# NOVEL STRATEGIES FOR EVALUATING ANTIBIOTIC USE

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**Duke** University
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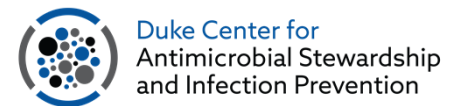
# Disclosures

Research grants – AHRQ, NIH/NIAID, CDC

Royalties – UpToDate

Several slides borrowed from Tom Holland and Scott Evans

- Antibacterial Resistance Leadership Group (ARLG)

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# Outline

## Background

- Limitations of traditional approaches

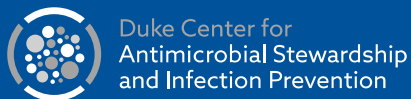## Desirability of Outcome Ranking (DOOR) – a novel paradigm to assess outcomes

- Basics
- Examples
- Build a DOOR!

## Future directions

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# Background

**Shorter is Better!**

**Less is Better!**

**Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy**

| Disease | Treatment, Days | |
|---|---|---|
| | Short | Long |
| Community-acquired pneumonia[1-3] | 3-5 | 7-10 |
| Nosocomial pneumonia[6,7] | ≤8 | 10-15 |
| Pyelonephritis[10] | 5-7 | 10-14 |
| Intraabdominal infection[11] | 4 | 10 |
| Acute exacerbation of chronic bronchitis and COPD[12] | ≤5 | ≥7 |
| Acute bacterial sinusitis[13] | 5 | 10 |
| Cellulitis[14] | 5-6 | 10 |
| Chronic osteomyelitis[15] | 42 | 84 |

Abbreviation: COPD, chronic obstructive pulmonary disease.

The **JAMA** Network

# Example Stewardship Study

Prospective study evaluating post-prescription review of broad-spectrum antimicrobial agents

- Five academic centers

Primary outcome – days of therapy (DOT)/1000 pt-days

- Intervention period vs. baseline period

Conclusion – worked in some but not all

TABLE 1. Rate of Study and Total Antimicrobial (ABX) Use and Incidence Rate Ratios (IRR) in Each Study Period

|  | Hospital A | Hospital B[a] | Hospital C | Hospital D | Hospital E |
|---|---|---|---|---|---|
| ABX-days/1,000 patient-days |  |  |  |  |  |
| Study ABX |  |  |  |  |  |
| Baseline | 419.56 | 574.37 | 509.03 | 615.59 | 519.85 |
| Intervention | 469.62 | 533.84 | 497.28 | 512.62 | 596.07 |
| Follow-up | 446.33 | ... | 476.67 | 602.72 | 642.47 |
| Total ABX |  |  |  |  |  |
| Baseline | 395.63 | 548.02 | 474.07 | 522.25 | 473.46 |
| Intervention | 443.30 | 484.01 | 460.80 | 421.42 | 560.87 |
| Follow-up | 397.36 | ... | 425.20 | 500.57 | 605.77 |
| IRR (95% CI) |  |  |  |  |  |
| Study ABX |  |  |  |  |  |
| Intervention vs baseline | 1.12 (1.05–1.19) | 0.93 (0.88–0.98) | 0.98 (0.91–1.04) | 0.83 (0.79–0.88) | 1.14 (1.08–1.22) |
| Intervention vs follow-up | 0.95 (0.89–1.01) | ... | 0.96 (0.90–1.02) | 1.18 (1.12–1.24) | 1.08 (1.01–1.15) |
| Total ABX |  |  |  |  |  |
| Intervention vs baseline | 1.12 (1.06–1.18) | 0.88 (0.85–0.92) | 0.97 (0.92–1.03) | 0.81 (0.77–0.84) | 1.18 (1.13–1.25) |
| Intervention vs follow-up | 0.90 (0.85–0.95) | ... | 0.92 (0.87–0.97) | 1.19 (1.14–1.24) | 1.08 (1.03–1.13) |

Cosgrove et al. ICHE 2012; 33: 374-380.

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# Example – Setup

BASELINE

Design a study to determine the impact of stewardship intervention "X"

## Target antibiotics

- Piperacillin-tazobactam
- Carbapenems

## Utilization

- 2000 DOT/1000 ptd for 1 year

## Average LOS

- 4.5 days

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# Example – Setup

## BASELINE

Design a study to determine the impact of stewardship intervention "X"

Target antibiotics
- Piperacillin-tazobactam
- Carbapenems

Utilization
- 2000 DOT/1000 ptd for 1 year

Average LOS
- 4.5 days

## POST-INTERVENTION

Evaluate data from first 6 months after starting the intervention (n=100)

Utilization decreased
- 842 DOT/1000 ptd

LOS decreased
- 3 days

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# SUCCESS?

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# Example - Results

BASELINE

Mortality = 2%

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# Example - Results

BASELINE

POST-INTERVENTION

Mortality = 2%

Mortality = 35%

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# Example 2 - Setup

Two important outcomes to consider

- Efficacy (benefit)
- Toxicity

Running a trial comparing 3 stewardship interventions

- Restriction
- Time Out
- Post-Rx review

In this study, outcomes are binary

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# Example 2 – Analysis of Endpoints

| Restriction (n=100) | Time Out (n=100) | Post-Rx Review (n=100) |
|---|---|---|
| Benefit: 50% | Benefit: 50% | Benefit: 50% |
| Toxicity: 20% | Toxicity: 50% | Toxicity: 50% |

Which stewardship intervention was the best?

A               B               C

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# Example 2 – Analysis of Endpoints

| Restriction (n=100) | Time Out (n=100) | Post-Rx Review (n=100) |
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Which stewardship intervention was the best?

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|---|---|---|
| Benefit: 50% | Benefit: 50% | Benefit: 50% |
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Which stewardship intervention was the best?

C

# Example 2 – Analysis of Patients

| Restriction (n=100) | Time Out (n=100) | Post-Rx Review (n=100) |
|---|---|---|
| Benefit: 50% | Benefit: 50% | Benefit: 50% |
| Toxicity: 20% | Toxicity: 50% | Toxicity: 50% |

**Benefit**

|  | + | - |
|---|---|---|
| Tox + | 10 | 10 |
| Tox - | 40 | 40 |

**Benefit**

|  | + | - |
|---|---|---|
| + | 50 | 0 |
| - | 0 | 50 |

**Benefit**

|  | + | - |
|---|---|---|
| + | 0 | 50 |
| - | 50 | 0 |

**Benefit (without toxicity)**

40%            0%            50%

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# Could More Antibiotic Use be Good?

Under treatment/no treatment of serious infections

- Sepsis

Better adherence to guidelines

- *S. aureus* bacteremia
- Fungemia

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# Limitations – Competing Risks

Common endpoints can be distorted and are challenging to interpret

- Days in the hospital
- Days in the ICU
- Days of antibiotic use

Shorter is better…or is it?

Less is better…or is it?

The faster a patient dies, the fewer the days

Interpretation of these endpoints needs clinical context of other outcomes for the same patient

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# The Future of Clinical Trials

| | Today | Tomorrow |
|---|---|---|
| Endpoints | Many | Global patient outcome |
| Patient/Clinician preferences | Limited | Incorporated |
| Treatment effects | One | Many (personalized) |

Evans and Follman. Stat Biopharm Res 2016; 8: 386.

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# DOOR Advantages

Measure to evaluate the global patient outcomes

- More informative and pragmatic benefit:risk evaluation

Patient-level interpretation

Superiority design; avoids NI complexities

Reduction of sample size in some cases

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# Conceptual Framework

Ask if new strategies are BETTER than standard strategies

- Totality of intervention: benefits, harms, QoL
- Incorporate antibiotic use

Use an ordinal outcome to rank patients

Compare DOOR distributions between strategies

But…

- How to logically put together the important outcomes?
- Weighting outcomes is challenging

Evans et al. CID 2015; 61(5): 800-6.

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# Step 1: Ordinal Outcome

## Number and definition of levels is tailored to clinical disease

- Hierarchical layers are importantly different
  - Within layers are not importantly different
- Top and bottom categories are often obvious
  - Layers between?

| Generic Example - 5 Levels |
|---|
| 1. Benefit w/o toxicity |
| 2. Benefit w/ toxicity |
| 3. Survive, no benefit w/o toxicity |
| 4. Survive, no benefit w/ toxicity |
| 5. Death |

Evans et al. CID 2015; 61(5): 800-6.

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# Step 2: DOOR

All participants receive a DOOR

Two rules:

- If 2 patients with different clinical outcomes, the patient with the BETTER clinical outcome receives higher rank
- If 2 patients with same clinical outcomes, the patient with the SHORTER duration of antibiotics receives higher rank

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# Step 3: Evaluate Superiority of DOOR

## Compare DOOR distributions between strategies

- Estimate probability (with CI) that a randomly selected patient will have a better DOOR if assigned to a new strategy vs. a control
- >50% implies superiority

# Example

## DOOR – 3 LAYERS

1. Success without AE
2. Success with AE
3. Failure

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| Subject | Tx Arm | Clinical Outcome | Days of Abx Use | DOOR | Lower DOOR |
|---------|--------|------------------|------------------|------|------------|
| A | New | 2 | 5 | | |
| B | New | 1 | 3 | | |
| C | New | 1 | 4 | | |
| D | New | 2 | 4 | | |
| E | New | 3 | 3 | | |
| F | New | 2 | 3 | | |
| G | New | 3 | 5 | | |
| H | New | 3 | 4 | | |
| I | New | 1 | 7 | | |
| J | New | 2 | 8 | | |
| K | Control | 3 | 12 | | |
| L | Control | 2 | 7 | | |
| M | Control | 1 | 9 | | |
| N | Control | 2 | 8 | | |
| O | Control | 3 | 6 | | |
| P | Control | 2 | 11 | | |
| Q | Control | 1 | 10 | | |
| R | Control | 2 | 9 | | |
| S | Control | 3 | 9 | | |
| T | Control | 2 | 6 | | |

# Example

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| C | New | 1 | 4 | | |
| I | New | 1 | 7 | | |
| M | Control | 1 | 9 | | |
| Q | Control | 1 | 10 | | |
| A | New | 2 | 5 | | |
| D | New | 2 | 4 | | |
| F | New | 2 | 3 | | |
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| M | Control | 1 | 9 | | |
| Q | Control | 1 | 10 | | |
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| P | Control | 2 | 11 | | |
| E | New | 3 | 3 | | |
| H | New | 3 | 4 | | |
| G | New | 3 | 5 | | |
| O | Control | 3 | 6 | | |
| S | Control | 3 | 9 | | |
| K | Control | 3 | 12 | | |

# Example

DOOR – 3 LAYERS

1. Success without AE
2. Success with AE
3. Failure

| Subject | Tx Arm | Clinical Outcome | Days of Abx Use | DOOR | Lower DOOR |
|---------|--------|------------------|-----------------|------|------------|
| B | New | 1 | 3 | 1 | |
| C | New | 1 | 4 | 2 | |
| I | New | 1 | 7 | 3 | |
| M | Control | 1 | 9 | 4 | |
| Q | Control | 1 | 10 | 5 | |
| F | New | 2 | 3 | 6 | |
| D | New | 2 | 4 | 7 | |
| A | New | 2 | 5 | 8 | |
| T | Control | 2 | 6 | 9 | |
| L | Control | 2 | 7 | 10 | |
| J | New | 2 | 8 | 11.5 | |
| N | Control | 2 | 8 | 11.5 | |
| R | Control | 2 | 9 | 13 | |
| P | Control | 2 | 11 | 14 | |
| E | New | 3 | 3 | 15 | |
| H | New | 3 | 4 | 16 | |
| G | New | 3 | 5 | 17 | |
| O | Control | 3 | 6 | 18 | |
| S | Control | 3 | 9 | 19 | |
| K | Control | 3 | 12 | 20 | |

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# Example

DOOR – 3 LAYERS

1. Success without AE
2. Success with AE
3. Failure

| Subject | Tx Arm | Clinical Outcome | Days of Abx Use | DOOR | Lower DOOR |
|---------|--------|------------------|-----------------|------|------------|
| A | New | 2 | 5 | 8 | 8 |
| B | New | 1 | 3 | 1 | 10 |
| C | New | 1 | 4 | 2 | 10 |
| D | New | 2 | 4 | 7 | 8 |
| E | New | 3 | 3 | 15 | 3 |
| F | New | 2 | 3 | 6 | 8 |
| G | New | 3 | 5 | 17 | 3 |
| H | New | 3 | 4 | 16 | 3 |
| I | New | 1 | 7 | 3 | 10 |
| J | New | 2 | 8 | 11.5 | 5.5 |
| K | Control | 3 | 12 | 20 | **SUM=68.5** |
| L | Control | 2 | 7 | 10 | |
| M | Control | 1 | 9 | 4 | |
| N | Control | 2 | 8 | 11.5 | |
| O | Control | 3 | 6 | 18 | |
| P | Control | 2 | 11 | 14 | |
| Q | Control | 1 | 10 | 5 | |
| R | Control | 2 | 9 | 13 | |
| S | Control | 3 | 9 | 19 | |
| T | Control | 2 | 6 | 9 | |

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# Example

No. of control participants with a lower DOOR = 68.5

Probability of a better DOOR for a randomly selected participant from the new strategy

- Number of new strategy participants with higher door divided by number of pairwise comparisons
- 68.5/100 pair-wise comparisons = 68.5%

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# BUILD A DOOR

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# Build a DOOR

Compare two scenarios and select the one with the better global outcome

Consider five items:

1. Cure vs. Failure
   - Cure – global resolution of infection
   - Failure – lack of cure

2. Infectious complication – development of resistance AFTER intervention or recurrent/persistent infection

3. Ongoing symptoms

4. Adverse Events (AE) – temporally associated with the use of antibiotics but no judgement about causality

5. Survival

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# Patient #1

75 y/o man admitted from nursing home for pneumonia.

# Patient #1 – 75 y/o with pneumonia

Scenario A – transitioned from IV to PO antibiotics and has prompt recovery.  Returns to NH after 4 day hospitalization on supplemental oxygen.

Scenario B – develops *C. difficile* after receiving FQ and admitted to the ICU.  Develops acute renal failure and gets prolonged course of IV antibiotics.  Discharged to rehabilitation center on oxygen following 18 day hospitalization and now requires assistance with ADLs.

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# Patient #1 – 75 y/o with pneumonia

|  | Scenario A | Scenario B |
|---|---|---|
| **Cure?** | Yes | Yes |
| **Post-randomization infectious complications?** | No | *C. difficile* |
| **Ongoing symptoms?** | Yes | Yes |
| **AE Grade 4+?** | No | Yes |
| **Alive?** | Yes | Yes |

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# Better global patient outcome?

Scenario A – short hospitalization, oxygen

Scenario B – *C. difficile*, renal failure, assistance with ADLs

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# Patient #2

57 y/o female admitted for travel-associated pulmonary embolism, treated with heparin bridged to warfarin.

During admission, develops sepsis from line-associated MRSA BSI.

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# Patient #2 – 57 y/o with MRSA BSI

Scenario A – during treatment, she develops acute renal failure thought to be due to contrast nephropathy from the chest CT. She develops hyperkalemia and is *en route* to the ICU for urgent dialysis, however develops VT, suffers cardiac arrest and dies.

Scenario B – one week into treatment, the patient develops back pain and lumbar osteomyelitis is found on CT. She develops acute renal failure attributed to antibiotics, requires temporary dialysis, and is changed to another antibiotic.

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# Patient #2 – 57 y/o with MRSA BSI

| | Scenario A | Scenario B |
|---|---|---|
| **Cure?** | No | No |
| **Post-randomization infectious complications?** | No | Vertebral osteo |
| **Ongoing symptoms?** | N/A | No |
| **AE Grade 4+?** | Yes | Yes |
| **Alive?** | No | Yes |

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# Better global patient outcome?

Scenario A – renal failure, death

Scenario B – vertebral osteo, renal failure, alive

# Patient #3

53 y/o female admitted for elective hysterectomy.

During admission, develops *C. difficile* following receipt of ertapenem for antimicrobial prophylaxis prior to HYST.

# Patient #3 – 53 y/o with CDI

Scenario A – during treatment, develops toxic megacolon and requires colectomy.  Recovers but continues to have loose stools and persistent abdominal discomfort.

Scenario B – recovers well from *C. difficile* but develops acute renal failure after receiving IV contrast for an abdominal CT scan. Discharged on hemodialysis; nephrologists doubt will regain renal function.

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# Patient #3 – 53 y/o with CDI

| | Scenario A | Scenario B |
|---|---|---|
| **Cure?** | Yes | Yes |
| **Post-randomization infectious complications?** | **Colectomy** | **No** |
| **Ongoing symptoms?** | **Yes** | **No** |
| **AE Grade 4+?** | **No** | **Yes** |
| **Alive?** | Yes | Yes |

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# Better global patient outcome?

Scenario A – colectomy, persistent abdominal symptoms

Scenario B – hemodialysis

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# Clinician Survey to Develop BAC-DOOR

## 43 ID physicians (ARLG members)

- 72% adult ID, 28% peds ID

## 20 adult SA-BSI profiles

- Represent the range of experiences and outcomes encountered in clinical practice
- Profiles included information about efficacy, AEs, treatment adjustments during a theoretical trial comparing 2 treatment strategies

## Respondents instructed to rank the profiles based on global patient outcome

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Updated BAC-DOOR algorithm
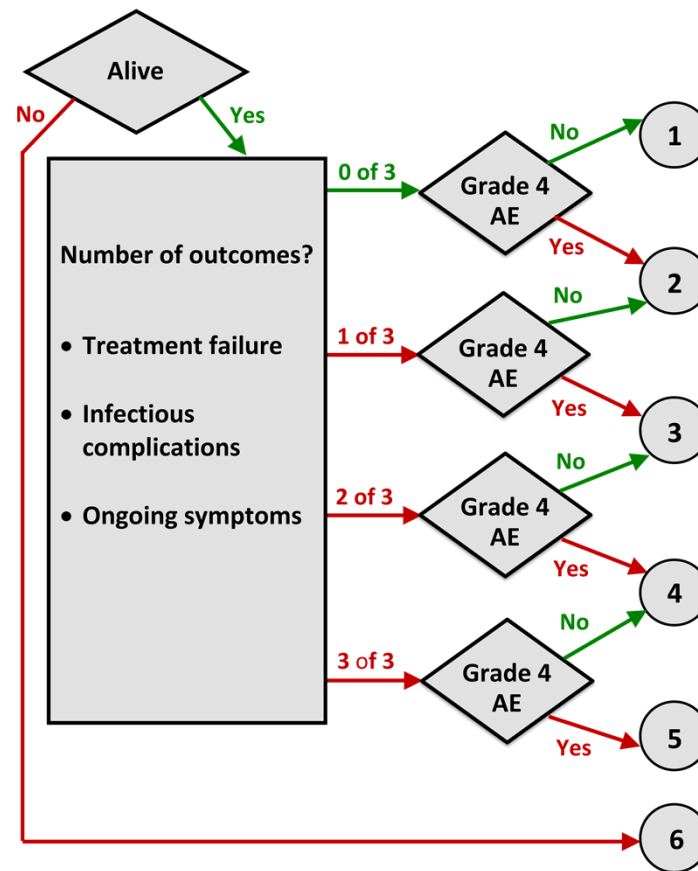
# Example 2 – Treatment of CRE

Retrospective review of prospectively enrolled patients

- 38 treated with Ceftaz-avi and 99 with colistin

Outcomes assessed at 30 days

| 4 Level DOOR | Colistin (n=46) | Caz-Avi (n=26) |
|---|---|---|
| 1. Alive, d/c home | 4 (9%) | 6 (23%) |
| 2. Alive; not d/c; no renal failure | 25 (54%) | 17 (65%) |
| 3. Alive; not d/c; renal failure | 5 (11%) | 1 (4%) |
| 4. Death | 12 (26%) | 2 (8%) |

IPTW-adjusted DOOR probability: 64% (53%, 75%)

Van Duin et al. *Clin Infect Dis* 2017; 8: 386.

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# DOOR Challenges

Cultural change

Construction of ordinal outcome is novel

Composite endpoint complexities
- Potentially too much influence given to certain components

Focus on randomization at patient-level

Solutions?
- Composite endpoint fundamentals
- Sensitivity analyses that reduce or eliminate influence of particular components deemed of lower importance
- Co-primary endpoints

# What's Next?

RADAR/DOOR approach being used in trial on abx use in pediatric patients with CAP
- SCOUT-CAP

First attempts at using in unit-level interventions

Ongoing work to refine, improve, and provide additional alternative approaches
- Partial Credit
- BED-FRAME
  - Diagnostic tools; prevalence
- COMPASS (Comparing personalized antibiotic stewardship strategies)
- DOOR STEPP (MRSA BSI outcomes based on vanco AUC)

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# Take Home Points

<u>Key message</u>: you need to measure more than antimicrobial use in your antimicrobial stewardship research

Novel strategies have been developed and are being further refined

- Focus first on composite patient outcome
- THEN, focus on antibiotic use (as a tie breaker)

Best news of all – great deal of work being done in the area

- Stay tuned for future updates

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# QUESTIONS?

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