

Improving Antimicrobial Use in the NICU

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Outline of Talk

- Antimicrobial Stewardship
- *CDC 12 Step Program to Prevent Antimicrobial Resistance among Hospitalized Children*
- Antimicrobial Stewardship in Pediatrics
- Pilot Study conducted in NICUs
- NIH-funded iNAP study

Definition of Antimicrobial Stewardship

“The optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection with minimal toxicity to the patient and minimal impact on subsequent resistance.”



Owens RC, Pharmacotherapy 2004

Antimicrobial Stewardship: Safety and Quality

- Dosing errors
- Inadequate treatment
- Toxicity
- Emergence of resistance
- Emergence of pathogens, e.g., *C. difficile* colitis



Adverse Consequences of Antibiotic Use in NICU Population

- *Hypothesis*: 3rd generation cephalosporins and carbapenems risk factor for invasive candidiasis.
- Cohort study: 12 NICUs conducted from 1998-2001
- Subjects: 3,722 ELBW infants \geq 72 hours of age
- RESULTS
 - Overall incidence candidiasis 7.7% (2.4%-20.4% per site)
 - Exposure to broad-spectrum antibiotics
 - ↑ candidiasis
 - OR: 2.2 (CI₉₅: 1.4-3.3)

Cotton CM et al. Pediatric 2006

Antibiotic Use in NICU Population

- One month cohort study, 75% of neonates received antibiotics within first 48 hrs of life. [Fonesca SN 2004]
- National point prevalence study in 29 NICUs, 43% of infants receiving antimicrobials on survey date. [Grohskopf LA 2005]
- Few national guidelines
- Antibiotics often initiated for non-specific signs and symptoms
- Opportunities for stewardship

GUIDELINES

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,¹ Robert C. Owens,² John E. McGowan, Jr.,³ Dale N. Gerding,⁴ Robert A. Weinstein,⁵ John P. Burke,⁶ W. Charles Huskins,⁷ David L. Paterson,⁸ Neil O. Fishman,⁹ Christopher F. Carpenter,¹⁰ P. J. Brennan,⁹ Marianne Billeter,¹¹ and Thomas M. Hooton¹²

¹Harborview Medical Center and the University of Washington, Seattle; ²Maine Medical Center, Portland; ³Emory University, Atlanta, Georgia; ⁴Hines Veterans Affairs Hospital and Loyola University Stritch School of Medicine, Hines, and ⁵Stroger (Cook County) Hospital and Rush University Medical Center, Chicago, Illinois; ⁶University of Utah, Salt Lake City; ⁷Mayo Clinic College of Medicine, Rochester, Minnesota; ⁸University of Pittsburgh Medical Center, Pittsburgh, and ⁹University of Pennsylvania, Philadelphia, Pennsylvania; ¹⁰William Beaumont Hospital, Royal Oak, Michigan; ¹¹Ochsner Health System, New Orleans, Louisiana; and ¹²University of Miami, Miami, Florida

Clin Infect Dis 2007

Components of Antimicrobial Stewardship Programs

- Core interdisciplinary team
- Content expertise from stake holders
- Buy-in from prescribers
- Collaboration between team, hospital epidemiology, Pharmacy & Therapeutics committee, and Clinical Microbiology Lab
- Support of administration and medical leadership

SHEA and IDSA “Best-practice” Recommendations

- Formulary restrictions and pre-authorization
- Guidelines and clinical pathways
- Dose optimization
- Prospective audit with intervention and feedback

Formulary Restrictions and Pre-authorization

- Drug approvals by Infectious Diseases physicians or PharmD's
- Restricted drugs at start of use

Guidelines and Clinical Pathways

- Develop evidence-based guidelines
 - Incorporate local epidemiology and antimicrobial resistance
 - Use national guidelines when available and appropriate
- Disseminate guidelines
- *Education **will** improve acceptance of stewardship program*
- *Education **will not** lead to sustained practice changes*

Audits, Intervention, Feedback

- Academic Detailing/ Prescriber Report Cards
- Antimicrobial order forms
- Computerized order entry
- Clinical decision support
- Computer-based surveillance
 - antimicrobial usage
 - resistance
 - hospital-acquired infections
 - adverse drug events

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Key Prevention Strategies for CDC 12 Step Program to Prevent Antibiotic Resistance in Hospitalized Children



- **Prevent infection**
- **Diagnose and treat infection effectively**
- **Use antimicrobials wisely**
- **Prevent transmission**

Clinicians hold the solution!



Campaign to Prevent Antimicrobial Resistance in Healthcare Settings

12 Steps to Prevent Antimicrobial Resistance: Hospitalized Children

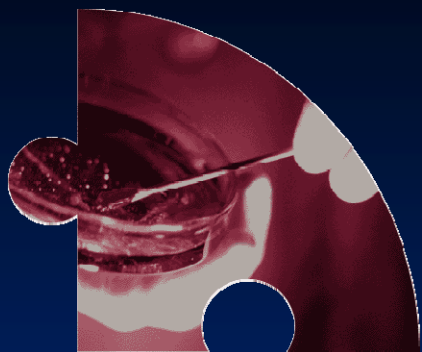
- 12 Hand hygiene
- 11 Infection control
- 10 Stop treatment
- 9 Know when to say "no"
- 8 Don't treat colonization
- 7 Use local data
- 6 Practice antimicrobial control
- 5 Access the experts
- 4 Target the pathogen
- 3 Use appropriate diagnostic methods
- 2 Get the catheters out
- 1 Vaccinate

Prevent Transmission

Use Antimicrobials Wisely

Diagnose & Treat Effectively

Prevent Infections



Diagnose & Treat Infections Effectively

Step 3: Use Appropriate Methods for Diagnosis

Fact :

Appropriate blood culture methods improves the reliability of results.

Actions :

- ✓ Use appropriate skin preparation
- ✓ Obtain at least 2 blood cultures
- ✓ Obtain at least 1 cc per bottle



Use Antimicrobials Wisely

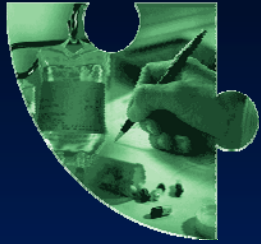
Step 9: Know when to say “no”

Fact:

Broad spectrum antibiotics such as vancomycin, extended-spectrum cephalosporins, and carbapenems overuse promotes emergence, selection, and spread of resistant pathogens.

Actions:

- ✓ Utilize antimicrobial stewardship
- ✓ Avoid routine use of these agents



Use Antimicrobials Wisely

Step 10: Stop antimicrobial treatment

Fact:

Failure to stop unnecessary antimicrobial treatment contributes to overuse and resistance.

Actions:

- ✓ Stop if cultures are negative and infection unlikely
- ✓ Stop when infection cured
- ✓ Stop if infection not diagnosed

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Systematic Review

- Studies of antibiotic stewardship conducted in pediatric populations
- Primary outcomes
 - Antibiotic use
 - Antimicrobial resistance

Patel S. et al, Pediatric Infect Dis J 2007

Antimicrobial Stewardship Studies

Intervention (n)	Setting	Primary outcome	Findings
Focused Educ (n=8)	6 out-pt. 2 in-pt.	Prescribing rates	8 improved prescribing rates
Dynamic Educ (n=4)	2 out-pt. 2 in-pt.	Prescribing rates	2 improved prescribing rates
Parent Educ (n=4)	4 out-pt.	Prescribing rates	2 improved prescribing rates
Restriction (n=6)	5 ICU	Colonization/ infection	3 decreased resistance
Ancillary tests (n=6)	4 NICU 2 in-pt.	Prescribing rates Clinical outcomes	6 decreased usage

Limitations of Current Studies

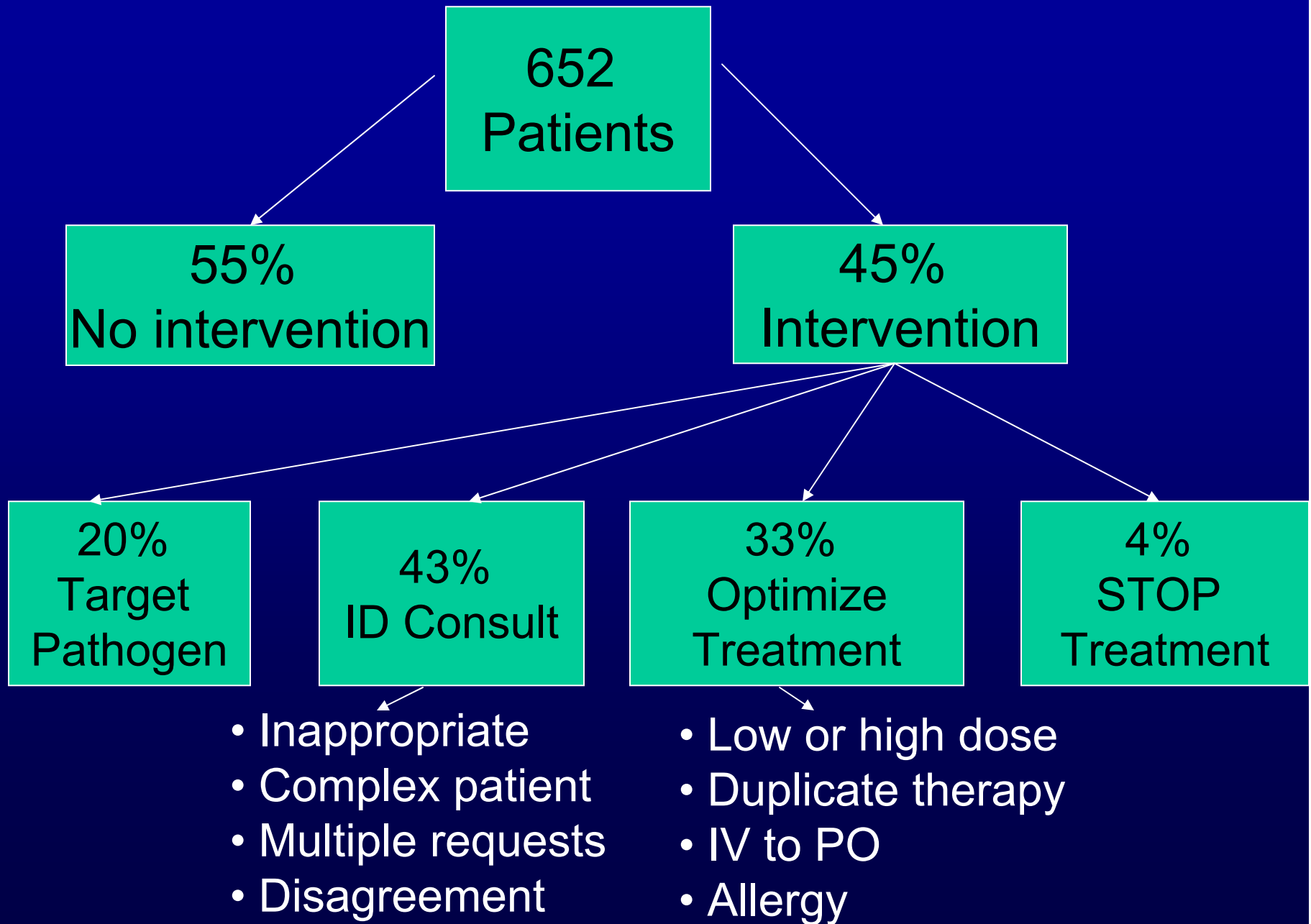
- Study design
 - Lack standardized study design
 - Inadequate descriptions of pre-/ post- intervention groups
 - Potential contamination between groups
- Interventions
 - Adherence to interventions not always measured
 - Multiple interventions used together
 - May be subversion of system
- Outcomes
 - Few direct measures of impact on antimicrobial resistance
 - Inadequate power
- Analysis
 - Inadequate pre-intervention data for time series
 - Sustainability not determined

Antimicrobial Stewardship Program – Children's Hospital of Philadelphia

- April – July 2005
- 652 patient requests
- 856 antibiotics requested
- 5-6 requests per day
- Most commonly requested:
 - vancomycin
 - 3rd generation cephalosporins

Metjian et al. Pediatr Infect Dis J 2008

ASP - CHOP



ASP-CHOP

Safety	Chart review 62 patients: <ul style="list-style-type: none">• 3 developed infection not covered by ASP recommendations or clinician request
Compliance	Overall 89% complied with ASP recommendations <ul style="list-style-type: none">• 94% complied to broaden• 96% complied to narrow• 73% complied with stop
Cost saving	\$50,090 saved in drug acquisition costs

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Pilot Study of Antimicrobial Use in the NICU

- Describe antibiotic prescribing patterns in 4 NICUs for infants ≥ 72 hours of age.
- Determine if antibiotic prescribing adhered to *CDC 12 Step guidelines*
- ***Identify opportunities for stewardship***

Patel et al. *Pediatr Infect Dis J* *in press*



Methods

- **Study Design:**
Retrospective, observational study of antibiotic use in 4 tertiary care Level III NICUs
- **Study Sites:**
Columbia, Cornell, CHOP, Christiana
- **Study Subjects:**
50 consecutive infants per site receiving IV antibiotics from Sept 1st 2005 - April 15th 2006
- **Data collection:**
 - Demographic, clinical, and microbiology data
 - Antibiotic use fulfilling inclusion criteria



Eligible Subjects and Antibiotic Use

	Inclusion Criteria	Exclusion Criteria
Subjects	Infants born at or transferred to study sites	Death within 24 hrs of antibiotic initiation
Antibiotic Use	≥ 1 intravenous antibiotic Administered ≥ 72 hours of age	Oral, intramuscular or inhaled antibiotics Antifungal or antiviral agents

Criteria for Inappropriate and Appropriate Antibiotic Use

- **Appropriate** use adhered to national or professional society recommendations, when available, or accepted clinical practice.
- **Appropriate use:**
 - Antibiotics initiated for empiric treatment of suspected infection
 - Antibiotics continued for culture-negative sepsis
- **Inappropriate** use did not adhere to 12-Step principles.





CDC 12 Step	Examples of Inappropriate Use
Step 4 Target the pathogen	<ul style="list-style-type: none">• Use of broad spectrum agent if narrower agent available.• Use of two agents if single agent is adequate.
Step 6 Practice antimicrobial control	<ul style="list-style-type: none">• Prolonged post-operative prophylaxis.• Prophylaxis of chest tubes.
Step 8 Don't treat colonization or contamination	<ul style="list-style-type: none">• Treatment of colonized central venous catheter.• Treatment of contaminated urine culture.
Step 9 Know when to say 'no'	<ul style="list-style-type: none">• Initial empiric therapy with broad spectrum agent.
Step 10 Stop if infection cured or unlikely	<ul style="list-style-type: none">• Prolonged duration of therapy.• Treating positive tracheal culture without pneumonia.

Characteristics of Study NICUs

Characteristics	NICU			
	1	2	3	4
Beds	58	50	50	60
Annual discharges	970	679	900	1100
Mean length of stay	18 d	18 d	20 d	15 d
Admissions < 1000 g	9%	8%	15%	12%
Prior approval for restricted antibiotics	Yes	No	Yes	No
48 hour 'pass' for empiric vancomycin	Yes	NA	Yes	NA

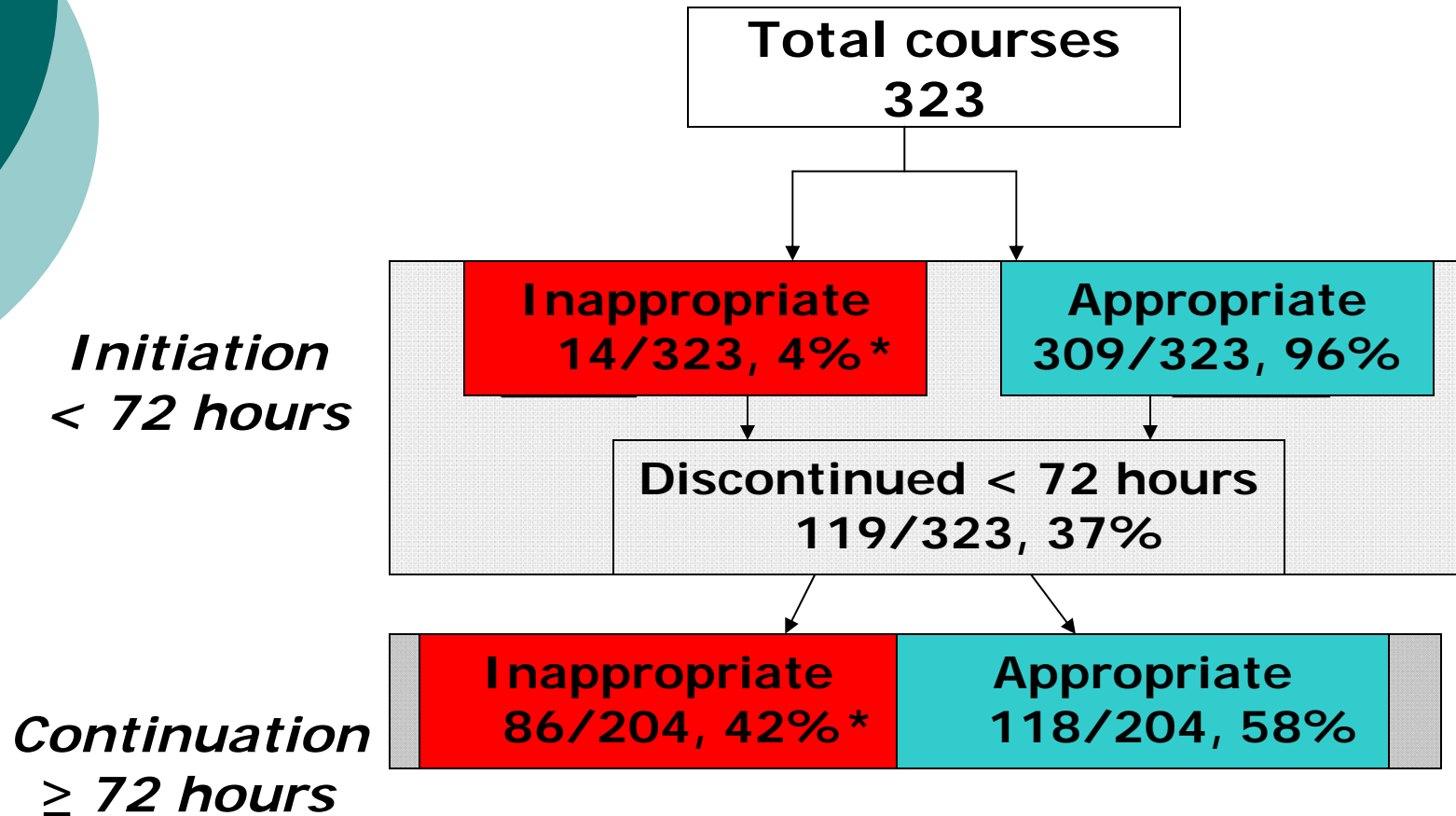


Inappropriate Antibiotic-Days Classified by CDC 12 Step

Inappropriate antibiotic-days:
806 (24%) of 3,334 days

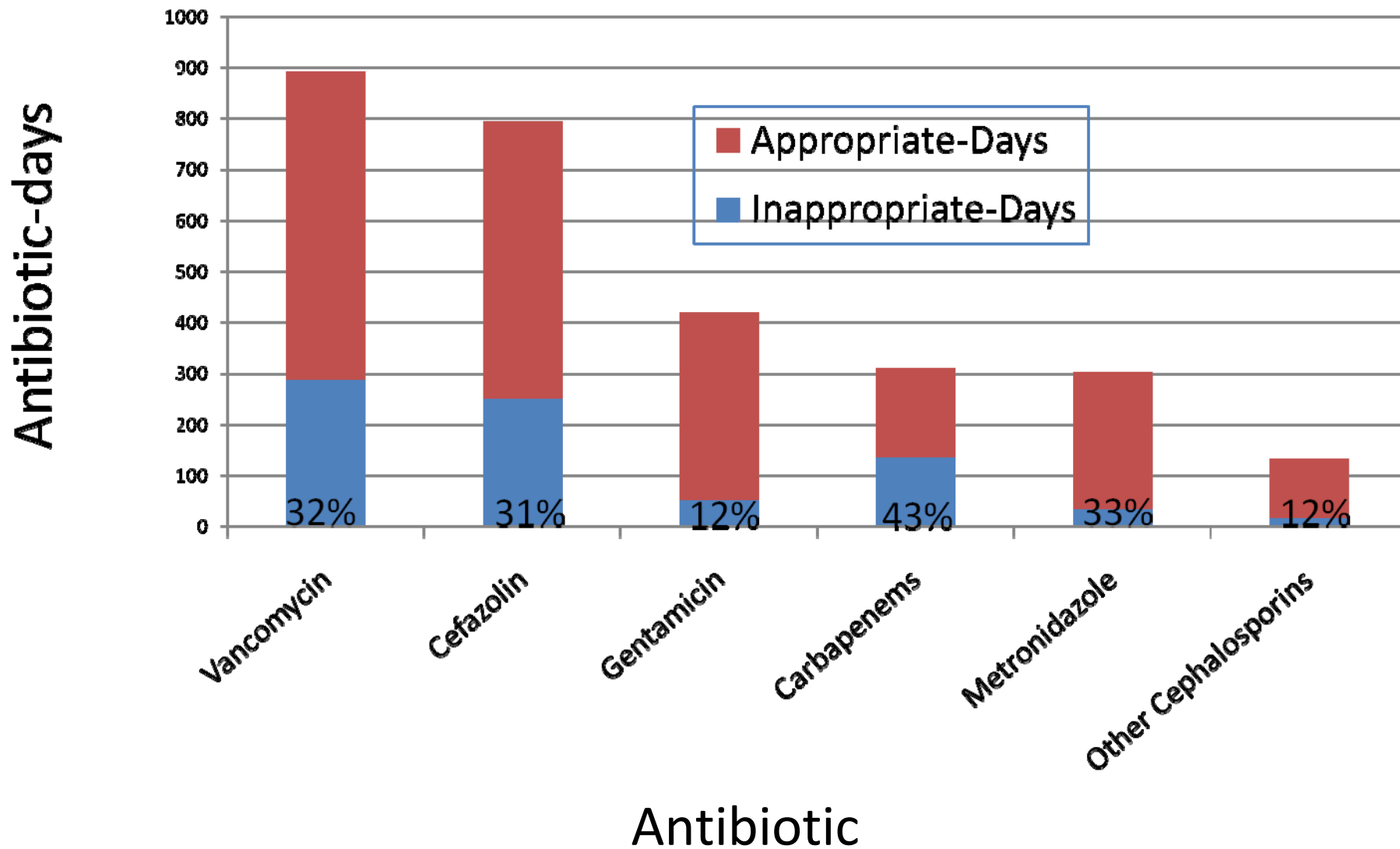
CDC 12-Step	Days	%
Target the pathogen	309	38
Practice antimicrobial control	167	21
Treating colonization/ contamination	130	16
Say 'no' to antibiotics	140	17
Stop treatment	60	8

Assessment of Antibiotic Use at Initiation and Continuation



* $p < 0.001$

Appropriate and Inappropriate Use Classified by Agent and Antibiotic-Days





Summary: Inappropriate Antibiotic Use

	Overall Use	Inappropriate Use
Courses	323	90 (28%)
Antibiotic-days	3,344	806 (24%)
Infants	200	70 (35%)

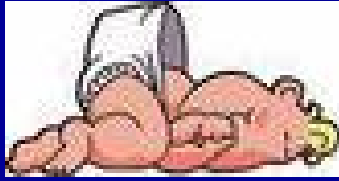


Summary and Conclusions

- The CDC's 12 Step Campaign is applicable NICU populations, but our findings may not be generalizable to other NICUs.
- Interventions more likely to be useful at continuation of antibiotics rather than initiation.
- Failure to "Target the Pathogen" (38%) and prolonged perioperative and chest tube prophylaxis (21%) were common.
- Understanding inappropriate use in the NICU population can promote development of interventions to improve antimicrobial prescribing.

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- Pilot Study conducted in NICUs
- **NIH-funded NAP study**

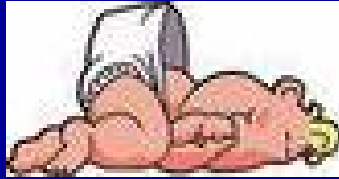


iNAP Study

interdisciplinary NICU Antimicrobial Prescribing Study

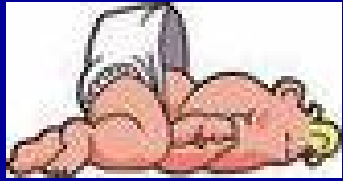
Multi-center quasi-experimental study to improve antimicrobial stewardship in the NICU population.

NINR R01 NR010821-01



iNAP STUDY Sites

- Columbia University Medical Center
 - Site PI: Lisa Saiman, MD MPH
- Weill Cornell University Medical Center
 - Site PI: Jeffrey Perlman, MD
 - Co-I: Patricia DelaMora, MD
- Children's Hospital of Philadelphia
 - Site PI: Theoklis Zaoutis, MD MSCE
- Christiana Care Health Sciences
 - Site PI: David Paul, MD



iNAP Study Specific Aims

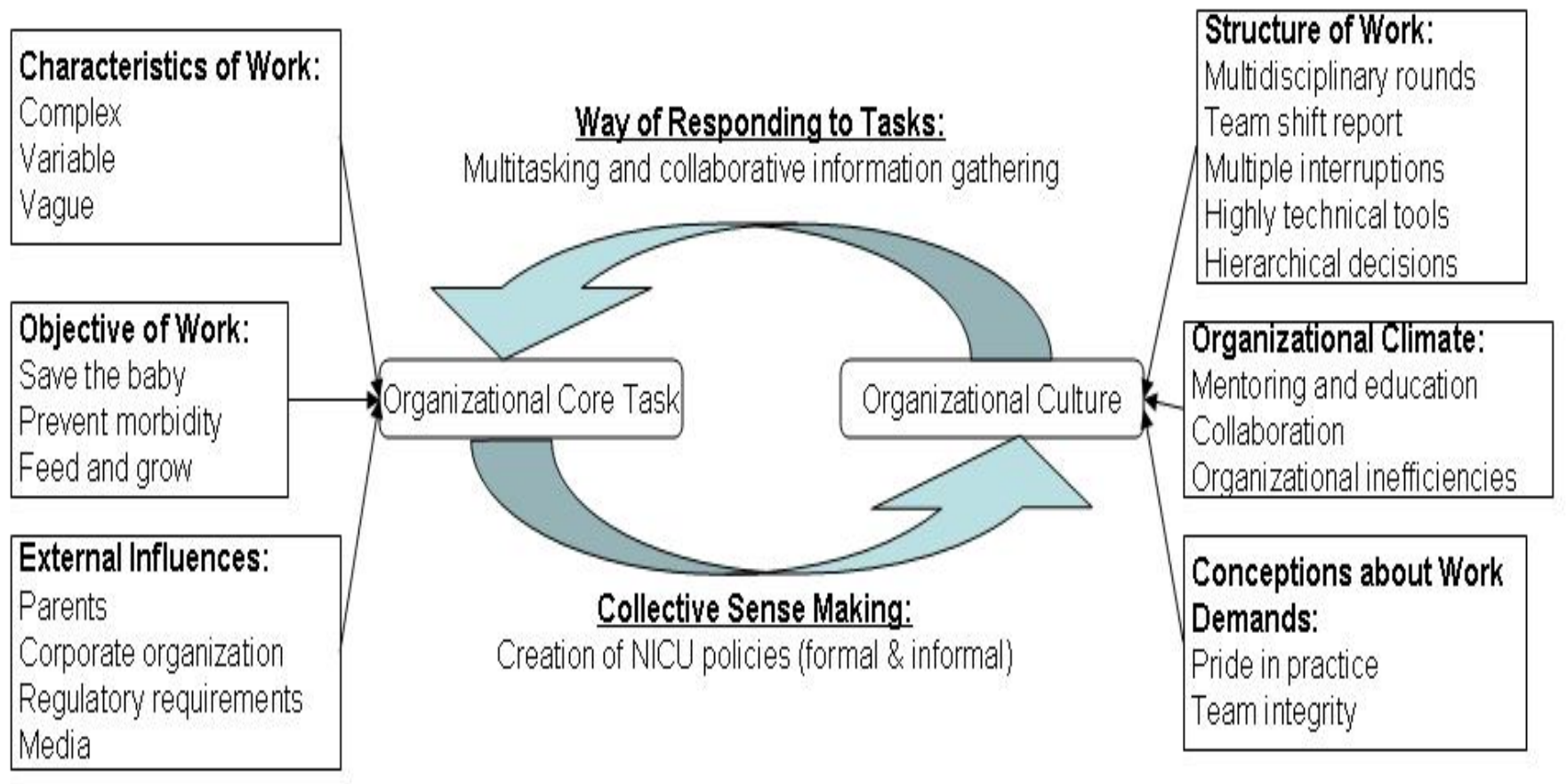
1. Impact of 3 interdisciplinary intervention bundles on inappropriate antimicrobial use categorized by *CDC 12 Step Campaign to Prevent Antimicrobial Resistance*.
2. Impact of 3 intervention bundles on antimicrobial resistance density, defined as changes in proportion of infant infections, infant colonization, and staff hand carriage with MDROs.
3. Cost effectiveness of interdisciplinary interventions in preventing BSIs caused by MDROs.

NAP Interdisciplinary Interventions

Randomized to Bundles	Education Plus	Clinical Decision Support	Audit and Prescriber Feedback
Usual Care	--	--	--
Intervention Bundle 1	<input checked="" type="checkbox"/>	--	--
Intervention Bundle 2	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	--
Intervention Bundle 3	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

Preliminary Results

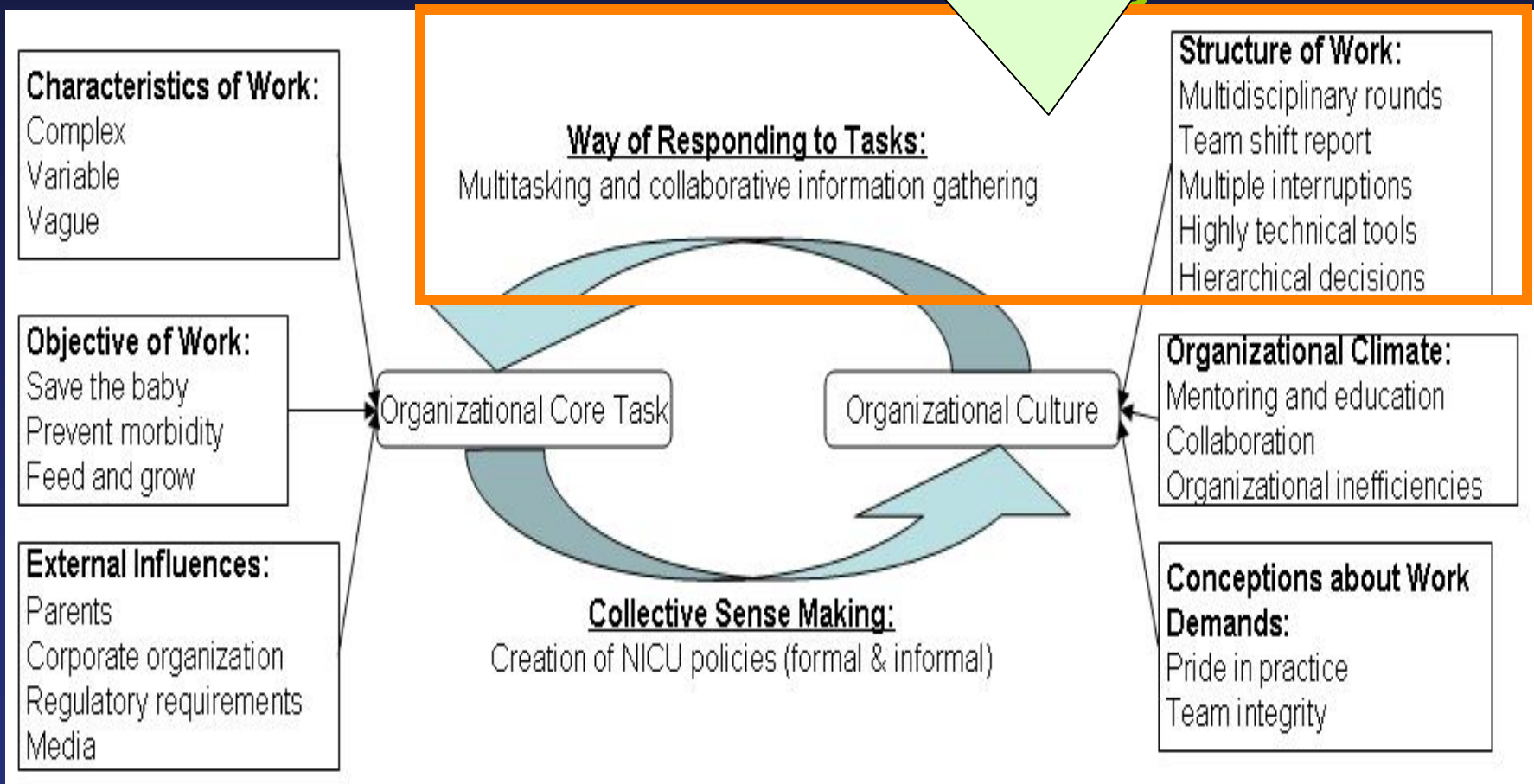
Sociotechnical Analysis



Sociotechnical model with factors contributing to the core task and factors contributing to organizational culture

Pre Sociotechnical

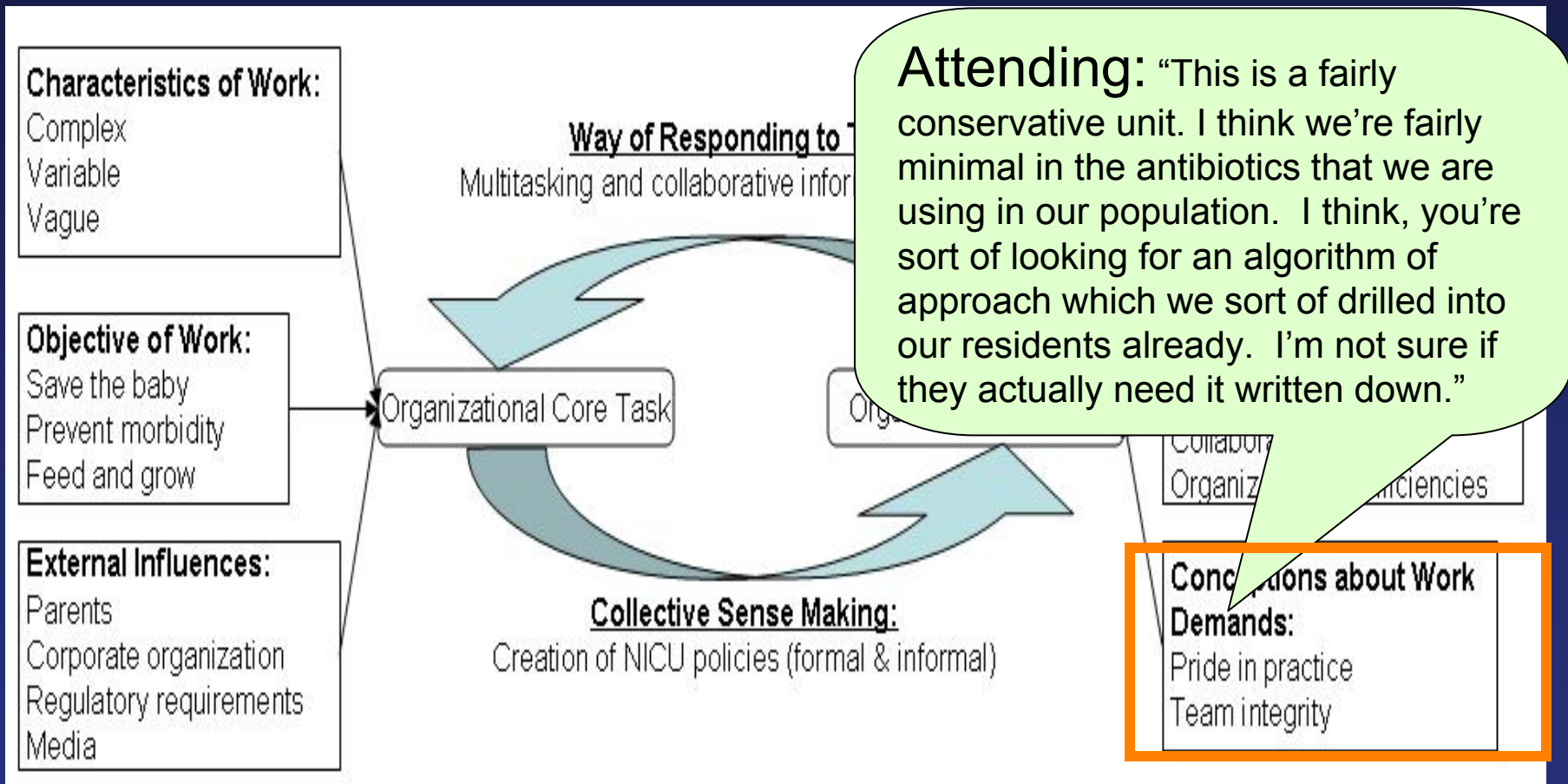
Resident: "Usually we do the ordering, the actual Eclipsys ordering and figuring out which dose to use based on usually Neofax, but most of the time the decision of which antibiotic we use comes from a higher level."



Sociotechnical model with factors contributing to the core task and factors contributing to organizational culture

Preliminary Results

Sociotechnical Analysis



Sociotechnical model with factors contributing to the core task and factors contributing to organizational culture

iNAP Study Timeline

Year 1 May 2009- April 2010	Year 2 May 2010- April 2011	Year 3 May 2011- April 2012
Baseline	Interventions Implemented	Interventions Continued Sustainability Determined

iNAP Outcomes

- **Primary Outcome:**

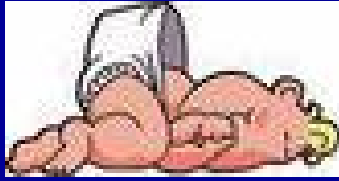
- Change in number of inappropriate antibiotic-days during pre-intervention period (baseline phase) compared with post-intervention period (intervention + sustainability phase).

- **Secondary Outcomes:**

- Proportion of infants receiving inappropriate antibiotics in pre- vs. post- intervention phases
- Proportion of inappropriate antibiotic use categorized by specific 12 Steps in pre- vs. post- intervention phases

iNAP Secondary Outcome: Resistance Density

- Defined as change in following MDROs:
 - Methicillin-resistant *S. aureus* (MRSA)
 - Vancomycin-resistant enterococci (VRE)
 - Extended spectrum β -lactamase (ESBL)-producing gram negative bacilli
 - Gentamicin-resistant gram negative bacilli
- Changes in MDROs measured in:
 - Infant infections
 - Infant colonization
 - Staff hand carriage



iNAP Study Subjects

- **Infants**
 - Hospitalized for ≥ 4 days – secular trends
 - Receive IV antibiotics ≥ 4 days of age
- **Attending Neonatologists**
 - Responsible antibiotic treatment
- **Permanent NICU Staff**
 - Direct patient contact

iNAP Study-related Procedures

- Infants
 - Review of medical records
 - Surveillance cultures at discharge if LOS \geq 14 days (informed consent)
 - Nares
 - Skin
 - Rectal verge
- NICU Attendings
 - Anonymous surveys
 - Review of medical records
 - Participate in relevant interventions (informed consent)
- Permanent NICU Staff
 - Anonymous hand cultures

Safety Measures

- Data Monitoring Committee
- Re-starting antibiotics ≤ 2 calendar-days after discontinuing antibiotics
- Rates:
 - Catheter-related BSIs
 - Bloodstream infections
 - Crude mortality
 - Candidemia

iNAP Study Designed to Overcome Limitations of Previous Studies

- Study design
 - Adequate descriptions of pre-/ post- intervention groups
 - Avoid contamination between groups
- Interventions
 - Measure adherence to interventions
 - Bundles allow assessment of different interventions
- Outcomes
 - Direct measures of impact on antimicrobial resistance
 - Adequate power
- Analysis
 - Adequate pre-intervention data for time series
 - Sustainability will be measured

Summary & Conclusions

- Antimicrobial stewardship critical to ensure:
 - effective treatment
 - patient safety
 - quality care
 - reduce resistance
 - reduce emergence of other pathogens
 - preserve efficacy of antimicrobial agents
- Proven to be cost effective
- Stewardship is inconsistently implemented

**THANK YOU for Considering
Participation in our Study**

