

# Dosing of Antimicrobials in the Neonatal Intensive Care Unit: Does Clinical Practice Reflect Published Recommendations?

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# Disclosures

- I have documented no financial relationships to disclose or conflicts of interest to resolve.
- I have documented that this presentation involves discussion of off-label use of meropenem and fluconazole in infants.

# Background

- Correct dosing in the NICU is important to avoid treatment failure and to prevent adverse events
- Neonatologists often use data extrapolated from adults and older children to guide drug dosing for infants
- Recent pharmacokinetics (PK) studies performed in infants provided optimized dosing recommendations for
  - Meropenem (2011)
  - Fluconazole loading dose (2011)
  - Fluconazole daily dose (2009)
- Whether these findings resulted in more appropriate dosing is unknown

# Objective

- Describe changes in dosing for meropenem and fluconazole in the NICU after publication of drug pharmacokinetics in infants



# Methods

- Cohort study using an electronic health records from 362 NICUs managed by the Pediatrix Medical Group between 1997-2013
- Inclusion criteria
  - Received meropenem or fluconazole
  - <90 days postnatal age (PNA) at start of drug course
- Exclusion criteria
  - Dosing unavailable
  - Dosing consistent with prophylactic administration
    - Fluconazole courses that started before day of life 5, lasted >7 days, and began prior to any positive fungal culture
    - Courses dosed less frequently than every 24 hours

# Methods

- Definition: “appropriate dosing”
  - Dose between 80% - 120% of the published recommendation

<b>Drug</b>	<b>Recommended Dose</b>
<b>Meropenem</b>	
<32 weeks GA and <14 days PNA	40 mg/kg/day
<32 weeks GA and ≥14 days PNA	60 mg/kg/day
≥32 weeks GA and <14 days PNA	60 mg/kg/day
≥32 weeks GA and ≥14 days PNA	90 mg/kg/day
<b>Fluconazole, loading dose</b>	25 mg/kg/day
<b>Fluconazole, daily dose</b>	12 mg/kg/day

# Methods

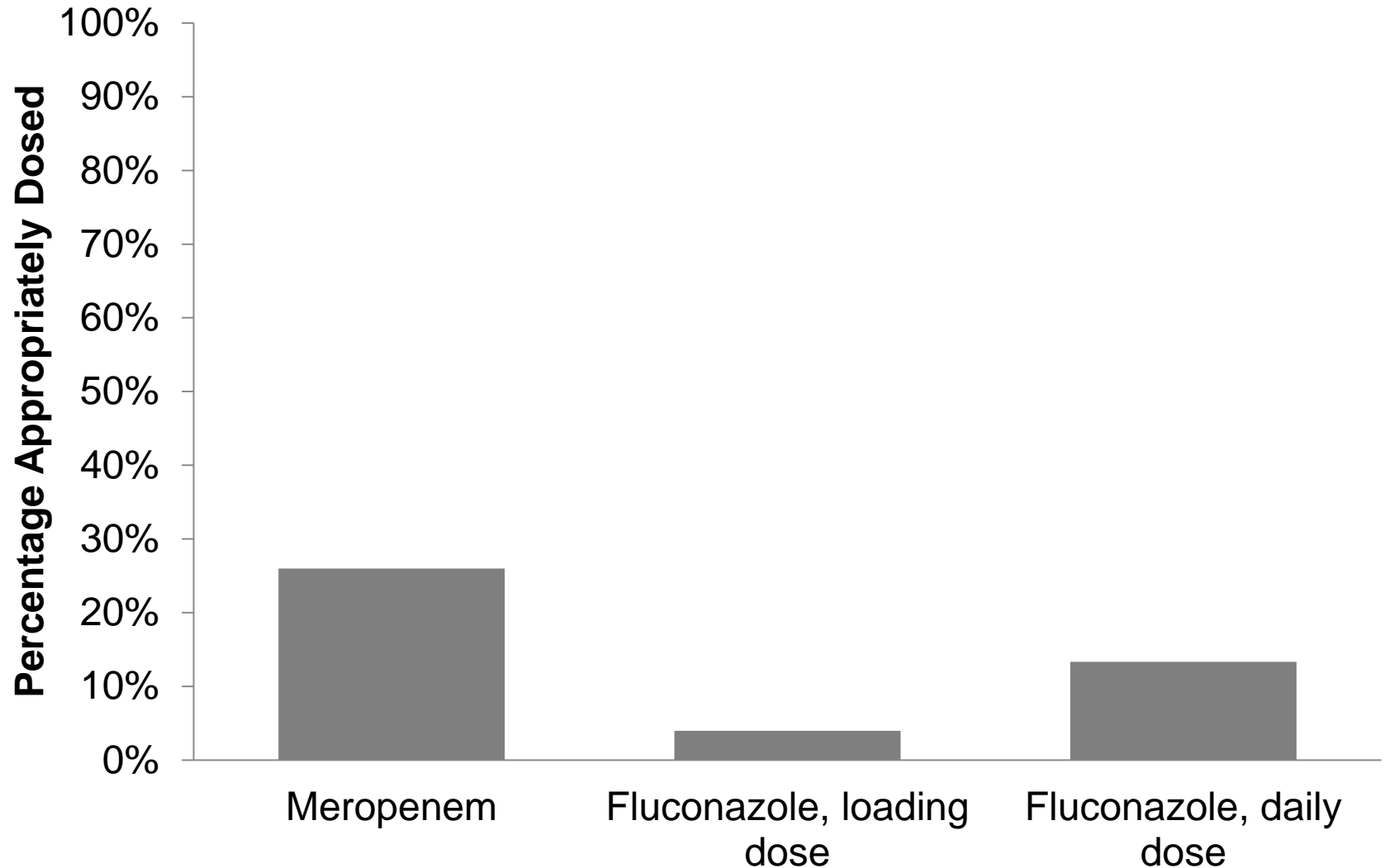
- Calculated the proportion of appropriately dosed courses
  - Overall
  - By discharge year
- Evaluated the change in appropriate dosing over time
  - Linear regression to predict proportion of appropriately dosed courses using discharge year
  - Chi-square statistic to test for linear trend

# Results

Drug	Courses n (%)
<b>Meropenem (N=784 courses)</b>	
<32 weeks GA and <14 days PNA	146 (19)
<32 weeks GA and ≥14 days PNA	441 (56)
≥32 weeks GA and <14 days PNA	112 (14)
≥32 weeks GA and ≥14 days PNA	85 (11)
<b>Fluconazole (N=805 courses)</b>	
<32 weeks GA and <14 days PNA	174 (22)
<32 weeks GA and ≥14 days PNA	406 (50)
≥32 weeks GA and <14 days PNA	56 (7)
≥32 weeks GA and ≥14 days PNA	169 (21)

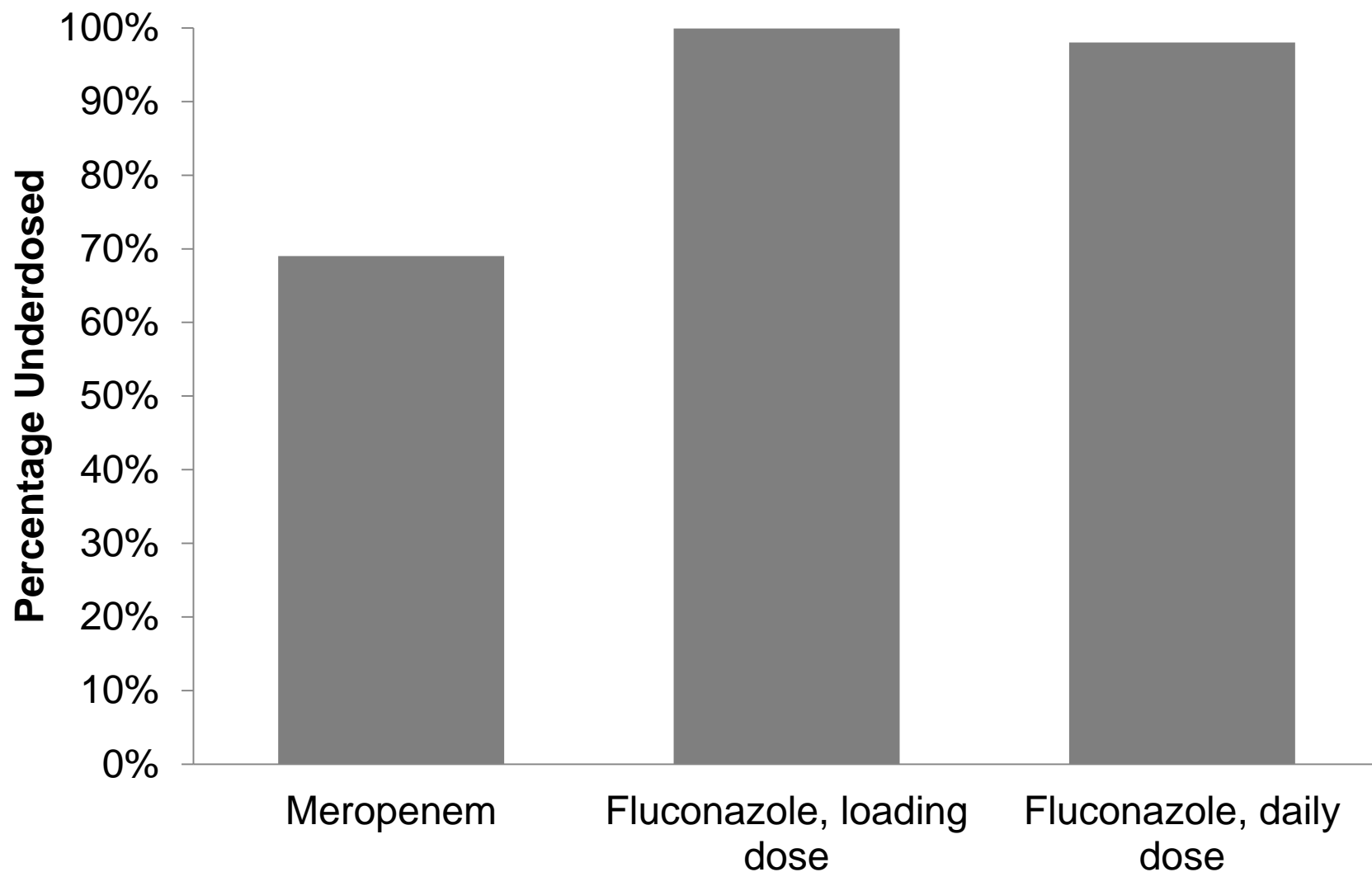


# Courses Dosed Appropriately

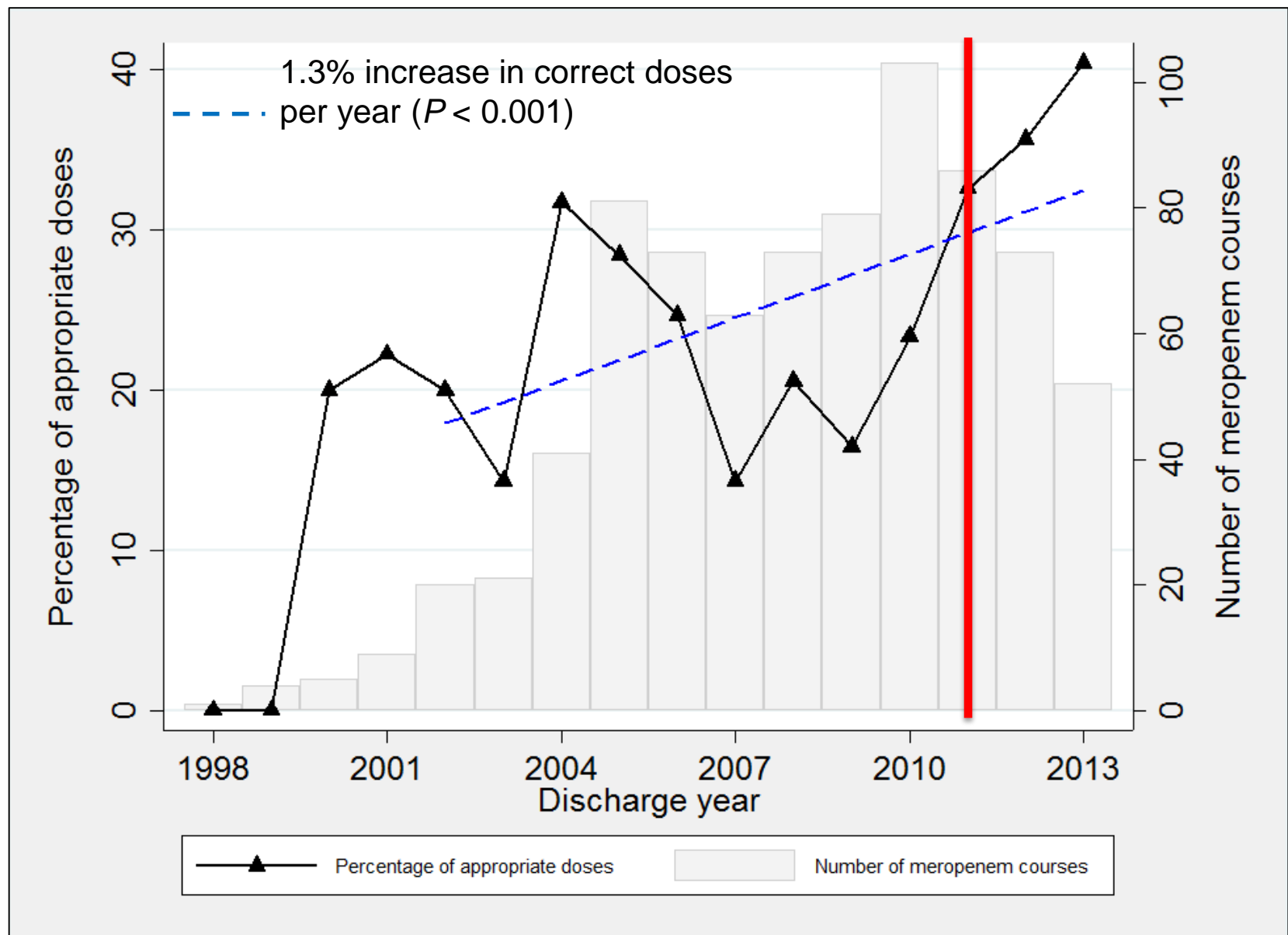




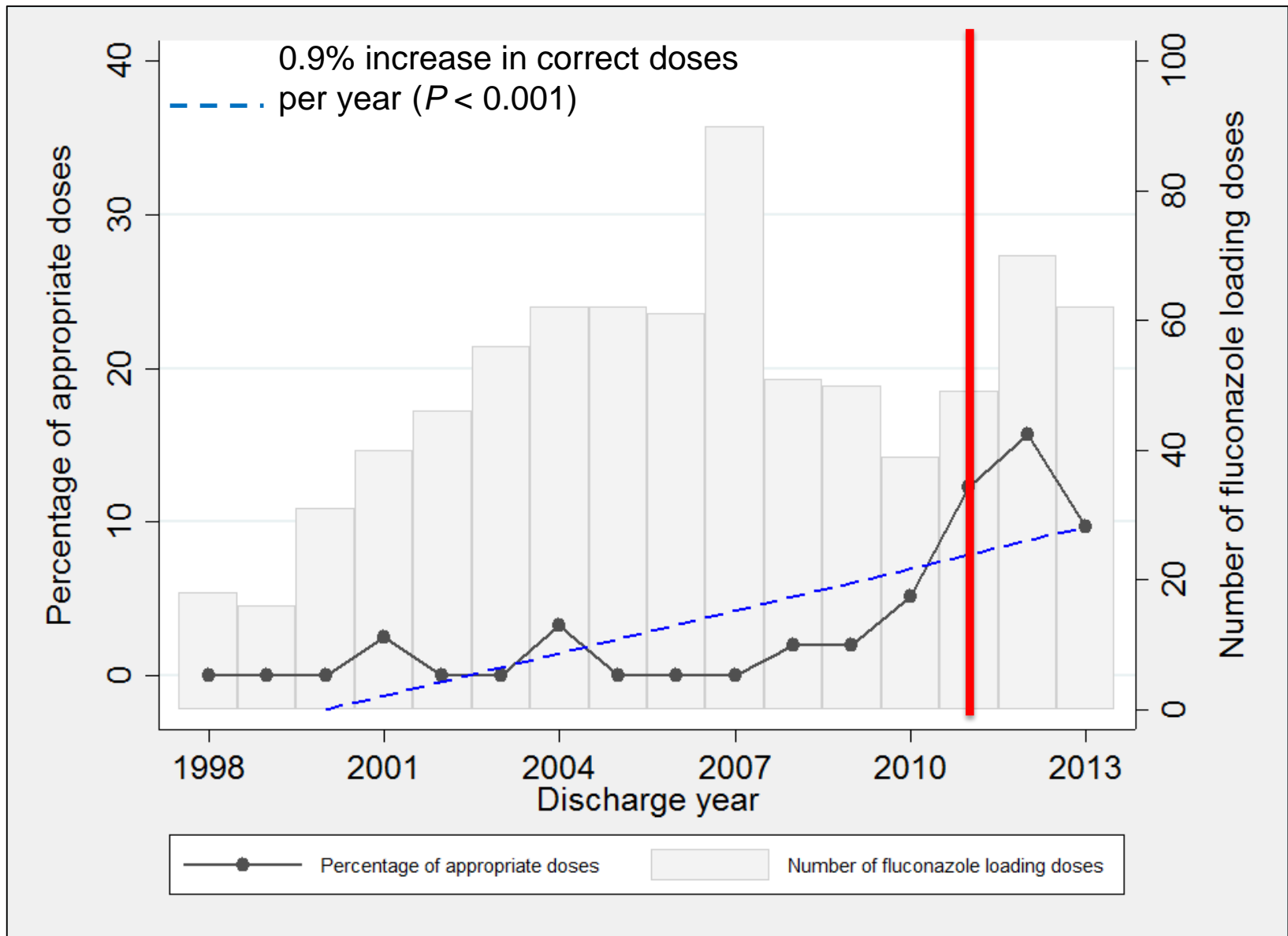
# Of Inappropriate Doses, Percentage Underdosed



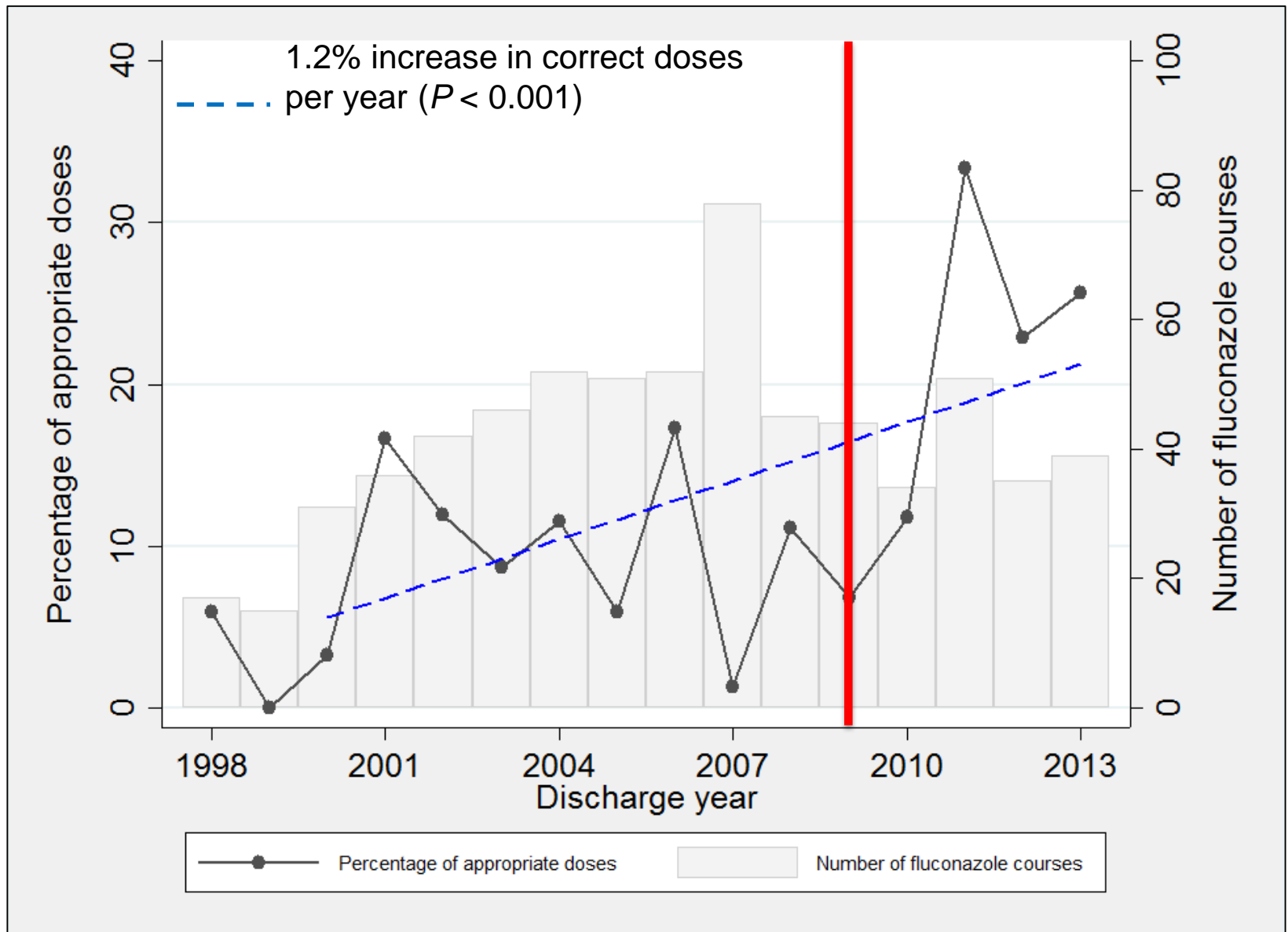
# Meropenem



# Fluconazole Loading Dose



# Fluconazole Daily Dose



# Conclusion

- Majority of infants in the NICU do not receive the recommended doses of meropenem or fluconazole (loading dose or daily dose)
- Publication of PK results was associated with more appropriate dosing

# Limitations

- Appropriate dose adjustments for renal function not considered
- Data not monitored for accuracy
- Abstracts presented 1 year prior to publications
- Possible misidentification of fluconazole prophylaxis

# Future Studies

- Evaluate how antimicrobial dosing impacts safety and efficacy
- Quality improvement programs to improve accurate dosing through:
  - Increased education
  - Computerized order entry dosing guidelines



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