



Administration of Antibiotics in Neonates and in Neonatal Intensive Care Units

Sagori Mukhopadhyay M.D., M.M.Sc.

Division of Neonatology, Children's Hospital of Philadelphia

Associate Professor of Pediatrics

University of Pennsylvania Perelman School of Medicine

Sept 18-20th 2025

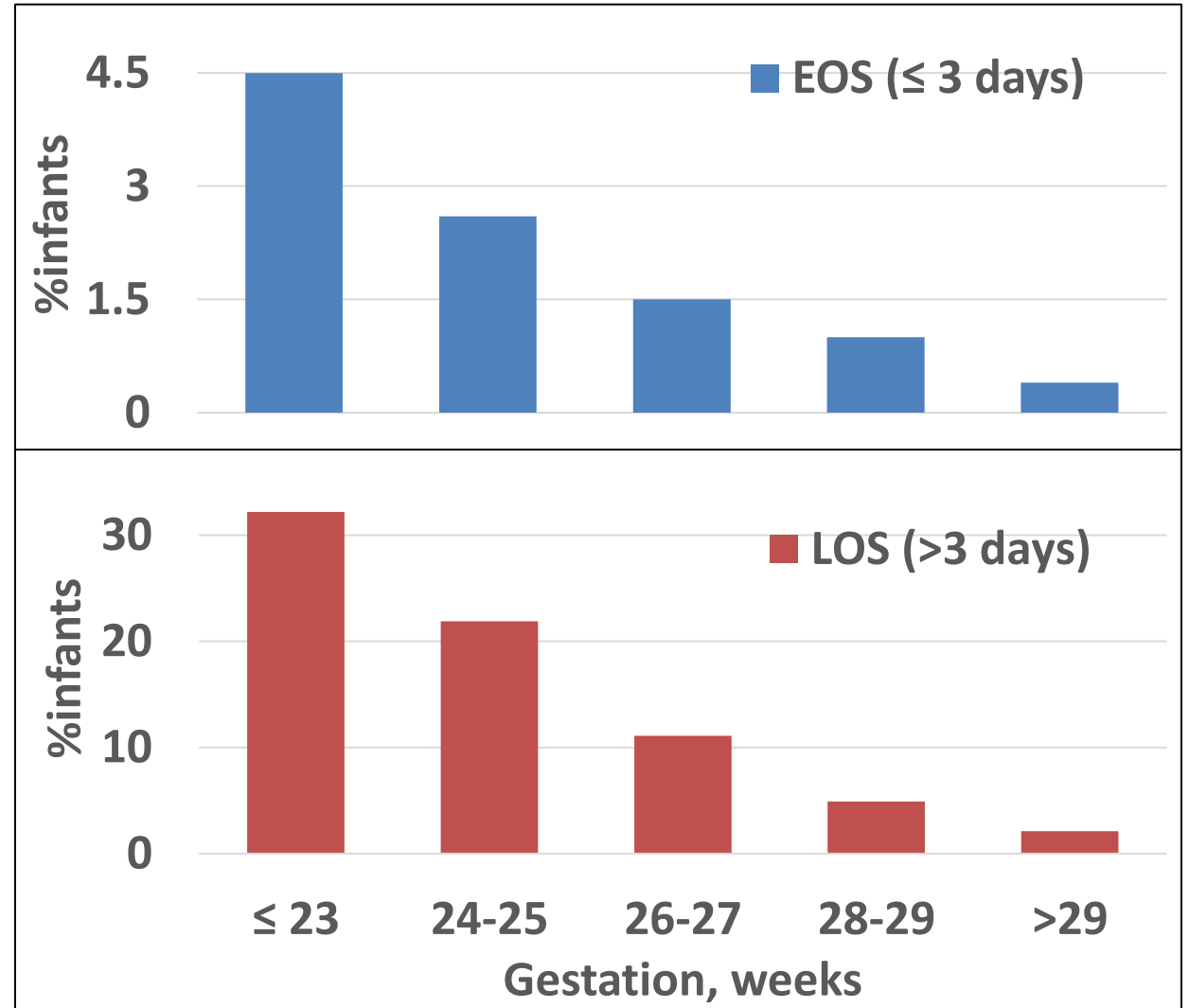
Congreso Internacional Epiclatino 2025

**I have no financial relationships to disclose
or Conflicts of Interest (COI) to resolve.**

Learning Objectives:

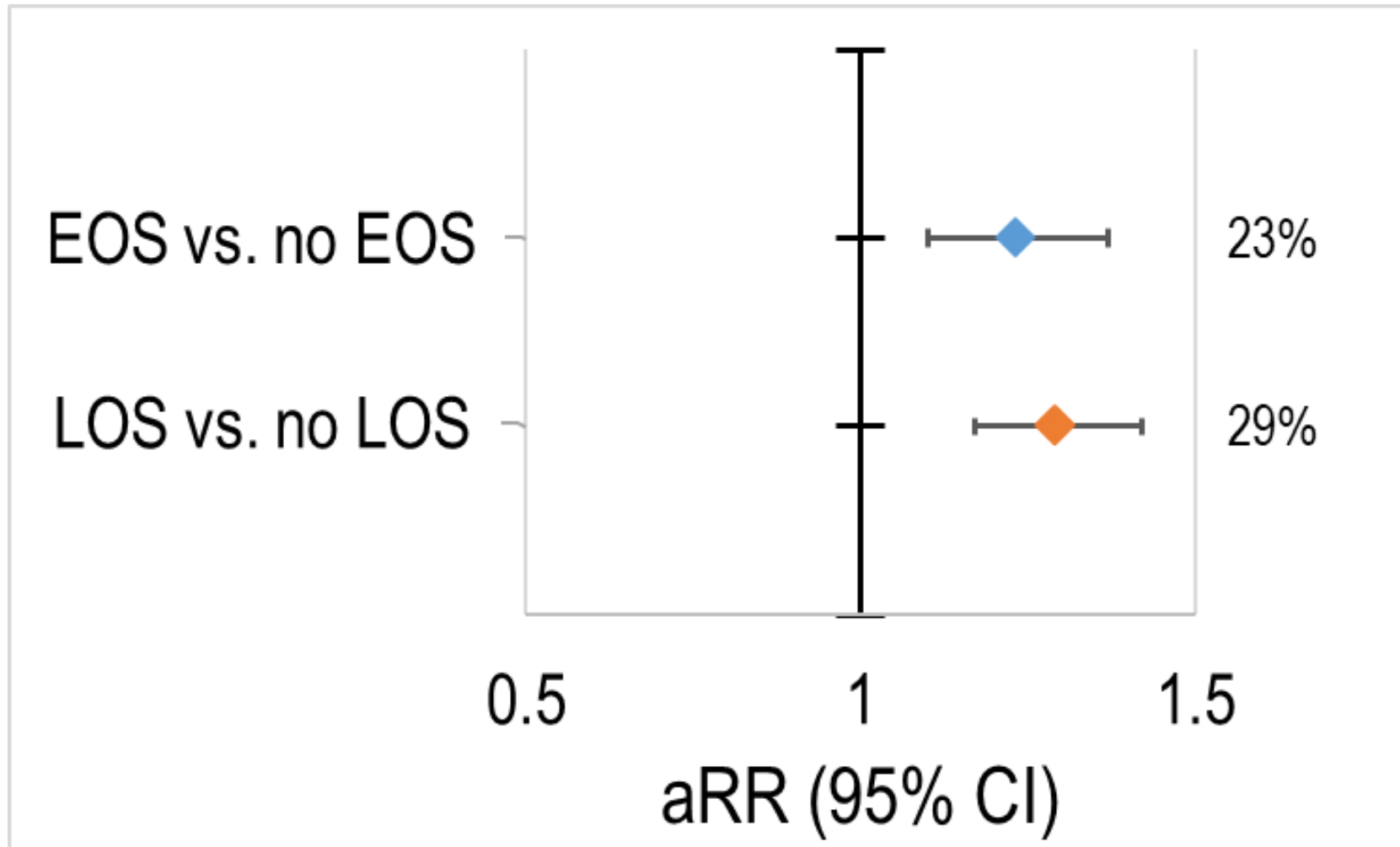
- **Discuss the need for antibiotic stewardship in healthcare**
- **Identify common stewardship strategies in the NICU**
- **Review the evidence supporting these strategies**

Neonatal Intensive Care and Risk of Infection



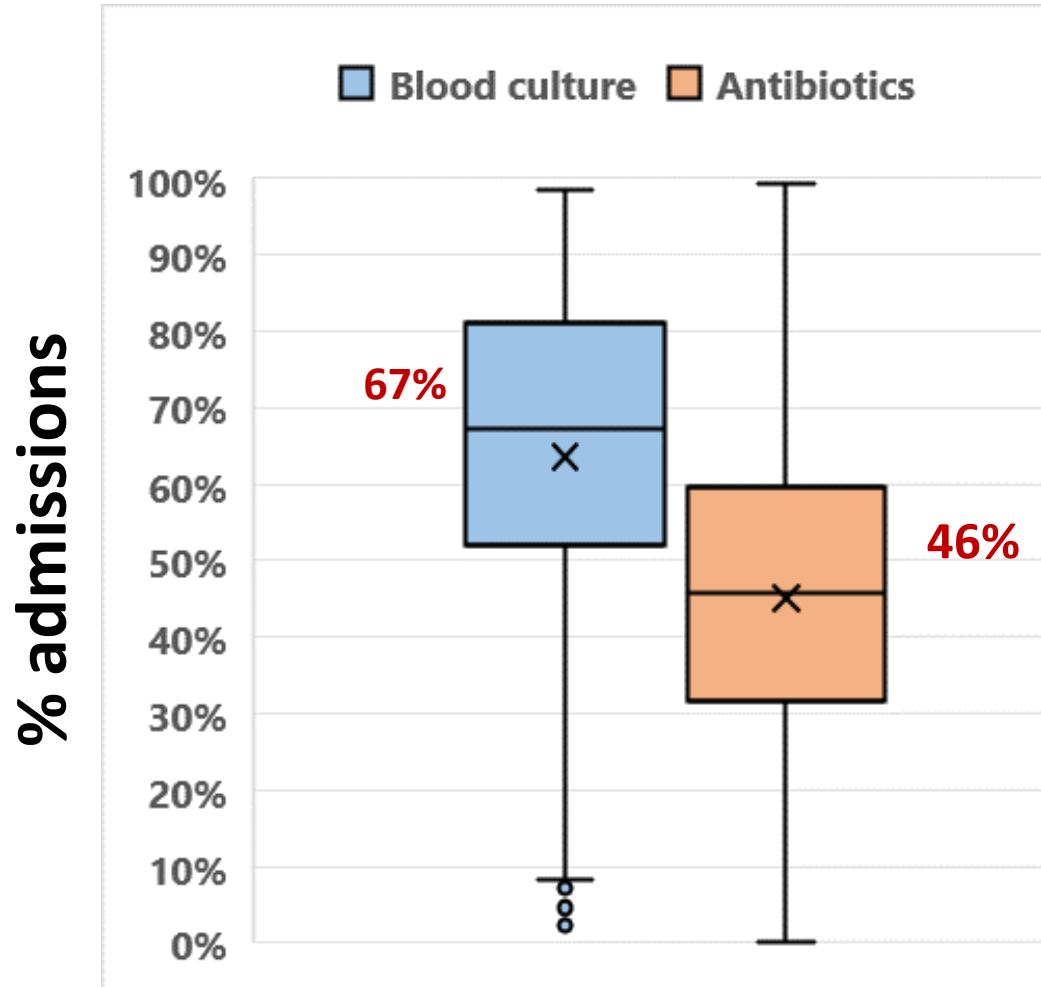
EOS – Early onset sepsis; LOS – Late onset sepsis

Death or Neurodevelopmental Delay at 2 years

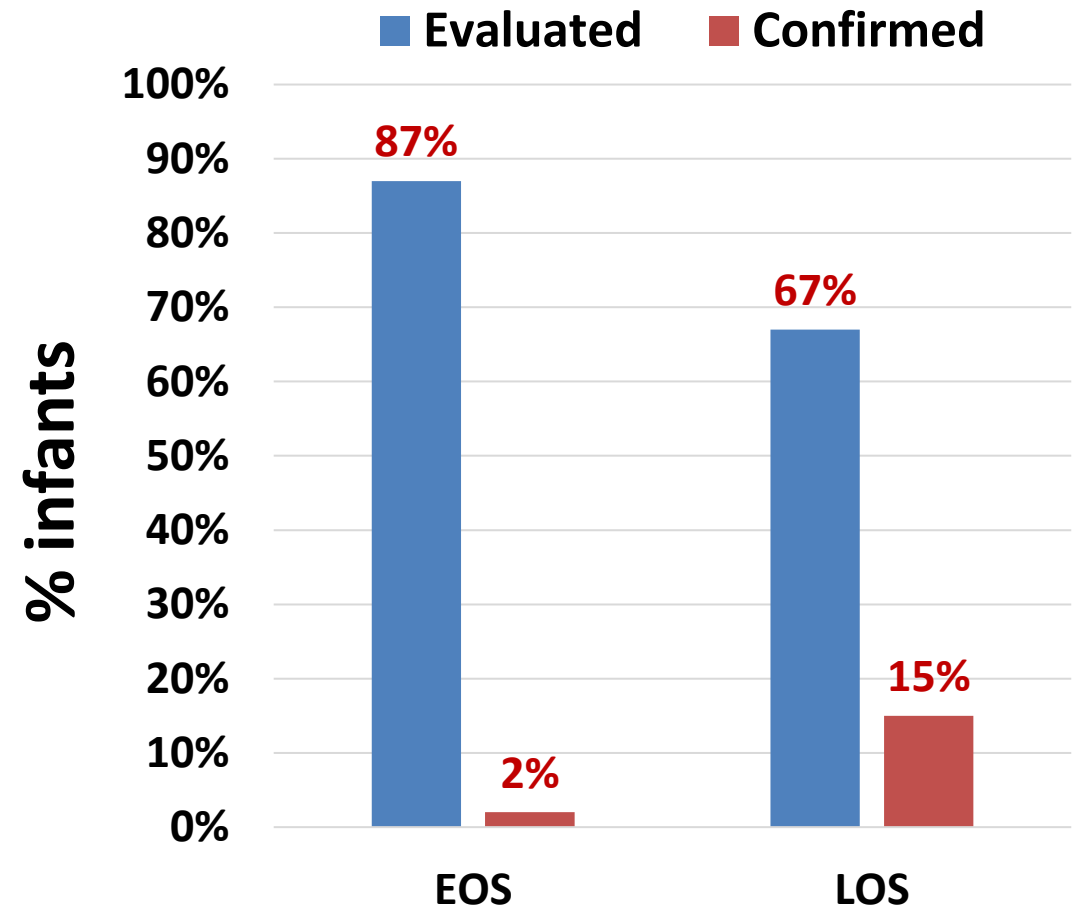


Infection Evaluation and Antibiotic Use is Common

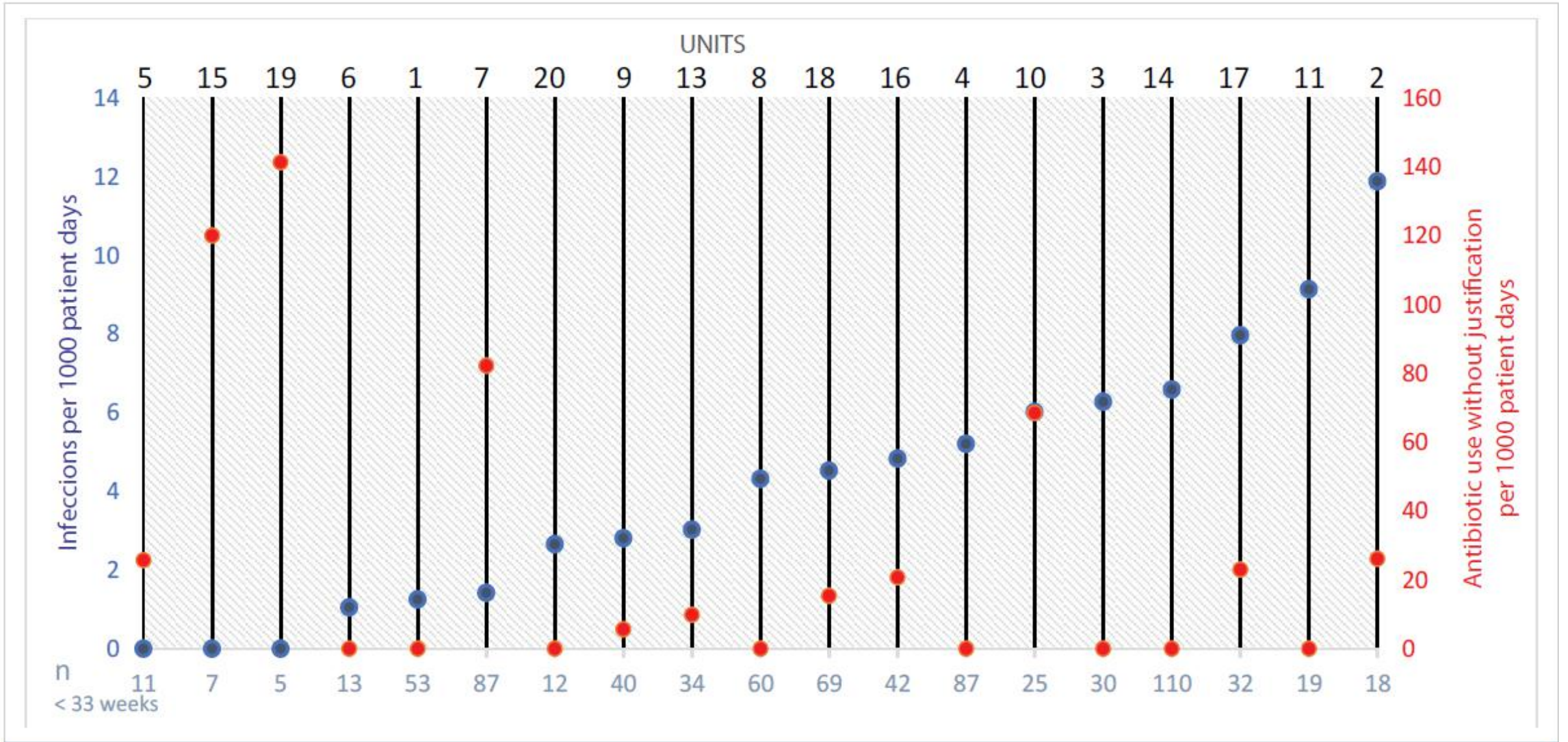
All gestations at admission



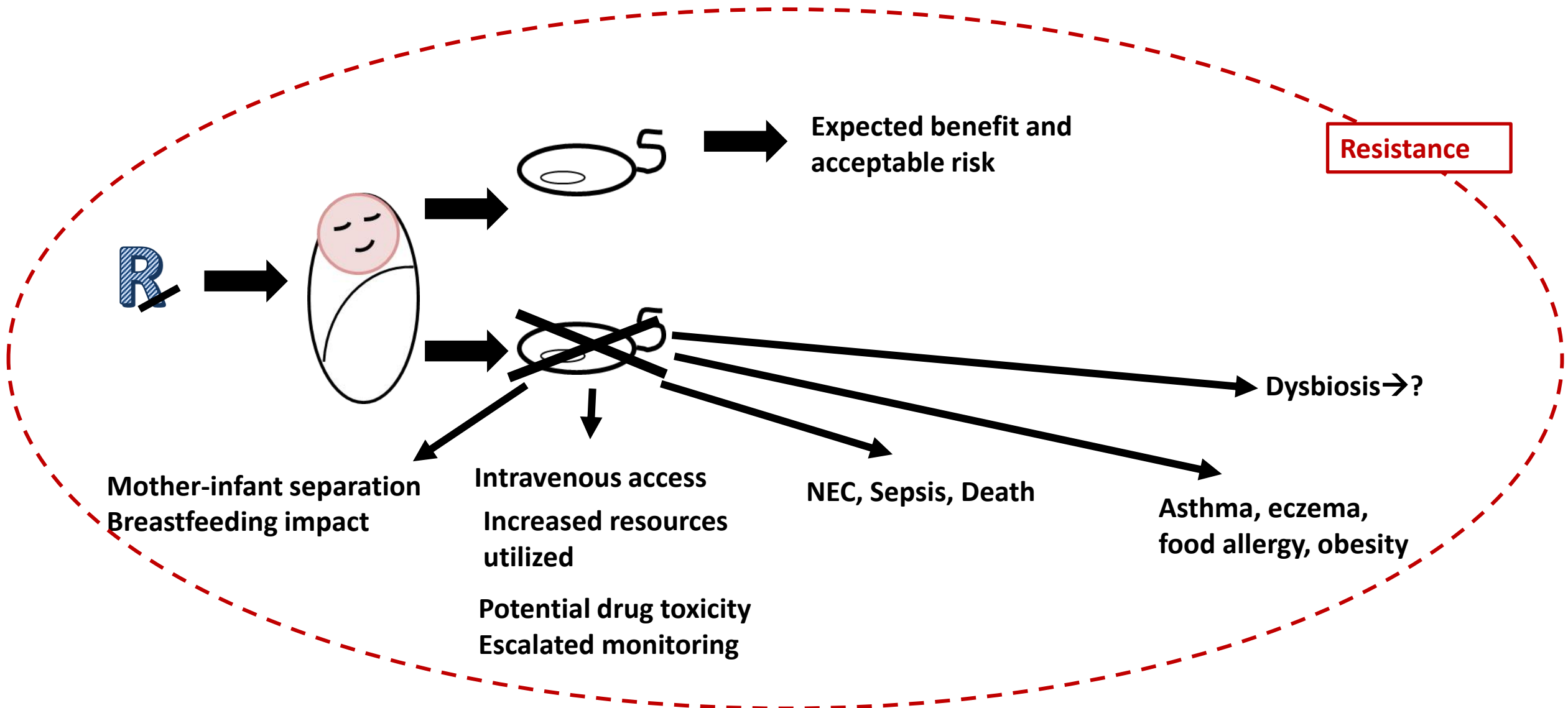
Extremely Preterm or low birthweight



Antibiotic use is variable and not always indicated



Antibiotic Stewardship is a commitment to always use antibiotics appropriately and safely



Mukhopadhyay *et al*, 2015 & 2014; Murk *et al*, 2011; Tsasok *et al*, 2013; Metsala *et al*, 2014; Vangay *et al*, 2015; Cotten *et al*, 2009; Kuppala *et al*, 2013; Deshmukh *et al*, 2014

Not Enough Increases Mortality

| Outcome | Inadequate Empiric N=2785 | Adequate Empiric N=12398 | aOR (95% CI) | P value |
|-----------------------|------------------------------|-----------------------------|------------------|-------------|
| Mortality | 488 (17.5) | 2011 (16.3) | 1.19 (1.03-1.37) | 0.02 |
| Acute Kidney Injury | 486 (17.5) | 2196 (17.7) | 1.02 (0.90-1.16) | 0.72 |
| <i>C diff</i> colitis | 207 (7.4) | 498 (4.0) | 1.19 (0.98-1.45) | 0.09 |

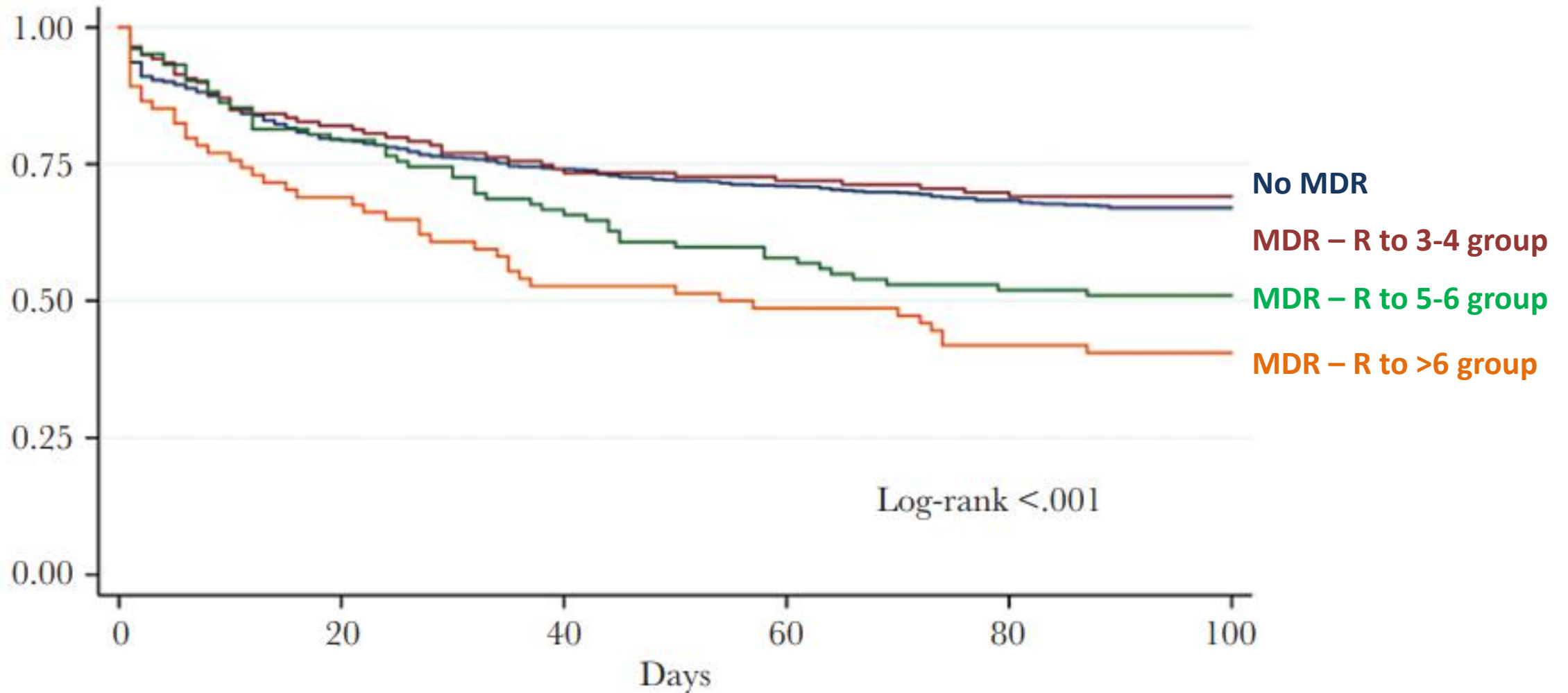
17,430 adults in 104 US hospital between 2009 - 2015

Too Much Increases Mortality

| Outcome | Unnecessarily Broad N=8405 | Not Unnecessarily Broad N=3993 | aOR (95% CI) | P value |
|-----------------------|-------------------------------|-----------------------------------|------------------|--------------|
| Mortality | 1575 (18.7) | 436 (10.9) | 1.22 (1.06-1.40) | 0.007 |
| Acute Kidney Injury | 1641 (19.5) | 555 (13.9) | 1.12 (1.00-1.26) | 0.05 |
| <i>C diff</i> colitis | 367 (4.4) | 131 (3.3) | 1.26 (1.01-1.57) | 0.04 |

17,430 adults in 104 US hospital between 2009 - 2015

When antibiotics do not work



1049 adult inpatients in a single US hospital – 28% MDR,

Antibiotics make NICU care possible



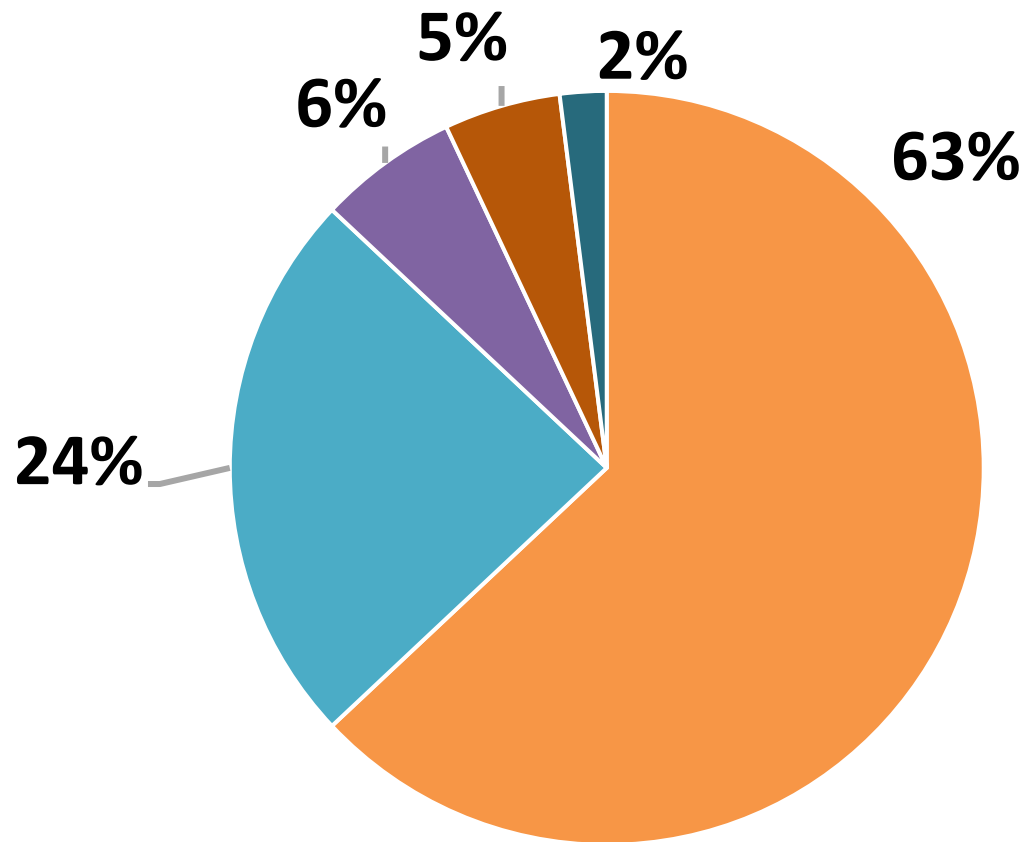
Appropriate antibiotic use is necessary not despite but because of the vulnerabilities of our patients

To give the right antibiotic at the right time for the right duration



What Drives Antibiotic use in the NICU?

79% initiations for risk of early onset sepsis (EOS)



- Empiric 'rule-out'
- Culture negative infection
- Prophylaxis
- Culture-confirmed infection
- NEC, cellulitis etc.

14 m single center surveillance
1607 infants and 343.2 Days of therapy (DOT)/1000 Patient-days

Antibiotic use in the NICU

'Suspect always and start often'

Empiric "rule-out"

- **High incidence & mortality with infection**
- **Clinical lability inherent to prematurity**
- **Long turn-over time for culture results**

'Just to be safe'

Culture negative infection:

- **Blood culture skepticism**
- **Reliance on immune markers**
- **Antibiotic prolongation is beneficial**
- **Antibiotic risks are manageable**

Strategies Targeting Major Contributors

General Stewardship and Infection Prevention Practices

Empiric “rule outs”

- **Start less:** Risk-stratification
- **Stop early:** Reduce empiric therapy duration
- **Select wisely:** Narrow the spectrum of empiric therapy

Culture-negative therapy

- **Avoid prolongation**
 - Monitor reliability of diagnostic tests
 - Question the risk-benefit of prolonged antibiotics

Strategies Targeting Major Contributors

General Stewardship and Infection Prevention Practices

Empiric “rule outs”

- **Start less:** Risk-stratification
- **Stop early:** Reduce empiric therapy duration
- **Select wisely:** Narrow the spectrum of empiric therapy

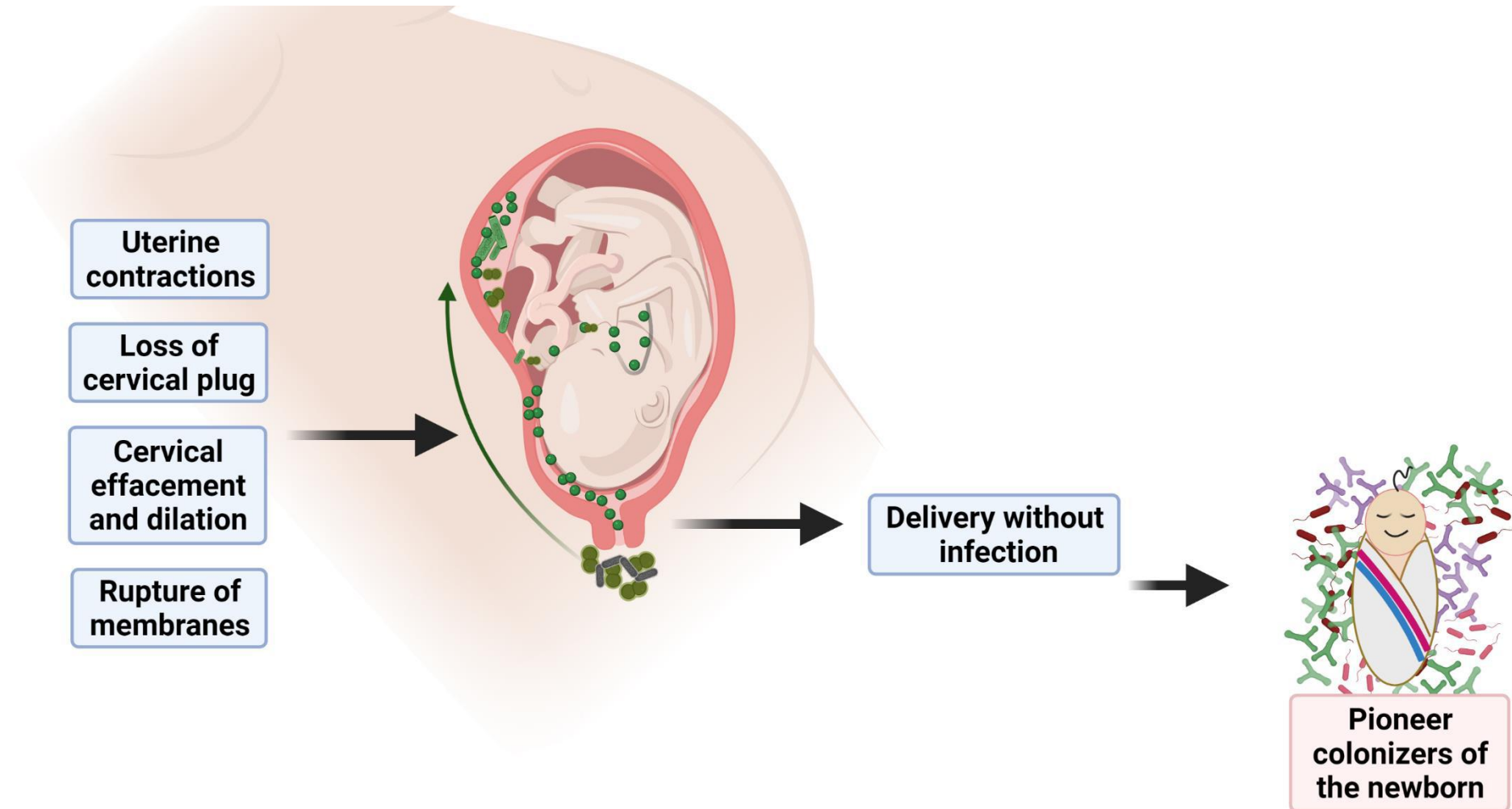
Culture-negative therapy

- Avoid prolongation
- Monitor reliability of diagnostic tests
- Question the risk-benefit of prolonged antibiotics

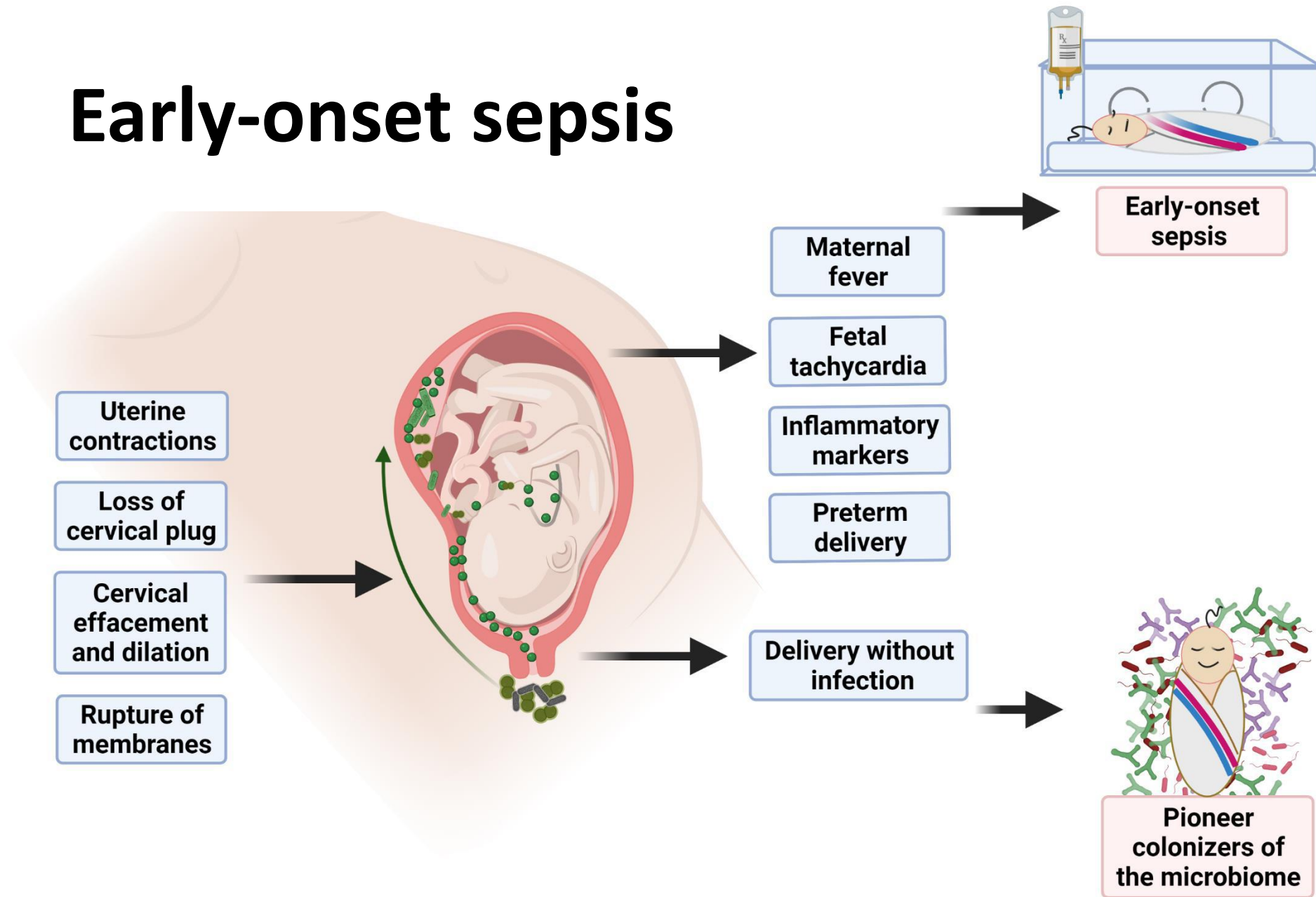
Risk-Stratification for suspected EOS

1. START LESS

Mother to child microbial transfer



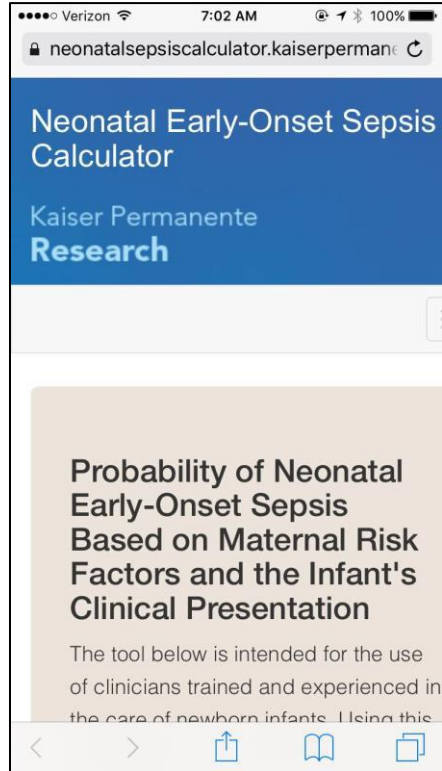
Early-onset sepsis



Approach risk-stratification via a Multivariate Model

| VARIABLE | ODDS RATIO |
|---|---|
| GBS status | 1.78 (1.11 – 2.85) |
| Gestational age | 0.001 (0.0001 – 0.014) |
| Duration of ROM | 3.41 (2.23 – 5.20) |
| Highest intrapartum maternal temperature | 2.38 (2.05 – 2.77) |
| <ul style="list-style-type: none">• No intrapartum abx• GBS IAP or any abx <u>not</u> given on time• Broad-spectrum abx given on time | Reference 0.35 (0.23 – 0.53) 0.31 (0.13 – 0.71) |

Neonatal Sepsis Risk Calculator



Verizon 7:02 AM 100%
neonatalesepsiscalculator.kaiserpermanente.org

Please enter details below.

| Predictor | Scenario |
|---|---|
| Incidence of Early-Onset Sepsis | <input type="text"/> |
| Gestational age | <input type="text"/> weeks <input type="text"/> days |
| Highest maternal antepartum temperature | <input type="text"/> Fahrenheit |
| ROM (Hours) | <input type="text"/> |
| Maternal GBS status | <input type="radio"/> Negative <input type="radio"/> Positive <input type="radio"/> Unknown |

- **Clinical care algorithms updated to include implementation work done at KPNC since 2014 publication**
- **Threshold for blood culture: >1/1000**
- **Threshold for antibiotics: >3/1000**

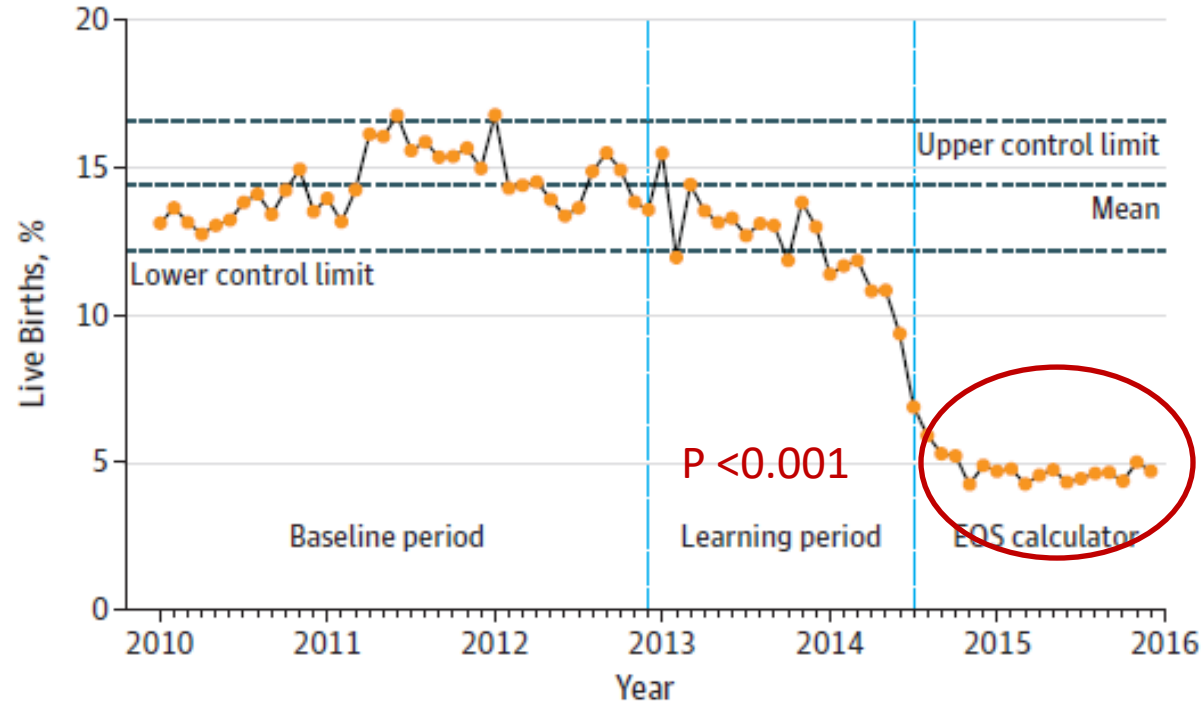
New website: <http://neonatalesepsiscalculator.kaiserpermanente.org>

Also reached at: <http://kp.org/eoscalc>

Credits for websites: Soora Wi, MPH; Allen Fischer, MD, Regional Director of Neonatology; Michael Kuzniewicz, MD, Director, Perinatal Research Unit Kaiser Permanente Northern California

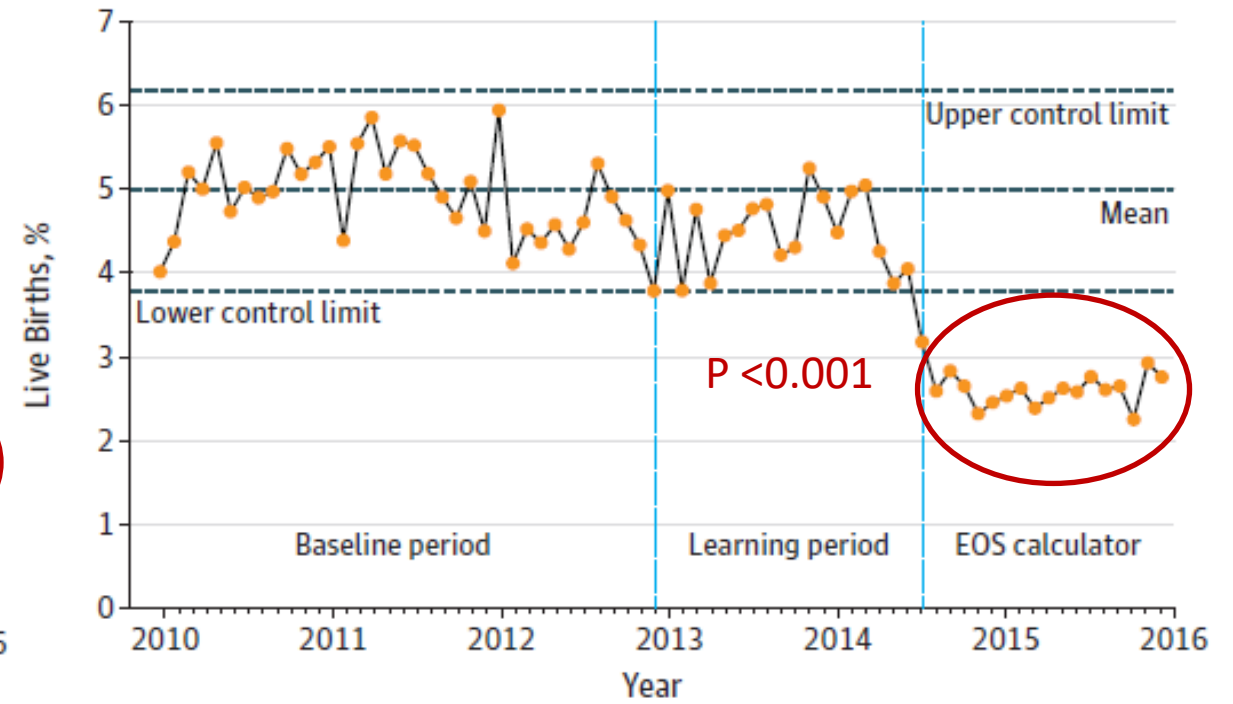
Kaiser Permanente Northern California implementation

Figure 1. Monthly Early-Onset Sepsis (EOS) Evaluation Rate



Monthly percentage of infants born at 35 weeks' gestation or later undergoing EOS evaluation with a blood culture performed in the first 24 hours of life.

Figure 2. Monthly Antibiotic Treatment Rate



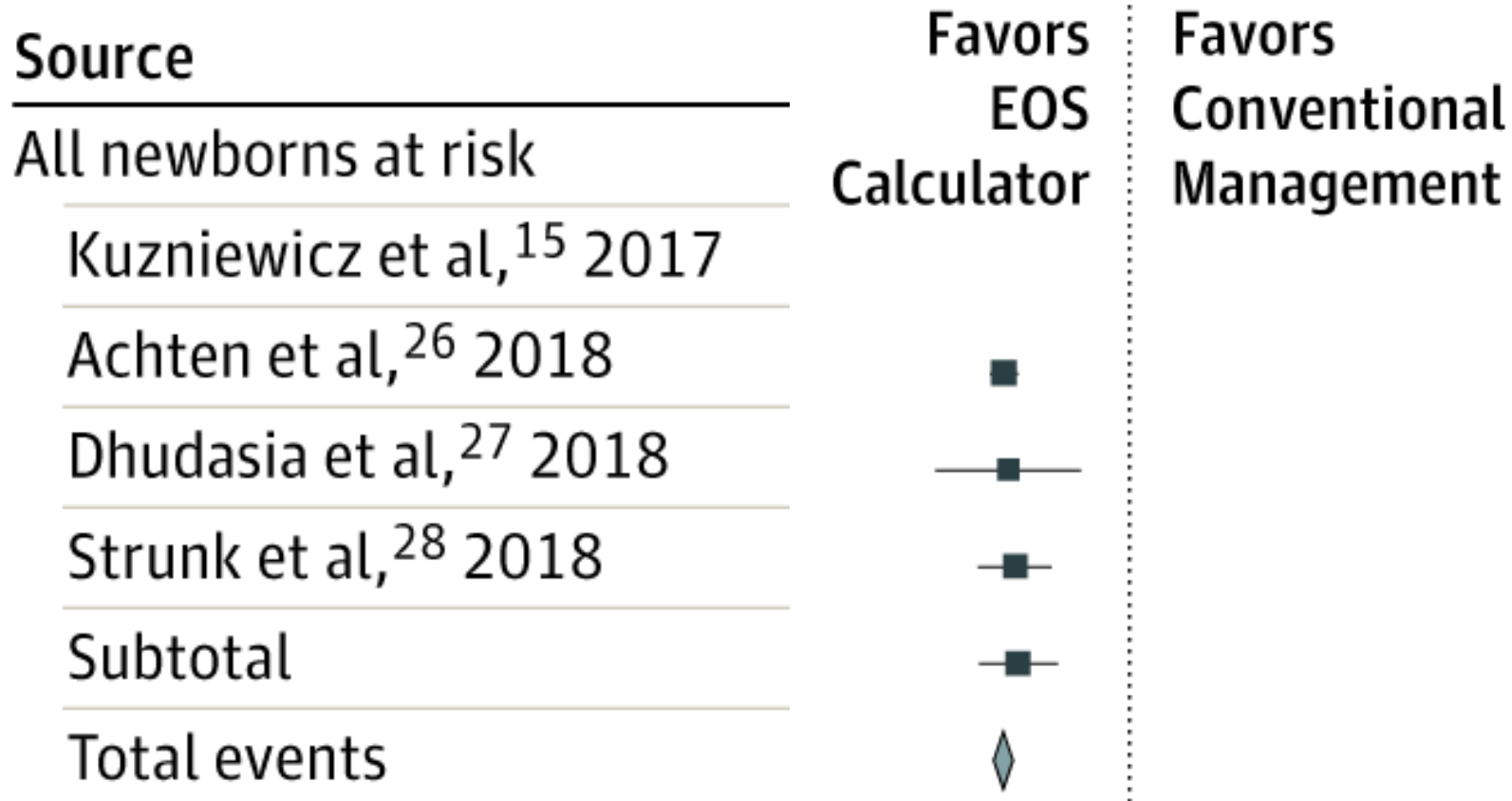
Monthly percentage of infants born at 35 weeks' gestation or later receiving intravenous antibiotic therapy in the first 24 hours of life. EOS indicates early-onset sepsis.

Measures of Safety

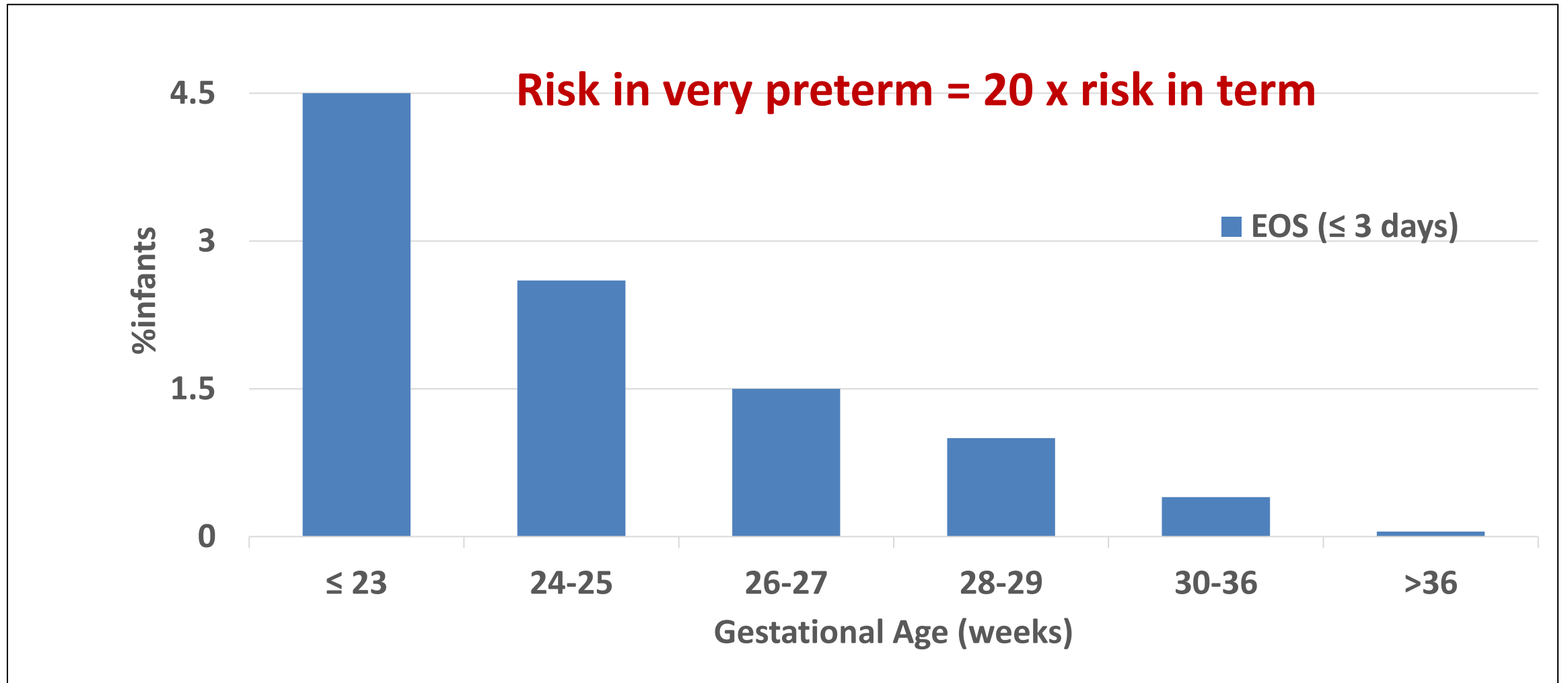
| Time Period | CDC N=95,343 | Calculator N=56,261 |
|--|-------------------------|--------------------------------|
| Total Cases | 24 (0.03%) | 12 (0.02%) |
| Symptomatic at Birth | 12 (50%) | 6 (50%) |
| Critically Ill | 2 | 1 |
| Death | 0 | 1* |
| Readmission \leq 7 days of life with EOS | 5.2/100,000 | 5.3/100,000 |

*Infant with severe HIE treated with antibiotics, ECMO and cooling from birth

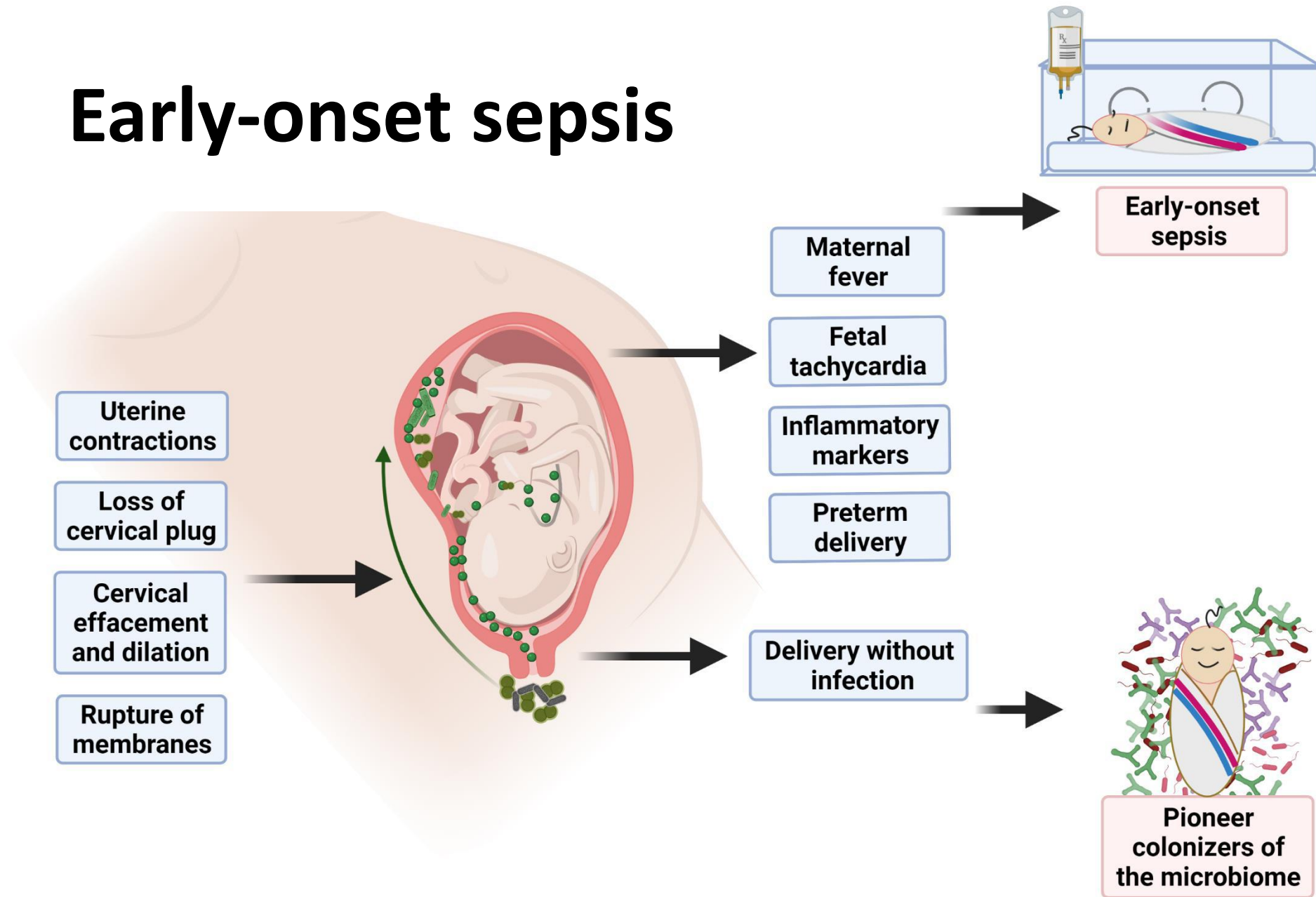
Consistent Safe Antibiotic Reduction



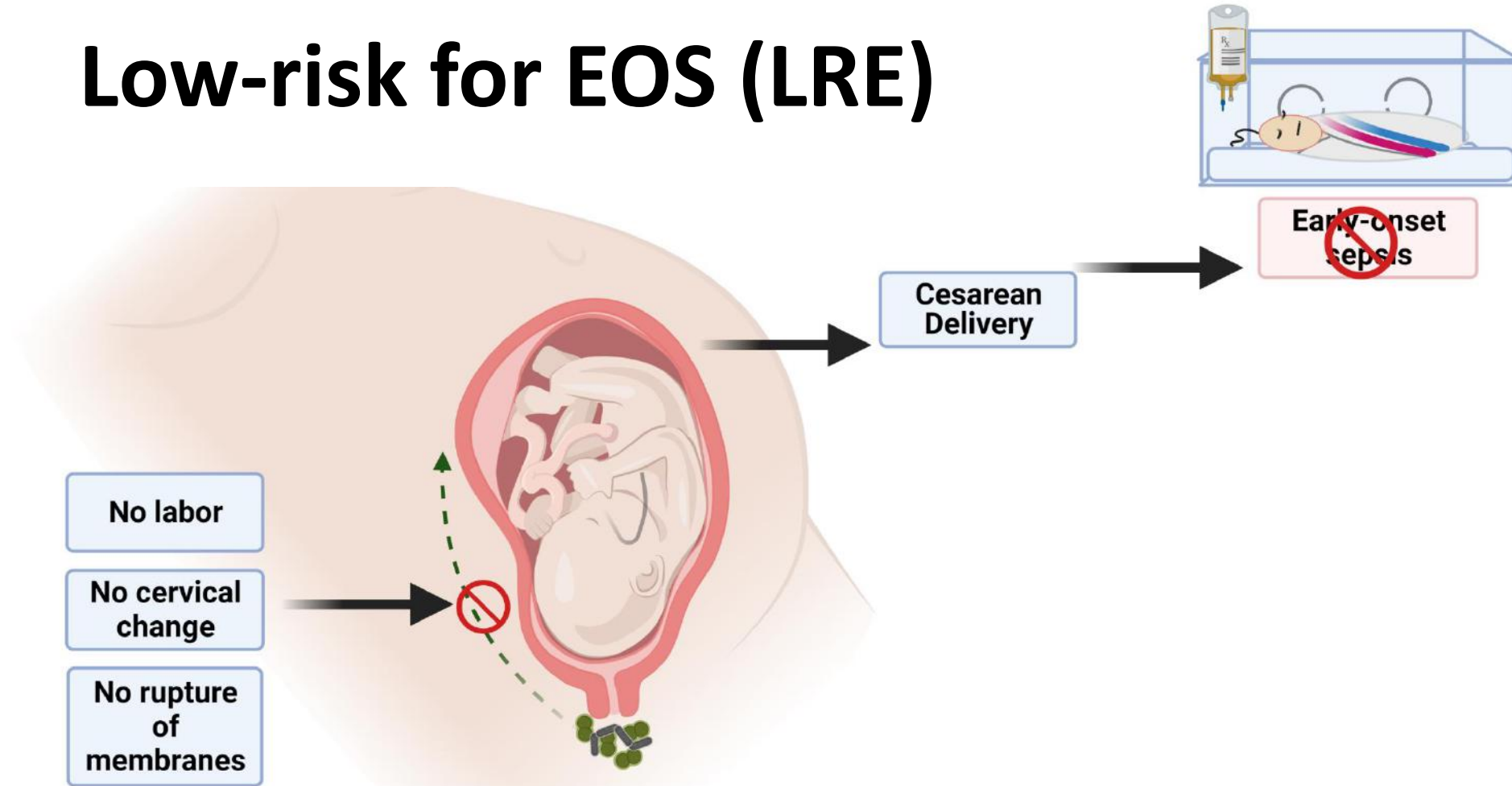
Limits of EOS Risk Factor Based Approach in Preterm Infants



Early-onset sepsis



Low-risk for EOS (LRE)



When the pathogenesis of EOS is absent can we safely avoid antibiotic rule-outs?

The LRE phenotype has low rates of EOS

Single center

25 y single center

- 109 EOS cases
- 3 cases in LRE infants
 - *L. monocytogenes* in two

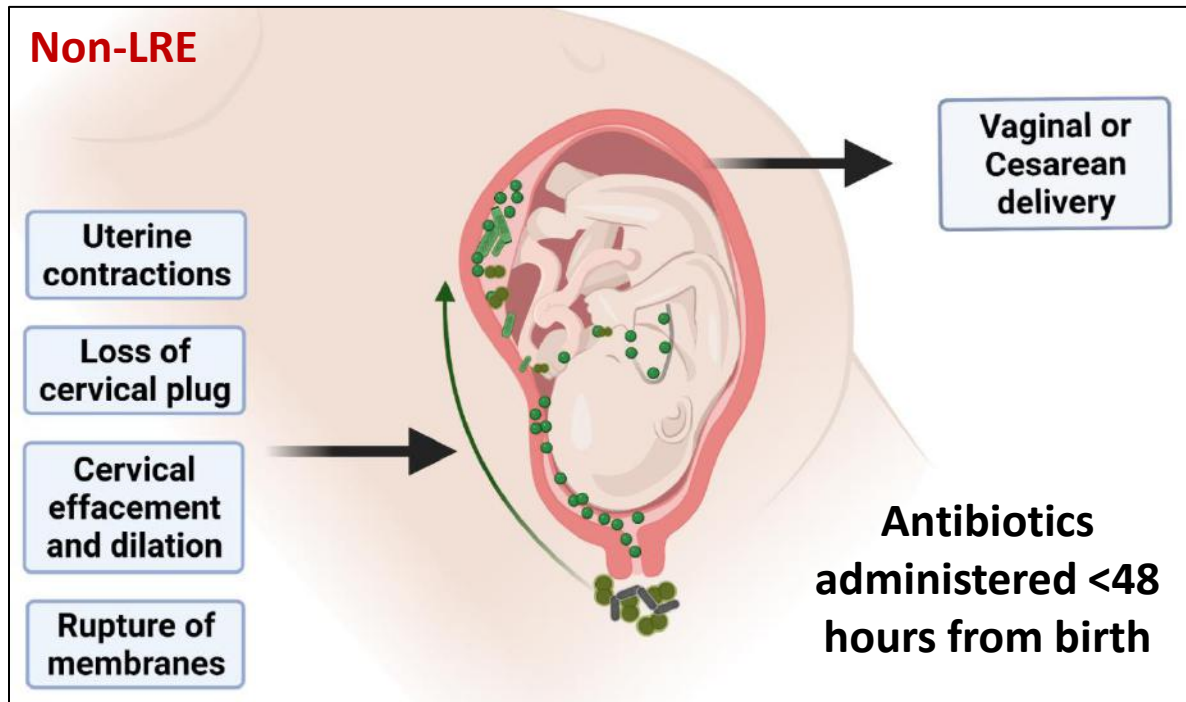
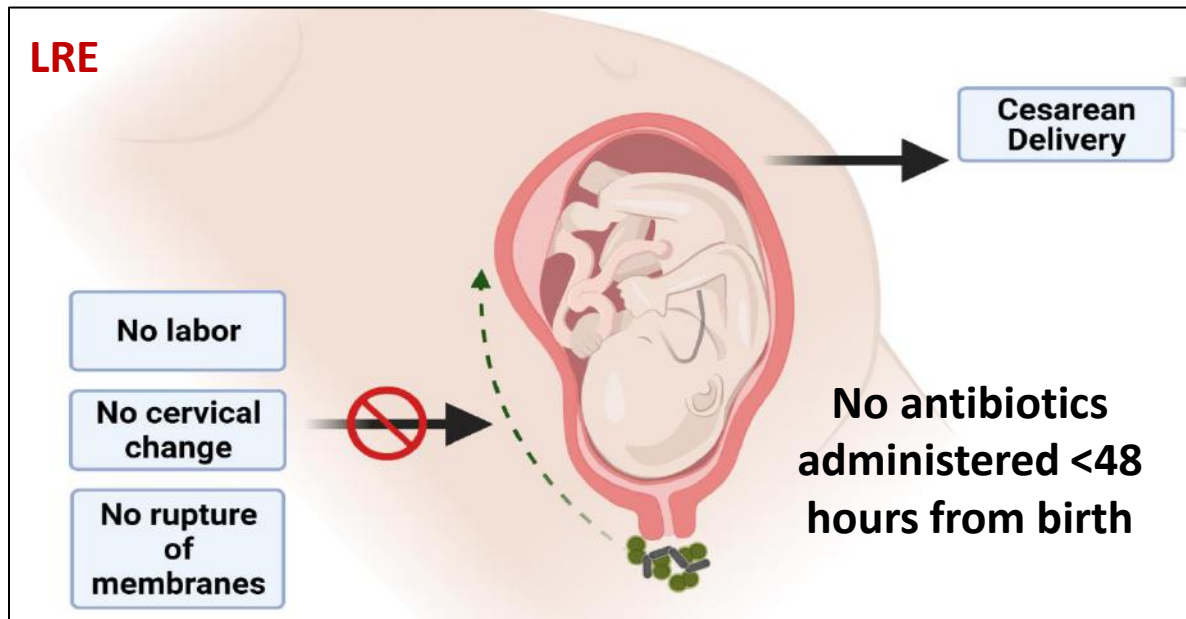
11 y at another center

- 41 EOS cases
- None among LRE infants

Neonatal Research Network

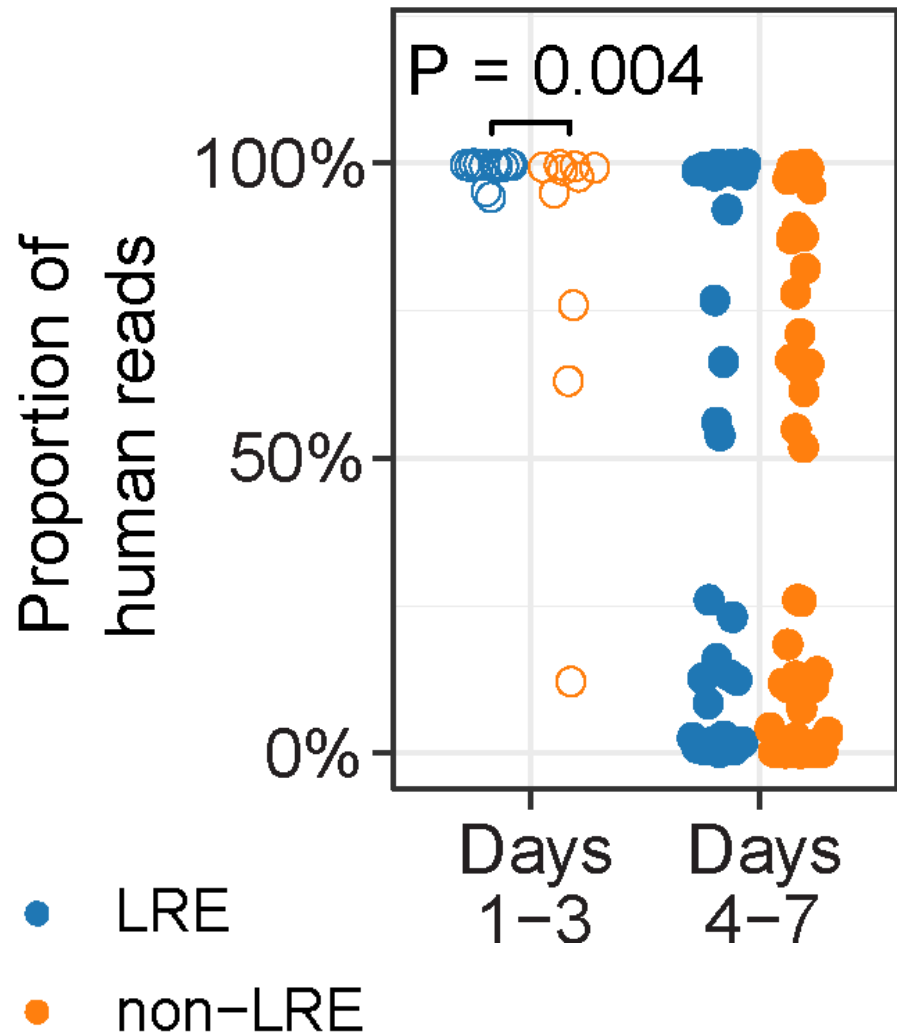
9 y in 22 centers

- 37% were LRE infants (n=5759)
- LRE infants had a 76% lower adjusted risk of EOS
- Yet 33% of them were administered prolonged antibiotics >5 days in duration



To provide molecular evidence for this epidemiological observation we conducted shotgun metagenomic sequencing of fecal sample in first days from birth in LRE and non-LRE infants

Difference in bacterial acquisition at birth



- **LRE infants have significantly lower proportion of bacterial DNA after birth**
- **Both groups have low bacterial reads**
- **Both groups gain in relative microbial mass rapidly**

AAP COFN Clinical Report

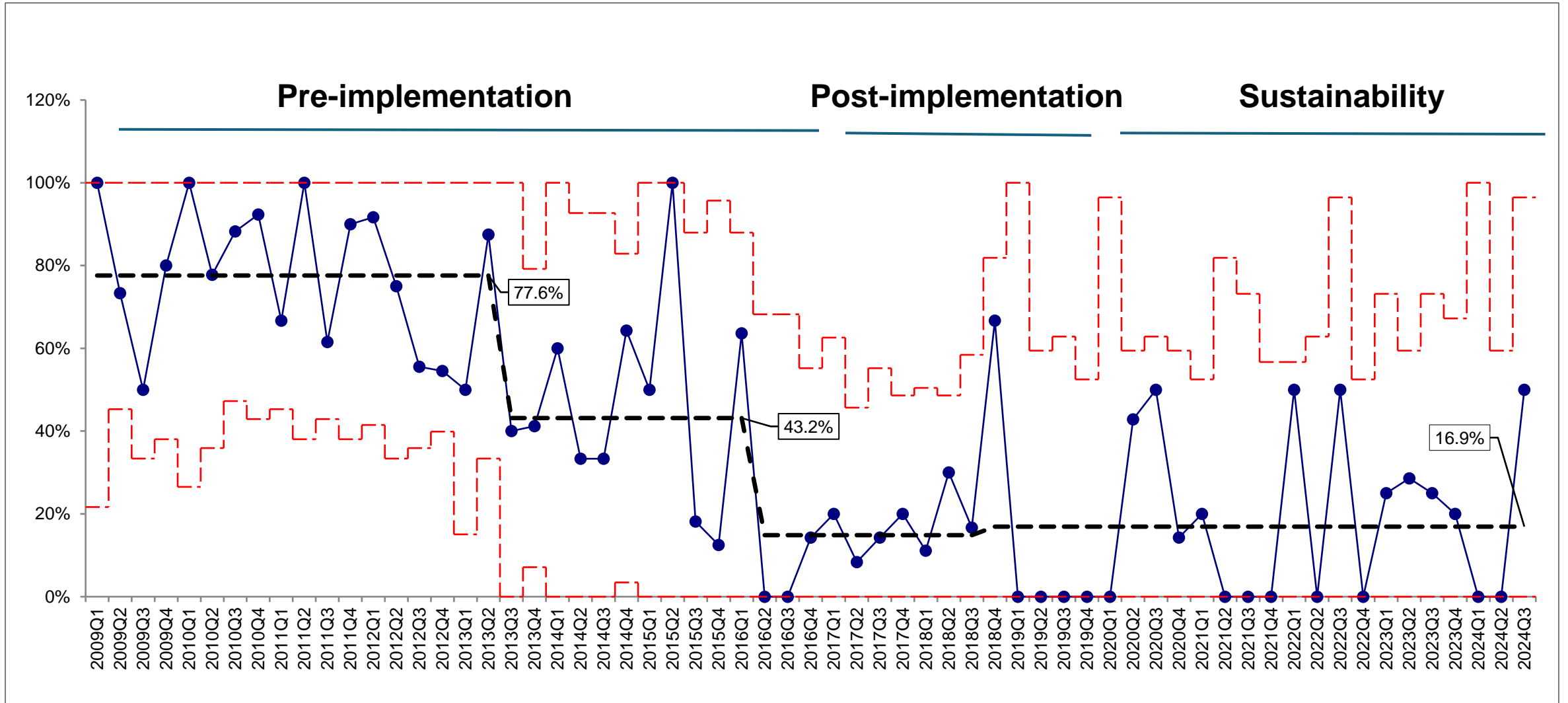
Endorsed LRE phenotype based on delivery criteria

- **Preterm infants at a lower risk for EOS:**
 - Obstetric indications for preterm birth (such as preeclampsia)
 - Birth by cesarean delivery
 - Absence of labor, attempts to induce labor
 - Membrane rupture at time of delivery
- **Management for these infants**
 - No laboratory evaluation, no empirical antibiotic therapy
 - Or, blood culture and no empirical antibiotic therapy

Implementation of LRE-based EOS evaluation

| N (%) or Median (Q2, Q3) | Pre Period 1 n=727 | Implementation Period 2 n=191 | Sustainability Period 3 n=277 | <i>P</i> 1 vs. 2 | <i>P</i> 2 vs. 3 |
|--|-----------------------------------|--|--|---------------------------------|---------------------------------|
| Birth weight (g) | 1085 (820 – 1320) | 1105 (795 – 1335) | 1065 (815 -1340) | 0.74 | 0.98 |
| Gestational age (wks) | 28 (26, 30) | 28 (26, 30) | 28 (26, 30) | 0.98 | 0.75 |
| Female | 365 (50.2) | 107 (56.0) | 138 (49.8) | 0.15 | 0.19 |
| Cesarean delivery | 564 (77.6) | 137 (71.7) | 201 (72.6) | 0.09 | 0.84 |
| Rupture of membranes at delivery | 491 (67.5) | 128 (67.0) | 181 (65.3) | 0.89 | 0.71 |
| Infants meeting low-risk criteria | 298 (41.0) | 83 (43.5) | 103 (37.2) | 0.54 | 0.17 |

Antibiotic Initiation in Low-Risk VLBW infants



No Increase In Adverse Outcomes in Days 4-7

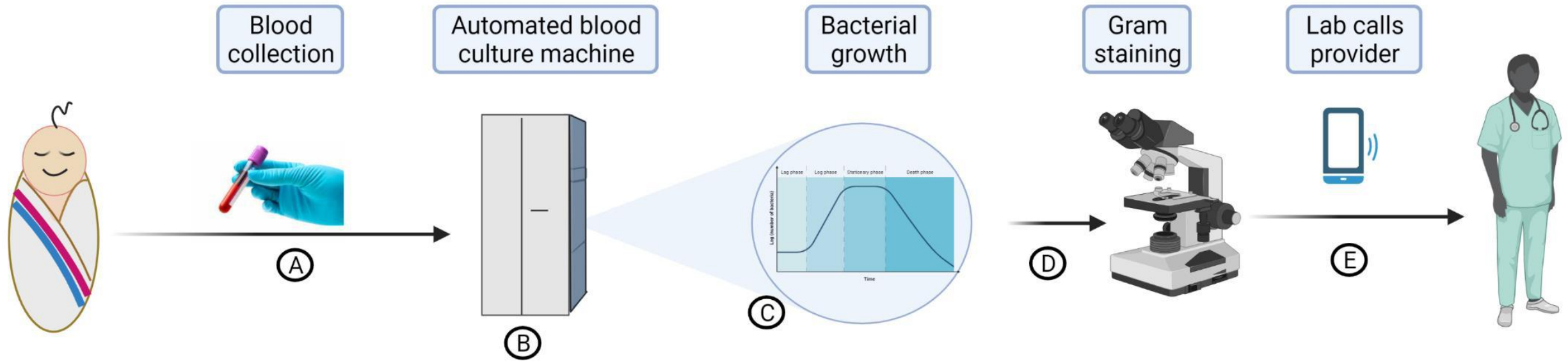
| N (%) or Median (IQR) | Pre Period 1 | Implementation Period 2 | Sustainability Period 3 | P value 1 vs. 2 | P value 2 vs. 3 |
|-------------------------------|-----------------|----------------------------|----------------------------|--------------------|--------------------|
| All VLBW | 727 | 191 | 277 | | |
| Blood culture obtained | 130 (17.9) | 25 (13.1) | 17 (6.1) | 0.12 | 0.01 |
| Antibiotic initiation | 67 (9.2) | 22 (11.5) | 16 (5.8) | 0.34 | 0.03 |
| Blood culture positive | 15 (2.1) | 3 (1.6) | 3 (1.1) | 1.0 | 0.69 |
| Deceased/Transferred | 36 (5.0) | 10 (5.2) | 14 (5.1) | 0.87 | 0.93 |
| LRE VLBW | 298 | 83 | 102 | | |
| Blood culture obtained | 61 (20.5) | 9 (10.8) | 6 (5.9) | 0.05 | 0.22 |
| Antibiotic initiation | 34 (11.4) | 9 (10.8) | 6 (5.9) | 0.89 | 0.22 |
| Blood culture positive | 6 (2.0) | 1 (1.2) | 0 | 1.0 | 0.45 |
| Deceased/Transferred | 11 (3.7) | 2 (2.4) | 2 (2.0) | 0.74 | 1.00 |

Summary - Strategies For Starting Less

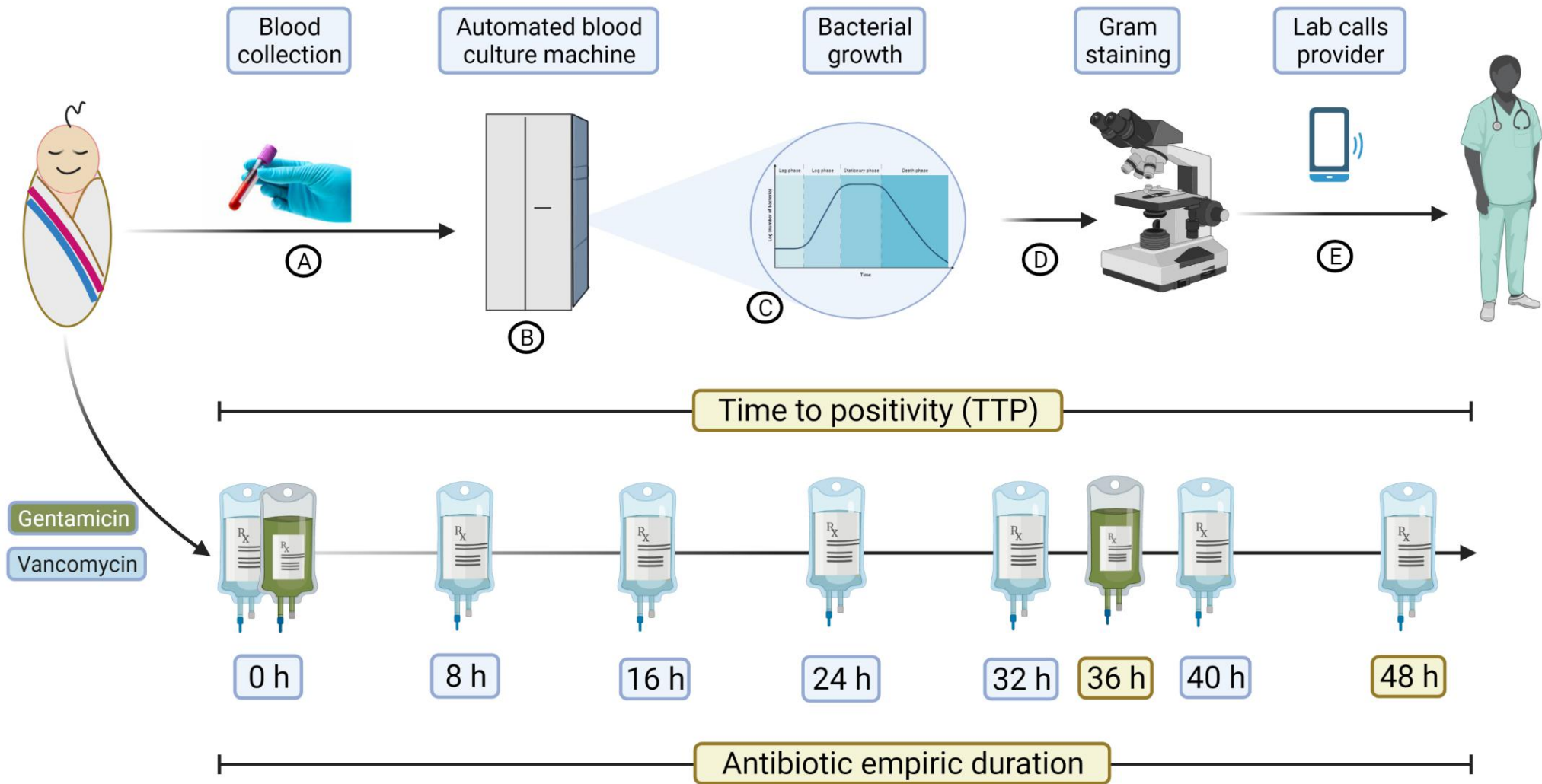
- **Risk factors can be modelled in term infants to give a probability of EOS**
 - Use of the Sepsis Risk Calculator has reduced antibiotic initiations across United States without increased adverse events
- **Lack of risk factors can be used in preterm infants to allow management without antibiotics**
 - Implementing a LRE based approach is feasible and can reduce antibiotics without increase in adverse events

Reducing duration of empiric therapy

2. STOP EARLY



Time to positivity (TTP) – time from collecting the blood culture to when the lab confirms growth in the bottle



Empiric antibiotic duration is based on time to positivity (TTP) for *the majority* of confirmed cases

Determine TTP for Blood Cultures

Early-Onset

19 NICUs
1995-2017

BacT/Alert[®] Pediatric FAN
BD BACTEC[™] systems

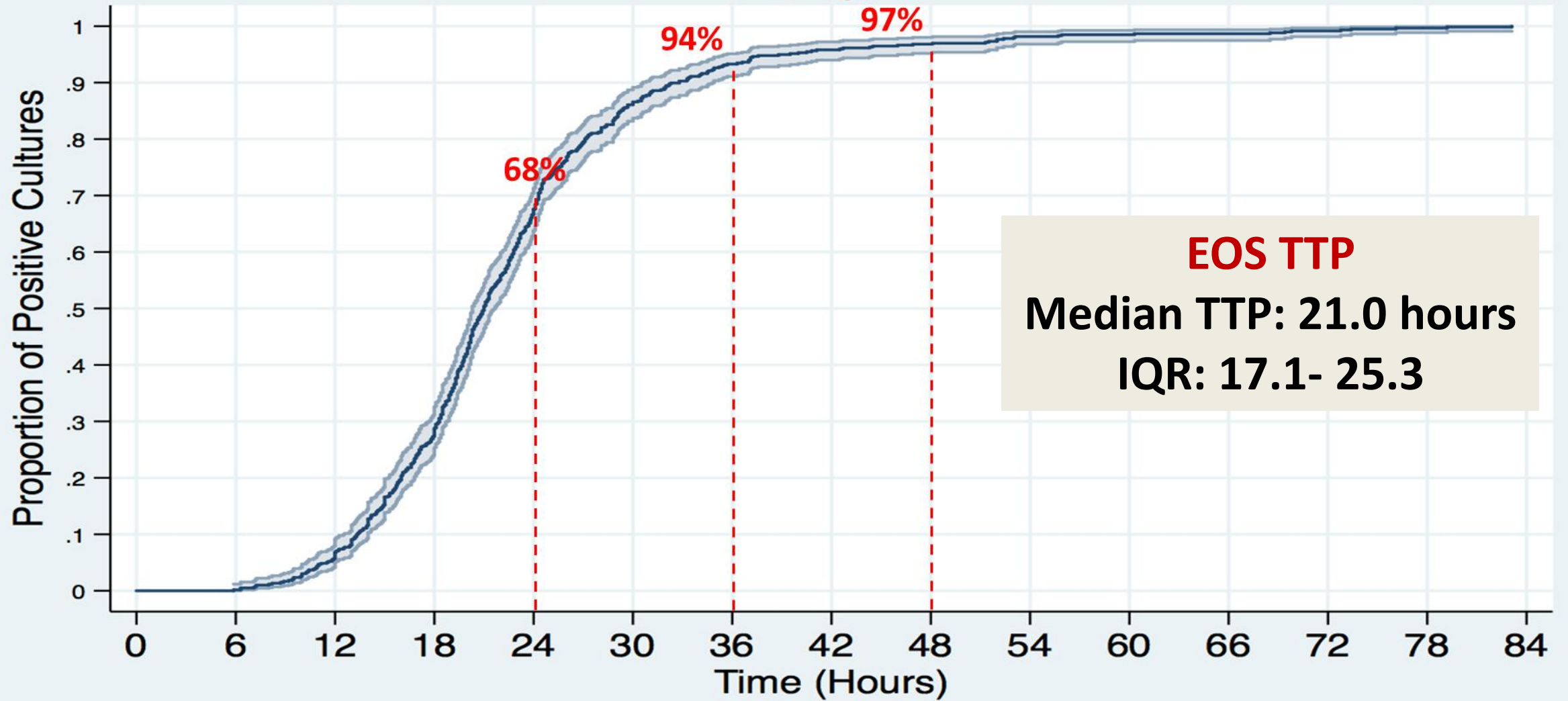
1624/71,345 (2%)
positive cultures

Late-Onset

16 NICUs
2009-2020

BacT/Alert[®] Pediatric FAN
BD BACTEC[™] systems

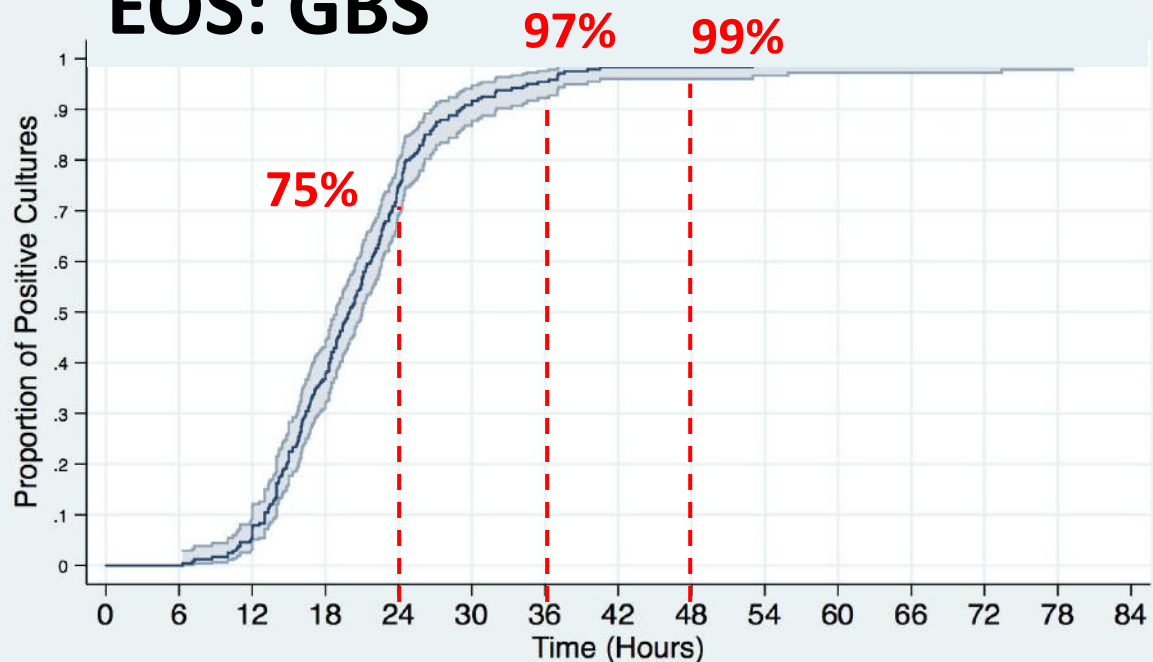
1082/10235 (10%)
positive cultures



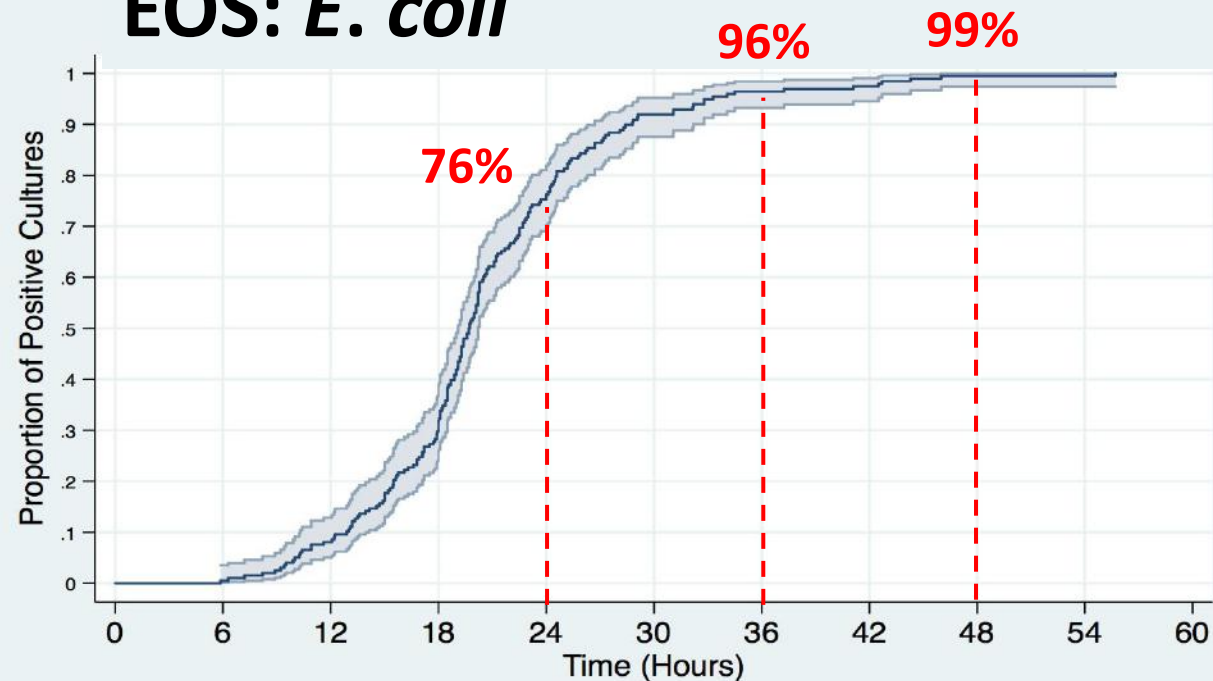
EOS TTP
Median TTP: 21.0 hours
IQR: 17.1- 25.3

95% CI Time to Positivity

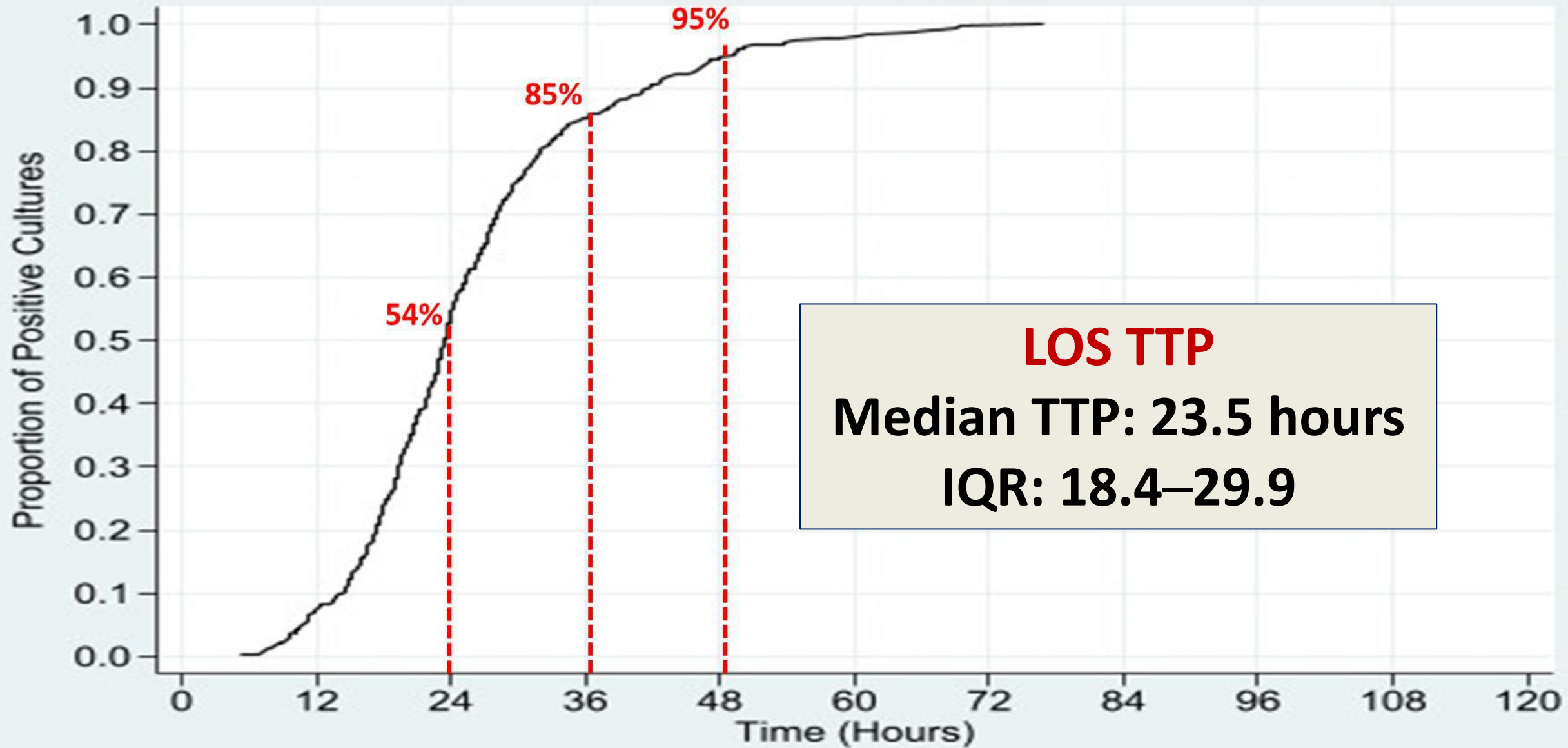
EOS: GBS



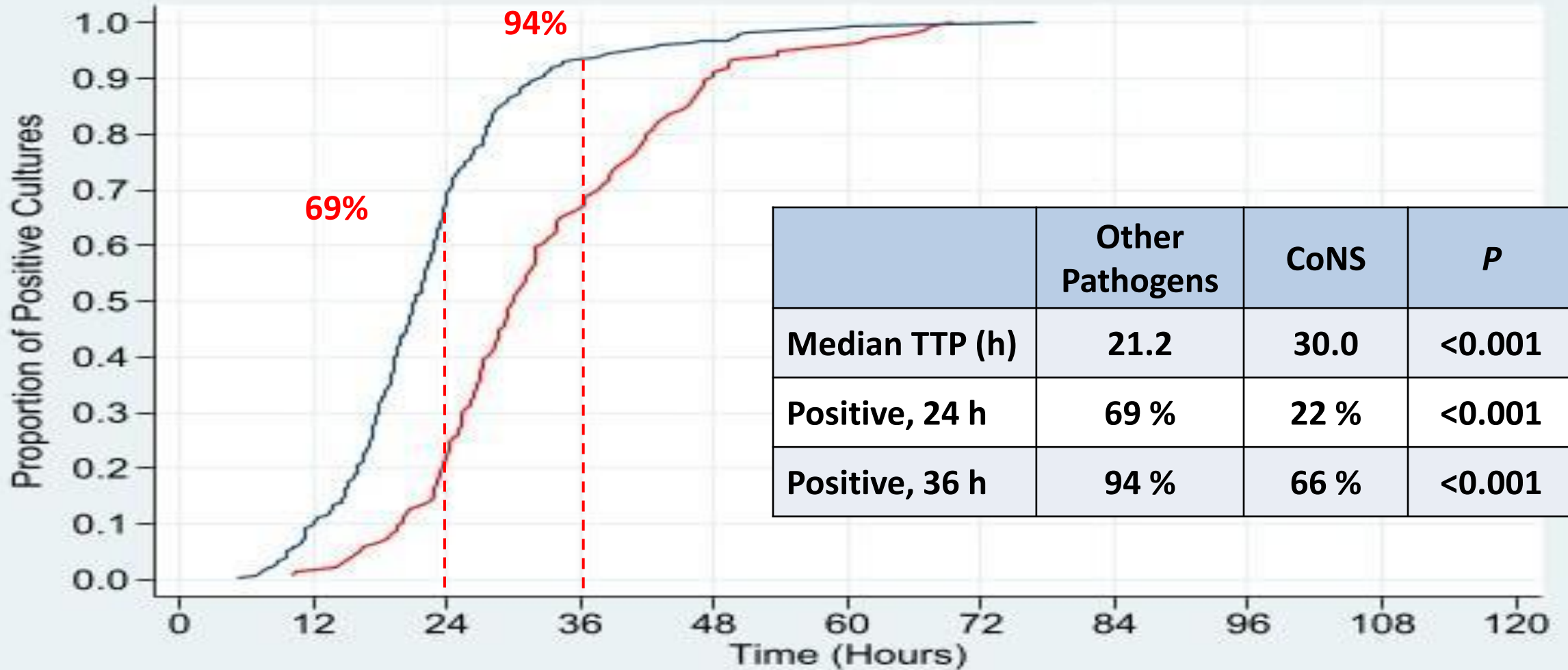
EOS: *E. coli*



| | GBS | <i>E. coli</i> | P value |
|----------------|------|----------------|---------|
| Median TTP (h) | 20.0 | 19.7 | 0.9 |
| Positive, 24 h | 75% | 76% | |
| Positive, 36 h | 97% | 96% | |

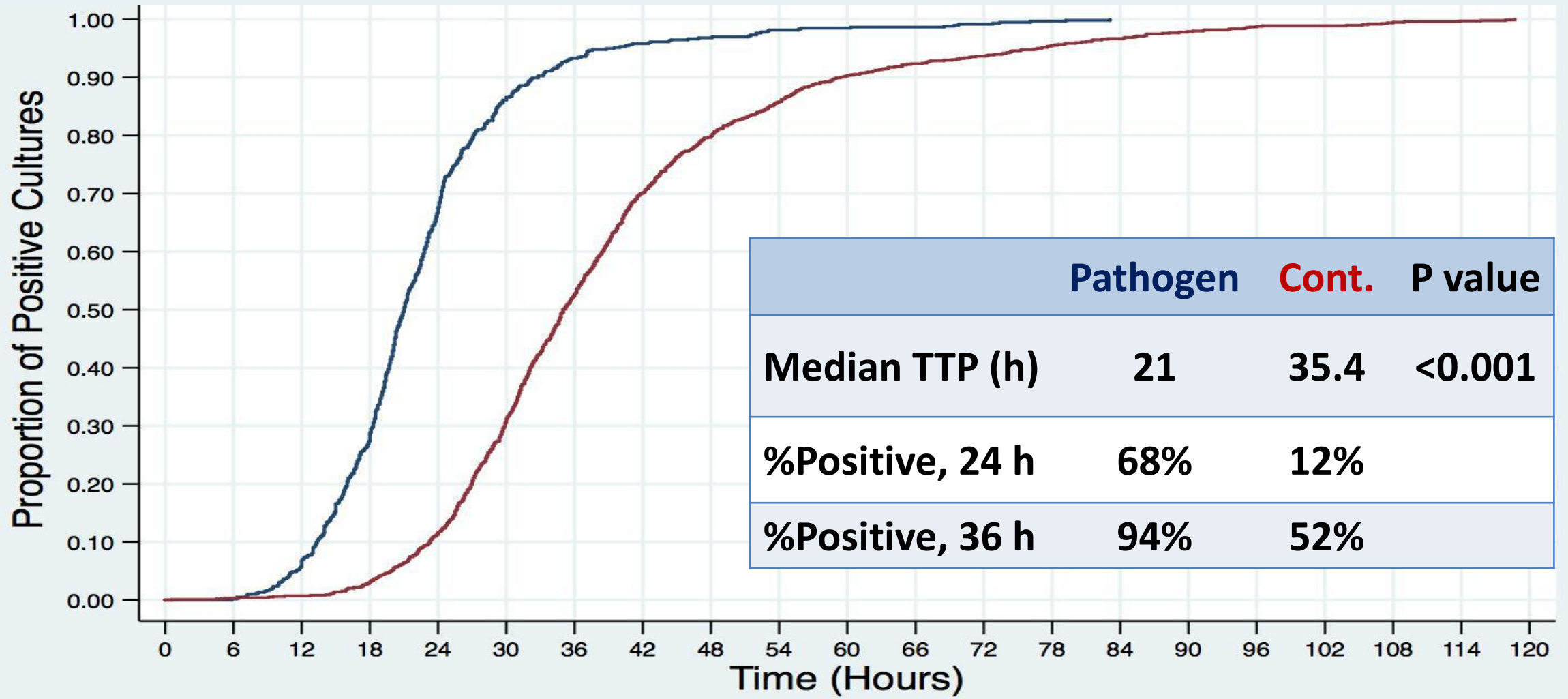


LOS: CoNS vs Other Pathogens



| | Other Pathogens | CoNS | <i>P</i> |
|----------------|-----------------|------|----------|
| Median TTP (h) | 21.2 | 30.0 | <0.001 |
| Positive, 24 h | 69 % | 22 % | <0.001 |
| Positive, 36 h | 94 % | 66 % | <0.001 |

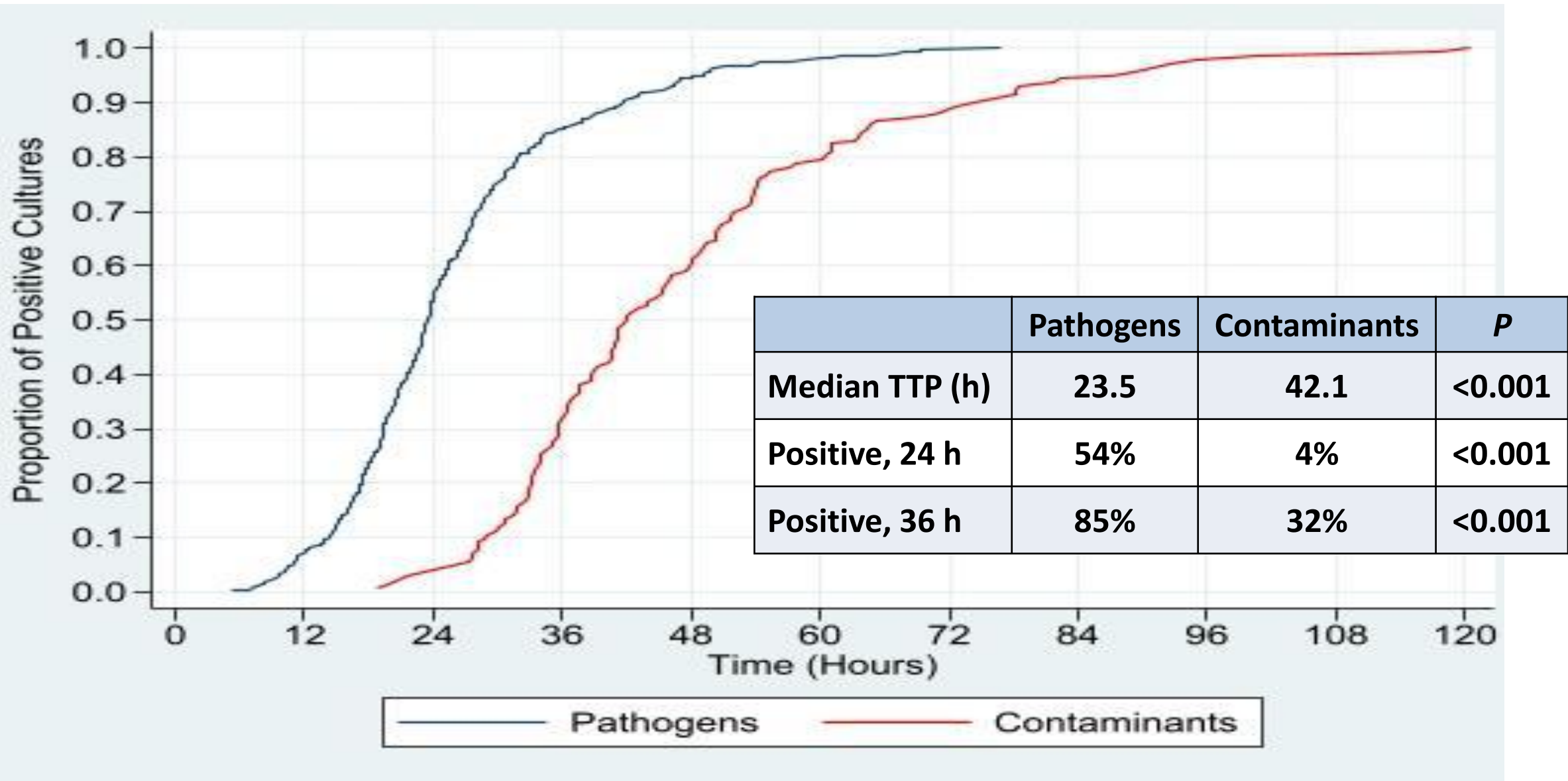
EOS: Pathogen vs. Contaminant



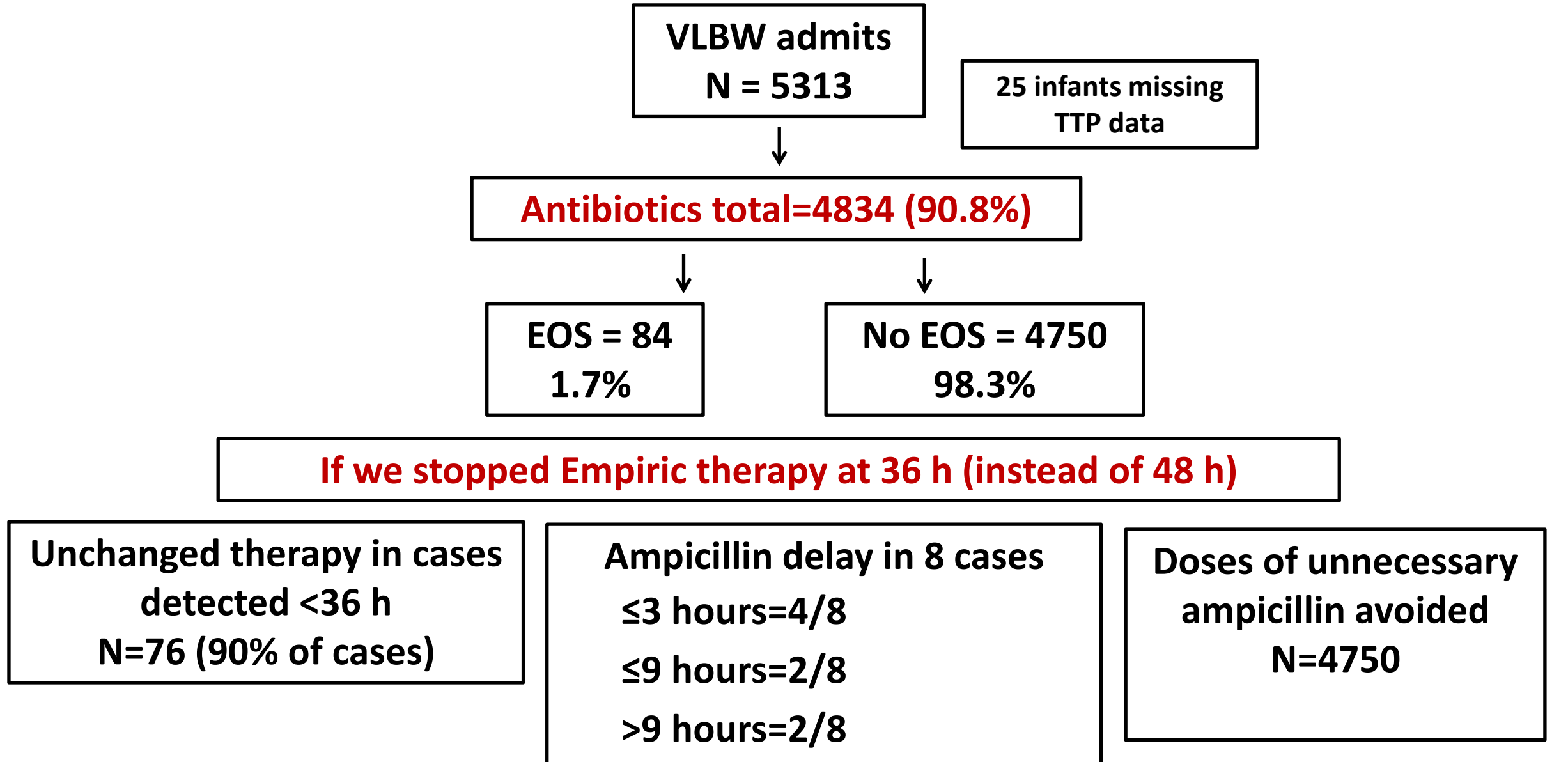
| | Pathogen | Cont. | P value |
|-----------------|----------|-------|---------|
| Median TTP (h) | 21 | 35.4 | <0.001 |
| %Positive, 24 h | 68% | 12% | |
| %Positive, 36 h | 94% | 52% | |

— Pathogens — Contaminants

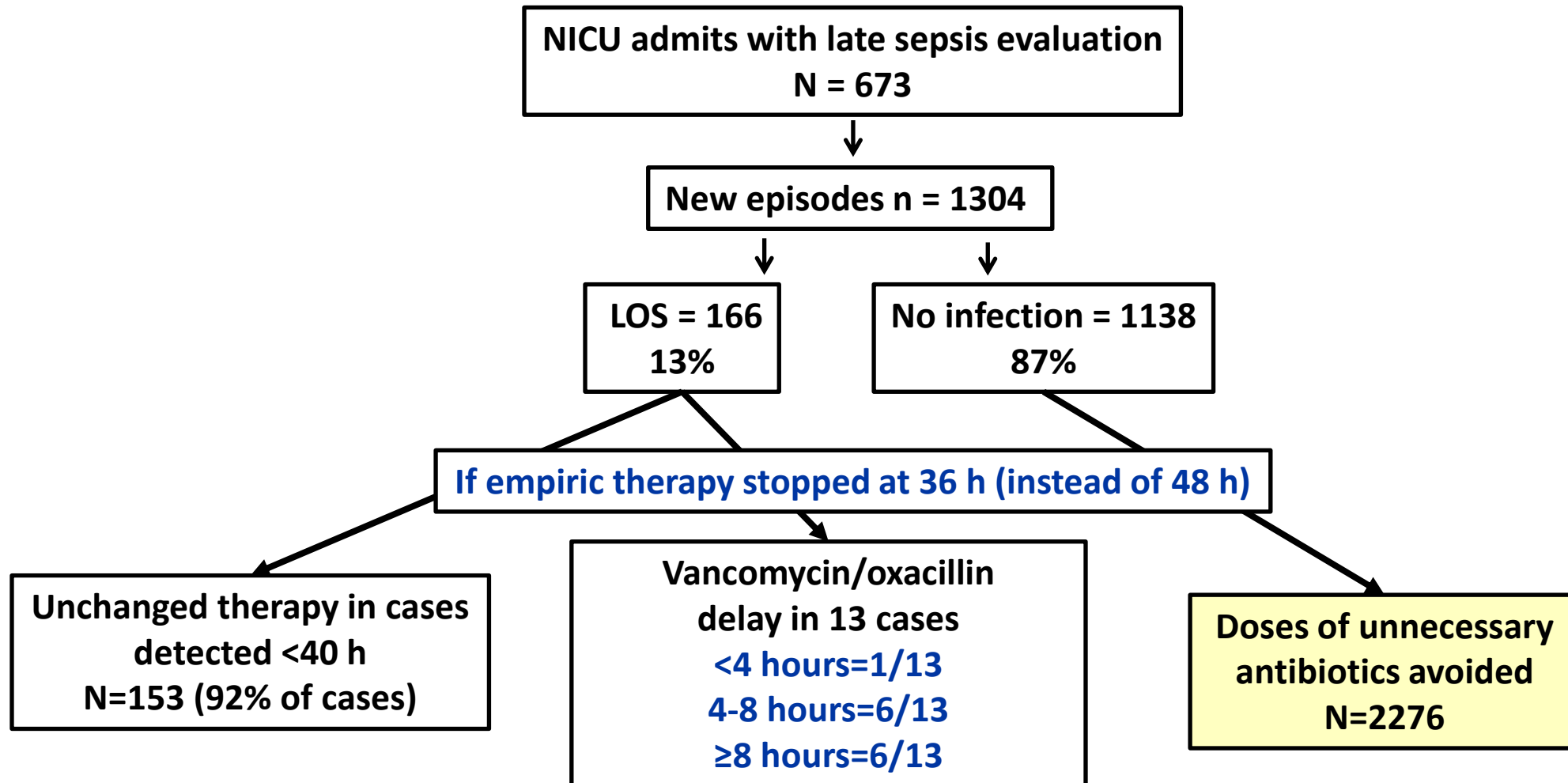
LOS: Pathogens vs Contaminants



Projected Impact at one center over 25 years



Projected Impact on Antibiotic Use



Summary – Strategies for Stopping Early

- **Majority (94%) of early- and late-onset pathogens are identified within 36 hours after blood culture collection**
- **After 36 hours, chances of positive results being a contaminant sharply increase**
- **Reducing empiric ‘rule-out’ duration from 48 to 36 hours can avoid thousands of antibiotic doses**

Narrow spectrum antibiotics for empiric therapy

3. SELECT WISELY

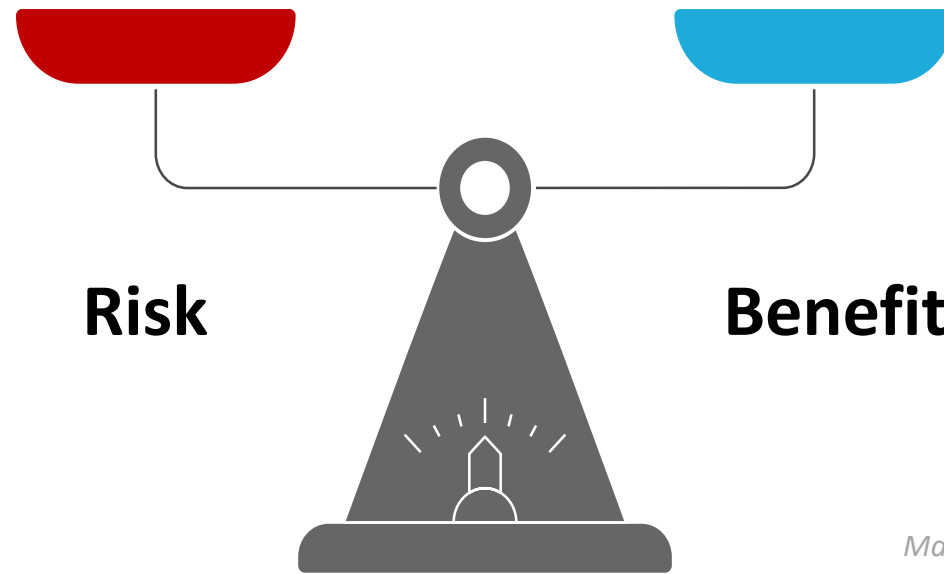
How Broad Should First Line Empiric Antibiotics be?

**No benefit only harm
if uninfected**

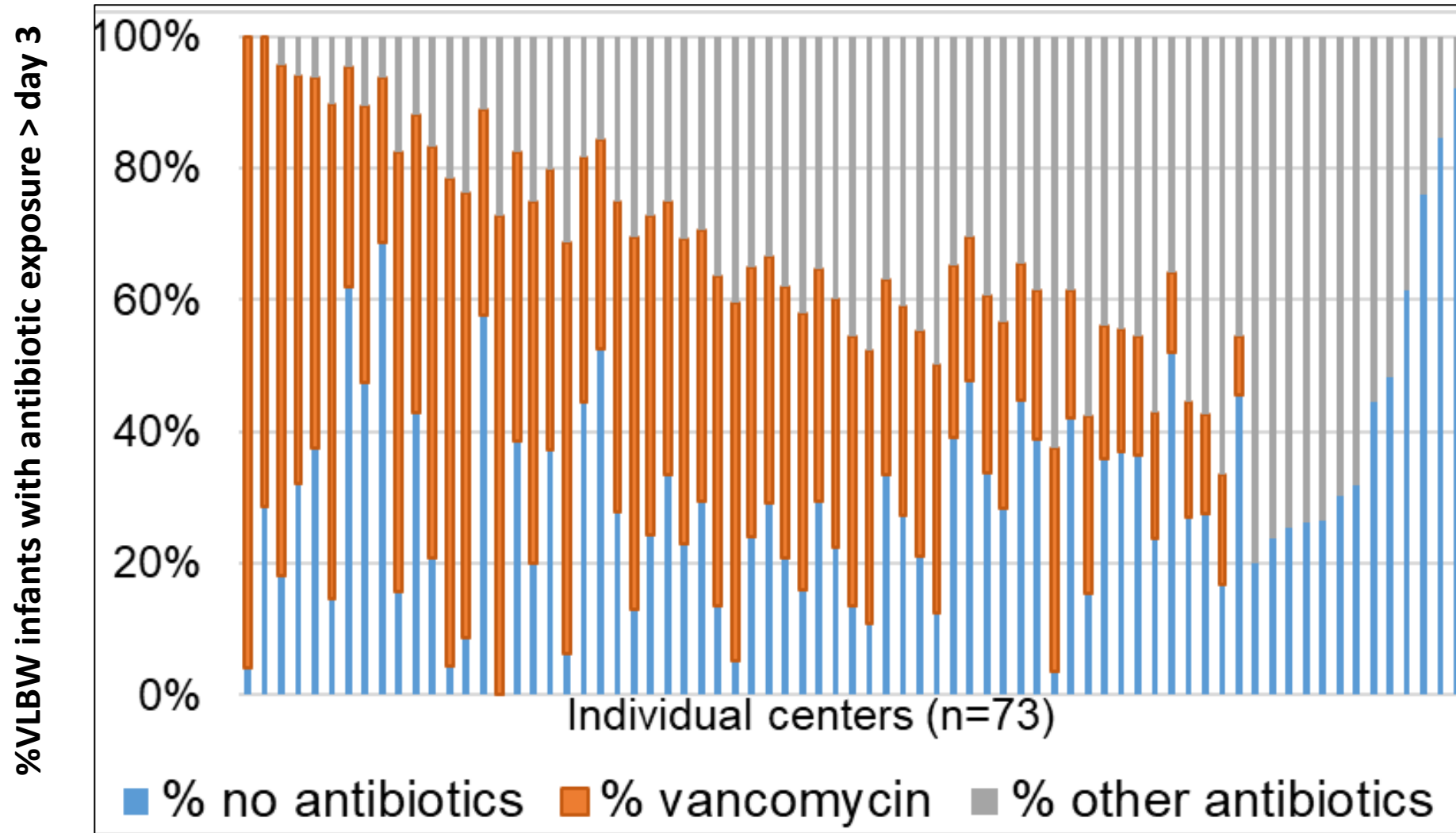
**Majority evaluations
are negative**

Improved survival

**If infected, reduced
time to treatment**

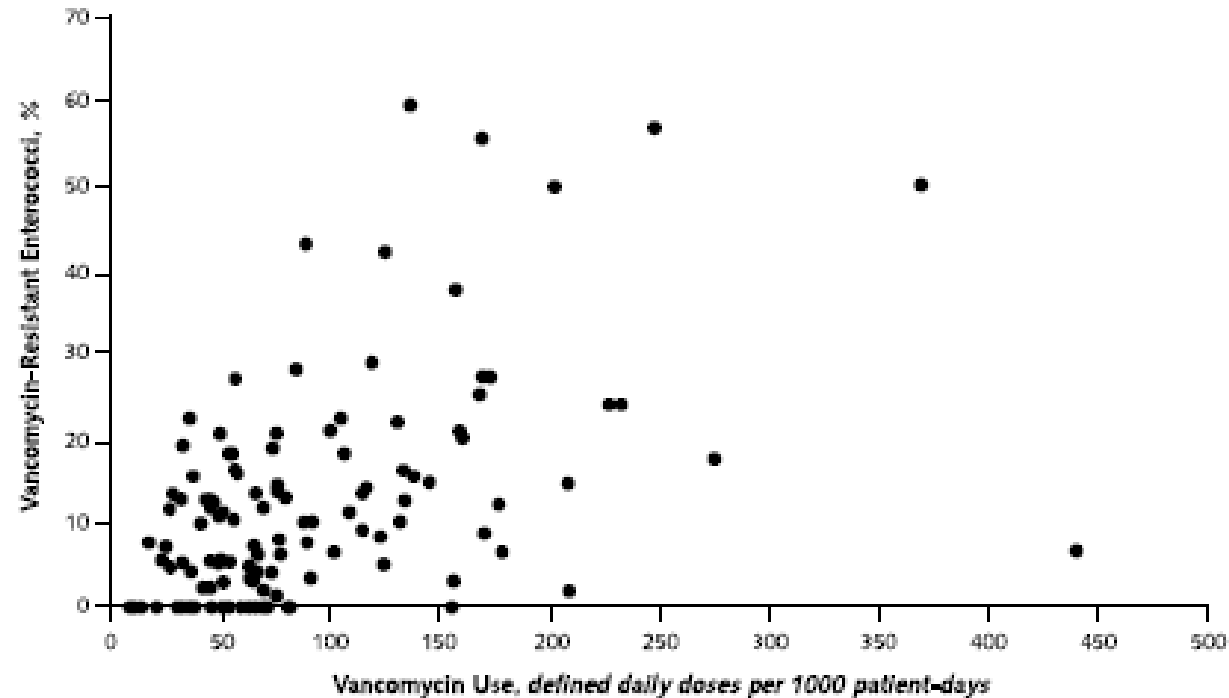


Vancomycin Is A Broad-spectrum Antibiotics Commonly Used As First-line Empiric Therapy

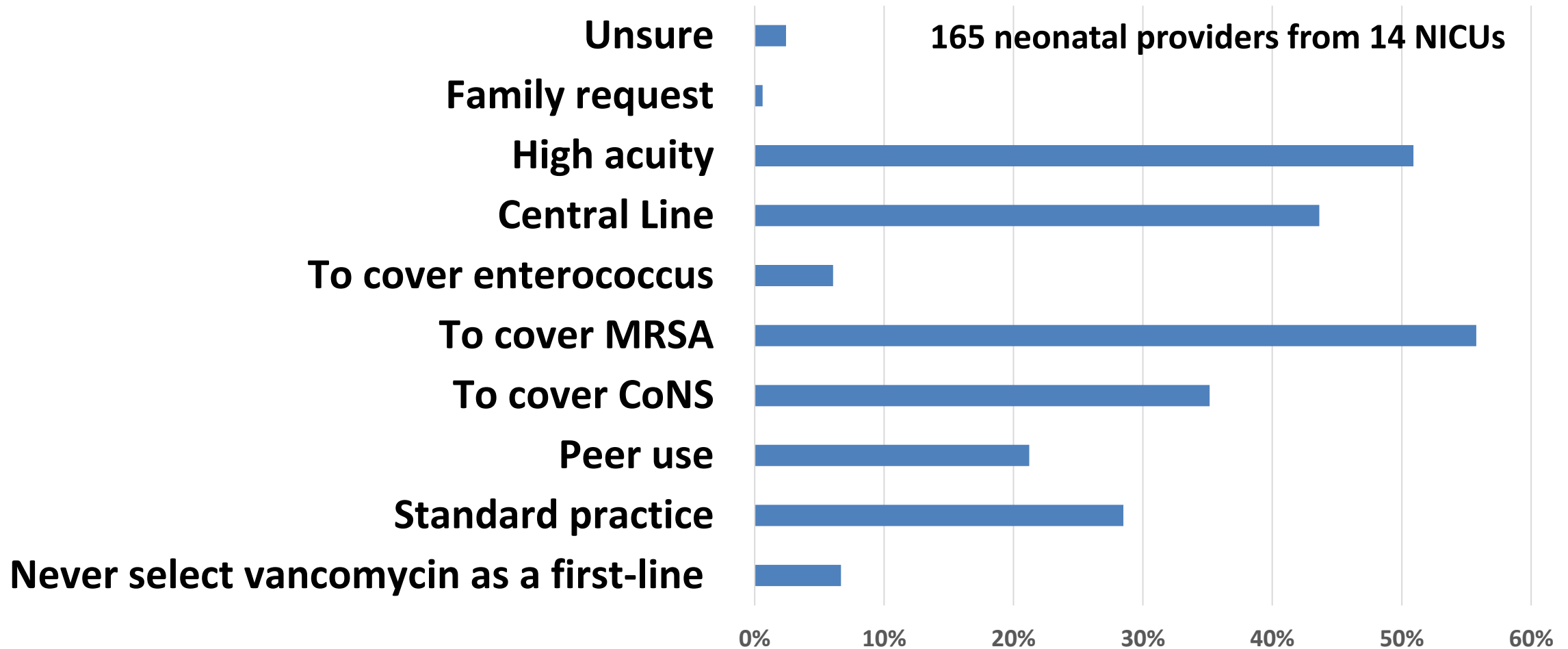


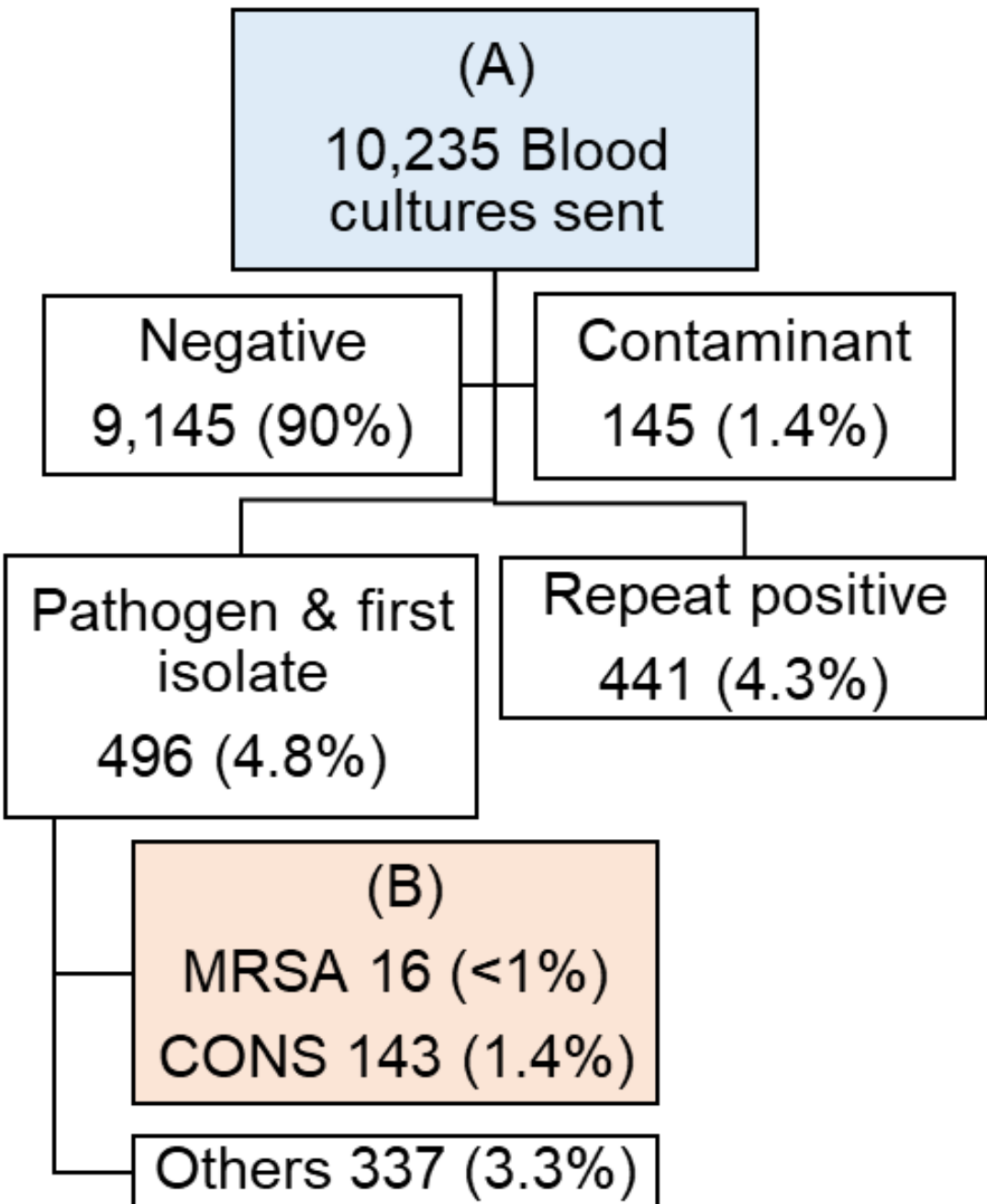
Vancomycin is recommended for *targeted therapy*, not *routine empiric therapy*

- The World Health Organization and the American Academy of Pediatrics recommends against the use of vancomycin as an empiric first-line antibiotic.
- Increased vancomycin use correlated with selection of resistant pathogens



Reasons for choosing vancomycin

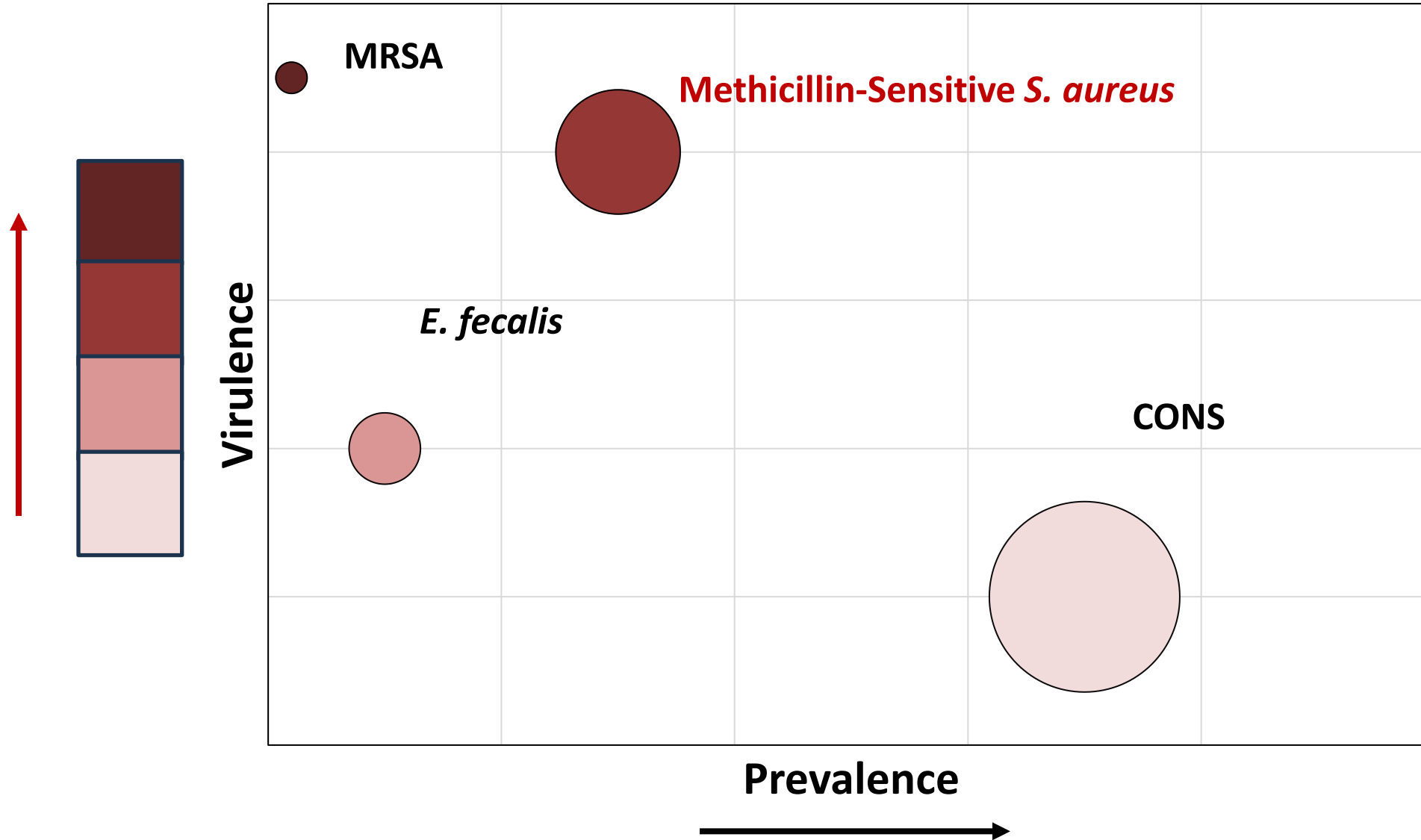




Do you really need Vancomycin?

Less than 2% of all evaluations (A) will ultimately need vancomycin (B) as treatment

Cover the most prevalent AND virulent



Advantages of beta-lactams as empiric therapy

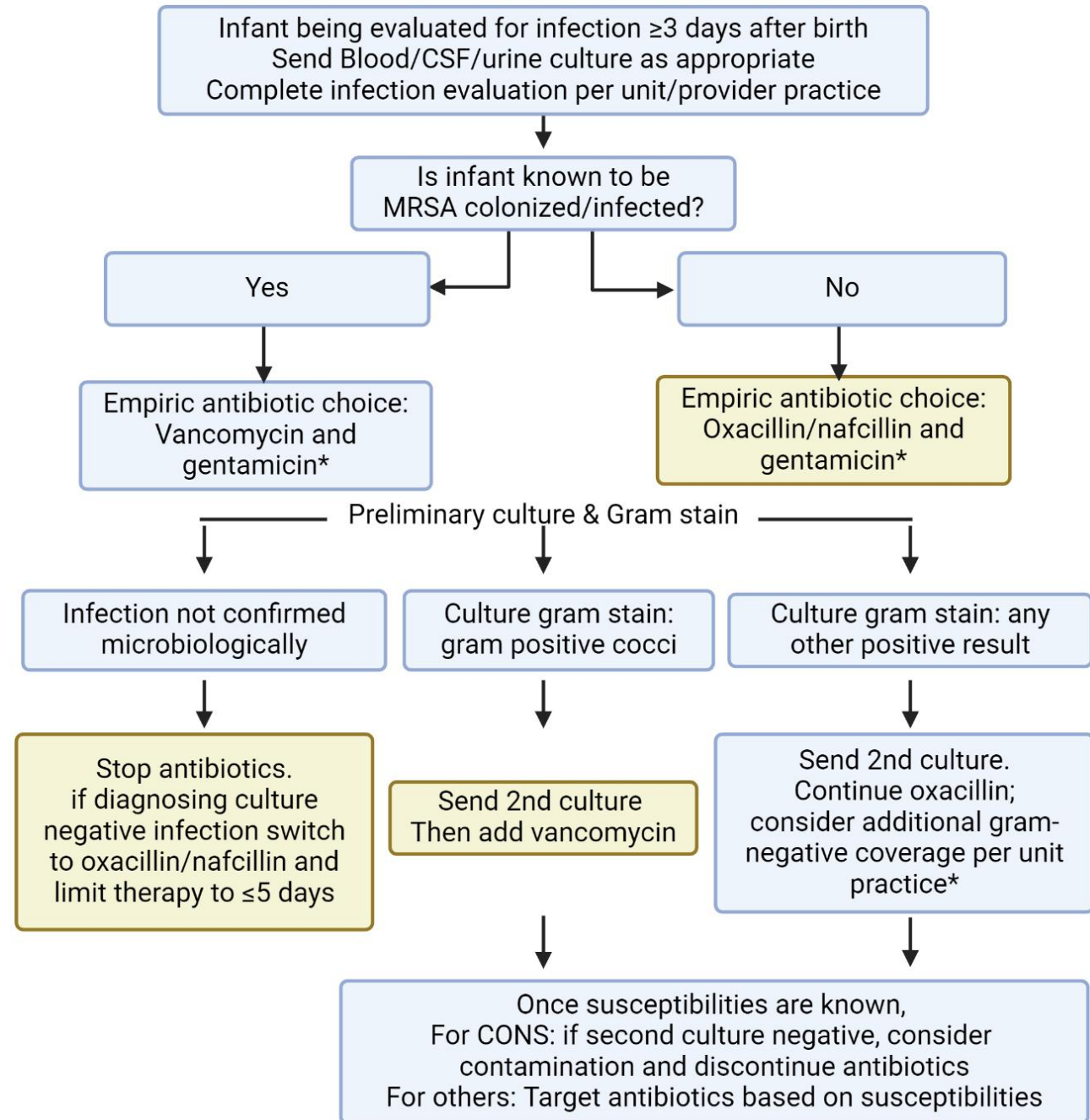


Vancomycin Reducing Practice (VRP): A more balanced approach to LOS evaluation

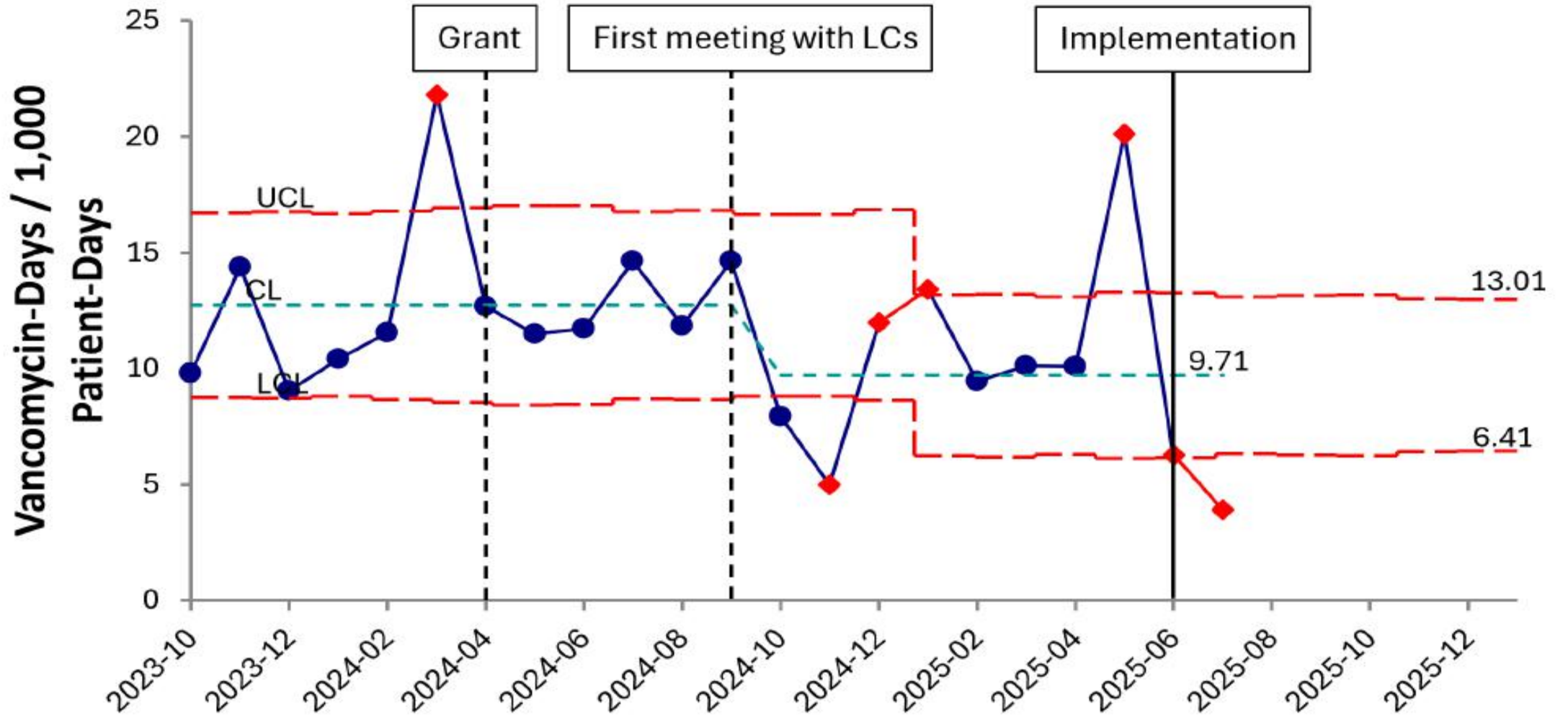
- 1. Initiate oxacillin/nafcillin (Ox/naf) when evaluating for LOS, unless meeting specific criteria for vancomycin**
- 2. If gram-positive cocci (GPCs) are identified in culture: obtain repeat cultures before adding vancomycin so contamination may be distinguished from true infection**
- 3. Stop all antibiotics if cultures are negative at 36-48 hours incubation; if antibiotics are administered despite sterile cultures, use Ox/naf and limit duration to ≤ 5 days**

*Vancomycin alternates for gram-positive coverage, e.g. ampicillin or cephalosporin monotherapy may be selected based of unit-specific epidemiology

VRP Algorithm



Implementation of VRP in 14 centers

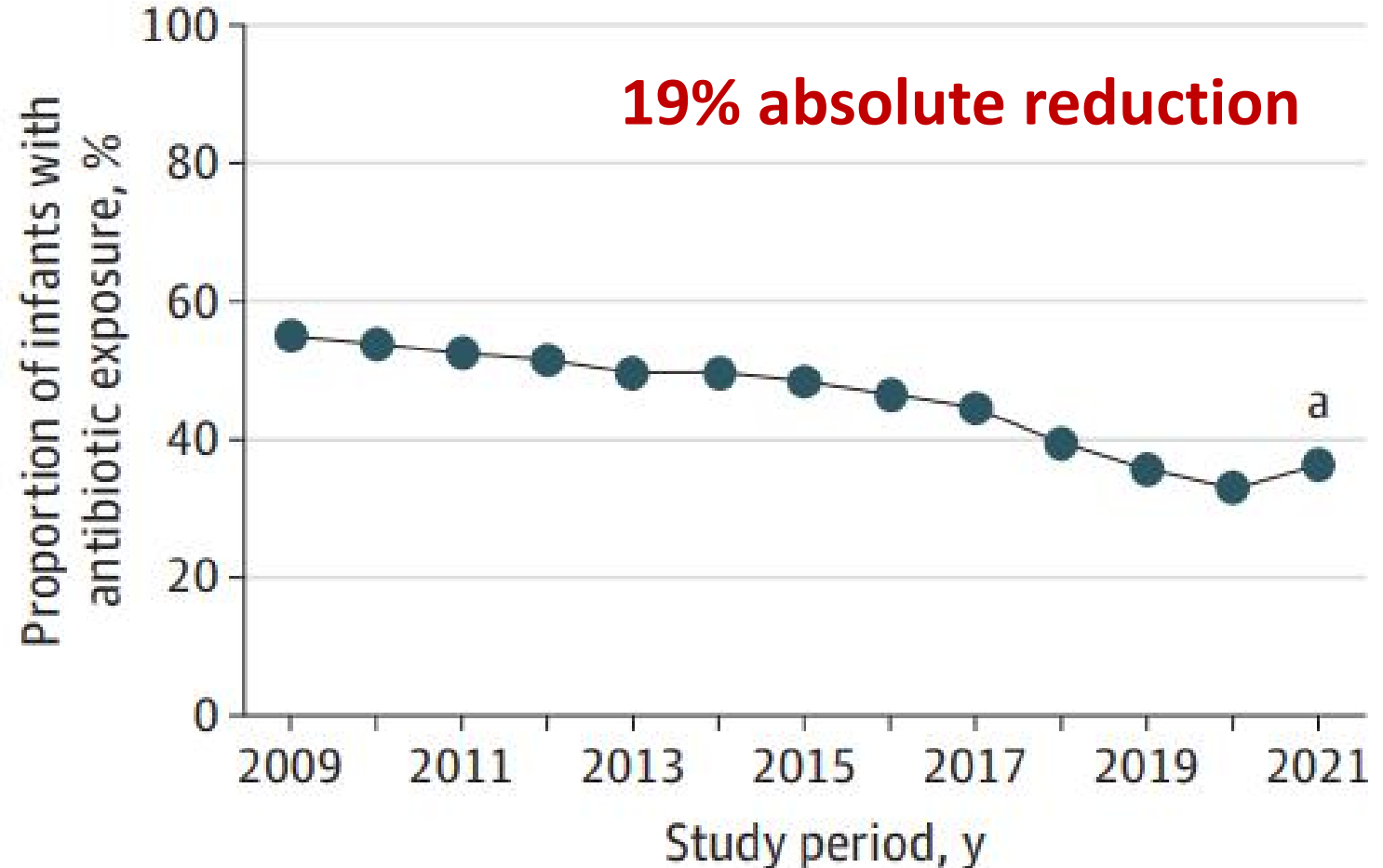


Summary: **Strategies for Selecting Wisely**

- **Assess the following in selecting empiric antibiotics**
 - **Antibiogram**
 - **Rates of evaluation and empiric antibiotic use**
 - **Rates of pathogen identification**
- **Select the narrowest spectrum allowed by the above**
- **Follow an algorithm to identify thresholds for broadening**

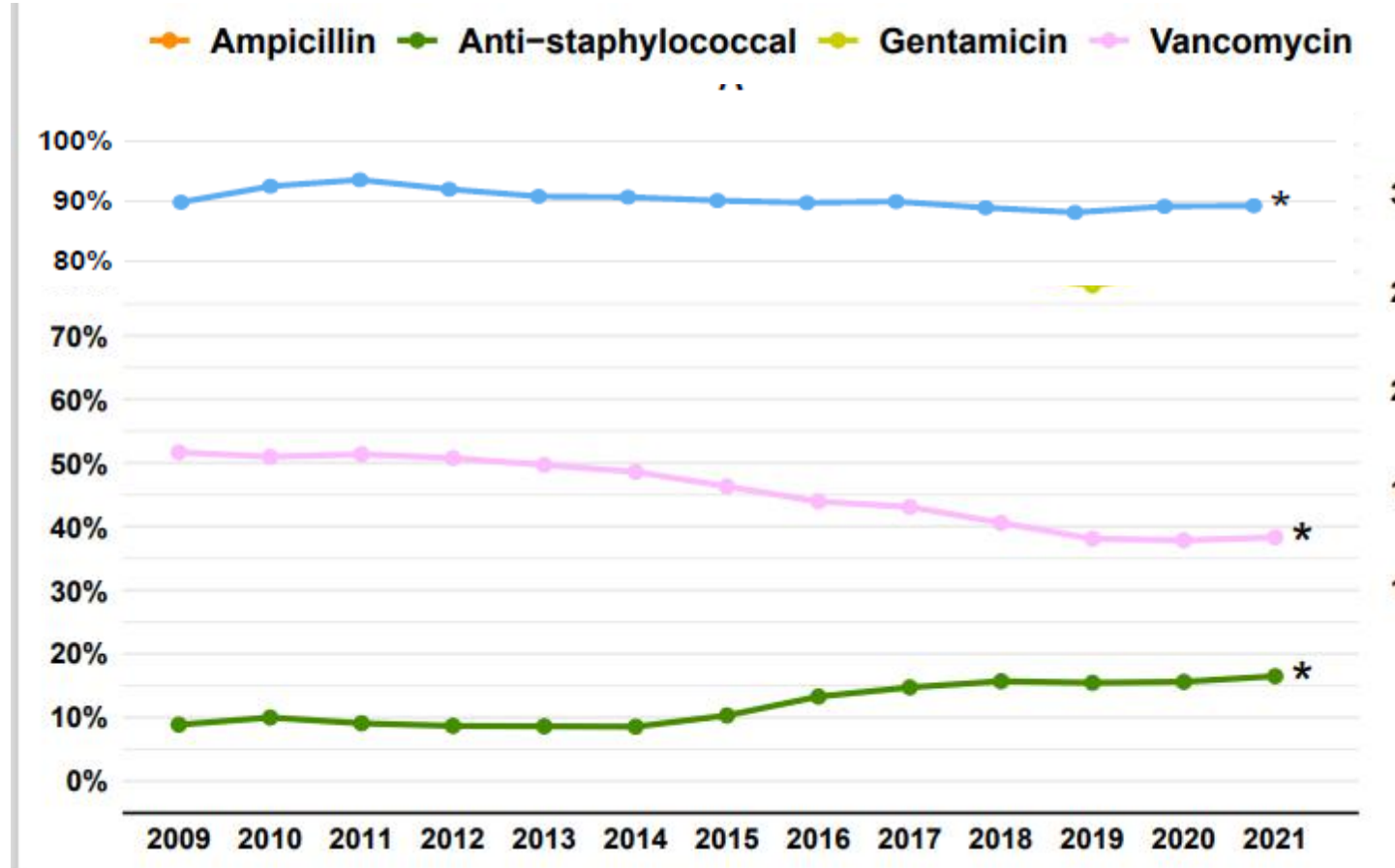
NICU Antibiotic Use has Reduced

- 735 NICUs
- % infants initiated on antibiotics

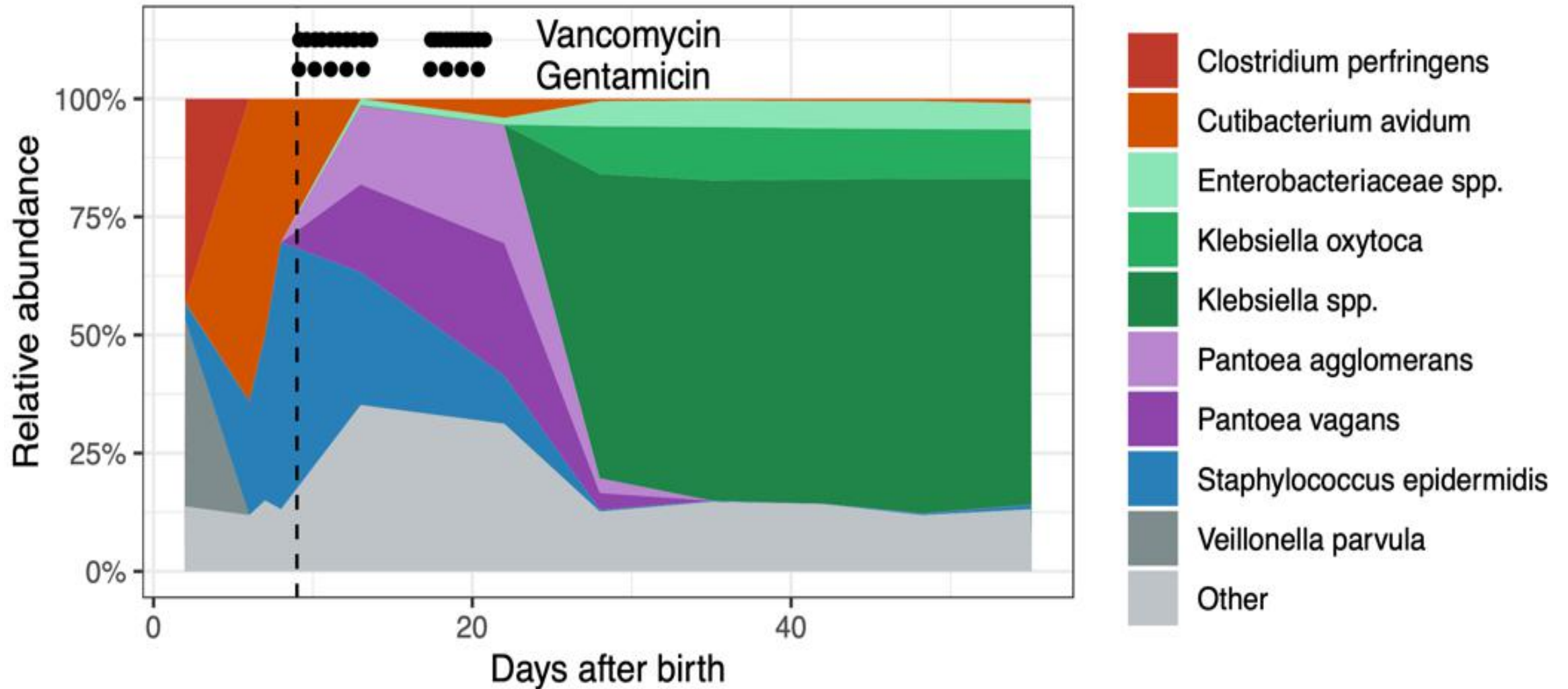


Slower Change in ELBW Infants

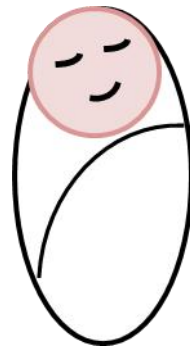
- Days of therapy have reduced overall
- Slow but significant reduction in vancomycin



Yet Preterm Infants need Optimization the Most



**Antibiotic stewardship in the NICU supports
healthier infants today and effective
treatments for tomorrow**





Acknowledgements



- **Research Team**

- Miren Dhudasia, MBBS, MPH
- Hanna Rosewod, BS
- Erica Hartman, MA
- Maddie Pfeifer, MS
- Alvaro Zevallos Barboza, MPH

- **Collaborators:**

- Karen M Puopolo, MD, PhD
- Jeffery Gerber, MD, PhD, MSCE
- Dustin Flannery, DO, MSCE
- Michael Kuzniewicz, MD
- Corinna Koebnick, PhD (Kaiser Permanente)
- Kyle Bittinger, PhD

- **Supporting Institutes**

- Eric Eichenwald, MD. Division Chief, Neonatology, CHOP
- Clinical Futures, CHOP
- PennCHOP Microbiome Program

- **Sponsors**

- NICHD - K23HD088753
- AHRQ - 1R01HS029500
- Gerber Foundation
- Society of Pediatric Research
- Centers for Disease Control & Prevention
- Institute for Translational Medicine and Therapeutics, Penn



<https://research.chop.edu/people/sagori-mukhopadhyay>
CPPID Team | CHOP Research Institute





Questions?

mukhopadhs@chop.edu