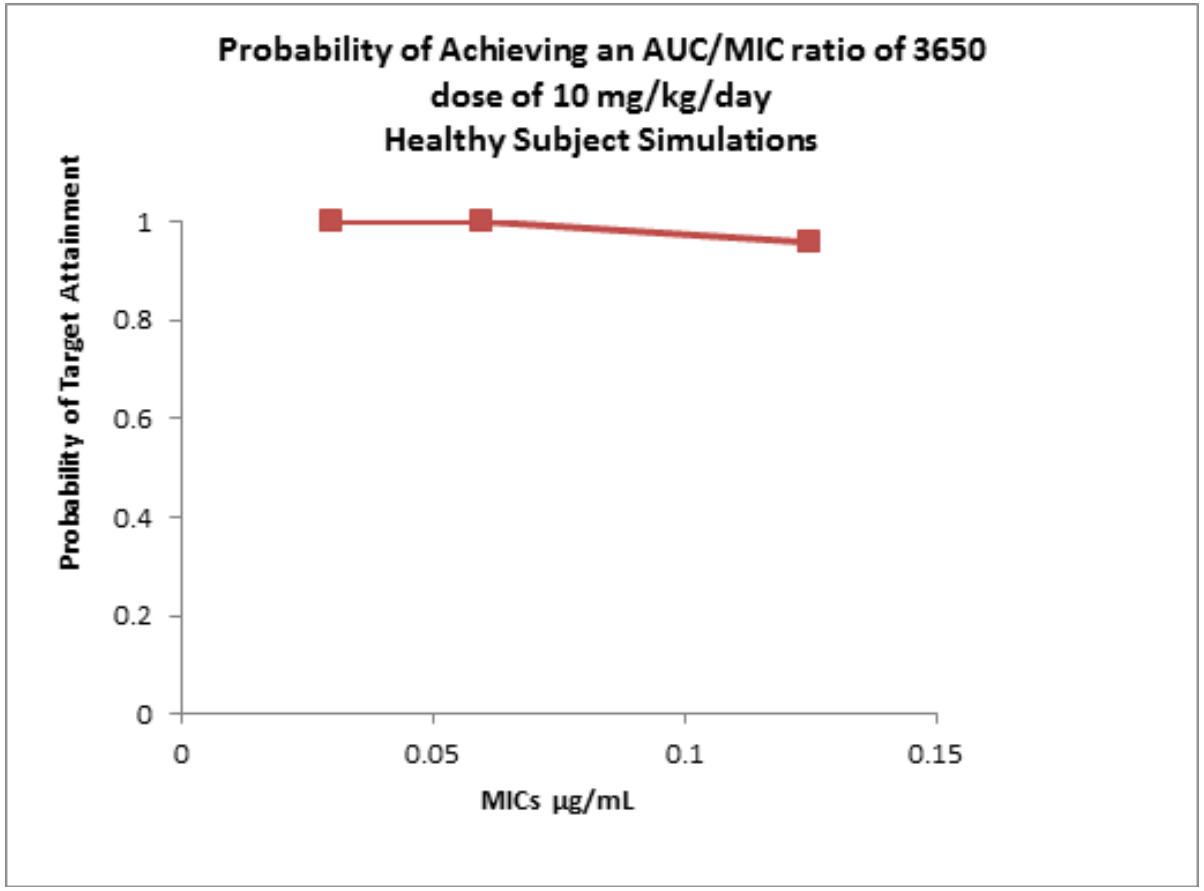
- Retested all available Phase 3 (cSSSI studies and HABP/VABP studies) clinical isolates with revised MIC methodology (n= 2,157)

- *S. aureus :*
  - cSSSI Clinical isolate data (n=1132)
    - Only 1 *S. aureus* isolate with MIC of 0.12 µg/mL
    - No (0) *S. aureus* isolates with MIC of 0.25 µg/mL
  - HABP/VABP Clinical isolate data (n=647)
    - 61 *S. aureus* isolates with MIC of 0.12 µg/mL
    - 3 *S. aureus* isolates with MIC of 0.25 µg/mL
      - Isolates re-tested in triplicate, all 3 isolates re-tested at 0.12 µg/mL

JMI Study 11-THE-01: Activity of TLV against baseline Gram-positive isolates from Ph3 clinical studies

- Using the new testing methodology, the PK/PD target AUC/MIC increased from 219 to 3650
- Free drug AUC/MIC 365 due to 90% protein binding
- MIC of the MRSA test strain decreased from 1 ug/ml to 0.06 ug/ml.

# Probability of Target Attainment Re-Analysis




- 10mg/kg/day dose is approved telavancin dose*
  - >90% Target attainment at 0.12 µg/mL

*dose adjustments are required in renally impaired patients

- The following motion was made and seconded:
- Approve the FDA breakpoints for MICs only, with a vote of Yes=9; No=0; Abstain = 3
- Suggested table 1 placement
  - *Staphylococcus* spp. - group B
  - *Streptococcus* spp. – group C
  - *Enterococcus* spp. – group B

# Achaogen Informational Presentation