

EFFECT OF FLUCONAZOLE PROPHYLAXIS ON FLUCONAZOLE *CANDIDA* SUSCEPTIBILITY IN PREMATURE INFANTS

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Pediatric Trials Network
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Disclosures

- Nothing to disclose

Fluconazole prophylaxis and resistance

- Invasive candidiasis
 - Extremely premature infants <750g birth weight at increased risk¹
 - Fluconazole prophylaxis is safe and effective in reducing invasive candidiasis^{2, 3}
- The effect of prophylactic fluconazole on the selection of fluconazole resistant *Candida* is an ongoing concern
 - Azole resistance mechanisms: target modification or overexpression, efflux pumps⁴
 - No emergence of fluconazole-resistant *Candida* sp in premature infants in neonatal studies⁵

Objective

- Evaluate the effect of fluconazole prophylaxis on fluconazole susceptibility of *Candida* isolates.

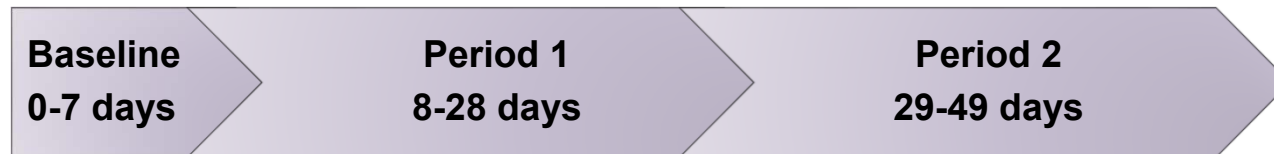
Methods

- Analysis of *Candida* isolates from a multicenter, randomized, placebo-controlled trial of fluconazole prophylaxis¹
 - 32 NICUs in the US
 - 2008-2011
 - Infants <750g birth weight and ≤5 days
 - Randomized (1:1) - fluconazole 6 mg/kg or placebo twice a week for 42 days

¹Benjamin JAMA 2014

Methods

- *Candida* from 2 sources
 - Surveillance cultures
 - umbilical-groin areas, rectum, and endotracheal secretions or nasopharynx



- Standard of care cultures
 - Normally sterile sites (blood, cerebral spinal fluid, urine obtained by sterile catheterization or suprapubic tap, peritoneal fluid)
 - Non-sterile sites: surface swabs (skin, wound) or urine obtained from urine bag
- Fluconazole minimum inhibitory concentration (MIC) was tested using broth microdilution¹

¹CLSI M27-A3

Methods

Species	CLSI Breakpoint MIC (mg/L) for fluconazole resistance ¹
<i>C. albicans, tropicalis, parapsilosis, kefyr, lusitaniae, biodinii</i>	≥8
<i>C. glabrata</i>	≥64
<i>C. krusei</i>	Intrinsically resistant

- MIC and proportion of fluconazole resistance were compared between the 2 treatment groups
 - Primary analysis: Colonizing *Candida spp*
 - Secondary analysis: standard of care culture
- A χ^2 test or Fisher's exact test for discrete variables and Wilcoxon rank sum test for continuous variables were used to assess any differences between treatment groups.

¹CLSI M27-A3

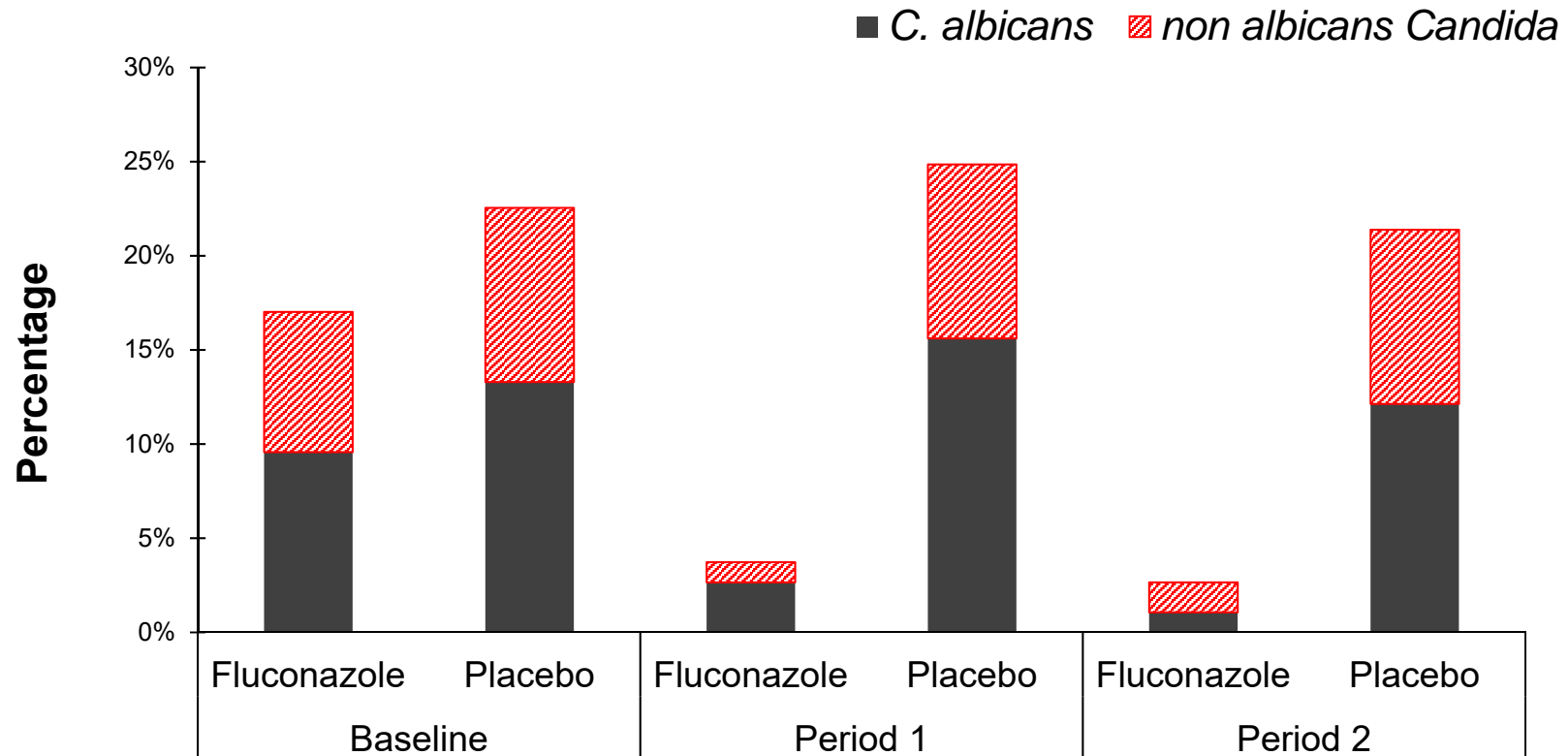
Results

- 361 infants

Median (range)*	Fluconazole (N=188)	Placebo (N=173)
Gestational Age (weeks)	25 (23, 31)	25 (22, 30)
Birth Weight (g)	653 (310, 794)	640 (350, 791)
Female, n(%)	109 (58%)	98 (57%)

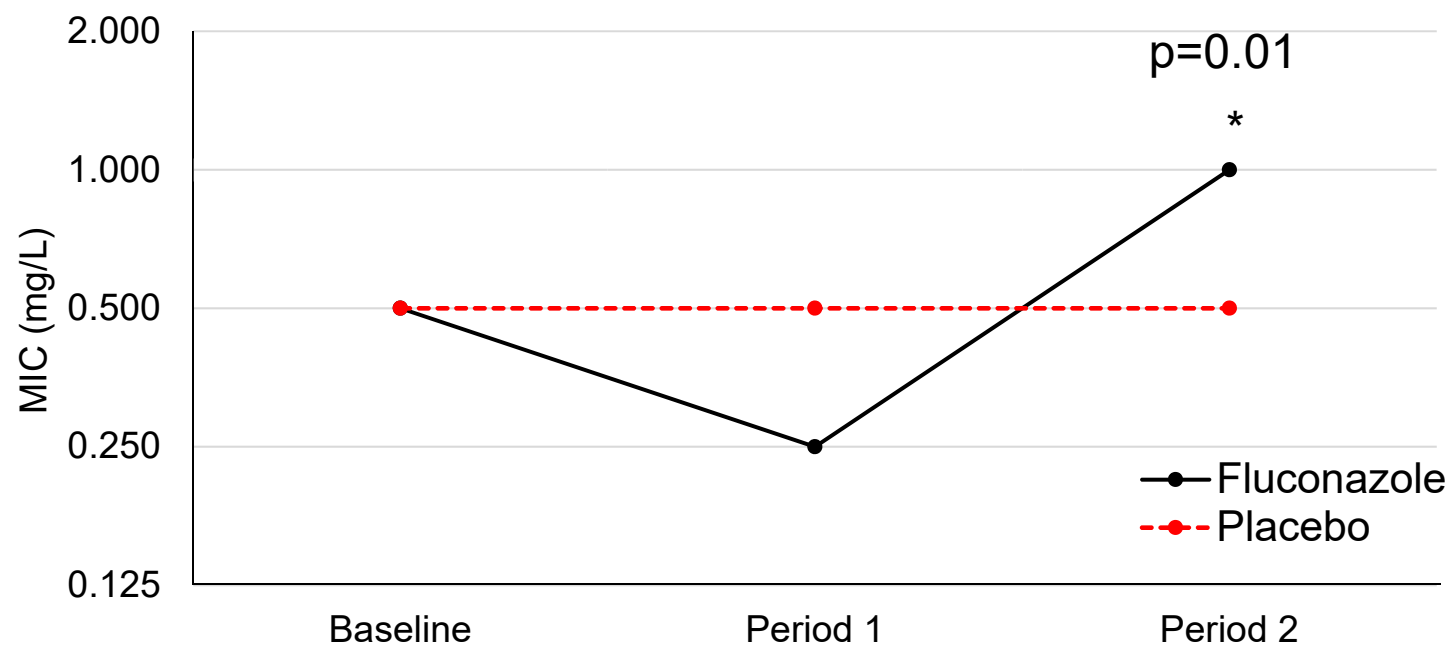
*unless otherwise stated

Candida colonization by treatment group



	Baseline		Period 1		Period 2	
Infants colonized, n	F	P	F	P	F	P
	27	35	7	38	4	36

Median fluconazole MIC over time for colonizing *Candida spp*



	Baseline		Period 1		Period 2	
	F	P	F	P	F	P
Infants colonized, n	27	35	7	38	4	36

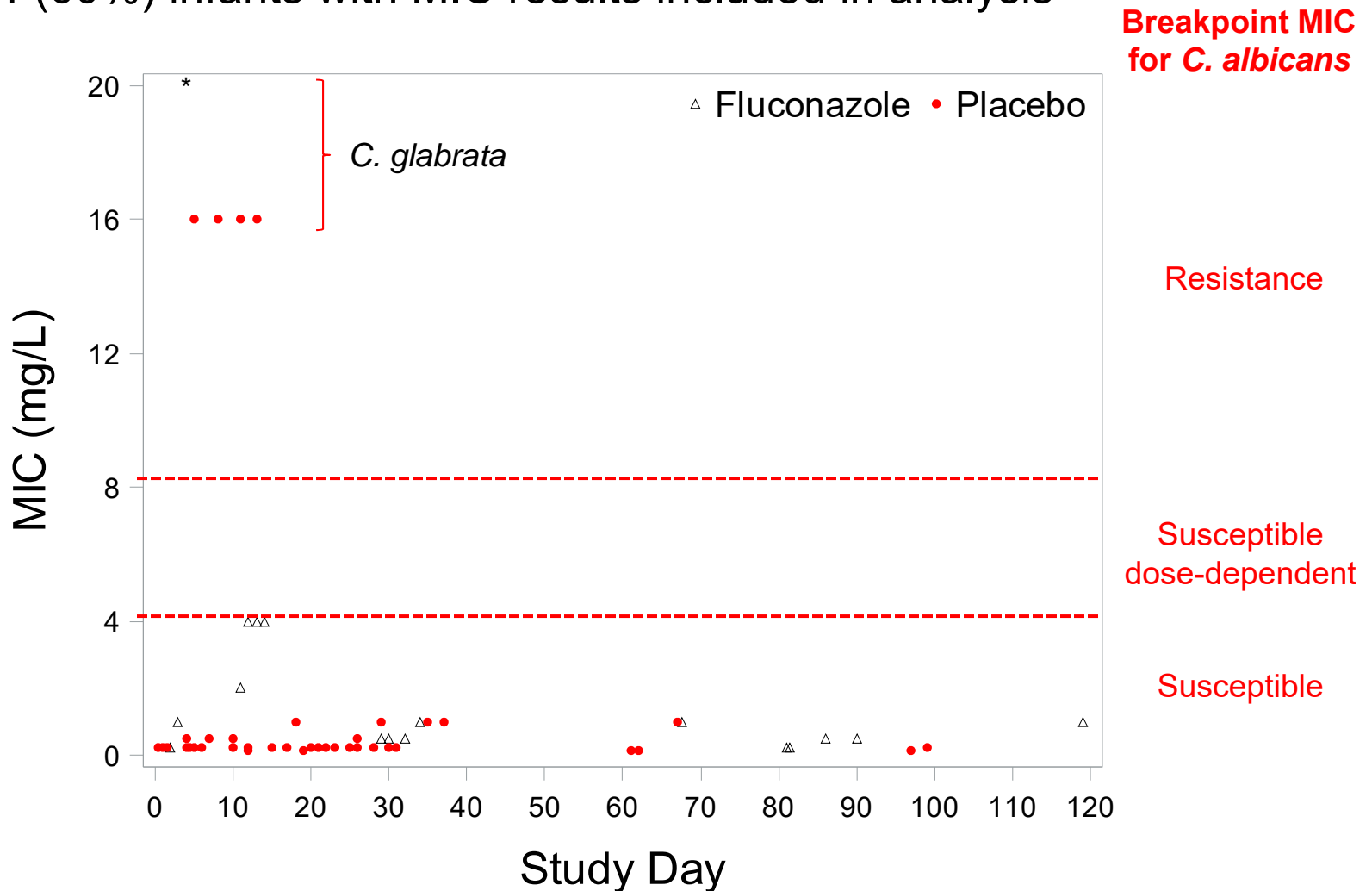
Fluconazole resistance among colonizing *Candida spp*

- After baseline, 4 infants (1%) were colonized with a fluconazole resistant *Candida* (2 in each treatment group)

	Candida species	Fluconazole MIC (mg/L)	Study period
Fluconazole	<i>C. albicans</i>	16	1
	<i>C. krusei</i>	32	1 and 2
Placebo	<i>C. parapsilosis</i>	8	2
	<i>C. biodinii</i>	16	1

Candida from standard of care cultures

- 40 (11%) infants had a positive standard of care culture
 - 24 (60%) infants with MIC results included in analysis



Discussion

- Limitations
 - Short duration of follow-up (49 days)
 - Limited sample size
 - Observation of colonization patterns but no tracking of resistance in one isolate
 - Fluconazole prophylaxis may have an effect on the local antifungal susceptibility pattern
 - High proportion of standard of care culture without MIC results
- Factors affecting the emergence of resistance
 - Antifungals used in NICUs
 - Duration of drug therapy/prophylaxis
 - Dosing regimen

Conclusion

- In this randomized placebo-controlled trial, fluconazole resistance was rare (1%) among extremely premature infants and similar in both treatment groups
- MIC of colonizing *Candida* isolates increased in the fluconazole group, but most remained in the susceptible range
- Clinical impact of colonizing *Candida* with higher fluconazole MIC remains to be established

Acknowledgement

- We thank the principal investigators and research teams in their support of this trial.

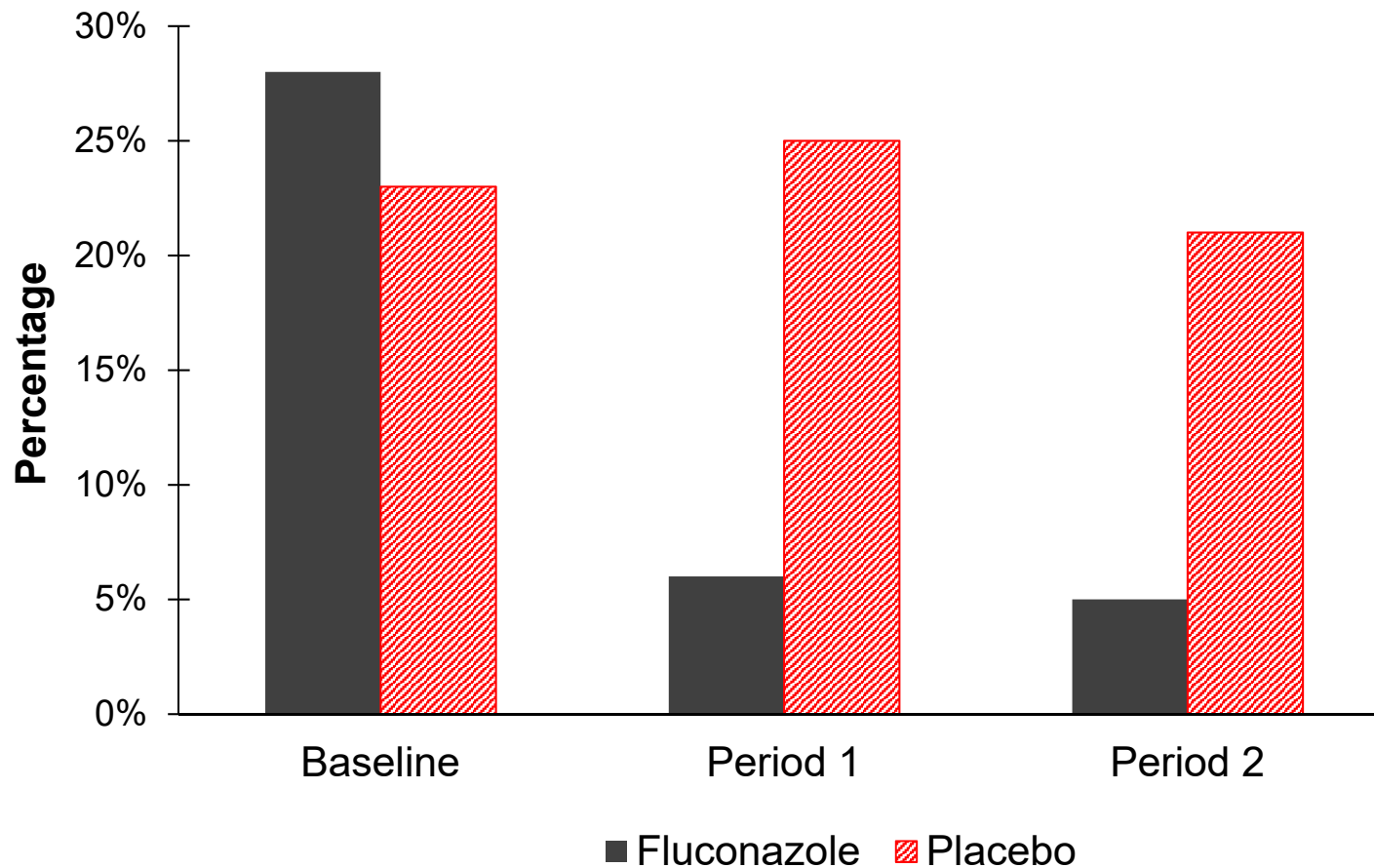
Site PI	City	State
MacGilvray, Scott	Greenville	NC
Wade, Kelly	Philadelphia	PA
Bidegain, Margarita	Durham	NC
Toms, Rune	Birmingham	AL
Finer, Neil	San Diego	CA
Burchfield, David	Gainesville	FL
Stewart, Dan	Louisville	KY
Arrieta, Antonio	Orange	CA
Duara, Shahnaz	Miami	FL
Shankaran, Seetha	Detroit	MI
NedreLOW, Jonathan	Fort Worth	TX
White, Robert	South Bend	IN
Kantak, Anand	Akron	OH
Shattuck, Karen	Galveston	TX
Pammi, Mohan	Houston	TX
Kennedy, Kathleen	Houston	TX
Sanchez, Pablo	Dallas	TX

Site PI	City	State
Bendel, Catherine	Minneapolis	MN
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Bloom, Barry	Wichita	KS
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Perenyi, Agnes	Brooklyn	NY
Neu, Natalie	New York	NY
Ezeanolue, Echezona	Las Vegas	NV
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Hudak, Mark	Jacksonville	FL
Ross, Ashley	Little Rock	AR
Mundakel, Gratias	Brooklyn	NY
Pandit, Paresch	Voorhees	NJ
Ross, Ashley	Little Rock	AR
Poindexter, Brenda	Indianapolis	IN
Gordon, Phillip	New Orleans	LA

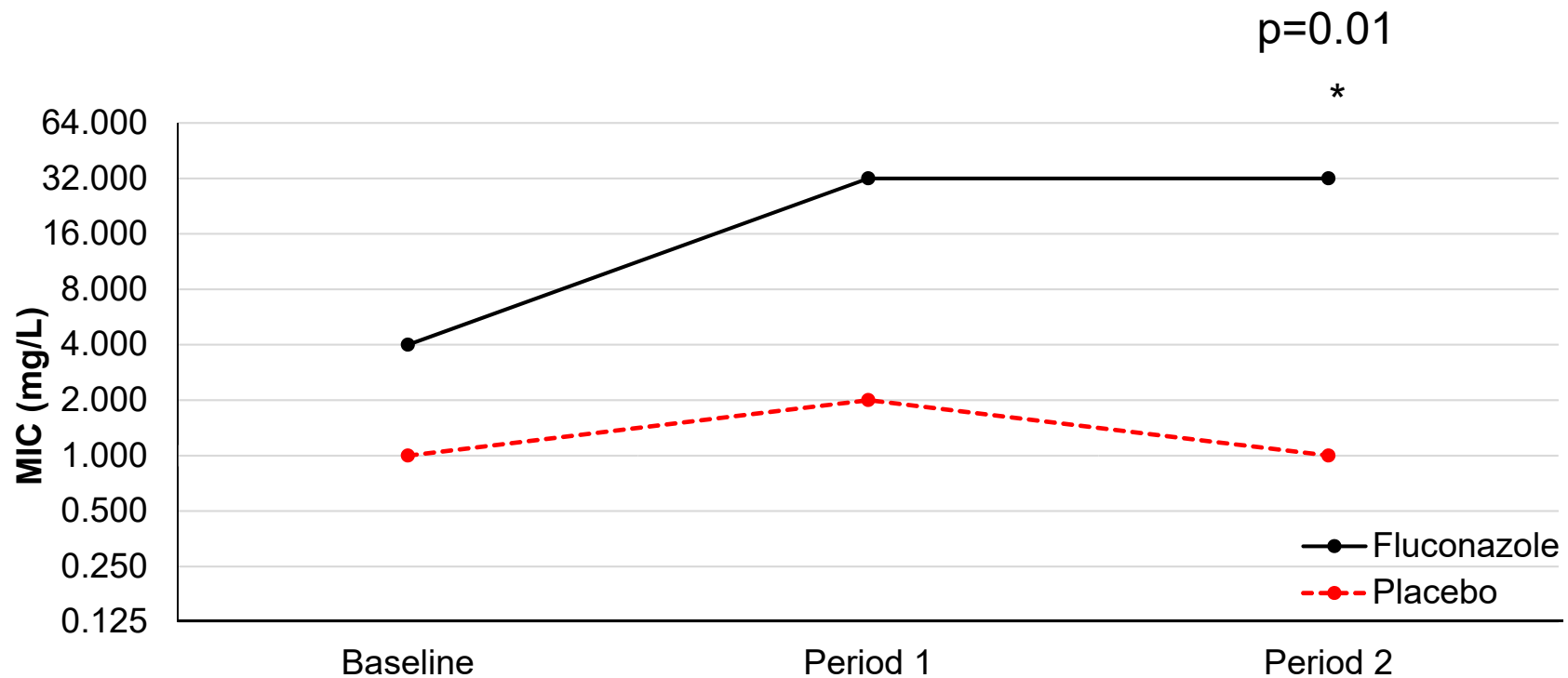
Additional slides

Candida colonization by treatment group

- 93 (26%) infants had *Candida* colonization
 - 92 infants with MIC results included in analysis.

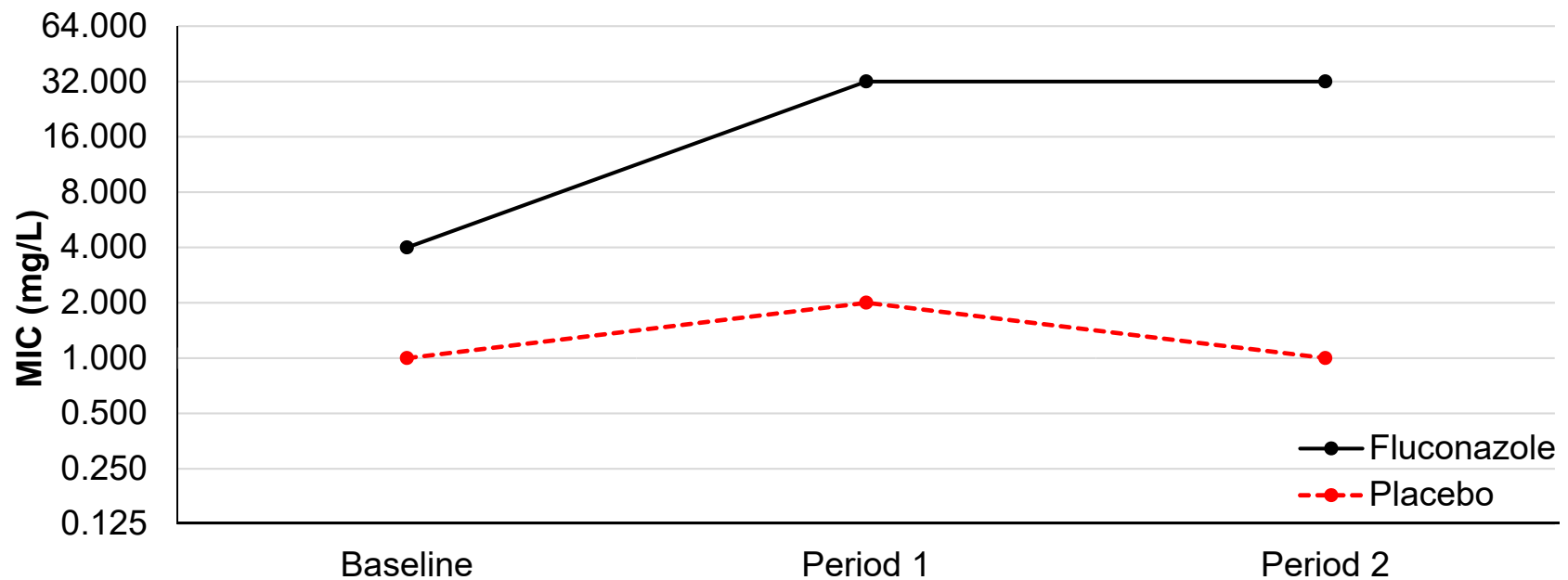


Fluconazole MIC₉₀ over time for colonizing *Candida spp*



Infants colonized, n (%)	Baseline		Period 1		Period 2	
	F	P	F	P	F	P
	27 (14)	35 (20)	7 (4)	38 (22)	4 (2)	36 (21)

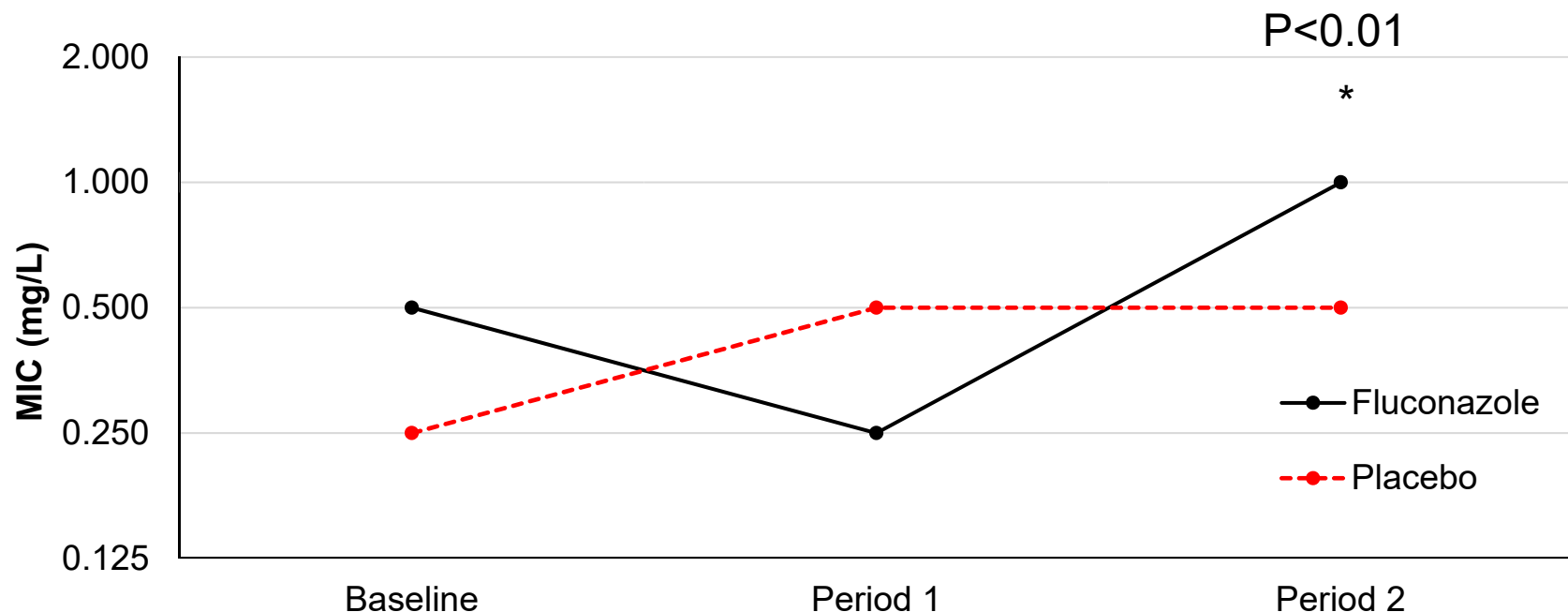
Fluconazole MIC₉₀ over time for colonizing *Candida spp*



MIC₉₀ 95% confidence intervals (mg/L)

	Baseline	Period 1	Period 2
Fluconazole	1-64	2-32	NA
Placebo	1-16	1-16	1-8

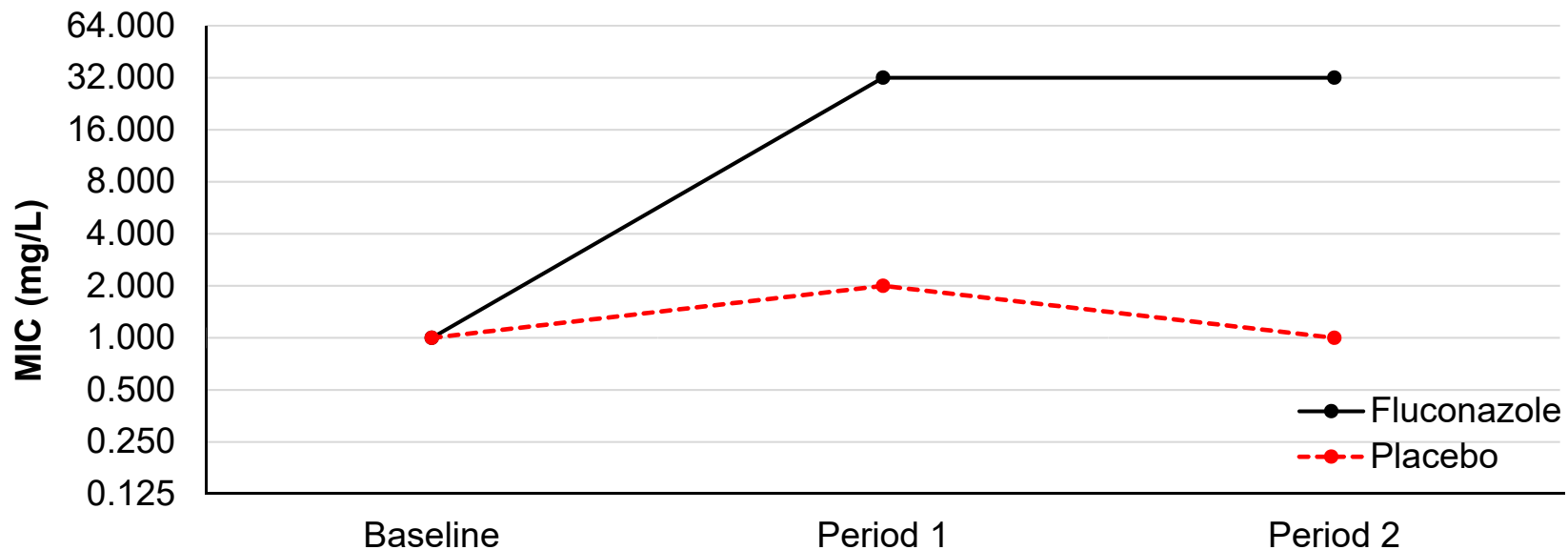
Median fluconazole MIC over time for colonizing *Candida spp* (excluding *C. glabratas*)



Median MIC 95% confidence intervals (mg/L)

Fluconazole	0.25-1	0.125-32	1-32
Placebo	0.25-0.5	0.25-0.5	0.25-0.5

Fluconazole MIC₉₀ over time for colonizing *Candida spp* (excluding *C. glabratas*)



Median MIC 95% confidence intervals (mg/L)

Fluconazole

1-4

2-32

NA

Placebo

1-1

1-16

1-8