Antibiotic Stewardship: Beyond the Sepsis Calculator

Karen Puopolo, MD, PhD

ILPQC
Illinois Perinatal Quality Collaborative

Illinois Perinatal Quality Collaborative

9th Annual Conference

October 28, 2021

Antibiotic Stewardship Among Preterm Infants

Karen M. Puopolo M.D., Ph.D.

Division of Neonatology, Children's Hospital of Philadelphia

Chief, Section on Newborn Medicine, Pennsylvania Hospital

Associate Professor of Pediatrics

University of Pennsylvania Perelman School of Medicine

DISCLOSURE STATEMENT

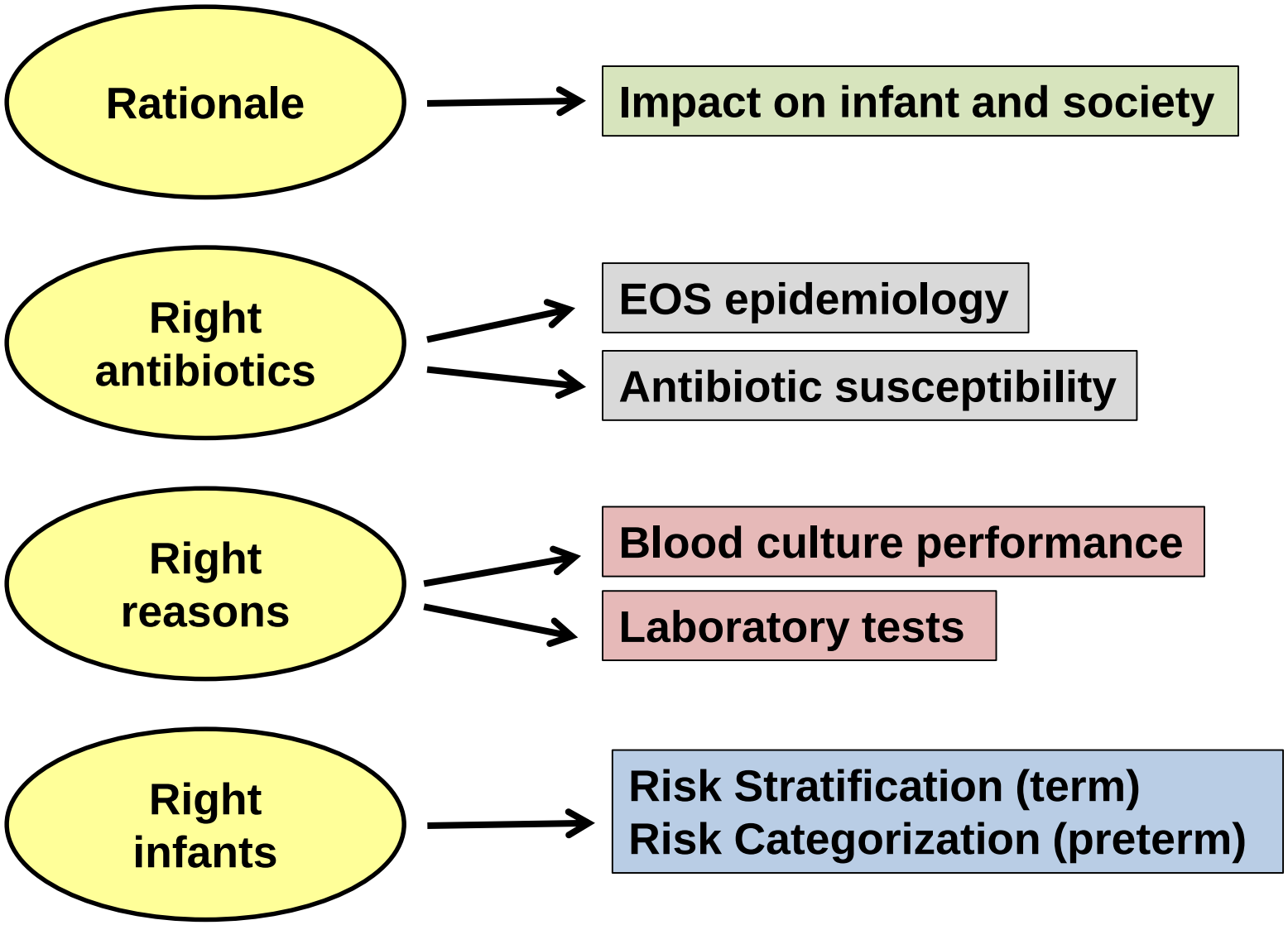
Karen M. Puopolo MD, PhD

- **I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity**
- **I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation**

What are the Real Goals of Neonatal Antibiotic Stewardship?

- **Some babies need antibiotics**
- **Some babies need a lot of antibiotics**
- **Antibiotic stewardship is NOT just about giving fewer antibiotics**
- ***Antibiotic stewardship is about giving the right antibiotics, to the right babies, for the right reasons (and at the right dose)***

Neonatal Antibiotic Stewardship

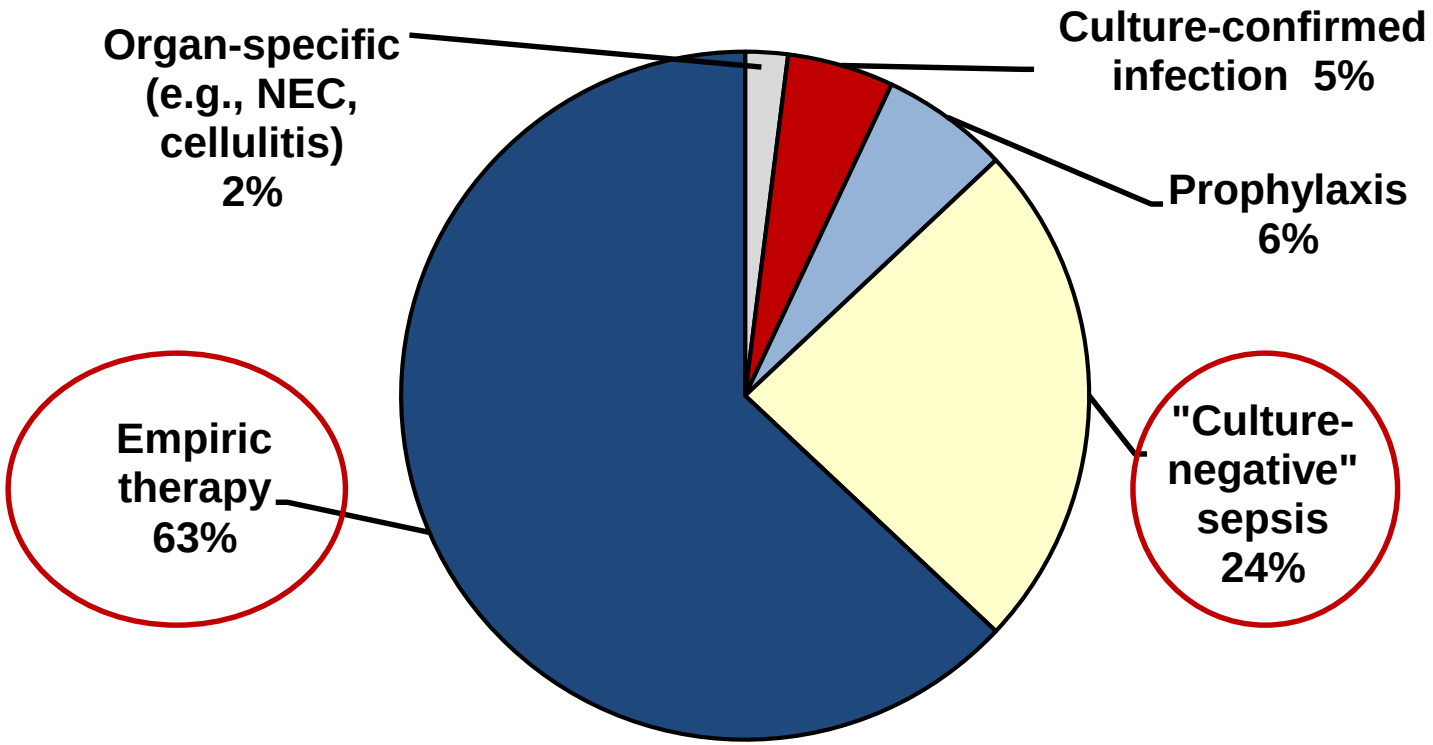


The Rationale

CPPID
CHOP/PENN PERINATAL INFECTIOUS DISEASES

LEGES SINE MORIBUS VANAE

What Drives Antibiotic Use in the NICU?

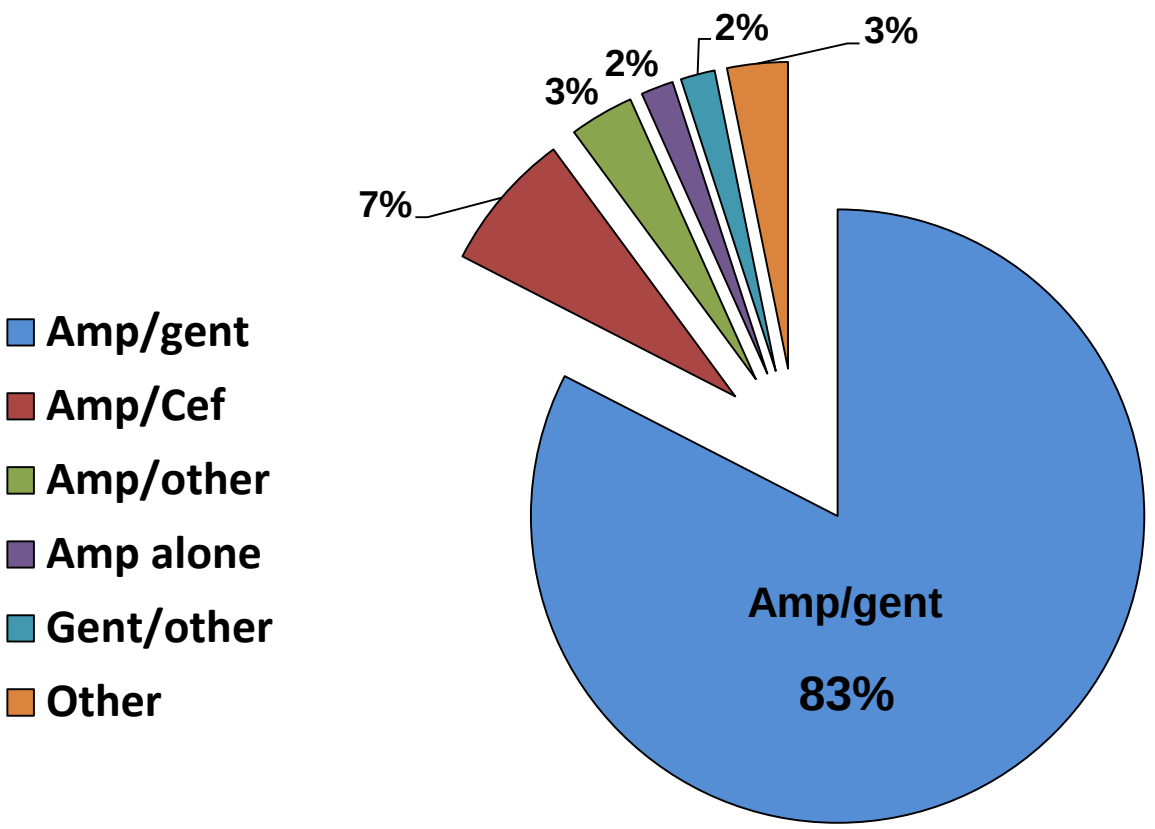


79% initiations for risk of Early-onset Sepsis

- 14 month single center surveillance
- 1607 infants and 343 Days of therapy/1000 Patient-days

Cantey et al. (2015) *Pediatr Infect Dis J*

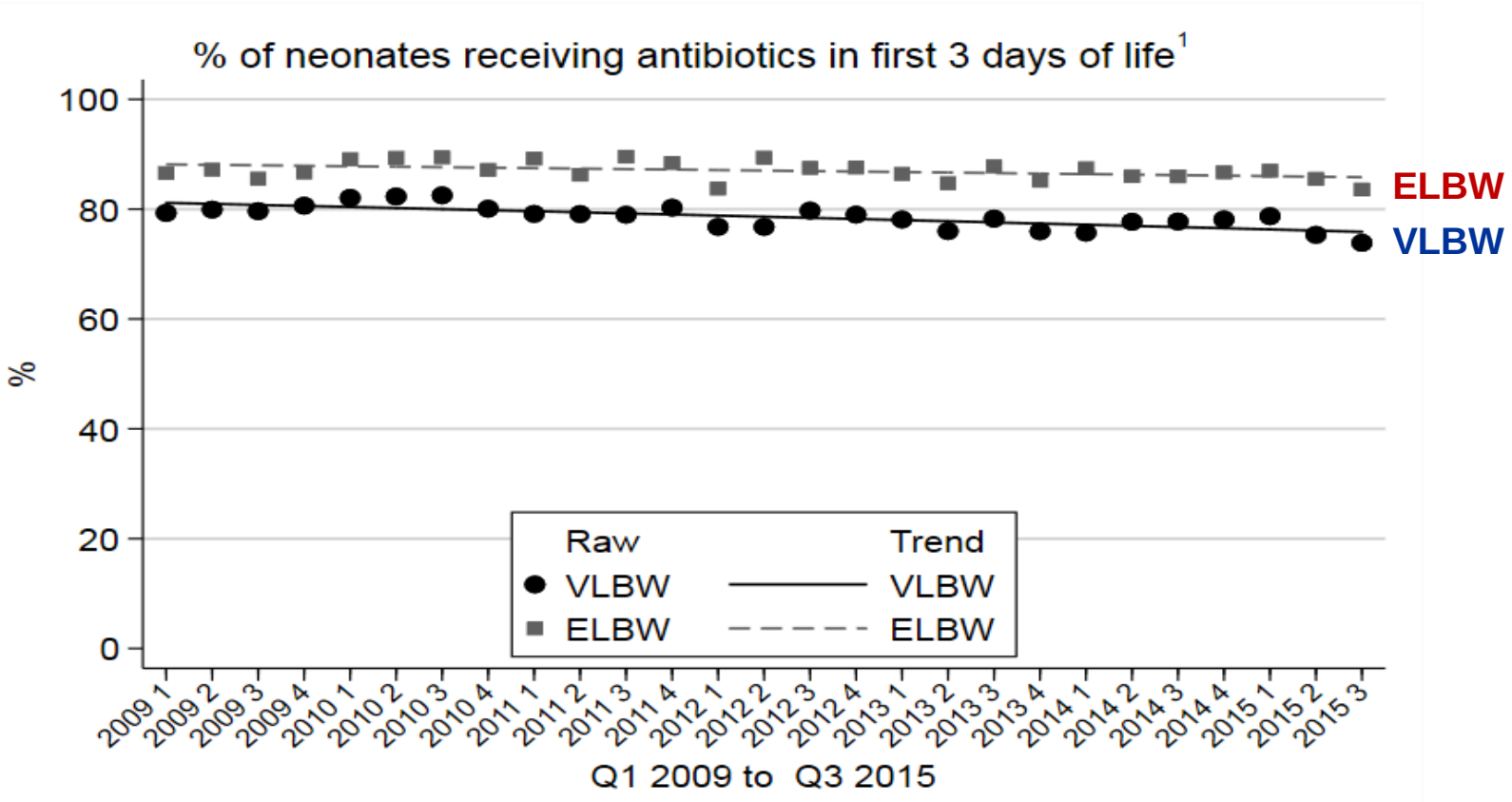
Antibiotic Initiation and Extension



- **NICHD Neonatal Research Network, 1998-2001**
- **5693 infants with BW < 1000 grams**
- ***98% received antibiotics in the first 3 days of life***
- ***53% of uninfected infants received early antibiotics ≥5 days***

Cotten et al (2009) *Pediatrics*

Contemporary National Data on Early Antibiotic Use Among Preterm Infants



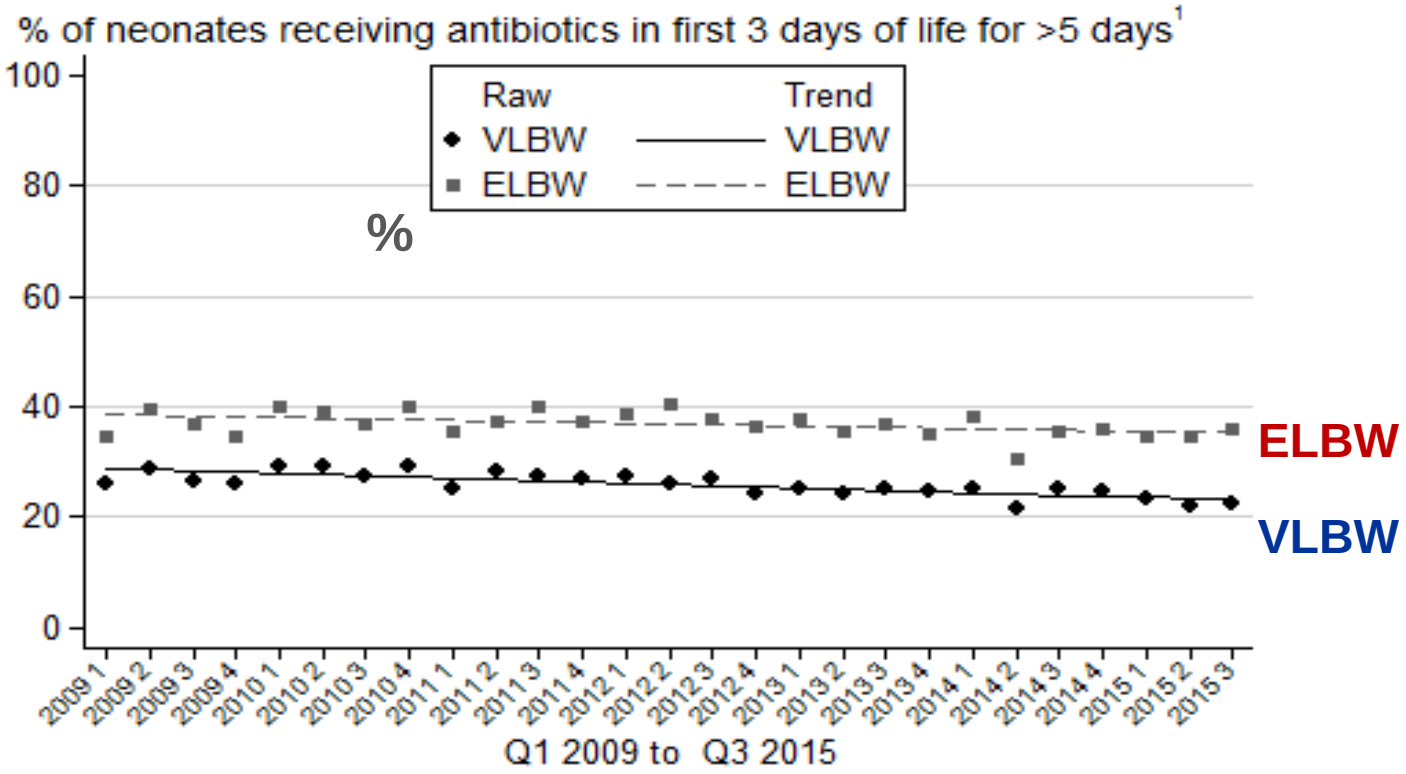
ELBW

VLBW

- Premier database
- 297 centers including 40,364 infants
- Antibiotic administered ≤3 days of age
  - 87% ELBW
  - 79% VLBW
- No change 2009-2015

Flannery et al (2018) *JAMA Netw Open*

And Once We Start…



- **Early antibiotics extended >5 days**
  - **ELBW: 38%**
  - **VLBW: 27%**
- **Significant decrease over time for VLBW infants**
- **Rates of EOS**
  - **ELBW: 2.1%**
  - **VLBW: 1.4%**

Flannery, et al (2018) *JAMA Netw Open;* Flannery, et al (2021) *Pediatrics*

Prolonged Empiric Antibiotic Exposure and Risk of NEC and Death

4039 ELBW infants
1998-2001

53% early antibiotics ≥5 days

NEC
61% early antibiotics ≥5 days

No NEC
51% early antibiotics ≥5 days

With each additional day of antibiotics

- ***7% increase in odds of NEC***
- ***16% increase in odds of mortality***

5730 ELBW infants
2008-2014

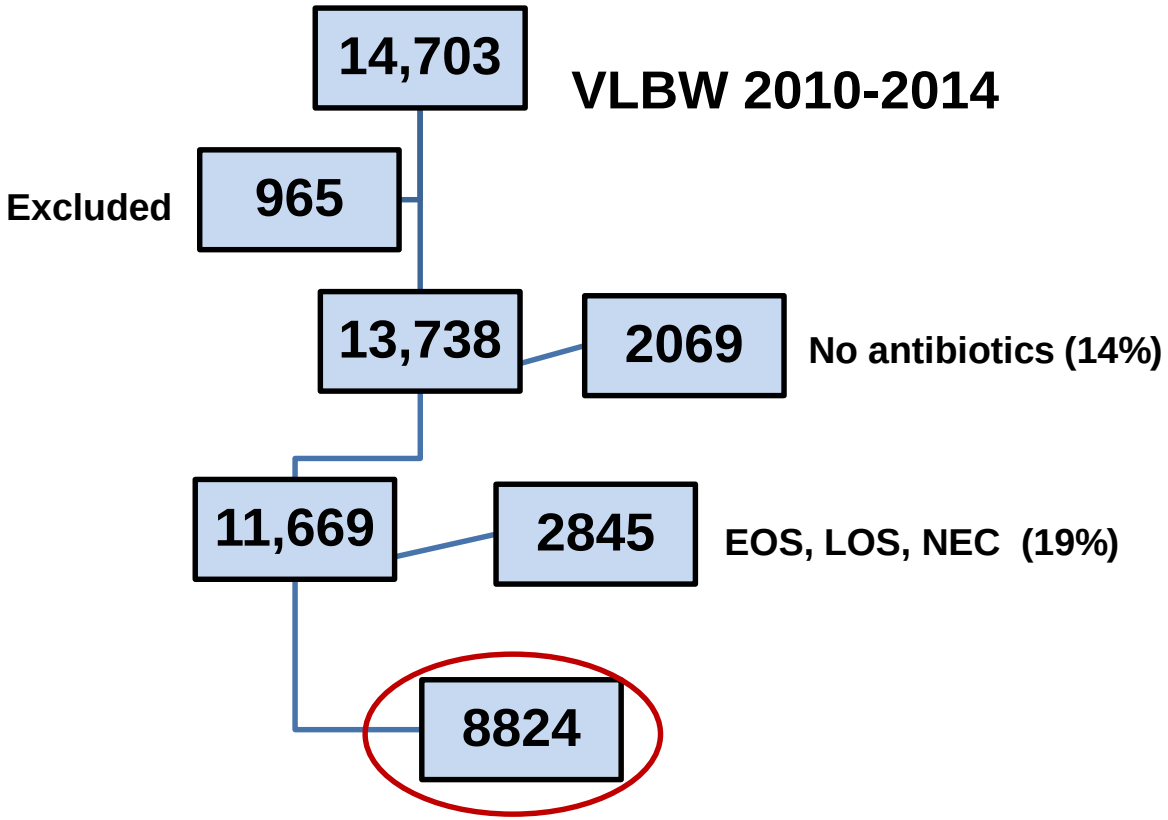
44% early antibiotics ≥5 days
49% in 2008 → 35% in 2014

Death/NEC

- **25% among those with early antibiotics ≥5 days**
- **20% among those without early antibiotics ≥5 days**

Cotten et al (2009) *Pediatrics;* Greenberg et al (2019) *Pediatr Res*

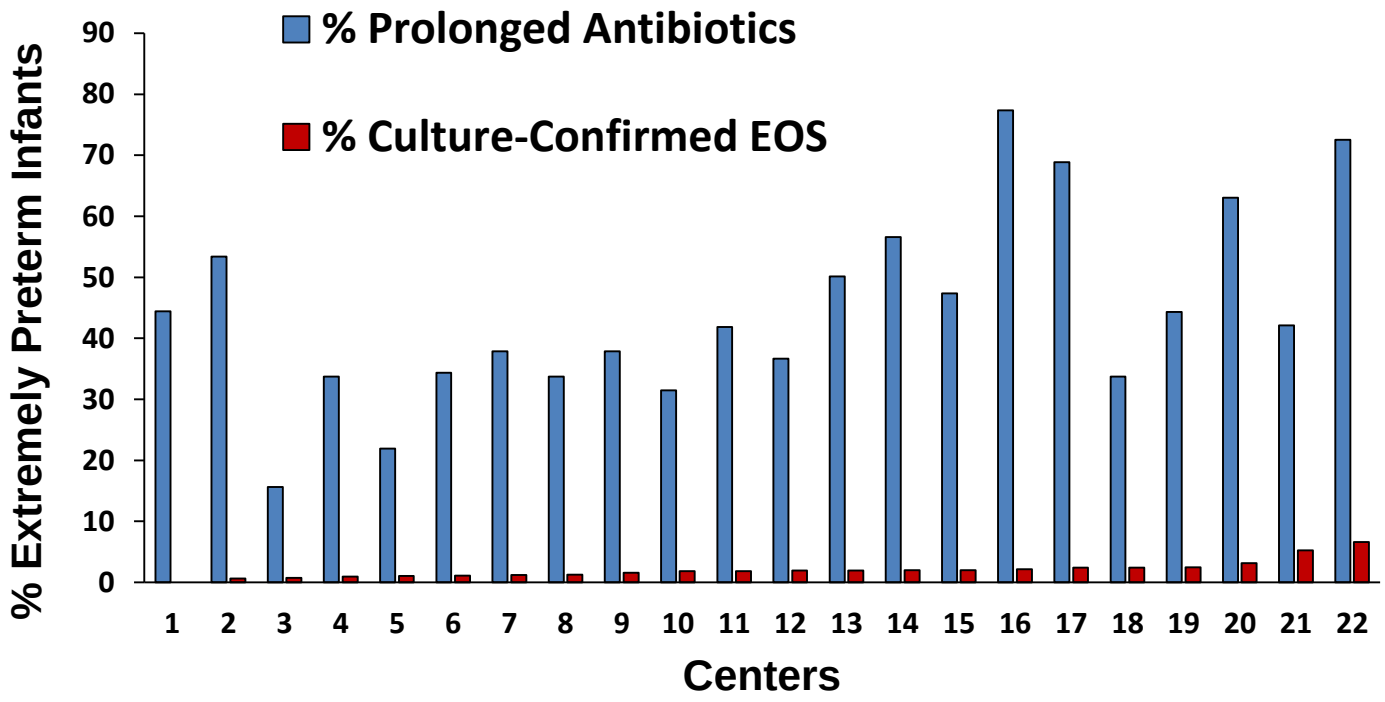
Antibiotics and Outcomes Among VLBW Infants



- Antibiotic Use Rate (AUR) decreased over time from 0.29 → 0.24
- Examined 8824 infants by AUR quartile
- *Mortality highest in highest AUR quartile*
- Overall adjusted risk (OR, 95% CI):
  - Mortality: 2.04 (1.87-2.21)
  - Major morbidity or mortality: 1.18 (1.13-1.23)

Ting, et al. (2016) *JAMA Pediatr*

Significant Variation in Use of Prolonged Early Antibiotics



There may be infants with similar clinical status who were managed differently – does this differential practice alter infant outcomes?

Puopolo et al (2017) *Pediatrics*

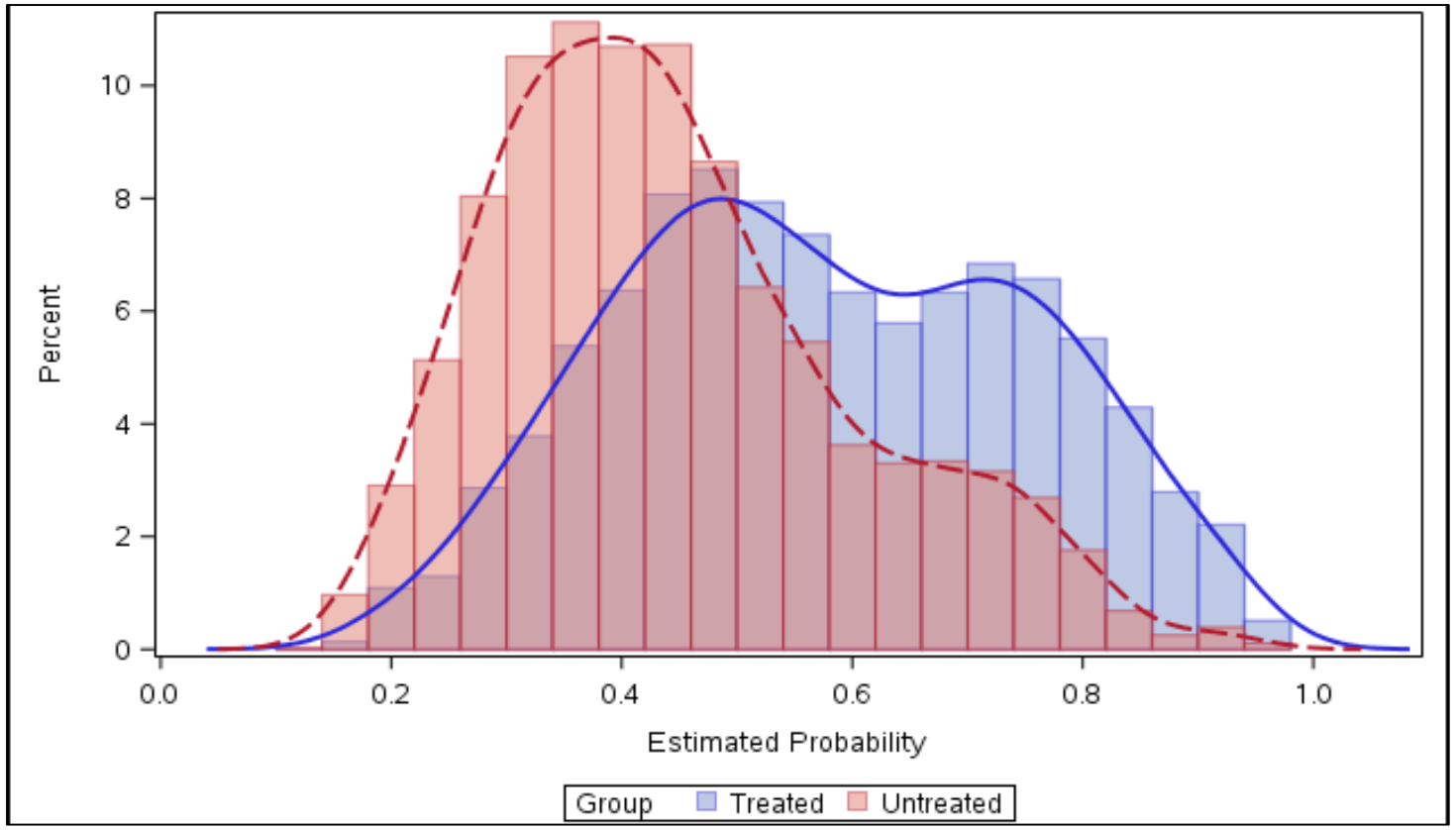
Propensity Score-Matched Comparison

- **7354 infants born at Neonatal Research Network centers 2006-2014 with GA <27 wks and BW <1000 g**
  - **1547 excluded (NEC/SIP, early death, missing data)**
  - **2978 received antibiotics ≥5 days from birth; 2829 did not**
- ***Using propensity score, matched 4362 infants***

- **GA, BW, Sex**
- **Chorioamnionitis**
- **Maternal antibiotics**
- **Antenatal steroids**
- **Cesarean delivery**
- **Membrane rupture >18 hours**
- **Respiratory support at 24 h**
- **Severe IVH at ≤ 7 days**
- **Intubation at birth**
- **First temperature**
- **Enteral feeds at ≤3 days**
- **Maternal hypertension**
- **Antepartum hemorrhage**
- **Race/ethnicity**
- **Maternal education and insurance**

Mukhopadhyay et al. (2020) *J Pediatr*

Propensity Score Match



- **Some babies everyone will treat with prolonged antibiotics**
- **Some babies no one will treat with prolonged antibiotics**
- **75% of the cohort matched**

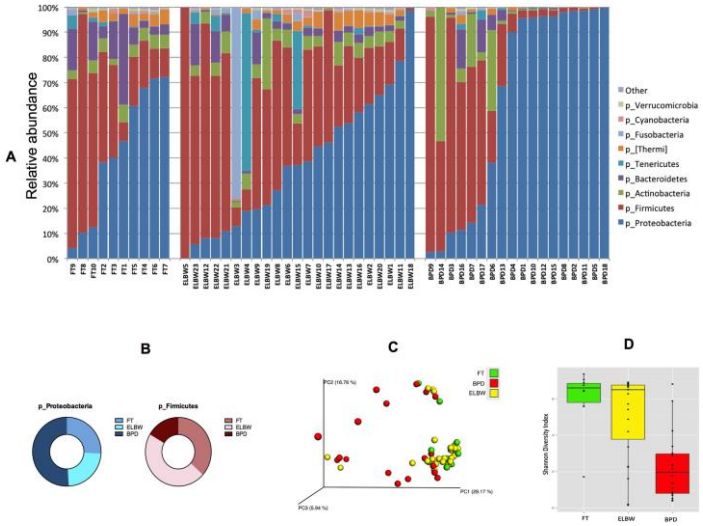
No Difference in Outcomes

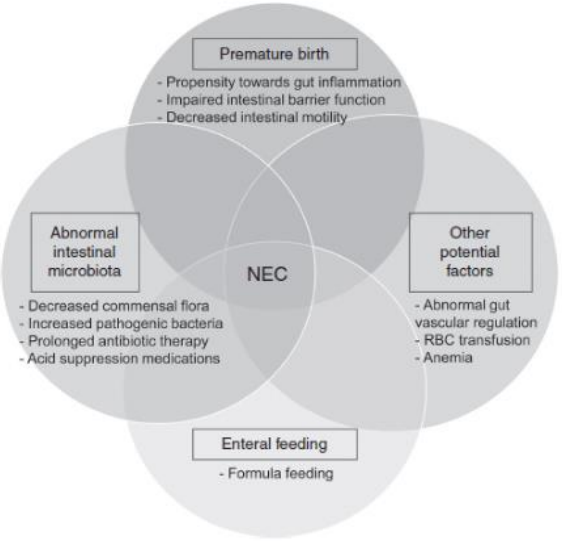
	Prolonged Abx n=2181	No Prolonged Abx n=2181	RR (95% CI)
Death/NDI	1,091 (50.0)	1,047 (48.0)	1.04 (0.98-1.11)
Death	512 (23.5)	469 (21.5)	1.09 (0.98-1.22)
NDI	579 (34.7)	578 (33.8)	1.03 (0.94-1.13)

- **Among clinically similar infants, management with or without prolonged antibiotic therapy did not reduce risk of death or NDI or the combined outcome**
- ***In the absence of benefit, prolonged antibiotic use exposes the infant only to the potential risks***

Evolving Understanding of the Role of Microbiome in Infection and Immunity

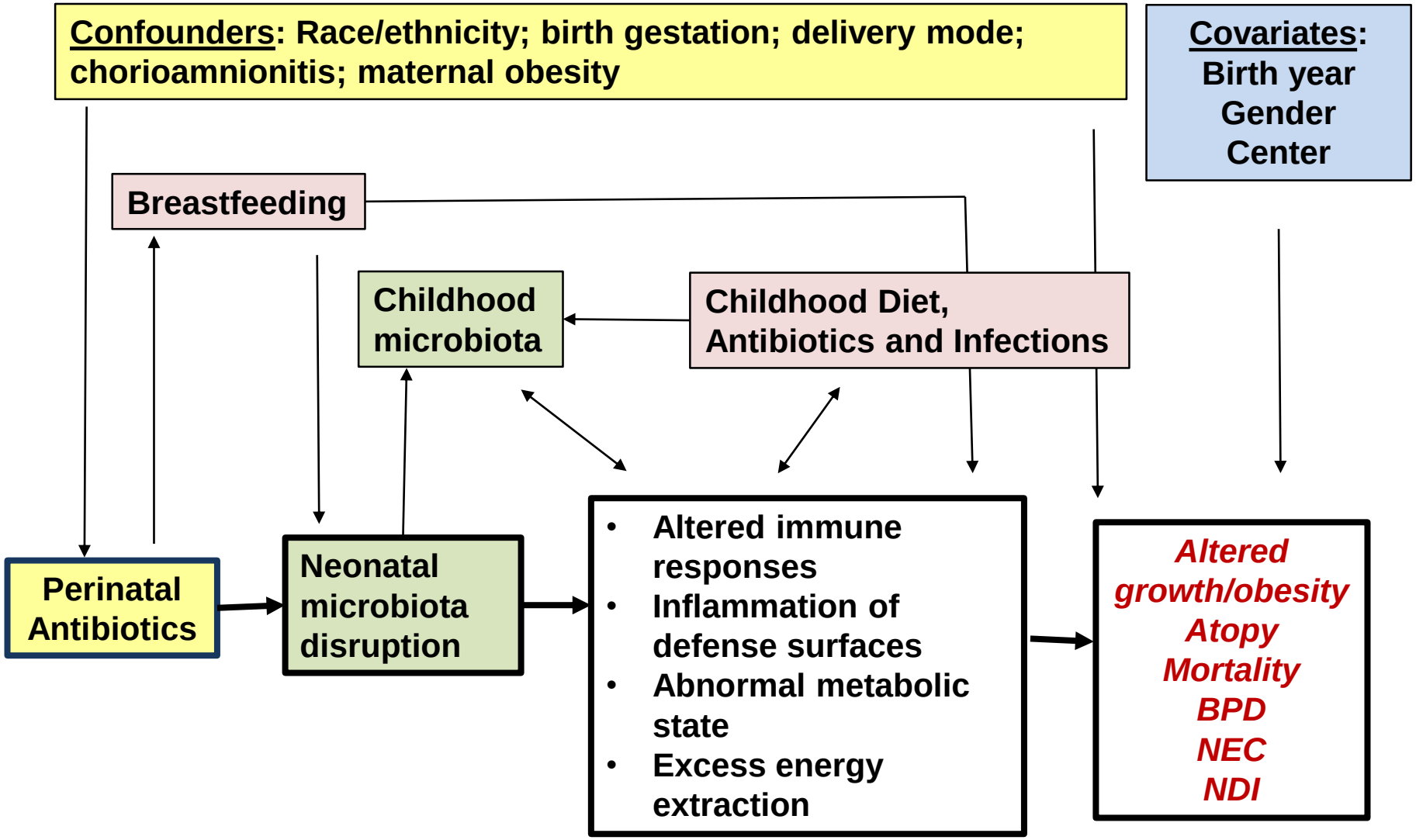
- Reduces biodiversity
- Reduces colonization with “normal flora”
- Promotes proliferation of pathogenic organisms
- Selects for antibiotic resistant organisms
- May promote pathologic immune responses leading to organ damage due to inflammation and altered growth and development





Patel and Denning (2015) *Pediatr Res;* Lal, et al (2016) *Sci Rpt*

Conceptual Model:
Perinatal Antibiotics and Infant/Child Outcomes



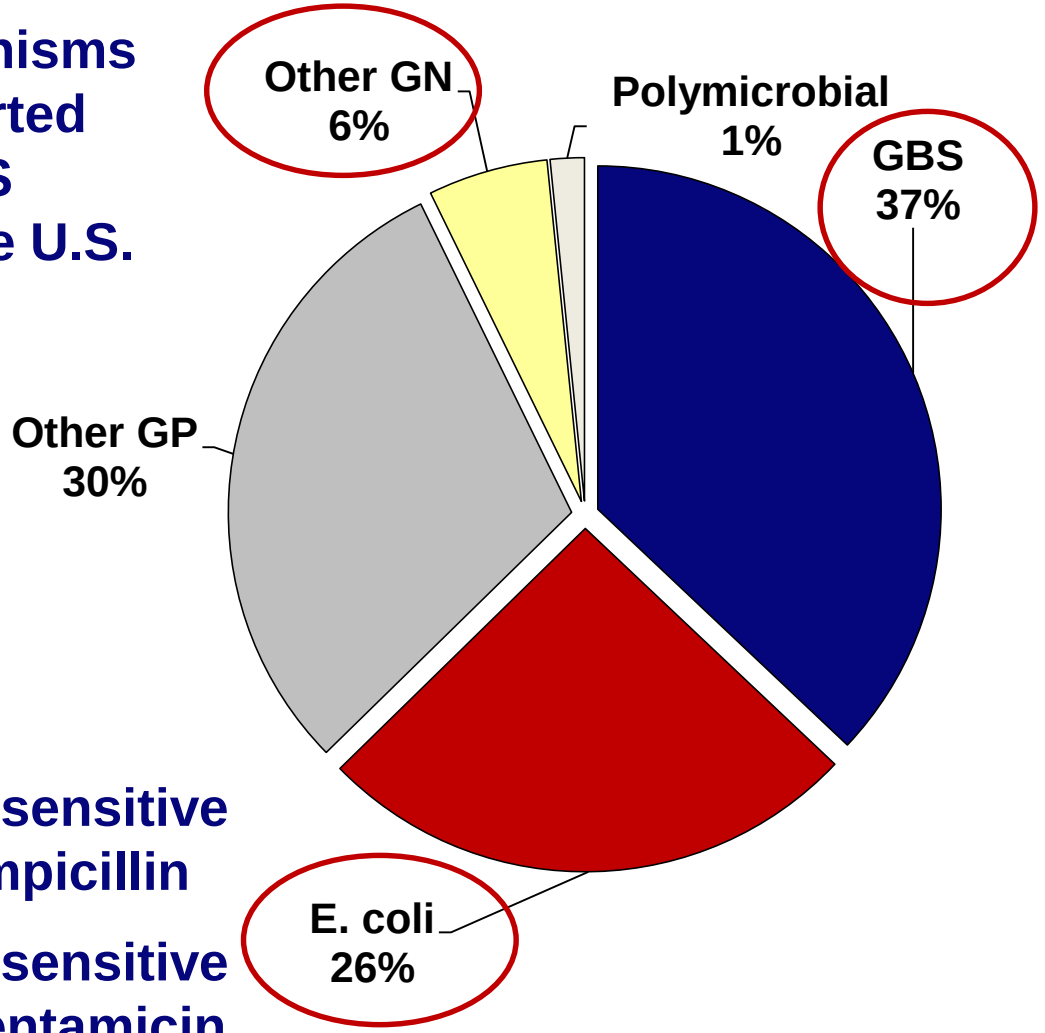
The Right Antibiotics

CPPID
CHOP/PENN PERINATAL
INFECTIOUS DISEASES

LEGES SINE MORIBUS VANAE

Antibiotic Susceptibilities

ESBL organisms rarely reported among EOS cases in the U.S.



All sensitive to ampicillin

34% sensitive to ampicillin

90% sensitive to gentamicin

U.S. Active Bacterial Core Surveillance

- **2005-2014**
- **~4,000,000 births**
- **1484 isolates**

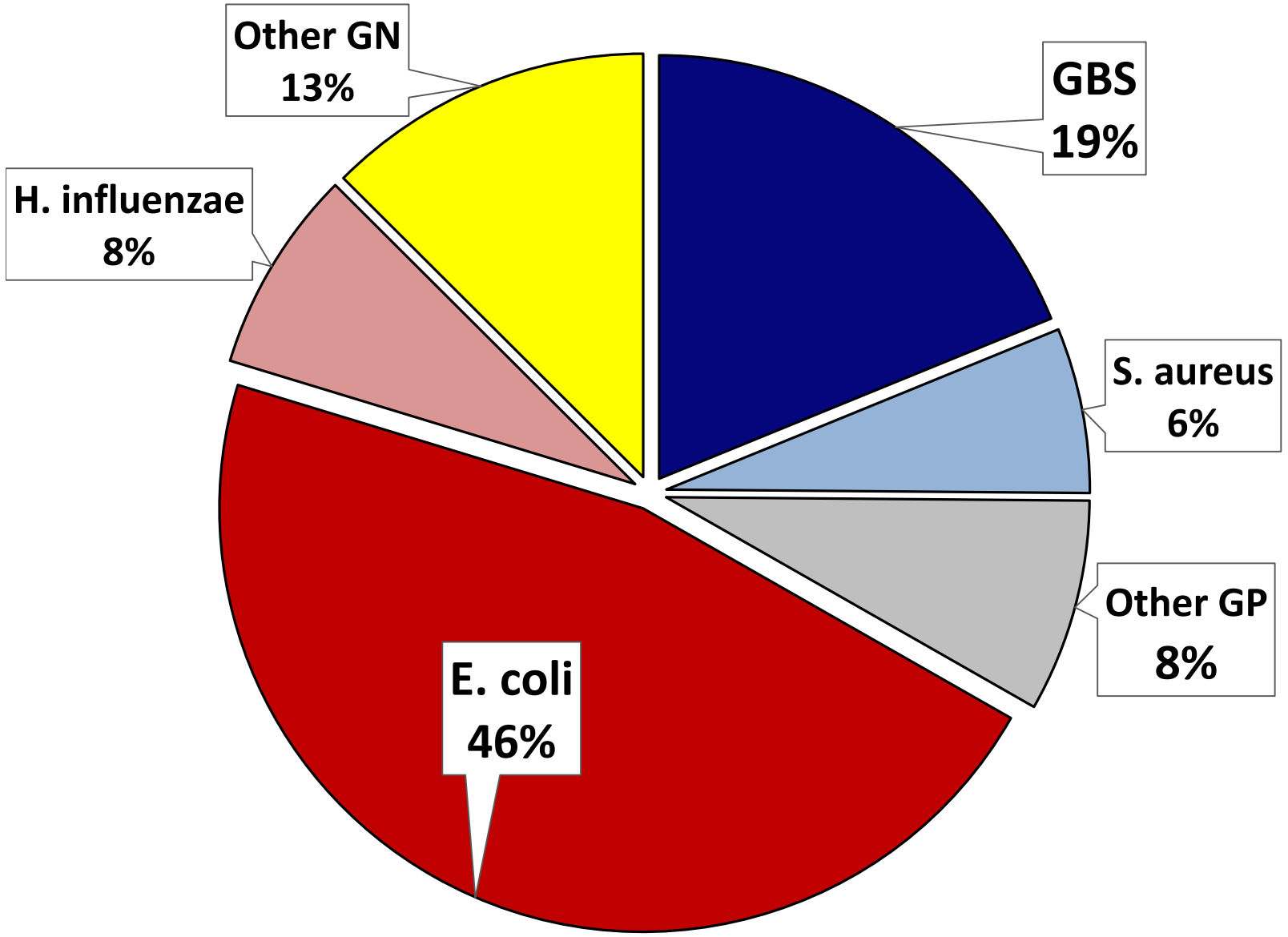
Schrag, et al. *Pediatrics 2016*

EOS Among VLBW Infants

- **Prospective observational study of 84,333 infants**
  - **753 centers participating in Vermont-Oxford Network**
  - **49 states and District of Columbia**
- **Gestational age 22-29 weeks (regardless of BW) *or***
- **Birth weight 401-1500 grams (regardless of GA)**
- **January 1, 2018 – December 31, 2019**

Flannery, et al. *Pediatrics* 2021

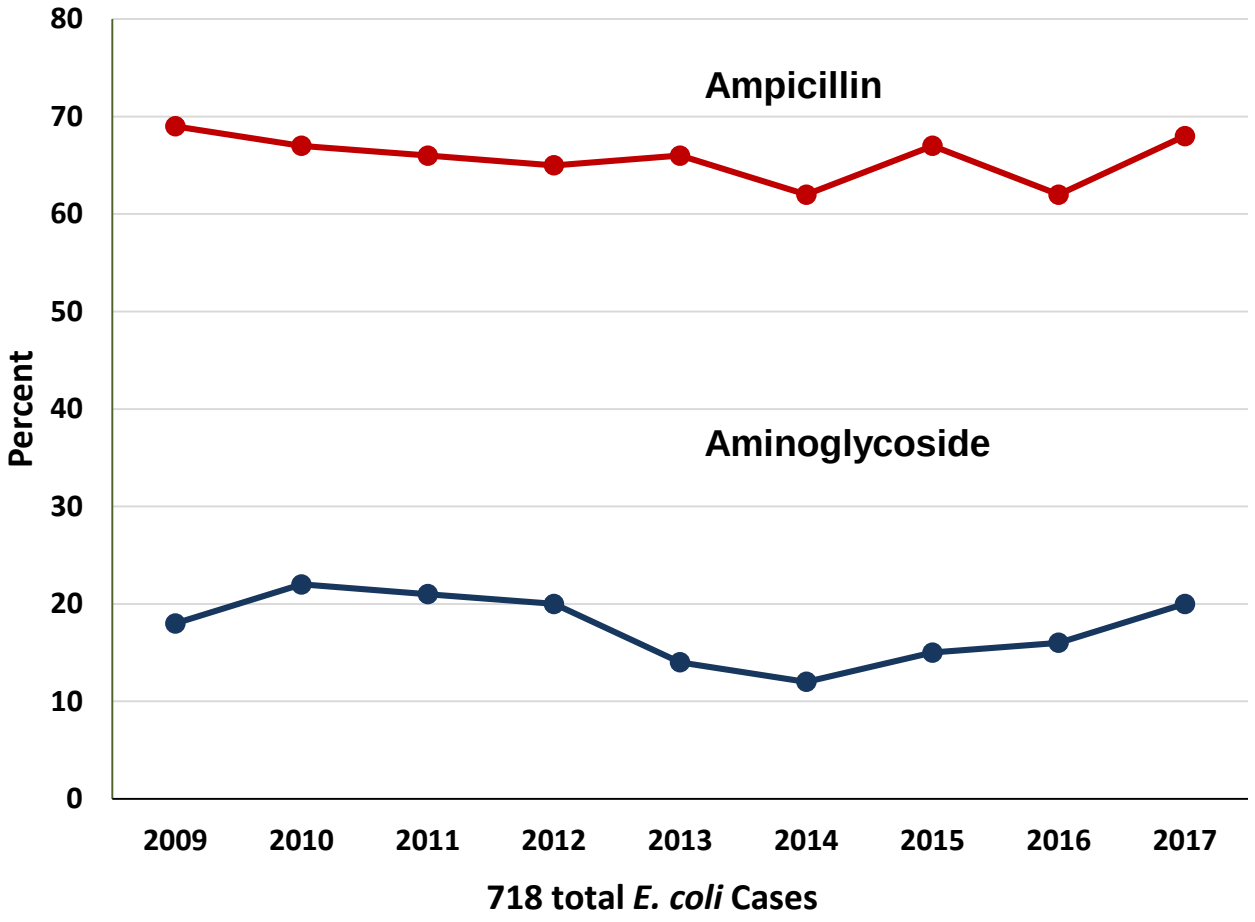
EOS Microbiology Among VLBW Infants



- 1158 isolates among 84,333 infants
- *E. coli* dominates
- HOWEVER, 1/3 of cases caused by an organism other than GBS or *E. coli*

Flannery, et al. *Pediatrics* 2021

Antibiotic Resistance in *E. coli*



Among 218 *E. coli* EOS cases

- **32% susceptible to both ampicillin and gentamicin**
- **58% resistant to ampicillin but sensitive to gentamicin**
- **10% resistant to both**
  - **12/89 (14%) among VLBWs**
  - **10/129 (8%) among infants with BW >1500 grams**

Flannery, et al. *JAMA Pediatrics* 2020

Other EOS Organisms and Antibiotic Susceptibility

Gram-positive	n	Gram-negative	n
Enterococcus	13	*Haemophilus*	9
Group A *Streptococcus*	9	*Klebsiella*	7
Viridans streptococci	7	*Morganella*	3
Streptococcus bovis	6	*Citrobacter*	1
Streptococcus sp.	5	*Enterobacter*	1
Streptococcus pneumoniae	3	Flavobacterium	1
CONS	2	*Proteus*	1
Listeria monocytogenes	3	*Pseudomonas*	1
Staphylococcus aureus	3	*E. coli* + other	3
Candida albicans	4	*Haemophilus* + other	1

Stoll et al. *JAMA Pediatrics* 2020; Flannery, et al. *Pediatr Infect Dis J* 2021; Puopolo et al. *Pediatrics* 2018

Other EOS Organisms and Antibiotic Susceptibility

Gram-positive	n	Gram-negative	n
Enterococcus	13	*Haemophilus*	9
Group A *Streptococcus*	9	*Klebsiella*	7
Viridans streptococci	7	*Morganella*	3
Streptococcus bovis	6	*Citrobacter*	1
Streptococcus sp.	5	*Enterobacter*	1
Streptococcus pneumoniae	3	Flavobacterium	1
CONS	2	*Proteus*	1
Listeria monocytogenes	3	*Pseudomonas*	1
Staphylococcus aureus	3	*E. coli* + other	3
Candida albicans	4	*Haemophilus* + other	1

- Ampicillin and gentamicin may not be effective empiric therapy for ~8% of isolates in NRN surveillance
- No single alternative would be effective in all cases
- ***Clinicians should use judgment to consider additional, broader-spectrum therapy until culture results are known***

Stoll et al. *JAMA Pediatrics* 2020; Flannery, et al. *Pediatr Infect Dis J* 2021; Puopolo et al. *Pediatrics* 2018

The Right Reasons

CPPID
CHOP/PENN PERINATAL INFECTIOUS DISEASES

LEGES SINE MORIBUS VANAE

Blood Culture Time to Positivity

- **“48-hour rule-out” based on daily examination of broth culture for visual turbidity and 12-hourly reviews of plate subcultures**
- **Current blood culture techniques rely on production of CO2 or change in gas pressure for continuous detection of bacterial growth**
  - **Optimized to detect very low levels of bacteremia**
  - **Neutralize antibiotics in circulation**

Pichichero and Todd (1979) *J Pediatr*

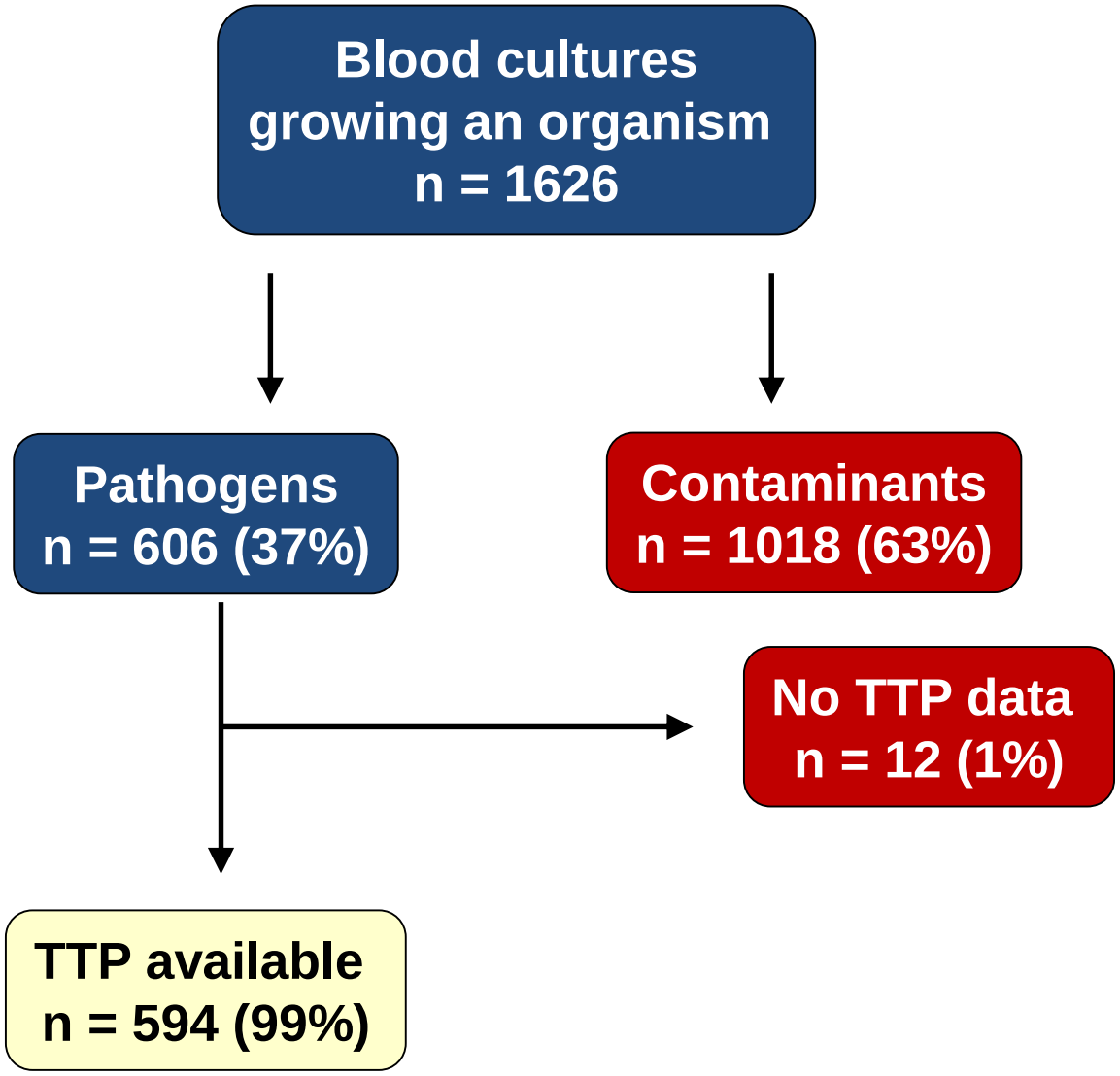
Blood Culture Time to Positivity

- **Study of time-to-positivity**
  - **Boston, Philadelphia, Northern California**
  - **Two different blood culture systems**
  - **Different laboratory services**
- **Study population consisted of a total 491,462 infants**
  - **71,345 blood cultures were obtained at <72 hours among the 429,442 infants born at 15 Kaiser-Permante Northern California centers, one Boston hospital and two Philadelphia hospitals (total culture number was not available for 2nd Boston hospital)**

Kuzniewicz, et al. (2020*) Pediatr Infect Dis J*

Blood Culture Time to Positivity

- **Boston, Philadelphia, Northern California 1993-2017**
- **Two different blood culture systems**
- **Total 491,462 infants / 72,000 blood cultures obtained at <72 hours among**



Kuzniewicz, et al. (2020) *Pediatr Infect Dis J*

Overall Time to Positivity

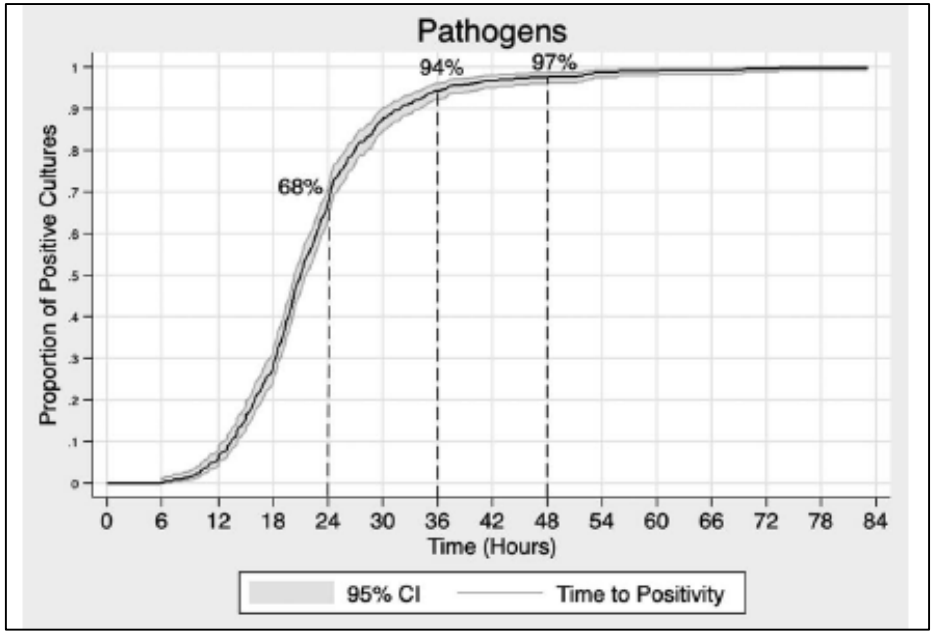


TABLE 1. Characteristics of Infants and Mothers, n = 594

Male, n (%)	302 (50.8)
Gestational age (weeks), median (IQR)	38 (34–40)
Gestational age (weeks), n (%)	
<28	74 (12.5)
28–31	51 (8.6)
32–34	45 (7.6)
≥35	424 (71.4)
Cesarean delivery, n (%)	124 (20.9)
Maternal intrapartum antibiotics, n (%)	195 (32.8)
Maternal GBS status, n (%)	
Positive	75 (12.6)
Negative	459 (77.3)
Unknown	60 (10.1)
Rupture of membranes ≥ 18 hours, n (%)	178 (30.0)
Hours after birth when culture was drawn, median (IQR)	1.4 (0.9–5.5)

- **68% positive by 24 hours**
- **94% positive by 36 hours**
- **97% positive by 48 hours**

Kuzniewicz, et al. (2020*) Pediatr Infect Dis J*

- **Longer TTP for contaminants**
- **Longer TTP at KPNC centers with off-site lab services**
- **NO difference in TTP by**
  - **organism**
  - **gestational age**
  - **culture system**
  - **whether or not mother received intrapartum antibiotics**

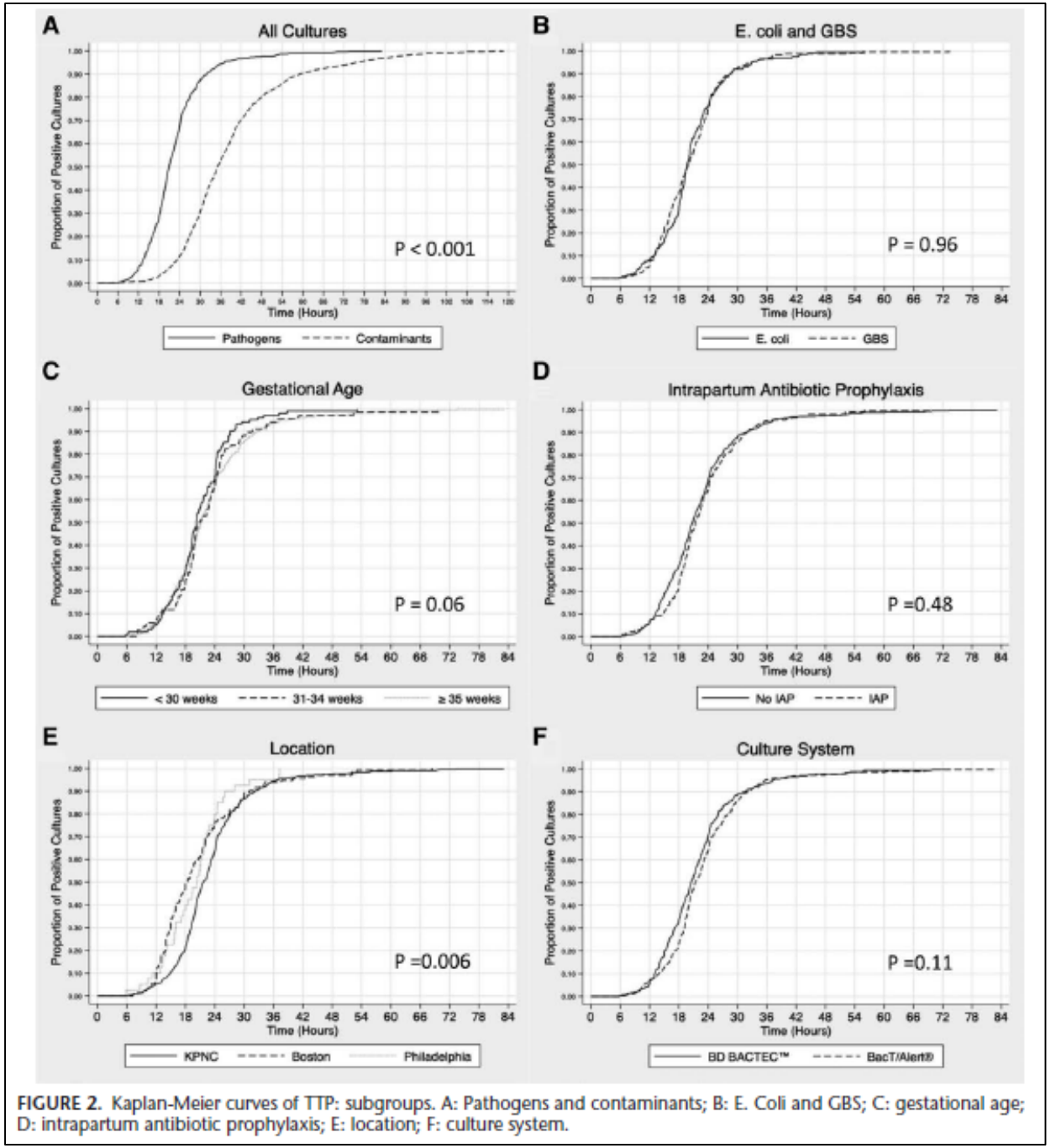


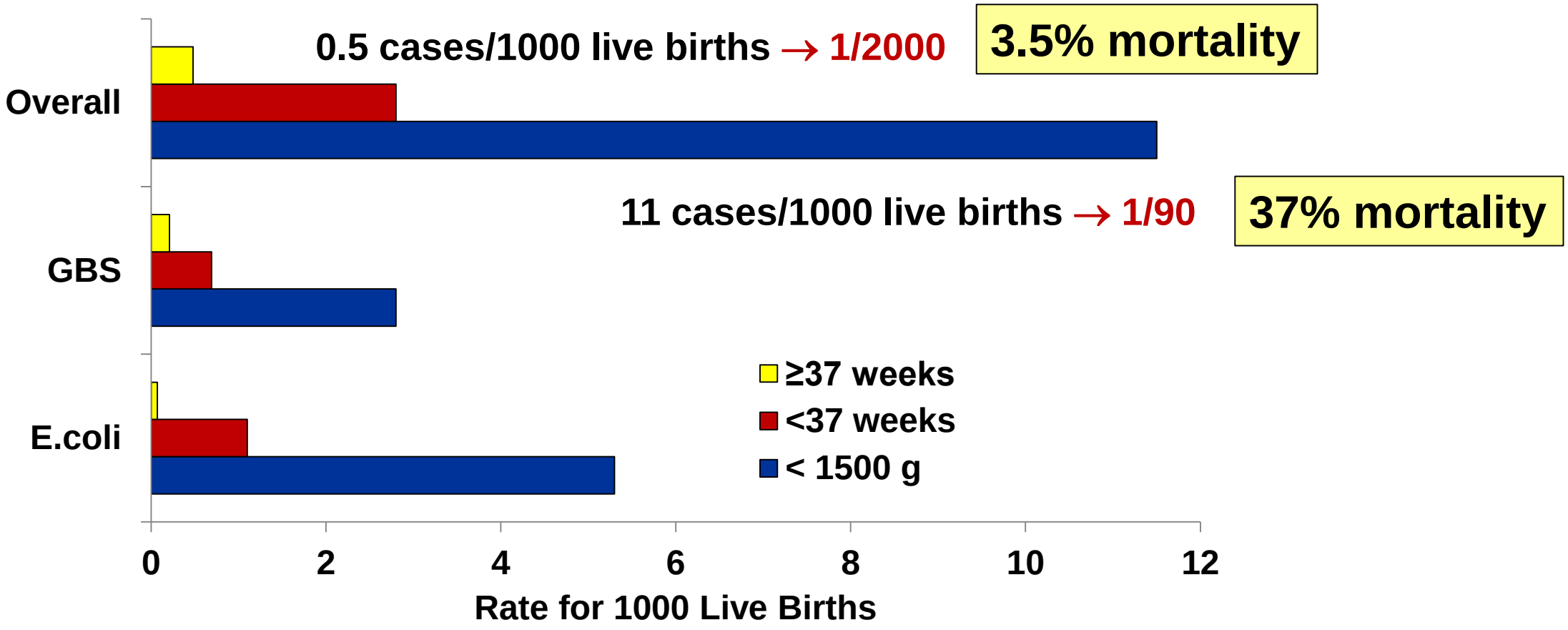
FIGURE 2. Kaplan-Meier curves of TTP: subgroups. A: Pathogens and contaminants; B: E. Coli and GBS; C: gestational age; D: intrapartum antibiotic prophylaxis; E: location; F: culture system.

Kuzniewicz, et al. (2020*) Pediatr Infect Dis J*

The Right Infants

CPPID
CHOP/PENN PERINATAL INFECTIOUS DISEASES

EOS Incidence ~20-fold Higher Among Preterm and VLBW Infants



Schrag, et al. *Pediatrics* 2016

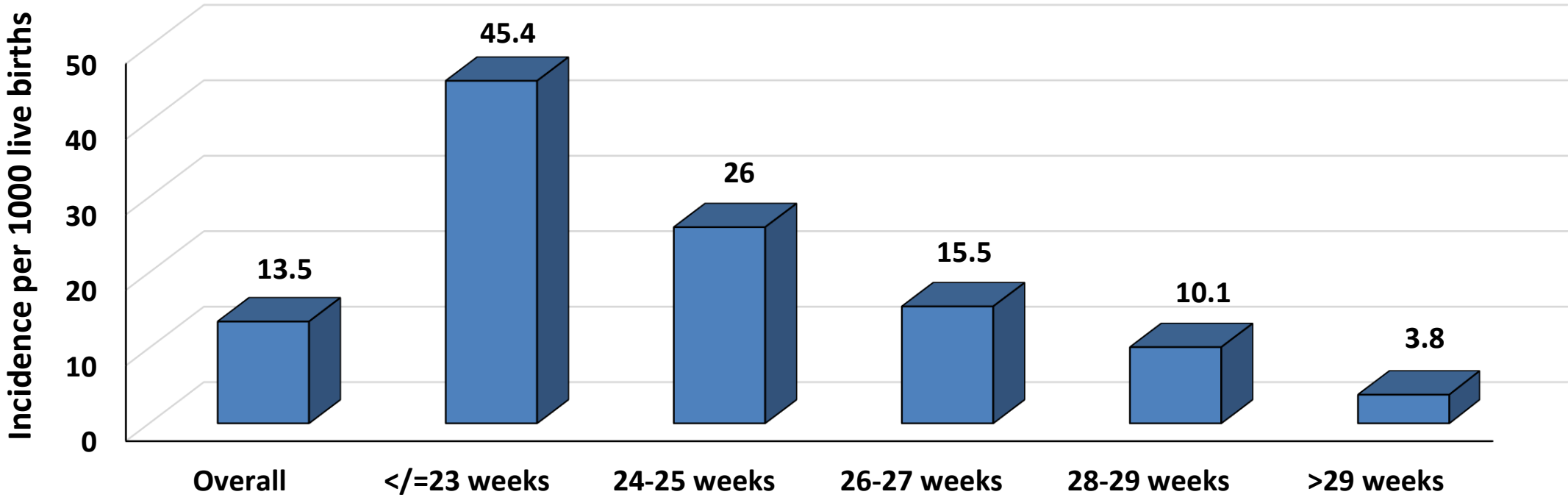
EOS Among VLBW Infants

- Prospective observational study of 84,333 infants
  - 753 centers participating in Vermont-Oxford Network
  - 49 states and District of Columbia
- Gestational age 22-29 weeks (regardless of BW) *or*
- Birth weight 401-1500 grams (regardless of GA)
- January 1, 2018 – December 31, 2019

Flannery, et al. *Pediatrics* 2021

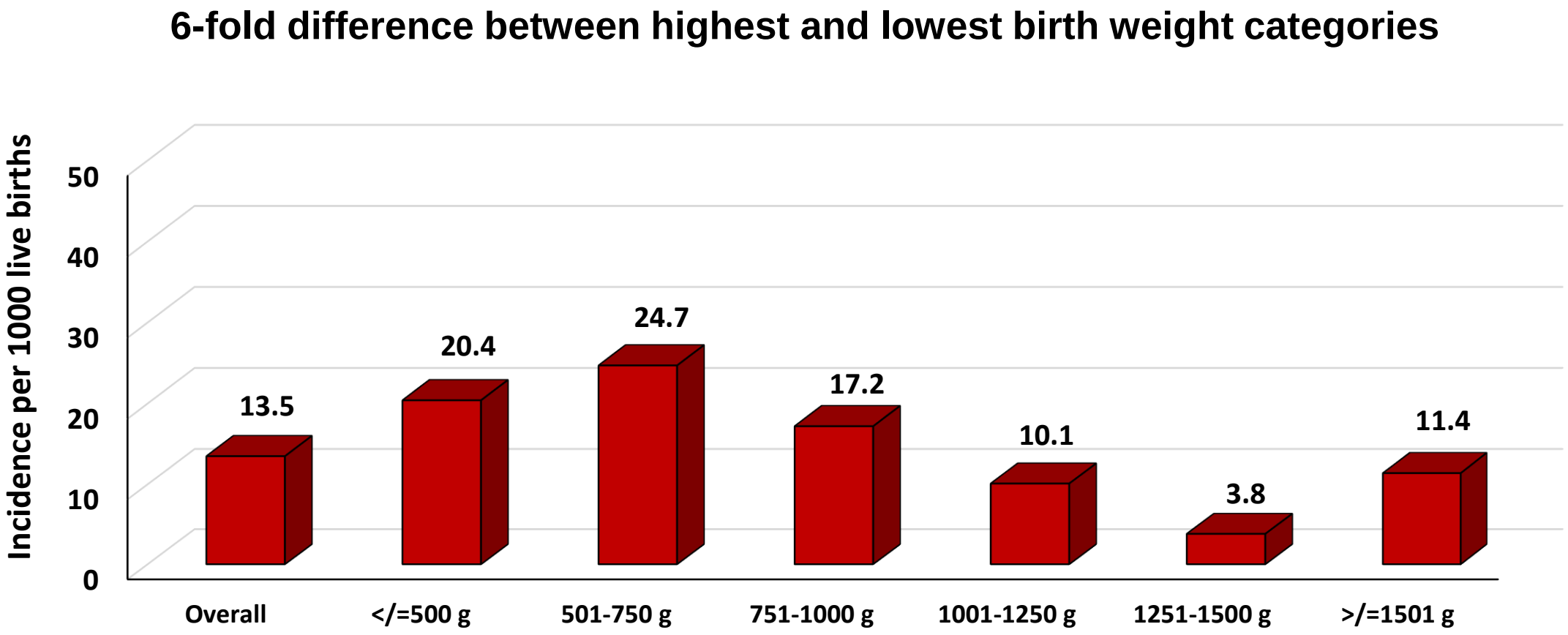
EOS Incidence and Mortality Varies by Gestational Age

12-fold difference between highest and lowest gestational age category



Flannery, et al. *Pediatrics* 2021

EOS Incidence and Mortality Varies Less by Birth Weight

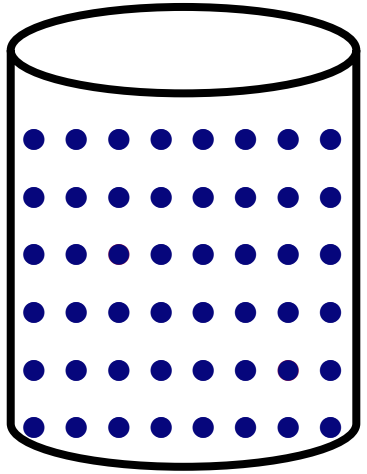


Flannery, et al. *Pediatrics* 2021

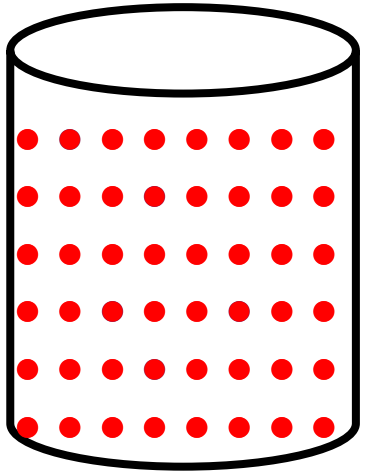
Could We Make a Sepsis Risk Calculator for Preterm Infants?

- **Bayesian approach to risk stratification makes some assumptions:**
  - **robust predictors derived from *cases***
    - ***Gestational age, preterm labor, preterm ROM, maternal intraamniotic infection, clinical instability***
  - **distinct prevalence in the *controls***
    - ***Everyone has risky GA; 2/3 born in setting of PTL or PPROM; maternal infection is suspected in all PTL/PPROM; most have clinical illness***
- **Room to differentiate**
  - **Baseline risk is 1:2000 → lots of room to adjust upward**
  - **Baseline risk is 1:90 → depending on your perspective, there may only be room to adjust downward**

Our Goal is Opposite that for Term Infants



Goal of EOS risk assessment among *term* infants is to determine who *should* receive empiric antibiotics



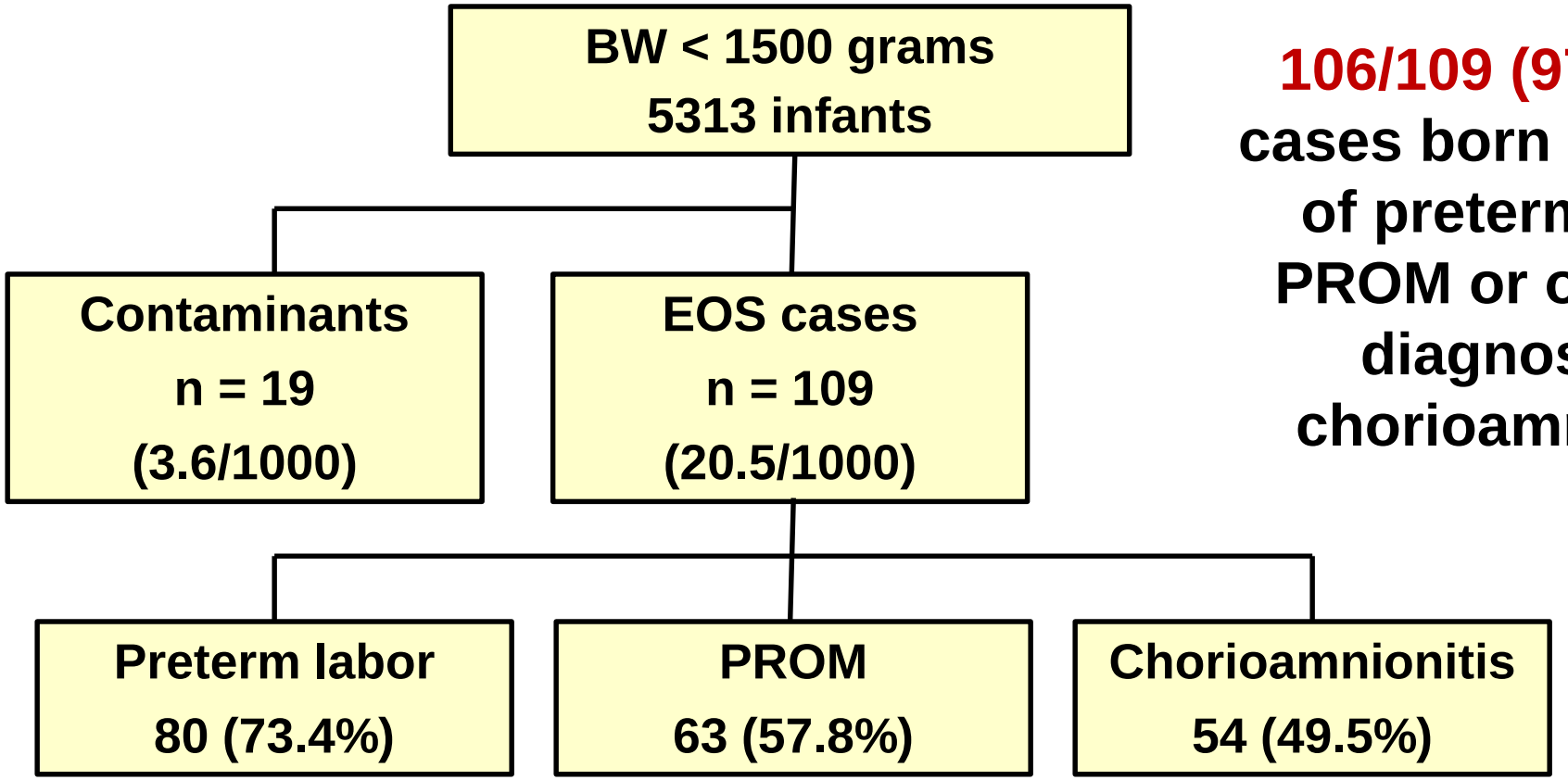
Goal of EOS risk assessment among *preterm* infants is to determine who might be *spared* empiric antibiotics– or at least, not subjected to prolonged culture-negative antibiotics

VLBW EOS Case Study

- Retrospective cohort study
- All live born infants with BW < 1500 grams
  - BWH 1990-2015
- Blood-culture proven bacterial or fungal infection occurring < 72 hours of age
- Detailed review of maternal and infant medical records and microbiology database

Mukhopadhyay and Puopolo (2017) *Pediatr Infect Dis J*

Delivery Characteristics of Cases



106/109 (97.2%) of cases born in setting of preterm labor, PROM or obstetric diagnosis of chorioamnionitis

Mukhopadhyay and Puopolo (2017) *Pediatr Infect Dis J*

Three Cases Occurred Without these Characteristics

- **In 2 cases, otherwise uncomplicated pregnancy presented with decreased fetal movement, with emergent delivery for poor fetal testing**
  - **Both cases grew *Listeria monocytogenes***
- **Final case of "EOS" was likely a contaminant**
  - ***Streptococcus mitis* grew in 1/2 culture bottles**
  - **Bacteremia cleared despite organism resistance to both administered antibiotics (ampicillin and gentamicin)**

Mukhopadhyay and Puopolo (2017) *Pediatr Infect Dis J*

What is the Risk in the Absence of these Characteristics?

- **Linked neonatal data with maternal ICD-9 codes (1999-2012)**
  - **2748 mother-infant pairs**
  - **605 (22%) with ICD-9 code for pre-eclampsia and delivery by C-section**

What is the Risk in the Absence of these Characteristics?

Linked neonatal data with maternal ICD-9 codes (1999-2012) for pre-eclampsia, chorioamnionitis and delivery by C-section

	PET/no Risk Factors (n = 605)	Others (n = 2143)	p-value
Blood culture, N (%)	591 (99.8)	2019 (99.7)	0.52
Antibiotics, N (%)	508 (85.3)	1990 (94.5)	<0.001
EOS cases, N (cases per 1000 live births)	1 (1.7)	45 (21.0)	0.001

Overall EOS rate: 16.7/1000 live births

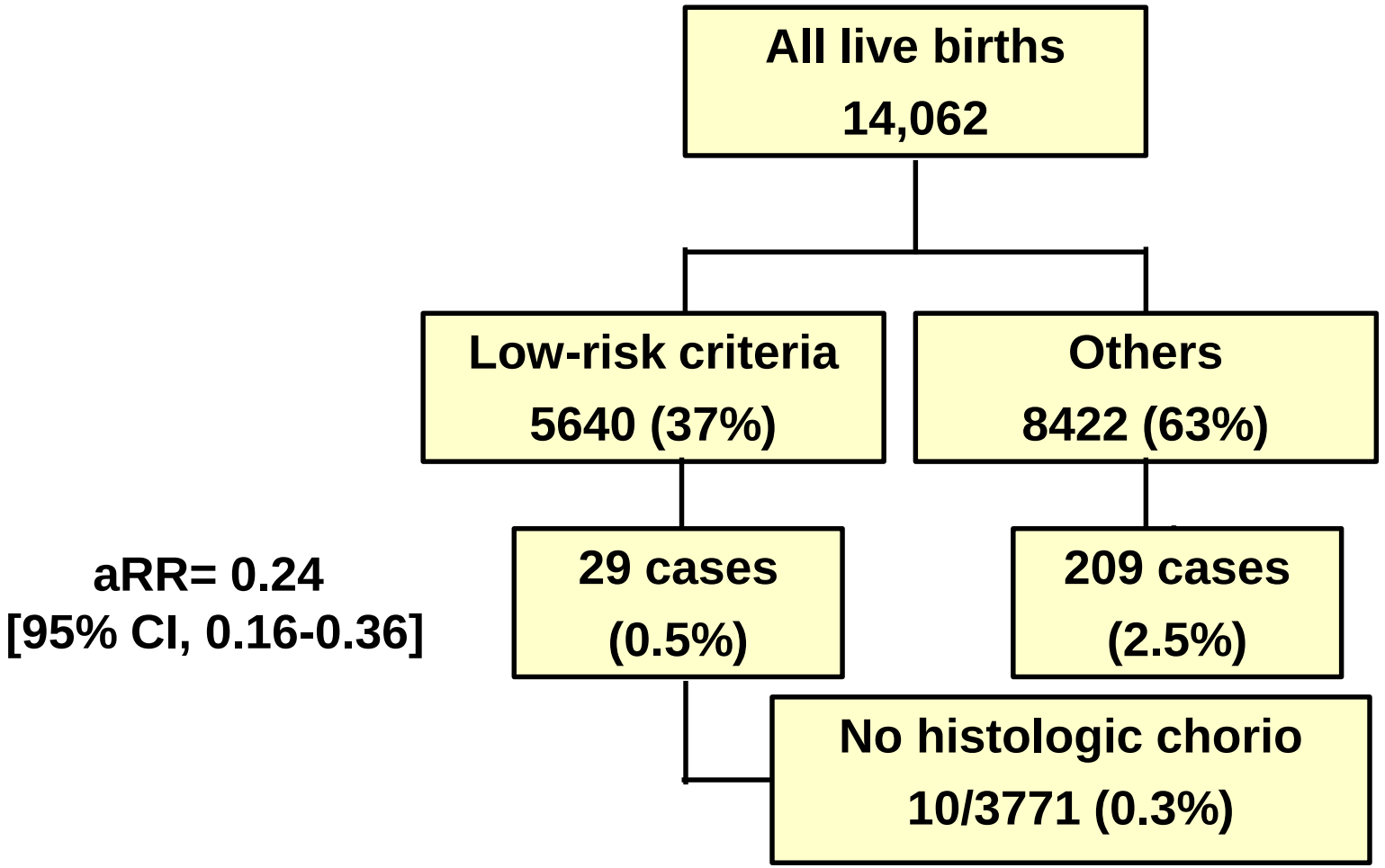
Mukhopadhyay and Puopolo (2017) *Pediatr Infect Dis J*

Can Delivery Characteristics Predict EOS Risk? Neonatal Research Network

- Infants born GA 22 0/7 -28 0/7 weeks and surviving > 12 hours
  - NRN centers 2006-2014
- NRN dataset does not collect “preterm labor”
- Hypothesized low-risk criteria
  - Birth by C-section
  - ROM at delivery
  - No obstetric diagnosis of chorioamnionitis

Puopolo, et al. *Pediatrics* 2017

Delivery Characteristics of ELBW Cases



Impact of Prolonged Antibiotics

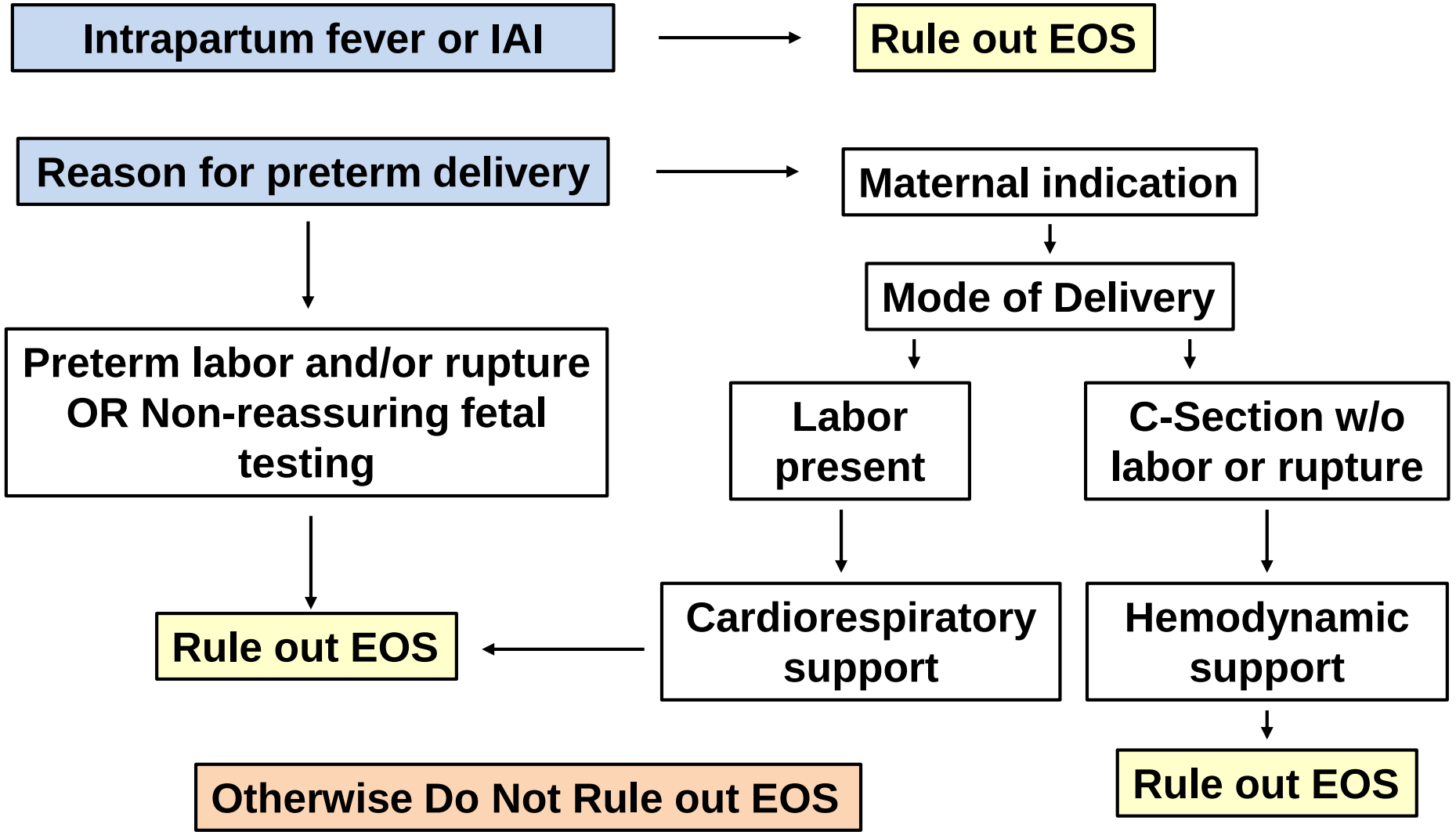
- **Prolonged antibiotics (≥ 5 days)**
  - **37.1% of low-risk group (66:1)**
  - **47.4% of others (19:1)**
- **Among low-risk infants, comparing those given or not give prolonged antibiotics**
  - **Death: aRR (95% CI): 1.52 (1.28-1.80)**
  - **BPD: aRR (95%CI): 1.28 (1.20-1.36)**

Puopolo, et al. *Pediatrics* 2017

Can We Do Better for Preterm Infants?

- **Can we *discriminate* better between at-risk infants?**
  - **Incidence of EOS markedly lower among preterm infants born in the absence of premature rupture of membranes, preterm labor or concern for chorioamnionitis**
- **Could we safely evaluate *fewer* infants and still identify the infected ones?**
  - **~25% of VLBW infants are at such low risk of EOS we could refrain from initiation of empiric antibiotics, or at least extension in the absence of culture-confirmed infection**

Preterm EOS Guideline Based on Delivery Criteria



Single Center Pre/Post Implementation Analysis

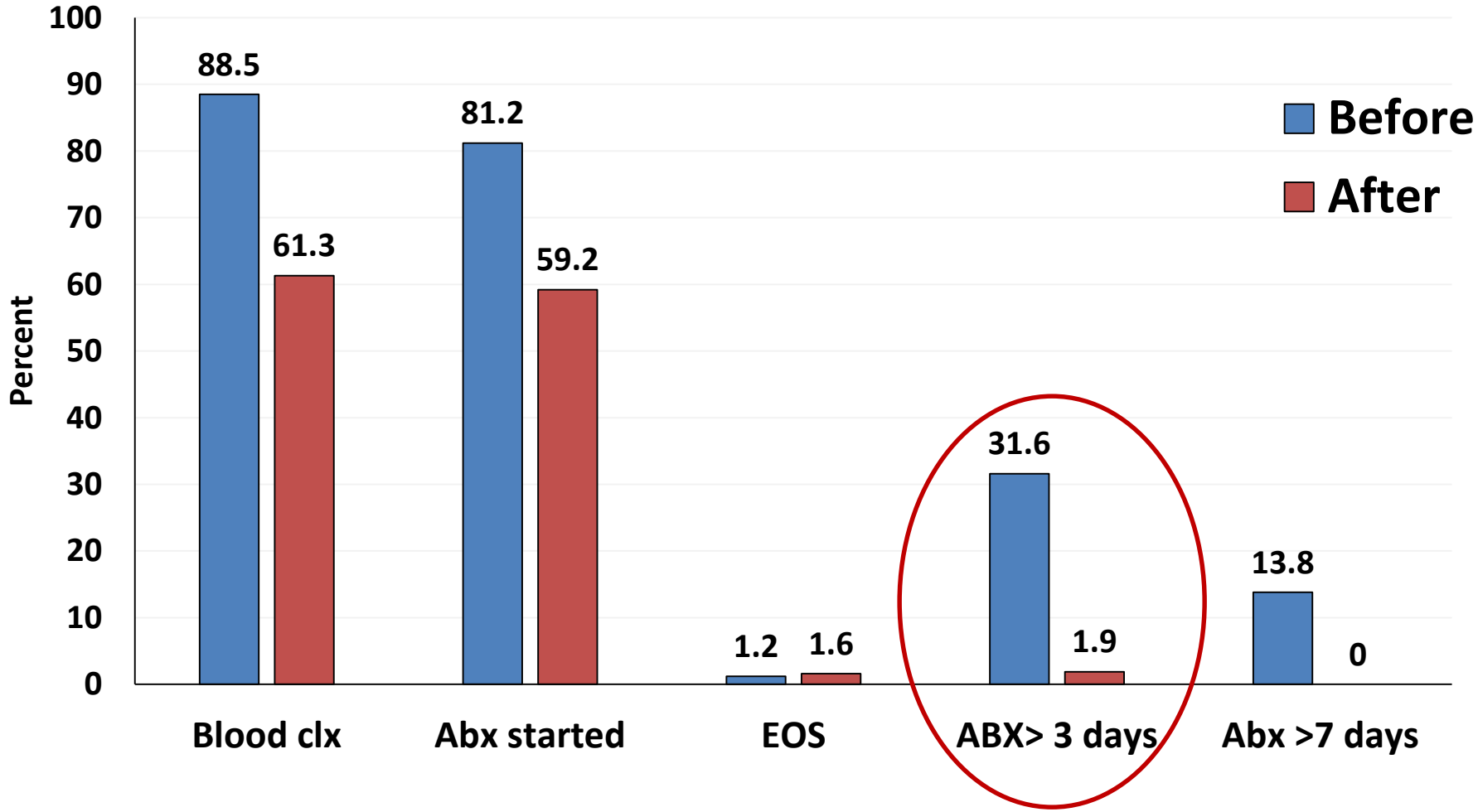
- Guideline discussed from 2015
- Formally implemented April 2017
- Compared antibiotic initiation and balance measures
  - Pre-implementation: 01/01/2009-03/31/2017 (n=727 infants)
  - Post-implementation: 04/01/2017 to 01/31/2020 (n=191 infants)
- Set balance measures
- Study approved with waiver of consent

Garber, et al. *J Perinatol* 2021

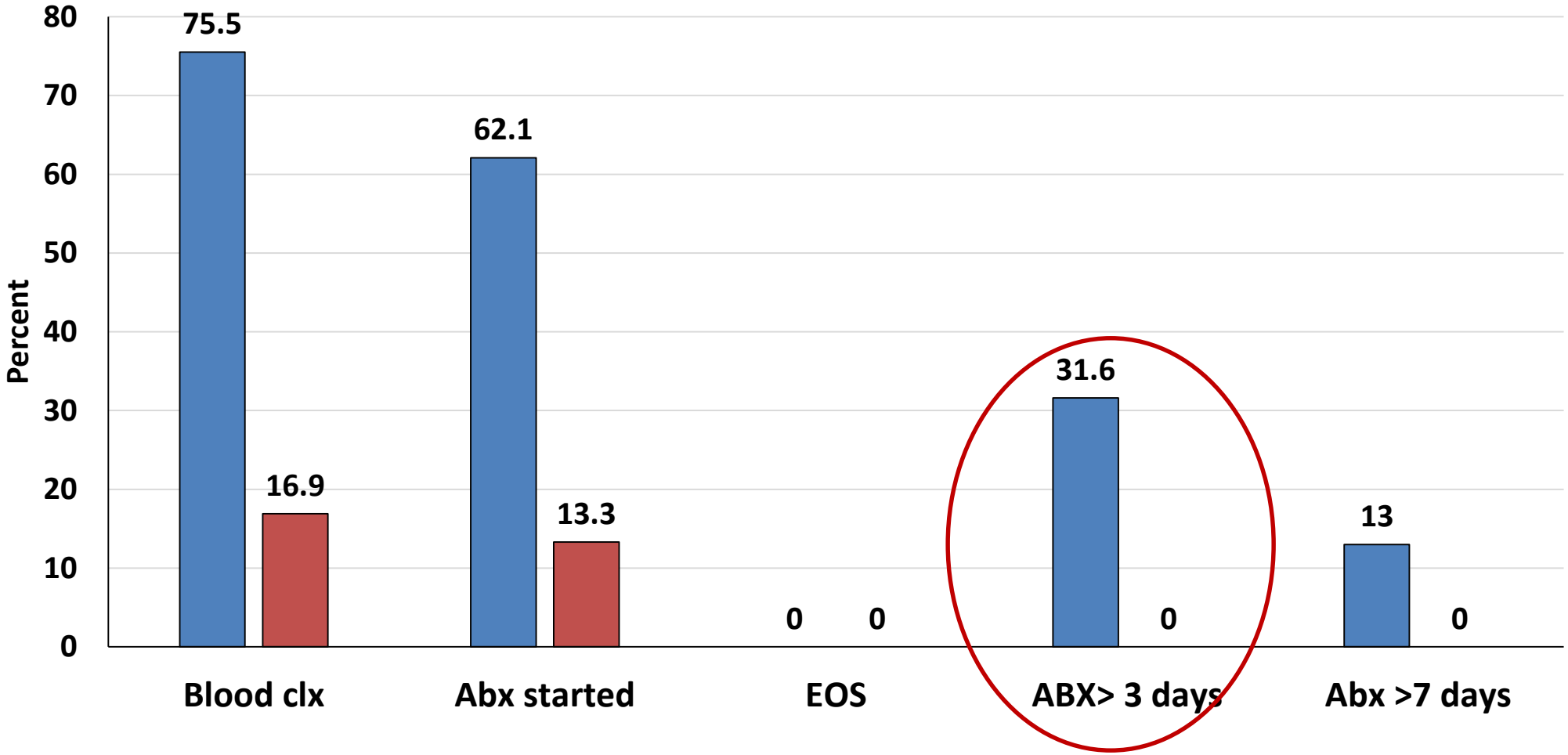
Demographics of Study Cohorts

	Pre n = 727	Post n = 191	p-value
BW (grams), mean (SD)	1056 (298)	1046 (312)	0.70
• ELBW, n (%)	297 (40.9)	85 (44.5)	0.36
GA (weeks), median (IQR)	28 4/7 (26 3/7 – 30 4/7)	28 5/7 (26 3/7 – 30 4/7)	0.98
Female, n (%)	365 (50.2)	107 (56.0)	0.15
Multiple birth, n (%)	233 (32.1)	41 (21.5)	0.004
Cesarean delivery, n (%)	564 (77.6)	137 (71.7)	0.09
ROM at delivery, n (%)	419 (57.6)	128 (67.0)	0.02
Any labor (spontaneous or induced), n (%)	425 (58.5)	92 (48.2)	0.01
Infants meeting low-risk criteria, n (%)	298 (41.0)	83 (43.5)	0.54

Impact Among All VLBW Infants



Impact Among Low-Risk VLBW Infants



Guideline Associated With Decreased Antibiotic Initiation Among ELBW Infants

	ELBW Infants		
	Pre	Post	p-value
Antibiotic initiation, all ELBW, n (%)	281/297 (94.6)	56/85 (65.9)	<0.001
Antibiotic initiation, low-risk ELBW, n (%)	105/120 (87.5)	8/36 (22.2)	<0.001

Balance Measures: Day 4-7 After Birth

	All VLBW Infants			Low-Risk VLBW Infants		
	Pre n = 727	Post n = 191	p-value	Pre n = 298	Post n = 83	p-value
Blood culture obtained, n (%)	130 (17.9)	25 (13.1)	0.12	61 (20.5)	9 (10.8)	0.045
Antibiotic initiation, n (%)	67 (9.2)	22 (11.5)	0.34	34 (11.4)	9 (10.8)	0.89
Blood culture +pathogen, n (%)	17 (2.3)	3 (1.6)	0.52	6 (2.0)	1 (1.2)	0.63
Deceased/Transfer by 7 days, n (%)	36 (5.0)	9 (4.7)	0.89	11 (3.7)	2 (2.4)	0.57

No significant differences in antibiotic initiation, infection or death/transfer later in the first week after birth

American Academy of Pediatrics Guidance

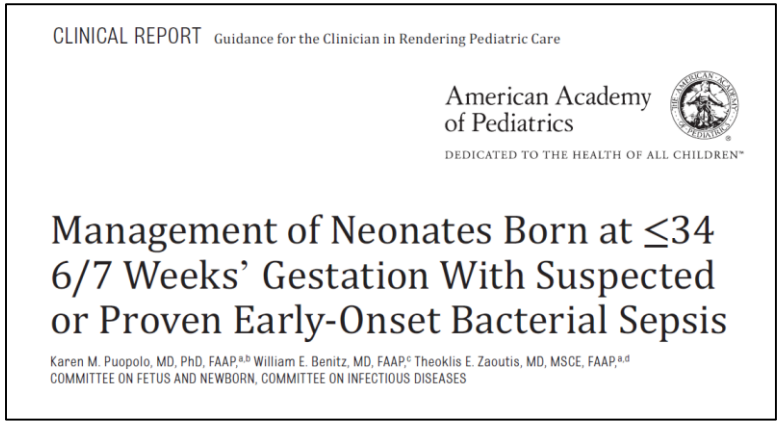

CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Management of Neonates Born at ≥35 0/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis

Karen M. Puopolo, MD, PhD, FAAP,[a,b] William E. Benitz, MD, FAAP,[c] Theoklis E. Zaoutis, MD, MSCE, FAAP,[a,d] COMMITTEE ON FETUS AND NEWBORN, COMMITTEE ON INFECTIOUS DISEASES


CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Management of Neonates Born at ≤34 6/7 Weeks' Gestation With Suspected or Proven Early-Onset Bacterial Sepsis

Karen M. Puopolo, MD, PhD, FAAP,[a,b] William E. Benitz, MD, FAAP,[c] Theoklis E. Zaoutis, MD, MSCE, FAAP,[a,d] COMMITTEE ON FETUS AND NEWBORN, COMMITTEE ON INFECTIOUS DISEASES


CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Management of Infants at Risk for Group B Streptococcal Disease

Karen M. Puopolo, MD, PhD, FAAP,[a,b] Ruth Lynfield, MD, FAAP,[c] James J. Cummings, MD, MS, FAAP,[d] COMMITTEE ON FETUS AND NEWBORN, COMMITTEE ON INFECTIOUS DISEASES

- **Clinical Reports published in December 2018 and August 2019 editions of *Pediatrics***
- **Recommend limited use of laboratory tests**
- **Endorse use of one of 3 methods for term risk stratification**
- **Endorse concept and use of "low-risk" preterm infant**

Summary

- **Understanding the impact of frequent antibiotic exposures can motivate preterm NICU antibiotic stewardship**
- **Data on epidemiology, microbiology and blood culture performance can inform antibiotic use**
- **Delivery characteristics can identify preterm infants who can be safely spared antibiotic initiation shortly after birth**
- ***Incorporating stewardship into national professional guidelines will (hopefully) mediate national change***

Thank you!

Questions?

Karen.Puopolo@pennmedicine.upenn.edu

puopolok@chop.edu