How do breakpoints relate to clinical everyday life?

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Central Hospital
Växjö, Sweden
Antimicrobial susceptibility testing of bacteria and fungi

• To choose appropriate therapy and predict clinical outcome in individual patients

• To obtain a basis for empiric therapy

• To screen for organisms with exceptional (spectacular) resistance (MRSA, VRE, ESBL, KPC, NDM, MDRTB etc)
  – Public health: to prevent dissemination in health care and community

• To determine the rate of resistance development
  – To understand and predict resistance development
  – To form strategies to counteract antimicrobial resistance development and to measure success and failures of strategies
Methods for susceptibility testing

- **Phenotypic test methods**
  - Based on antimicrobial activity (MIC) and breakpoints
  - MIC, disk diffusion, automated systems like Phoenix, Vitek2, Microscan
  - Predicts susceptibility and resistance
  - Quantifiable

- **Genotypic test methods**
  - Based on the detection of a resistance gene or its product
  - meca, vanA, vanB, ...PBP2, ... betalactamase detection (enzyme detection, Maldi Tof)
  - Predicts resistance, not sensitivity
  - Not quantifiable
  - Useful for epidemiological purposes

- **By deduction** — “expert rules”
  - If MRSA then report all betalactam antibiotics R — or soon not?
  - If ESBL-positive, then report betalactam antibiotics R — but not any longer!
  - If erythromycin-resistant, then report all macrolide antibiotics as R;
  - Some rules predict susceptibility, others resistance.
  - Unreliable!
  - Not quantifiable!
Phenotypic susceptibility testing are based on
Broth microdilution

Gradient tests
The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMA and ECDC. EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or infection control. The Steering Committee is the decision making body. It is supported by a General Committee with representatives from European and other countries, FESCI and ISC. The Steering Committee also consults on EUCAST proposals with experts within the fields of infectious diseases and microbiology, pharmaceutical companies and susceptibility testing device manufacturers.

EUCAST has a subcommittee on antifungal susceptibility testing. Subcommittees on expert rules for antimicrobial susceptibility testing and antimicrobial susceptibility testing of anaerobes have completed their tasks and have been disbanded.

Most antimicrobial MIC breakpoints in Europe have been harmonised by...
### Vancomycin MICs in S. aureus

**Median MIC of each population in yellow**

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>0</th>
<th>0</th>
<th>0.01</th>
<th>0.02</th>
<th>0.03</th>
<th>0.06</th>
<th>0.13</th>
<th>0.3</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
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<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

**Vancomycin / Staphylococcus aureus**

**EUCAST MIC Distribution - Reference Database 2011-04-21**

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.
Wild type MIC distribution

Organism with MIC above ECOFF:
- identification error
- MIC error
- resistance mechanism

MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L

ECOFF

3615 observations (11 data sources)
Clinical breakpoints: S ≤ 0.25 mg/L, R > 0.25 mg/L
Organism with MIC above ECOFF:
- identification error
- MIC-determination error
- resistance mechanism
Fluconazole / Candida albicans EUCAST
EUCAST MIC Distribution - Reference Database 2012-06-26

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

3756 observations (12 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 4 mg/L

MIC Epidemiological cut-off: WT ≤ 1 mg/L
EUCAST MIC distributions

WT, NWT and ECOFF

• The **ECOFF** is the breakpoint which provides the most sensitive measure of resistance. It does not change over time, origin of the isolates or with geography. It is tied to the agent, the species and a standardised method.

• Be prepared to ask (as a clinician) or answer (as the microbiologist) "if the isolate is wild type or non-wild type to the relevant drug".
Ciprofloxacin / Haemophilus influenzae
EUCAST MIC Distribution - Reference Database 2011-08-19

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

Reporting system utilising both ECOFFs and Clinical breakpoints.

MIC (mg/L)
- ≤ 0.002
- ≤ 0.004
- ≤ 0.008
- ≤ 0.015
- ≤ 0.03
- ≤ 0.06
- ≤ 0.12
- ≤ 0.25
- ≤ 0.5
- 1
- 2
- 4
- 8
- 16
- 32
- 64
- 128
- 256
- ≥ 512

% microorganisms
- ≤ 0.002
- ≤ 0.004
- ≤ 0.008
- ≤ 0.015
- ≤ 0.03
- ≤ 0.06
- ≤ 0.12
- ≤ 0.25
- ≤ 0.5
- 1
- 2
- 4
- 8
- 16
- 32
- 64
- 128
- 256
- ≥ 512

MIC
- Epidemiological cut-off: WT ≤ 0.064 mg/L
- Clinical breakpoints: S ≤ 0.5 mg/L, R > 0.5 mg/L

12794 observations (22 data sources)
Gentamicin / Enterococcus faecalis
EUCAST MIC Distribution - Reference Database 2012-03-28

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance.

MIC (mg/L)
- ≤ 0.002
- 0.004
- 0.008
- 0.015
- 0.03
- 0.06
- 0.12
- 0.25
- 1
- 2
- 4
- 8
- 16
- 32
- 64
- 128
- 256
- ≥ 512

% microorganisms

MIC: Epidemiological cut-off: WT ≤ 32 mg/L

Clinical breakpoints: Inappropriate

4783 observations (27 data sources)

$\mathbf{R^{WT}}$ $\mathbf{R^{NWT}}$
Clinical breakpoints are determined by

- breakpoint committees (EUCAST, CLSI)
- by medicines agencies (FDA, EMA, national medicines agencies) as part of the regulatory process.
EUCAST was formed in 1996 and reformed in 2001.

<table>
<thead>
<tr>
<th>Committee</th>
<th>Country</th>
<th>Regulatory agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUCAST ¹</td>
<td>Europe</td>
<td>Yes ¹</td>
</tr>
<tr>
<td>CLSI</td>
<td>USA</td>
<td>No</td>
</tr>
<tr>
<td>FDA²</td>
<td>USA</td>
<td>As part of the regulatory process</td>
</tr>
</tbody>
</table>

¹EUCAST is the umbrella for national breakpoint committees in Europe: BSAC, CA-SFM, CRG, (DIN), NWGA & SRGA and is the breakpoint committee of EMA.

²FDA has no committee; breakpoints are suggested by company and evaluated by individual rapporteurs as part of approval process.
Tools needed for determining CLINICAL BREAKPOINTS

1. Dose or doses
2. Clinical indications
3. Target organisms
4. Individual MIC-distributions for target organisms
   - breakpoints must not divide MIC-distributions of WT target organisms
5. Resistance mechanisms in target organisms
6. Pharmacokinetics (Cmax, AUC, T½, Protein binding, Vd..)
7. Pharmacodynamic properties (peak conc/MIC, AUC/MIC, TA, MCs)
8. Clinical outcome (clinical outcome vs. MIC)
9. Epidemiological cutoff values, Pk/Pd-indices and clinical data together determine the CLINICAL BREAKPOINT
When you have decided that organisms without resistance mechanisms (=WT) can be treated with the drug (at a defined dosage), the ECOFF will constitute the "safe" tentative clinical breakpoint!
Clinical breakpoints from EUCAST

• synthesis of the ECOFF, the Pk/Pd-cut off and the clinical cut-off, sometimes they point to the same value, sometime one needs to adjust one or several dilutions.

• The ECOFF is always available, but either or both of the other two may not be!

When this is the case, a “tentative clinical breakpoint”, based on (a) the evidence that the drug is successful against wild type isolates and (b) the ECOFF, may be decided on.

Here is one example:
Using the ECOFF to define the clinical breakpoint.
Here is an example where everyone tried to be clever:
Cefotaxime / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST

2001

S/I-breakpoints
I/R-breakpoints

MIC
Epidemiological cut-off: WT ≤ 0.25 mg/L
Clinical breakpoints: S ≤ - mg/L, R > - mg/L

6290 observations (12 data sources)
Cefotaxime / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST

S/I-breakpoints
I/R-breakpoints

2007

EUCAST
CLSI

MIC
Epidemiological cut-off: WT ≤ 0.25 mg/L
Clinical breakpoints: S ≤ - mg/L, R > - mg/L

6290 observations (12 data sources)
Cefotaxime / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST

2010

S/I-breakpoints
I/R-breakpoints

CLSI: no need to exclude ESBL production
EUCAST: no need to exclude ESBL production

MIC
Epidemiological cut-off: WT ≤ 0.25 mg/L
Clinical breakpoints: S ≤ - mg/L, R > - mg/L

6290 observations (12 data sources)
Susceptible (S)

• A micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success.

• A micro-organism is categorized as susceptible by applying the appropriate breakpoint in a defined phenotypic test system.

• Note: This breakpoint may be altered with legitimate changes in circumstances
Intermediate (I)

- A micro-organism is defined as intermediate by a level of antimicrobial activity associated with indeterminate therapeutic effect.

- A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system.

- Note: This breakpoints may be altered with legitimate changes in circumstances.
A micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.

A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances.
Breakpoints can fail in several ways!

• **Fail to predict failure (undercall resistance)**
  – CLSI piperacillin-tazobactam breakpoints in *Pseudomonas*
  – Imipenem breakpoints in MRSA

• **Fail to predict success (overcall resistance)**
  – Penicillin breakpoints in *S. pneumoniae* in pneumonia

• **Generally fail to be useful (lack of correlation with either success or failure)**
  – CLSI Erythromycin breakpoints in *H. influenzae* (dividing a WT population in three SIR-categories)
Breakpoints that failed to predict failures!

- Chloramphenicol in H.influenzae (70ies)
  - Lower breakpoint for H.influenzae from 8 to 2 mg/L
- Carbapenem in MRSA (80ies)
  - Breakpoints removed, expert rule, “test for MRSA”
- Cephalosporin in Enterobacteriaceae (1980 – 2010)
  1. Breakpoints only valid if ESBL excluded
  2. Later, lower breakpoint and report as tested
- Erythromycin in S.pneumoniae
  - Lower breakpoint
- Piperacillin-tazobactam in Pseudomonas (1990 – 2010)
  - Lower breakpoint from 64 to 16 mg/L
- Ciprofloxacin in systemic Salmonella infections (2005)
  - Lower ciprofloxacin breakpoint in Salmonella
- Vancomycin in S.aureus (2005)
  - See next slide
EUCAST General Committee
All European Countries

EUCAST Steering Committee
BSAC, CA-SFM, CRG, NWGA, SRGA
And 3 reps from the General Committee*

Subcommittees
Antifungals
(Expert Rules)
Resistance mechanisms

*Currently: Austria, Denmark and Spain

National Breakpoint Committees
F, N, NL, S, UK,

ESCMID Online Lecture Library
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European Medicines Agency
Science Medicine Health
12 voting members (industry, profession)*
12 advisors (industry, profession, CDC, FDA)

*Chairmen from industry and profession on rotation
<table>
<thead>
<tr>
<th>EUCAST</th>
<th>CLSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profession together with regulatory authorities</td>
<td>Industry, the profession, advisory regulators.</td>
</tr>
<tr>
<td>Funded by ESCMID, ECDC and national breakpoint committees.</td>
<td>Funded by industry and sales of output.</td>
</tr>
<tr>
<td>Industry consultative role.</td>
<td>Industry part of decision process</td>
</tr>
<tr>
<td>Decision by consensus.</td>
<td>Decision by vote.</td>
</tr>
<tr>
<td>Five meetings per year.</td>
<td>Two meetings per year.</td>
</tr>
<tr>
<td>EUCAST=EMEA brpt committee.</td>
<td>CLSI technical standing with FDA but breakpoints not accepted by FDA.</td>
</tr>
<tr>
<td>Clinical breakpoints and ECOFFs</td>
<td>Clinical breakpoints</td>
</tr>
<tr>
<td>Rationale for decisions published</td>
<td>Rationale for decisions not published.</td>
</tr>
<tr>
<td>Documents free of charge (on web)</td>
<td>Documents for sale</td>
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EUCAST and CLSI breakpoints are different

<table>
<thead>
<tr>
<th></th>
<th>Antibiotics compared</th>
<th>Identical breakpoints</th>
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<tr>
<td></td>
<td></td>
<td>S and R</td>
<td>Only S</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>33</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>16</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>10</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>27</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Strept A, B, C and G</td>
<td>13</td>
<td>2</td>
<td>2</td>
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<tr>
<td><em>S. pneumoniae</em></td>
<td>24</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Haemophilus</em> spp.</td>
<td>25</td>
<td>0</td>
<td>3</td>
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## The significance of vancomycin breakpoints

<table>
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<tr>
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<th>MIC mg/L</th>
<th>N=</th>
<th>Reference</th>
<th></th>
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<tbody>
<tr>
<td><strong>S. aureus bacteremia</strong></td>
<td>≤ 2</td>
<td>42</td>
<td>12 % mortality</td>
<td>Fridkin et al, 2003, CID; 36: 429</td>
</tr>
<tr>
<td></td>
<td>≥ 4</td>
<td>21</td>
<td>63 % mortality</td>
<td></td>
</tr>
<tr>
<td><strong>S. aureus bacteremia</strong></td>
<td>≤ 0.5</td>
<td>87</td>
<td>44 % failure</td>
<td>Sakoulas et al, 2004, JCM; 42: 2398</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td></td>
<td>90.5 % failure</td>
<td></td>
</tr>
<tr>
<td><strong>S. aureus bacteremia</strong></td>
<td>AUC/PAP ≤0.9</td>
<td>5</td>
<td>MIC 2-4mg/L had longer bacteraemia, more fever days but equivalent mortality at end of therapy</td>
<td>Charles et al, 2004, CID; 38: 448</td>
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<tr>
<td></td>
<td>vancomycin MIC</td>
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<tr>
<td></td>
<td>0.5-2mg/L</td>
<td>48</td>
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<tr>
<td></td>
<td>AUC/PAP &gt;0.9</td>
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<tr>
<td></td>
<td>vancomycin MIC</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2-4mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>S. aureus bacteremia</strong></td>
<td>&lt; 2</td>
<td>79</td>
<td>15% failure</td>
<td>Hidayat et al, 2006, Arch Intern Med; 166: 2138</td>
</tr>
<tr>
<td></td>
<td>&gt; 2</td>
<td></td>
<td>38% failure</td>
<td></td>
</tr>
<tr>
<td><strong>S. aureus bacteremia</strong></td>
<td>≥2</td>
<td>414</td>
<td>MIC ≥ 2 predicted mortality (OR 6.4)</td>
<td>Soriano et al, 2008, CID; 46: 193</td>
</tr>
<tr>
<td><strong>Nosocomial MRSA infections</strong></td>
<td>0.5–1</td>
<td>40</td>
<td>15 (10 % mortality)</td>
<td>Hidayat et al (2006)</td>
</tr>
<tr>
<td></td>
<td>1.5–2</td>
<td>39</td>
<td>38 (24 % mortality)</td>
<td></td>
</tr>
</tbody>
</table>

Vancomycin breakpoints for Staphylococci were recently revised by both CLSI and EUCAST
Trimethoprim-sulfamethoxazole an *H. influenzae*

Bacteriological failure in AOM

Based on data from Leiberman et al, PIDJ 2001

\[
\begin{array}{c c c}
\text{Cotrimoxazol MIC mg/l} & \text{N} & p=0.0002 \\
<0.5 & 28 & \\
\geq0.5 & 6 & 6 \\
\end{array}
\]
Azithromycin and *S. pneumoniae*

Bacteriological failure in AOM

Based on data from Dagan et al, PIDJ 2000; AAC 2000, IJID 2003

![Bar chart showing Azithromycin MIC mg/l](chart.png)

- Azithromycin MIC ≤ 0.25 mg/l: 35 cases
- Azithromycin MIC > 2 mg/l: 11 cases

\[ p < 0.0001 \]
EUCAST - breakpoints for new drugs with EMA

- Daptomycin  ✓
- Tigecycline  ✓
- Doripenem  ✓
- Telavancin  ✓
- Glycopeptides (one ongoing)
- Cefalosporines (activity against MRSA – two agents ongoing)
- Anti-Mtb (two agents - ongoing)

- Glycopeptide (withdrawn)
- Fluoroquinolone (withdrawn)
- Diaminopyrimidine (withdrawn)

- Extensions of indications (currently none)

EMA = European Medicines Agency
Miscellaneous organisms
Consultation with expert groups on breakpoints and methods

- Neisseria meningitidis (review) - 2012
- Moraxella catarrhalis (finalized) - 2011
- Helicobacter pylori (finalized) - 2011
- Clostridium difficile (finalized) - 2011
- Listeria monocytogenes (finalized) - 2011
- Campylobacter (on consultation) - 2012
- Pasteurella multocida (on consultation) - 2012
- Corynebacteria (ongoing) - 2012
- Yersinia (ongoing) - 2012
- Burkholderia cepacia (started) - 2012
- ...
The European Committee on Antimicrobial Susceptibility Testing - EUCAST

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EUCAST has a subcommittee on antifungal susceptibility testing and on methods for detection of resistance mechanisms of clinical and/or epidemiological importance.

Subcommittees on expert rules for antimicrobial susceptibility testing and antimicrobial susceptibility testing of anaerobes have completed their tasks and have been disbanded.

Most antimicrobial MIC breakpoints in Europe have been harmonised by EUCAST. Breakpoints for new agents are set as part of the licensing process for new agents through EMA. EUCAST breakpoints are available in devices for automated susceptibility testing but with some limitations, depending on the system. A disk diffusion susceptibility test method calibrated to EUCAST MIC breakpoints is also available.

EUCAST invites anyone with an interest in antimicrobial agents in general and antimicrobial breakpoints in particular to contact EUCAST, ESCMID or one of the National Breakpoint Committees.
### EUCAST breakpoint table

<table>
<thead>
<tr>
<th></th>
<th>MIC breakpoint</th>
<th>Disk content</th>
<th>Zone diameter</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>S ≤ 2 mg/L</td>
<td>R &gt;8 mg/L</td>
<td>Intermediate = 4-8 mg/L</td>
<td></td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>S ≥21 mm</td>
<td>R &lt;15 mm</td>
<td>Intermediate = 15-20 mm</td>
<td></td>
</tr>
</tbody>
</table>

*Example E. coli with Imipenem:*

- S ≤ 2 mg/L
- R >8 mg/L

Intermediate = 4-8 mg/L

- S ≥21 mm
- R <15 mm

Intermediate = 15-20 mm

---

**Note:** The intermediate column is not spelled out!
## Links in EUCAST breakpoint table

<table>
<thead>
<tr>
<th></th>
<th>MIC breakpoint</th>
<th>Disk content</th>
<th>Zone diameter</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbenems</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Doripenem</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Monobactams**          |                |              |               |       |
| **Aztreonam**            | 1 | 0 | 30 | 25 | 21 |

| **Fluoroquinolones**     |                |              |               |       |
| **Ciprofloxacin**        | 0.5 | 0.05 | 10 | 22 | 19 |
| **Levofoxacin**          | 0.5 | 0.1 | 1 | 19 | 10 |
| **Moxifloxacin**         | 0.5 | 0.1 | 1 | 19 | 10 |
| **Bactericidal  (spec) **| Note | Note | 30 |       |       |

| **Aminoglycosides**      |                |              |               |       |
| **Amikacin**             | 8 | 15 | 13 |       |       |
| **Gentamicin**           | 2 | 2 | 2 |       |       |
| **Tobramycin**           | 2 | 2 | 2 |       |       |

| **Glycopeptides**        |                |              |               |       |
| **Vancomycin**           |                |              |               |       |

**Click on antibiotic for Rationale Document**

**Click on MIC breakpoint for MIC distributions**

**Click on zone breakpoint for zone diameter distributions**
Thank you!

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