

Augmentin ES Bacteriological and
Clinical Efficacy in AOM

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Objectives

- Rationale
- Background
- Objectives, Design
- Results
 - Patients with *S. pneumoniae**, PRSP
 - Patients with *S. pneumoniae* isolates with amox/clav MIC = 4 mcg/mL
 - Patients with Beta-Lactamase Producing Pathogens
- Safety
- Overall Conclusions

*Represents "*S. pneumoniae* Alone or with Other Pathogens" throughout

Augmentin ES (14:1)

- Excellent bacteriological/clinical efficacy vs. PRSP
- Efficacy vs. *S. pneumoniae* with amox/clav
MIC \leq 4 mcg/mL
- Clinical/bacteriologic efficacy vs. beta-lactamase producing organisms
(e.g. *H. influenzae* and *M. catarrhalis*)

and

- Maintains the safety profile of the currently marketed formulation

Why was *Augmentin* ES Developed?

- Increasing *S. pneumoniae* Resistance Worldwide
- Few choices available for empiric pediatric treatment of PRSP
- Known safety of currently marketed *Augmentin* pediatric product
- Utility of increased amoxicillin dosage cited by members of the medical community

Rationale for 14:1 *Augmentin* ES Formulation

- PK/PD Data
- *in vivo* animal data
- Clinical Pharmacokinetic Data

Study Background

In response to discussions with the Agency, GSK designed a clinical trial:

"A non-comparative multi-center study to demonstrate bacteriologic efficacy of *Augmentin* ES in the treatment of AOM due to *S. pneumoniae*"

Study design & objectives, including primary efficacy parameter of on-therapy bacteriological response, were discussed with the Agency

Study Design

- Non-comparative, multi-center study conducted in: US, Israel, Costa Rica, Dominican Republic & Guatemala
- *Augmentin*® ES dosed at 90 mg/kg/day for 10 days
- Bacteriologically confirmed AOM (ie, tympanocentesis, otorrhea <24h)
- Repeat tympanocentesis:
 - on day 4 to 6 for all patients with *S. pneumoniae* isolated at baseline
 - clinical failures
 - at 3 sites for patients with any pathogens at baseline

Primary Objective

- Evaluation of bacteriological efficacy vs. *S. pneumoniae* with:
 - penicillin MICs ≥ 2 mcg/mL (PRSP)
 - amox/clav* MICs = 4 mcg/mL

* amoxicillin/clavulanic acid tested at a 2:1 ratio;
all MICs are expressed in term of the amoxicillin concentration

Enrollment Targets

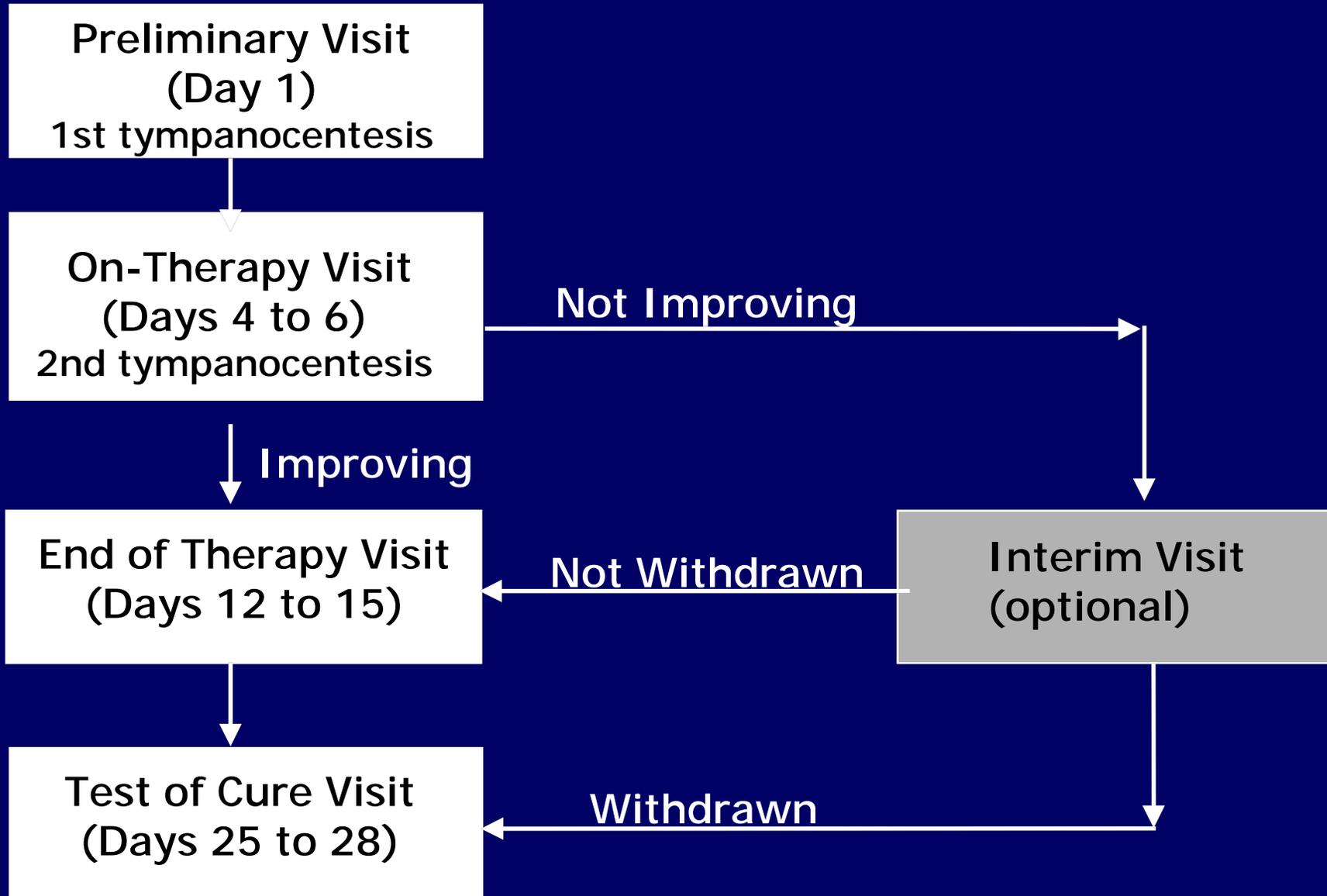
Goal:

- 20 pediatric patients with PRSP
(PCN MIC \geq 2 mcg/mL)
- Approximately 14 evaluable pediatric patients
with *S. pneumoniae* with amox/clav
MIC = 4 mcg/mL
- ~ 700 pediatric patients total

Enriched Study Population

- Included younger children than 'typical' AOM Studies, range 3 - 50 months
- Only excluded systemic antibiotics within 72 hrs of study entry; certain prophylaxis allowed, but discontinued on study entry
- No exclusion for recent/recurrent AOM
- No exclusion for "resistant" bacteria isolated at entry

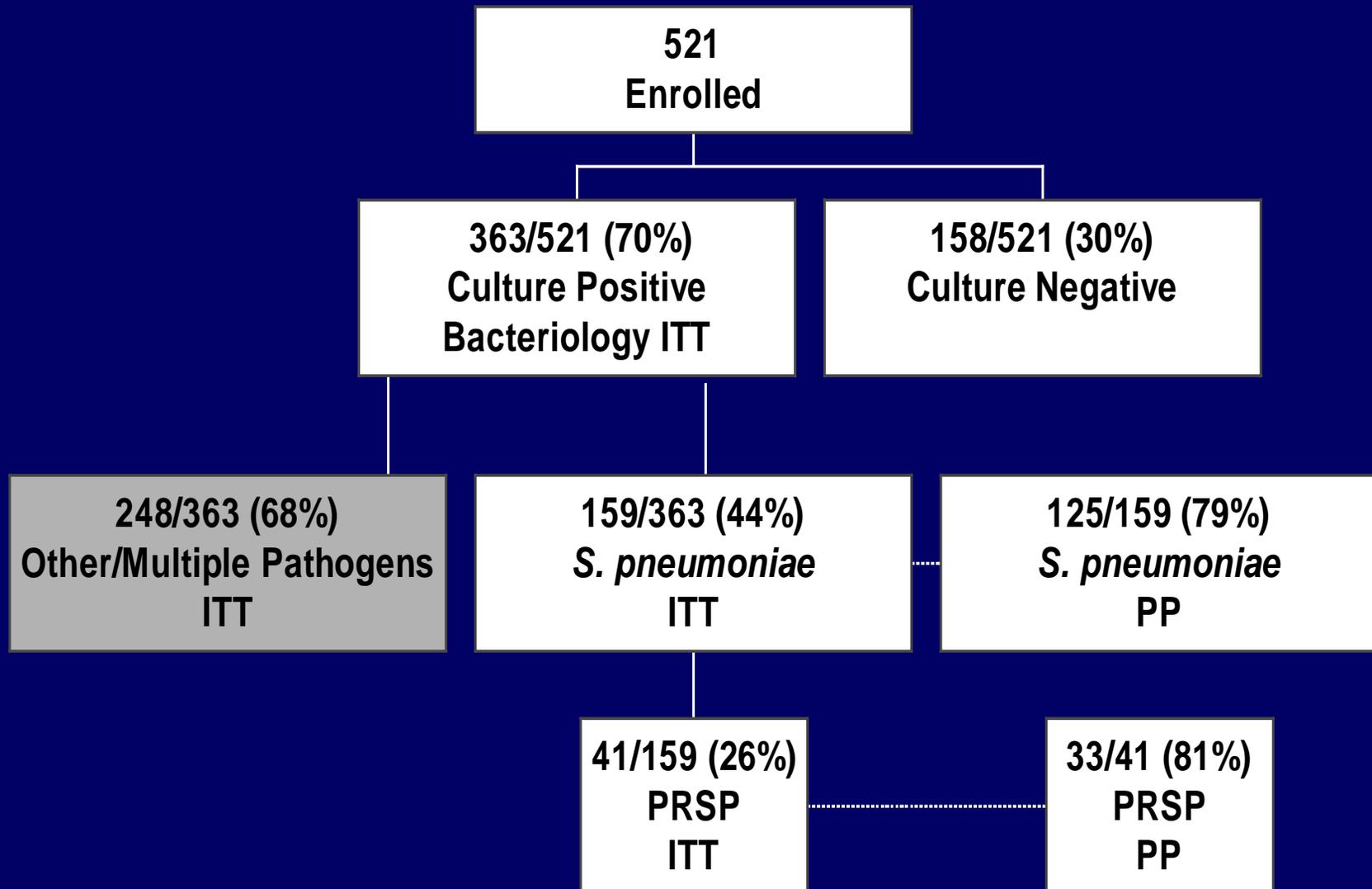
Study Plan



Demographic Characteristics

| | Clinical ITT N=521 | Bacteriological <i>S. pneumoniae</i> ITT N=159 |
|-------------------------------|-----------------------|--|
| Mean Age in Months (range) | 19 (3-50 mos.) | 18 (3-50 mos.) |
| Sex | 60% male | 57% male |
| Mean Weight | 10.8 kg. | 10.7 kg |
| Race | 60% Caucasian | 60% Caucasian |

Baseline Bacteriology



Baseline Bacteriology

**248/363 (68%)
Other/Multiple Pathogens
ITT**

**159/363 (44%)
S. pneumoniae
ITT**

**197/248 (79%)
H. influenzae
(36% beta-lactamase +)**

**31/248 (13%)
M. cattarhalis
(100% beta-lactamase +)**

**17/248 (7%)
*S. pyogenes***

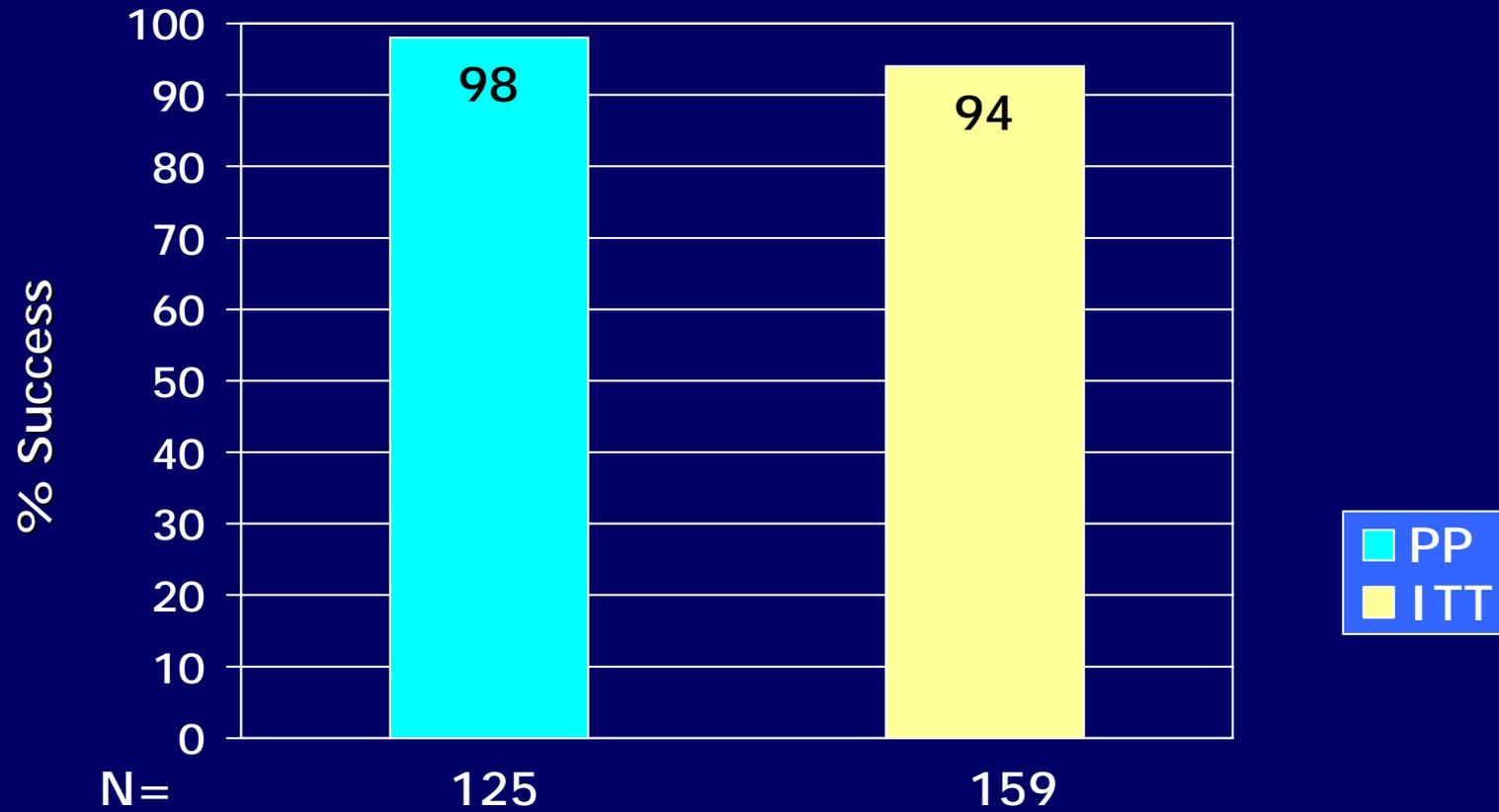
**51/248 (21%)
Multiple (>1) pathogens
present at baseline**

Efficacy Parameters

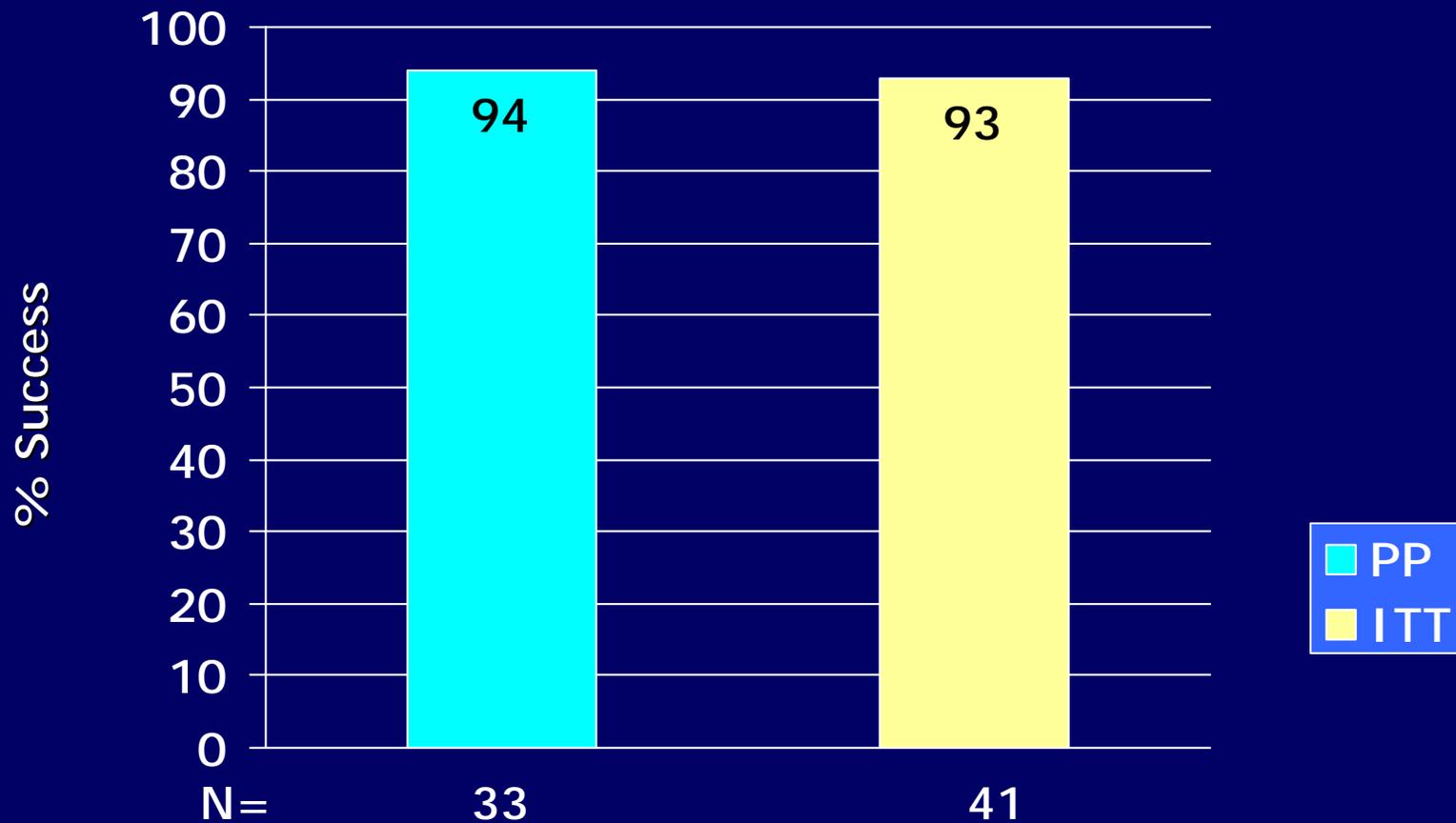
- Primary: Bacteriological response OT (days 4-6) in patients with *S. pneumoniae*
- Secondary:
 - Clinical response determined by primary investigator at EOT (days 12-15) in patients with *S. pneumoniae* (Key Clinical Endpoint)
 - Bacteriological (OT) and clinical responses (EOT) in patients with other pathogens
 - Clinical response determined by primary investigator at TOC (days 25-28, all pathogens)

What is the efficacy in patients
with *S. pneumoniae*?

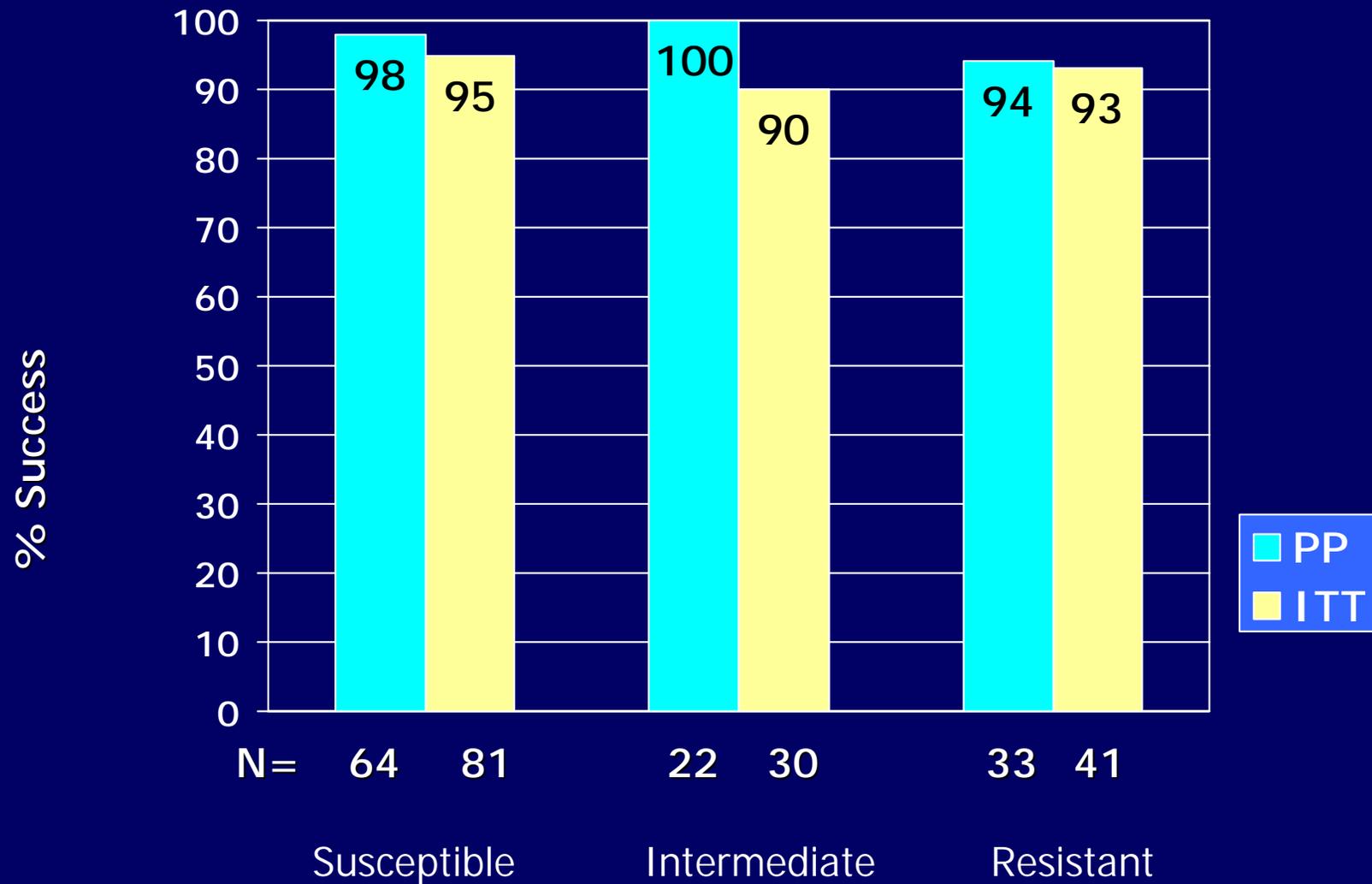
High Bacteriological Success Rates *S. pneumoniae*



High Bacteriological Success Rates Penicillin Resistant *S. pneumoniae* (Penicillin MIC \geq 2 mcg/mL)



Consistently High Bacteriological Success Rates Regardless of *S. pneumoniae* Susceptibility to Penicillin



**How do these data compare to the known
natural history of AOM?**

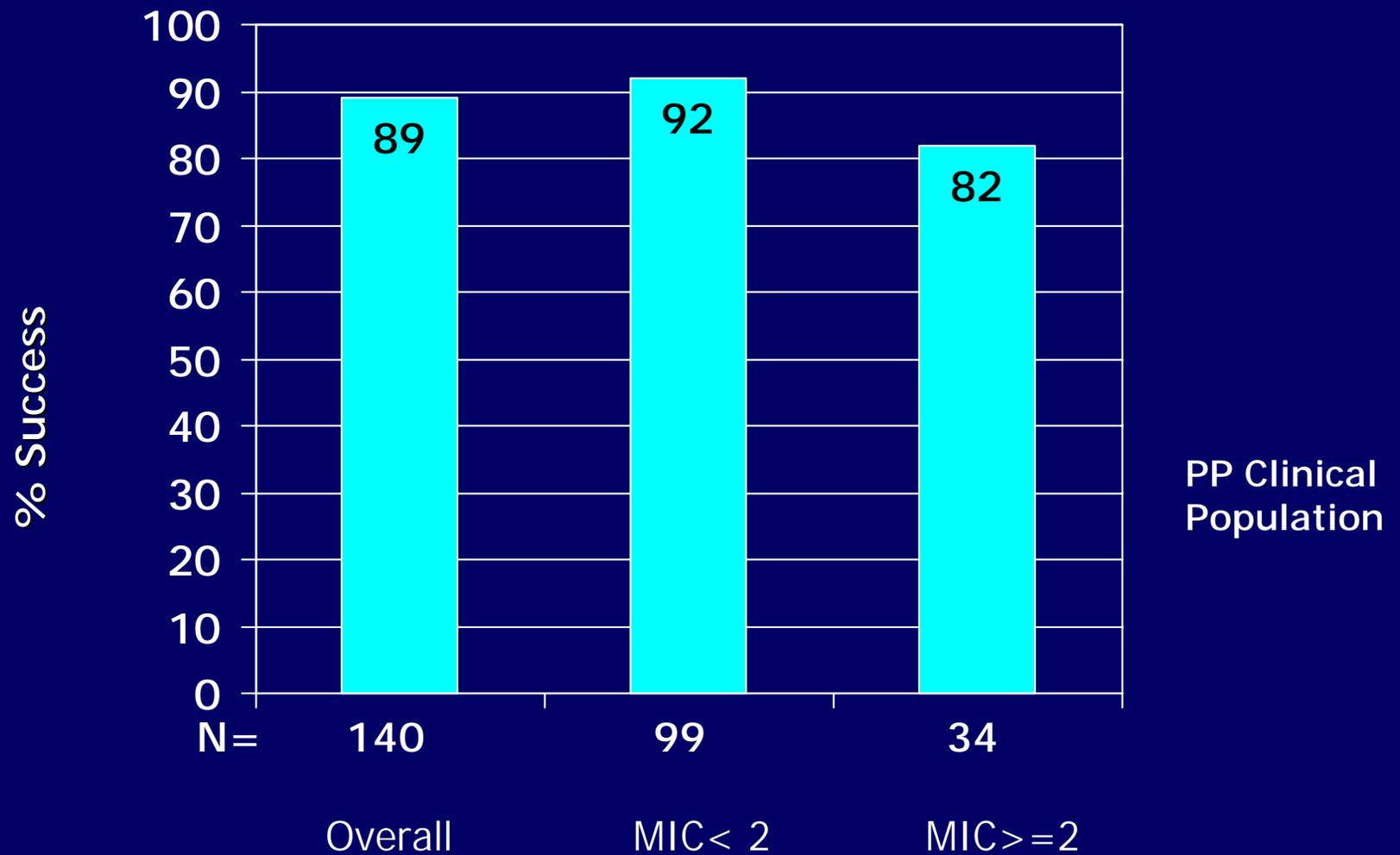
Natural History of AOM

- *S. pneumoniae* is least likely to resolve spontaneously
- *S. pneumoniae* spontaneous eradication rate of 20-30%
 - vs. 60-80% for other pathogens

Howie V. 1975. Natural History of AOM. *Ann Otol Rhino Laryn*
84: 67- 72.

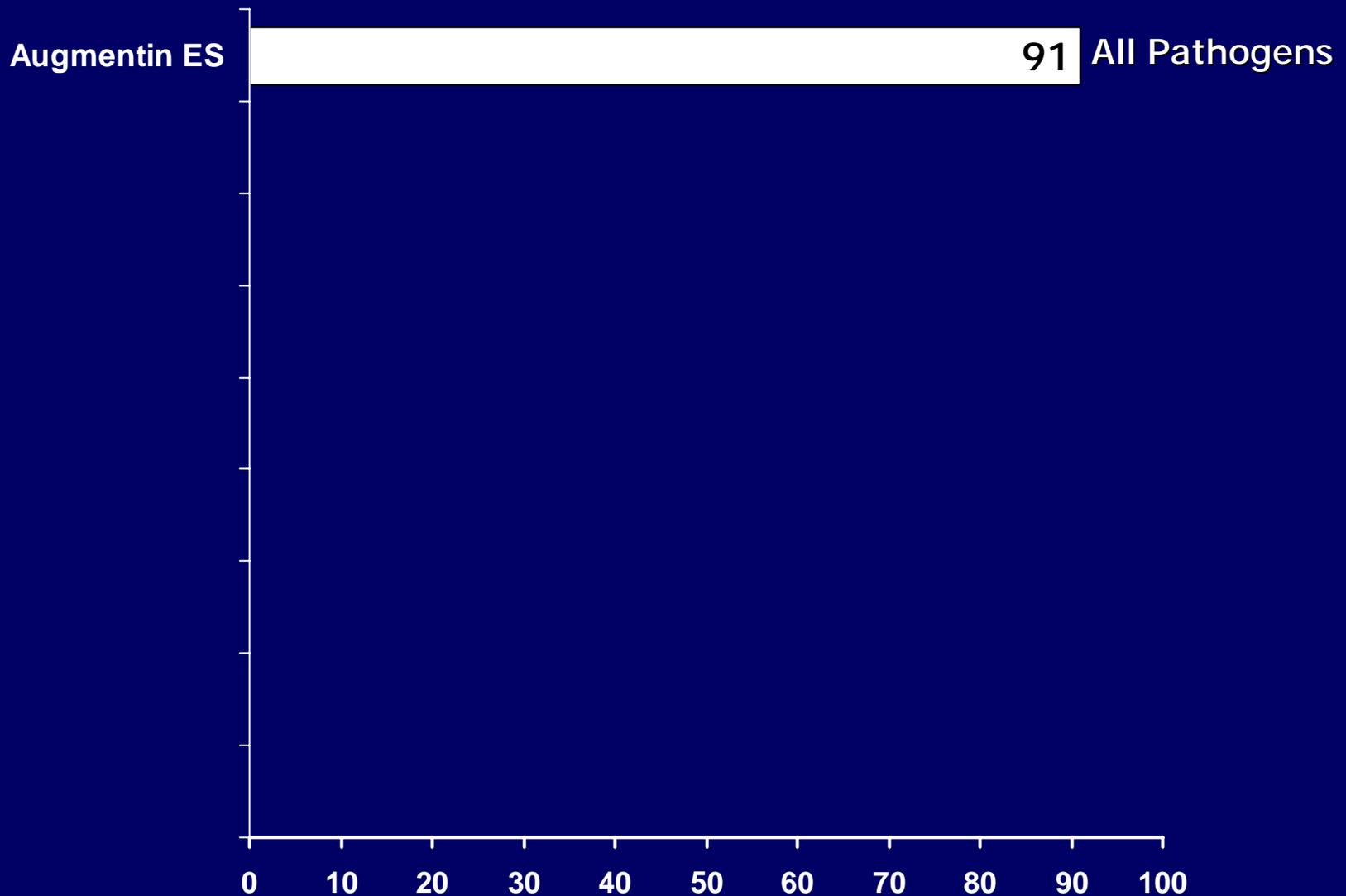
**Bacteriological efficacy is predictive of
clinical efficacy**

High Clinical Success Rates at EOT *S. pneumoniae* - Overall & by Penicillin MIC



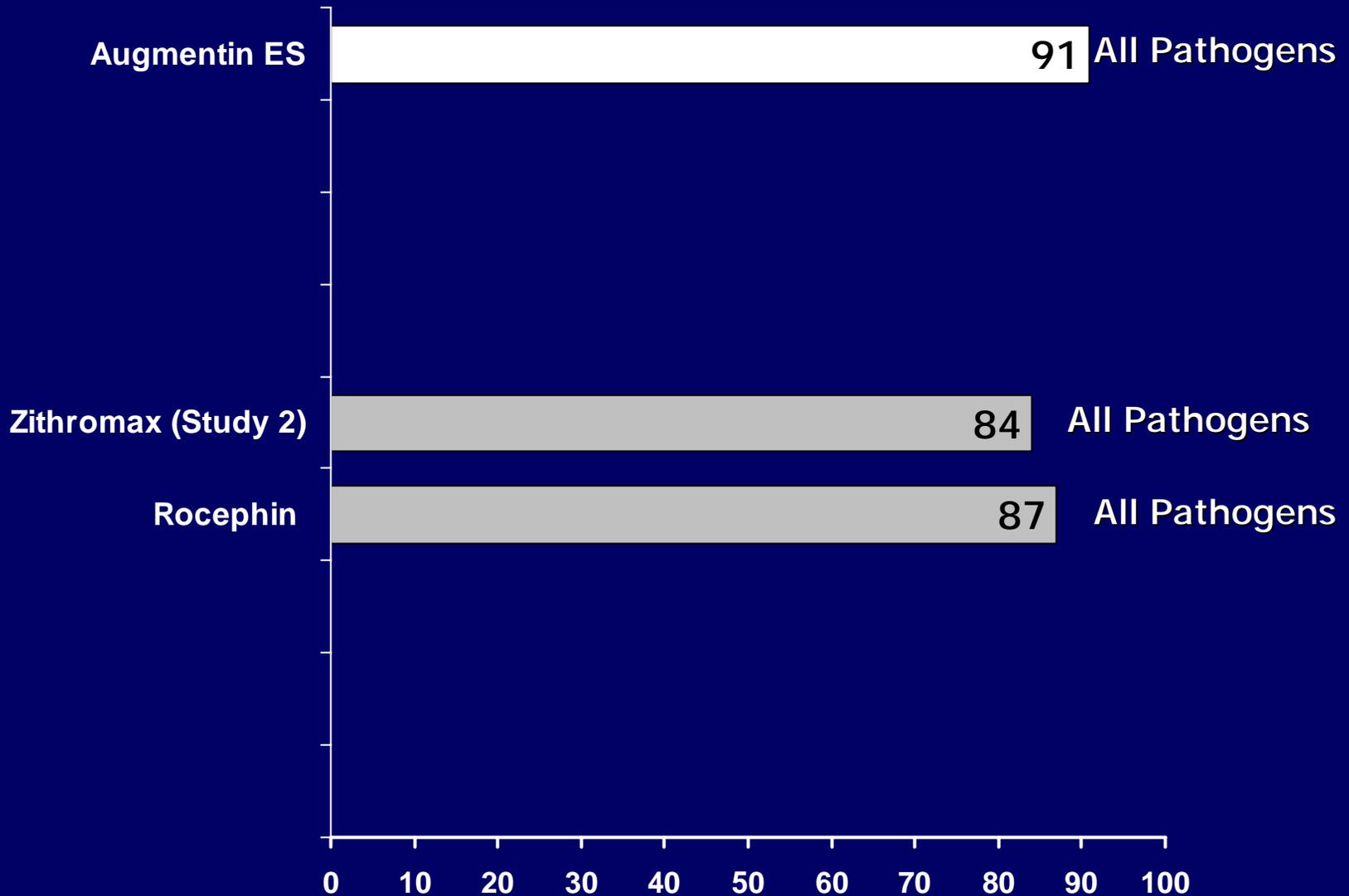
How does the EOT clinical efficacy of *Augmentin* ES compare to currently approved drugs?

High Clinical Success at EOT for *Augmentin ES*



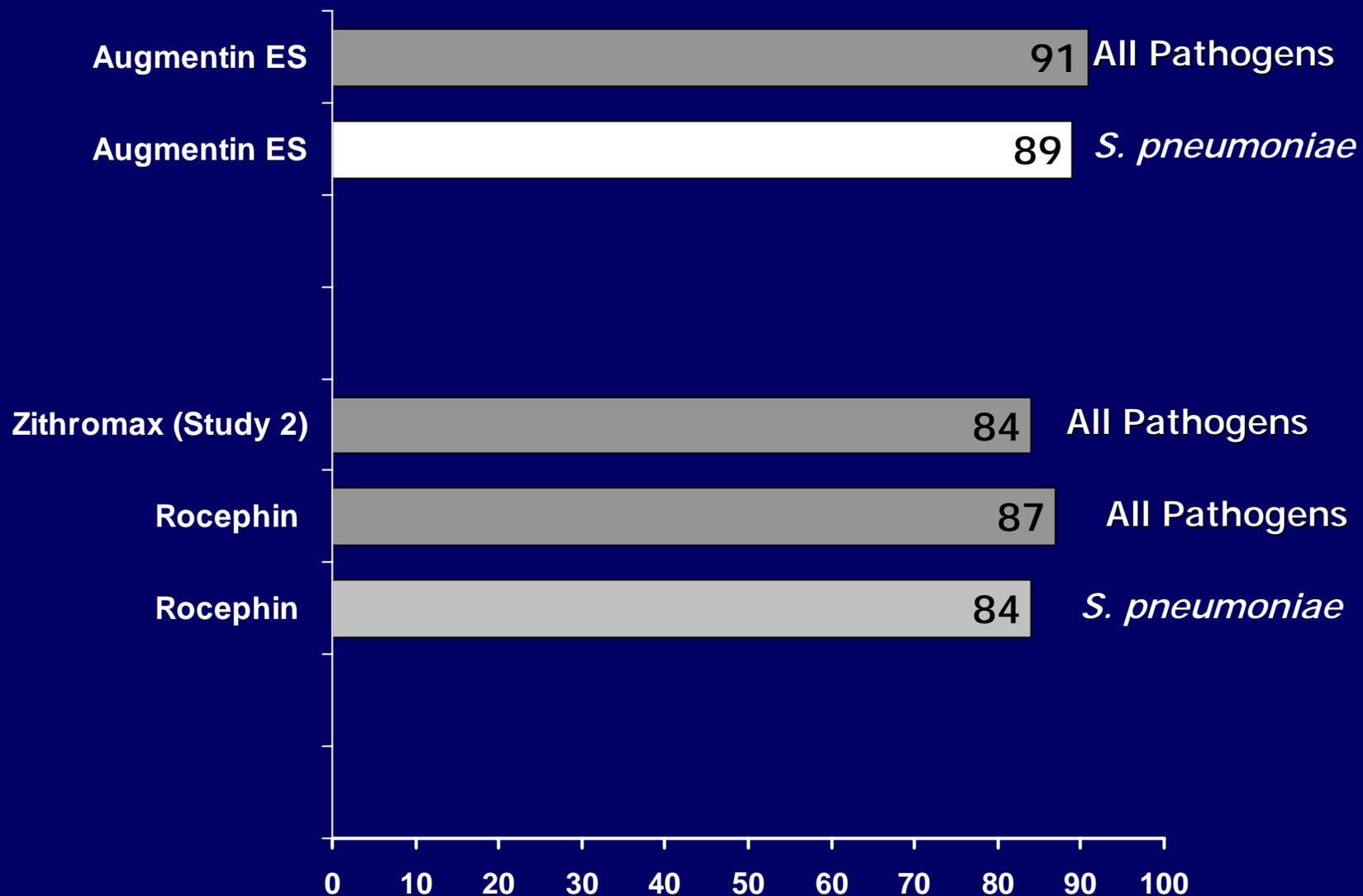
Note: comparator rates are taken from clinical trials of agents licensed for acute otitis media as reported in the product labeling or the SBA

High Clinical Success at EOT for *Augmentin ES* Compared to other Drugs (Studies w/ Bacteriology)



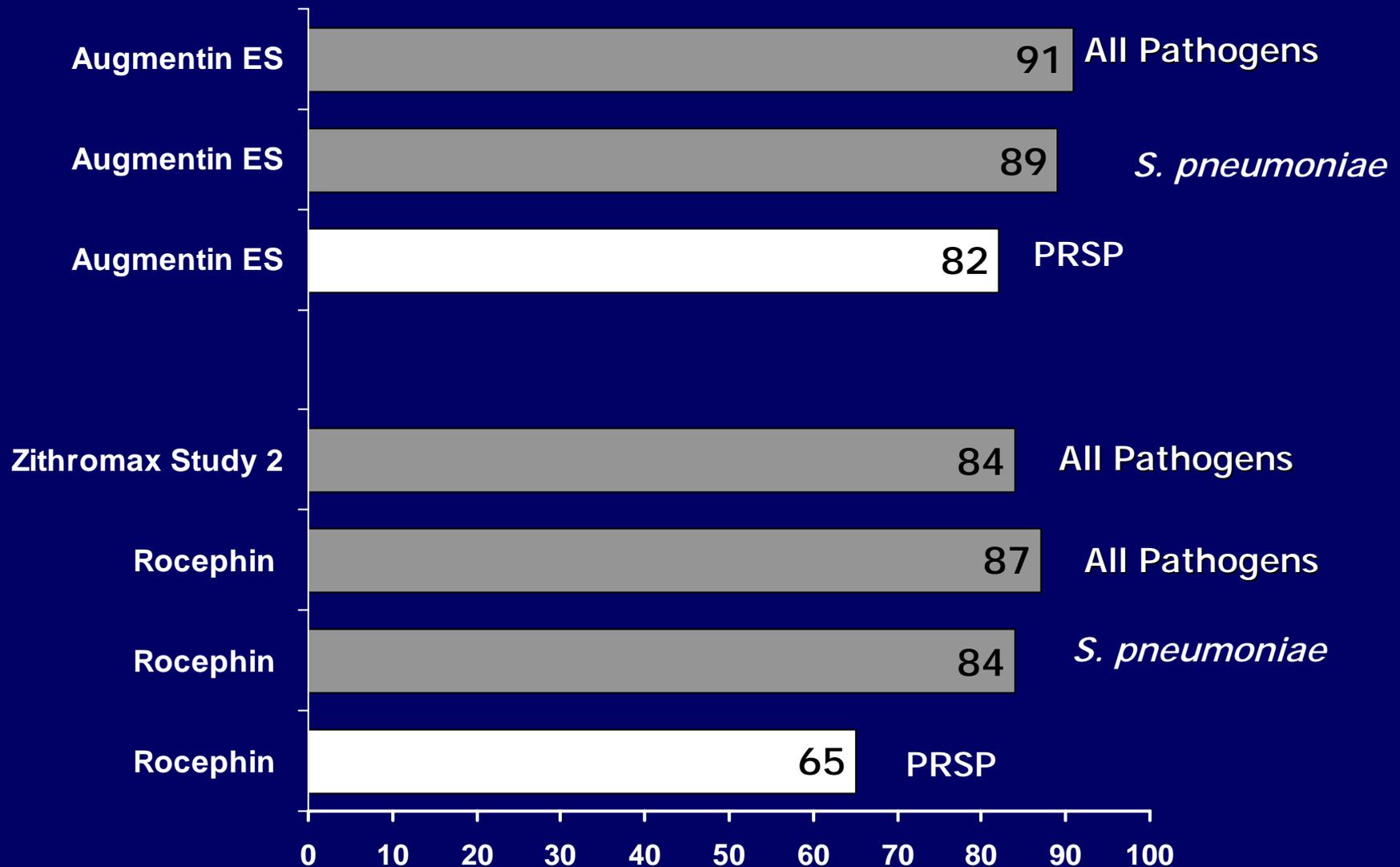
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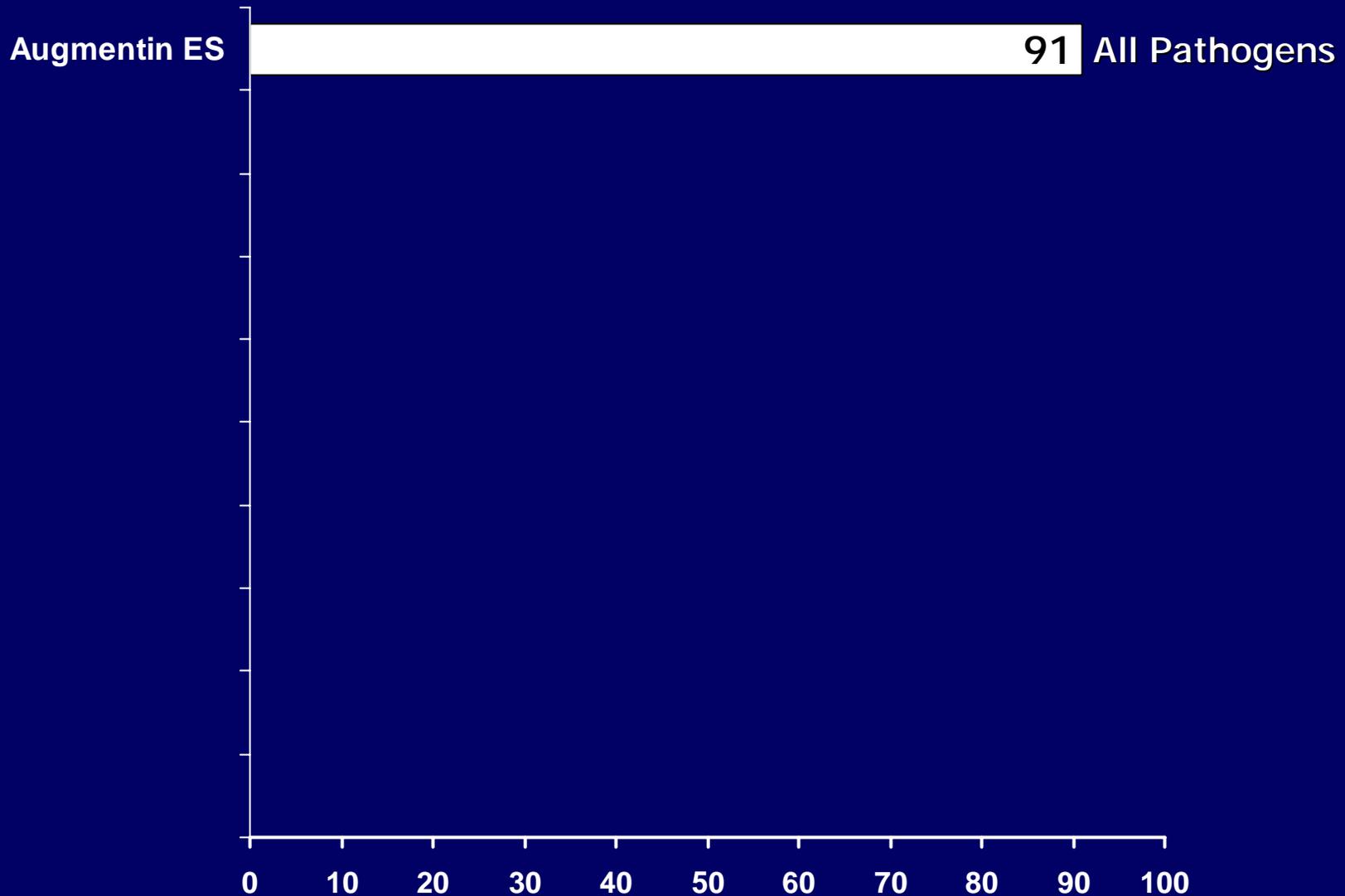
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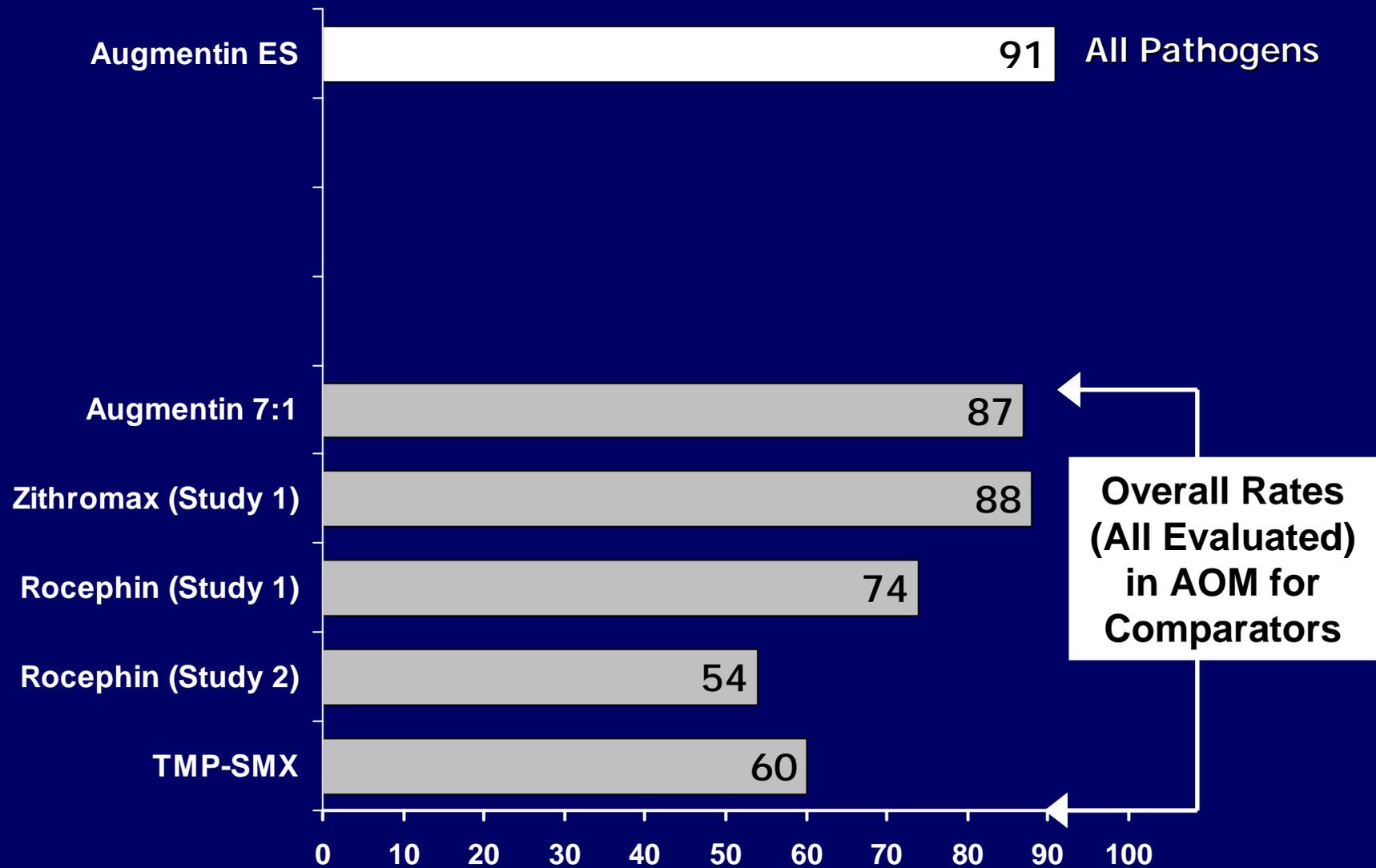
Clinical Studies
(All Evaluated, No Baseline Bacteriology)

High Clinical Success at EOT for *Augmentin ES*



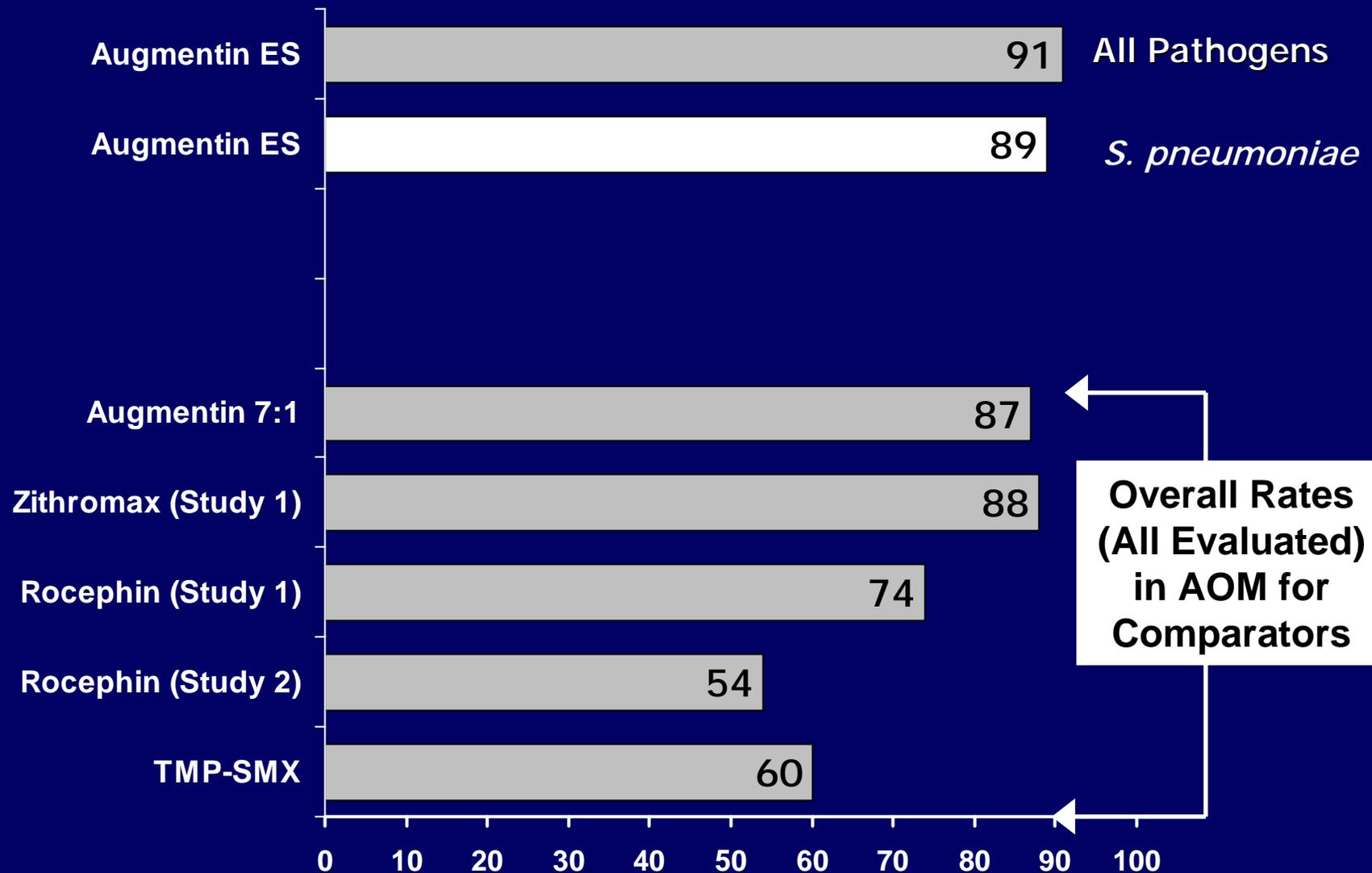
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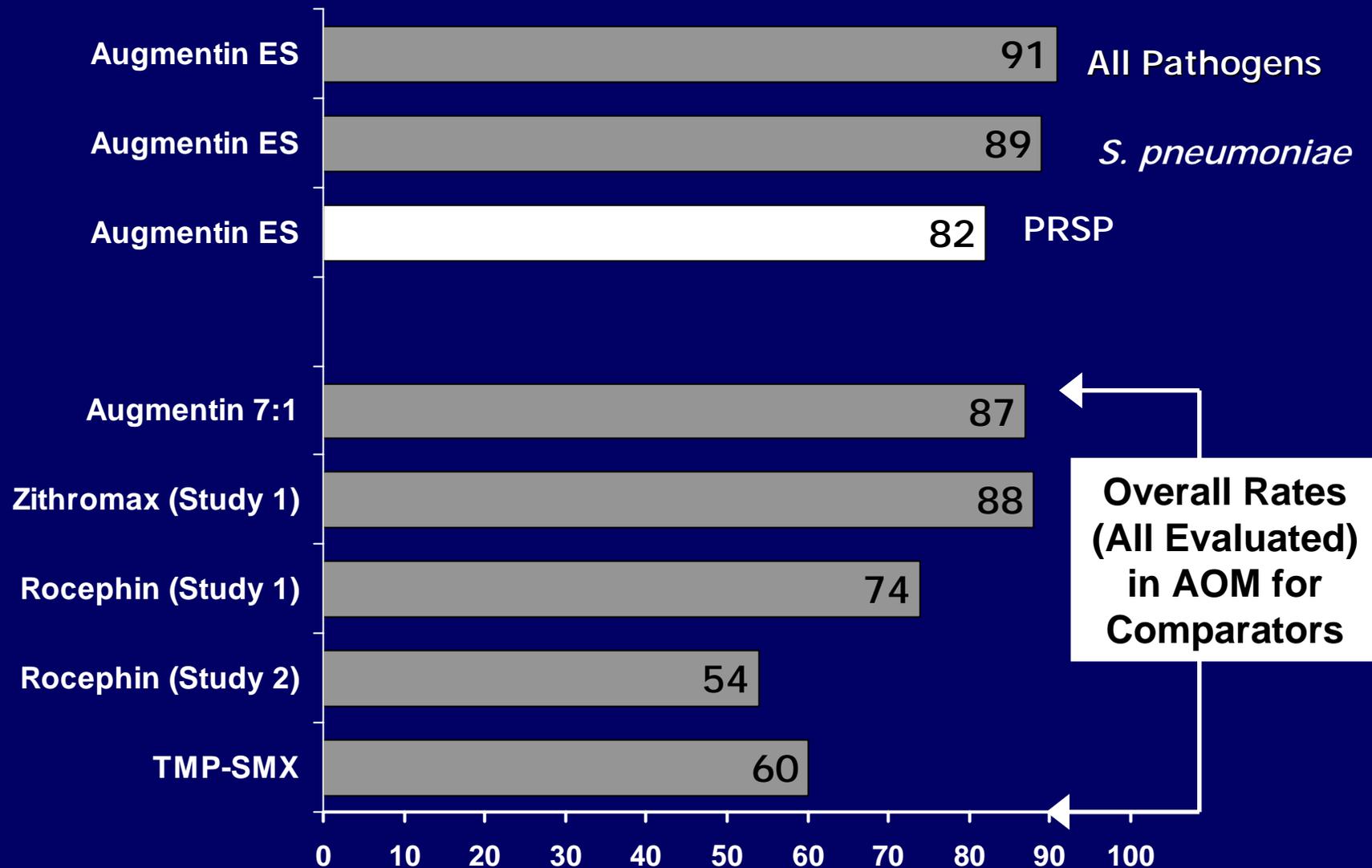
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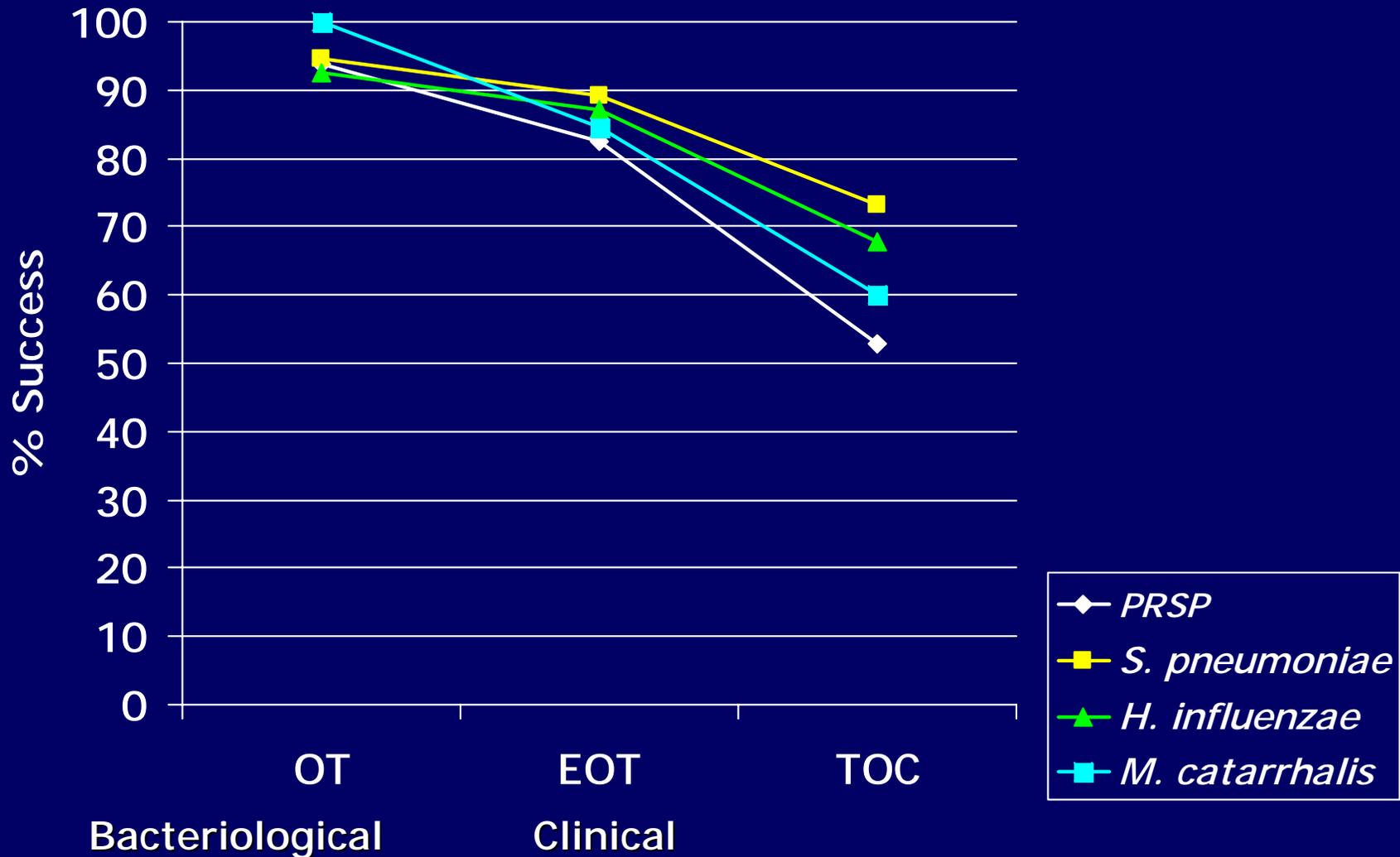
**What happens to clinical efficacy
after therapy stops?**

Historically Observed Rates for Reinfection in AOM

- Recurrences in 36 (35%) of 103 infants/children with AOM
- Of 29 children with repeat tympanocentesis:
 - 13 (45%) had no pathogen recovered
 - 12 (41%) had a new infection
 - 4 (14%) had a relapse with the same organism

Carlin et al. 1987. Early recurrences of OM: reinfection or relapse?
J. Pediatr, 110, 20-25.

Bacteriological Success (On-Therapy) and Clinical Success (EOT & TOC) by Baseline Pathogen



Respective PP Populations

Reinfection/recurrence is common in AOM patients in the weeks following successful treatment.

What factors contribute to higher rates of reinfection/lower clinical success rates observed at TOC for patients with PRSP?

Risk Factors for Recurrent AOM & PRSP

Risk Factors for Recurrent AOM

Age < 2 years

Age-related Siblings

Daycare Attendance

History of Recurrent AOM

Seasonal- Fall/Winter

Lower Socio-economic Class

Lack of Breastfeeding

Ethnic history

(Native American, Canadian Eskimo)

Exposure to Tobacco Smoke

Male

*Chartrand and Pong, Ped. Ann. 1998;
Klein, Clin. Inf. Dis. 1994*

Risk Factors for PRSP

Age < 2/3 years

Siblings

Daycare Attendance

History of Recurrent AOM

Winter

Recent treatment with
antibiotics/beta-lactams

*Chartrand and Pong, Ped. Ann. 1998;
Block, et al, Ped. Inf. Dis., 1995*

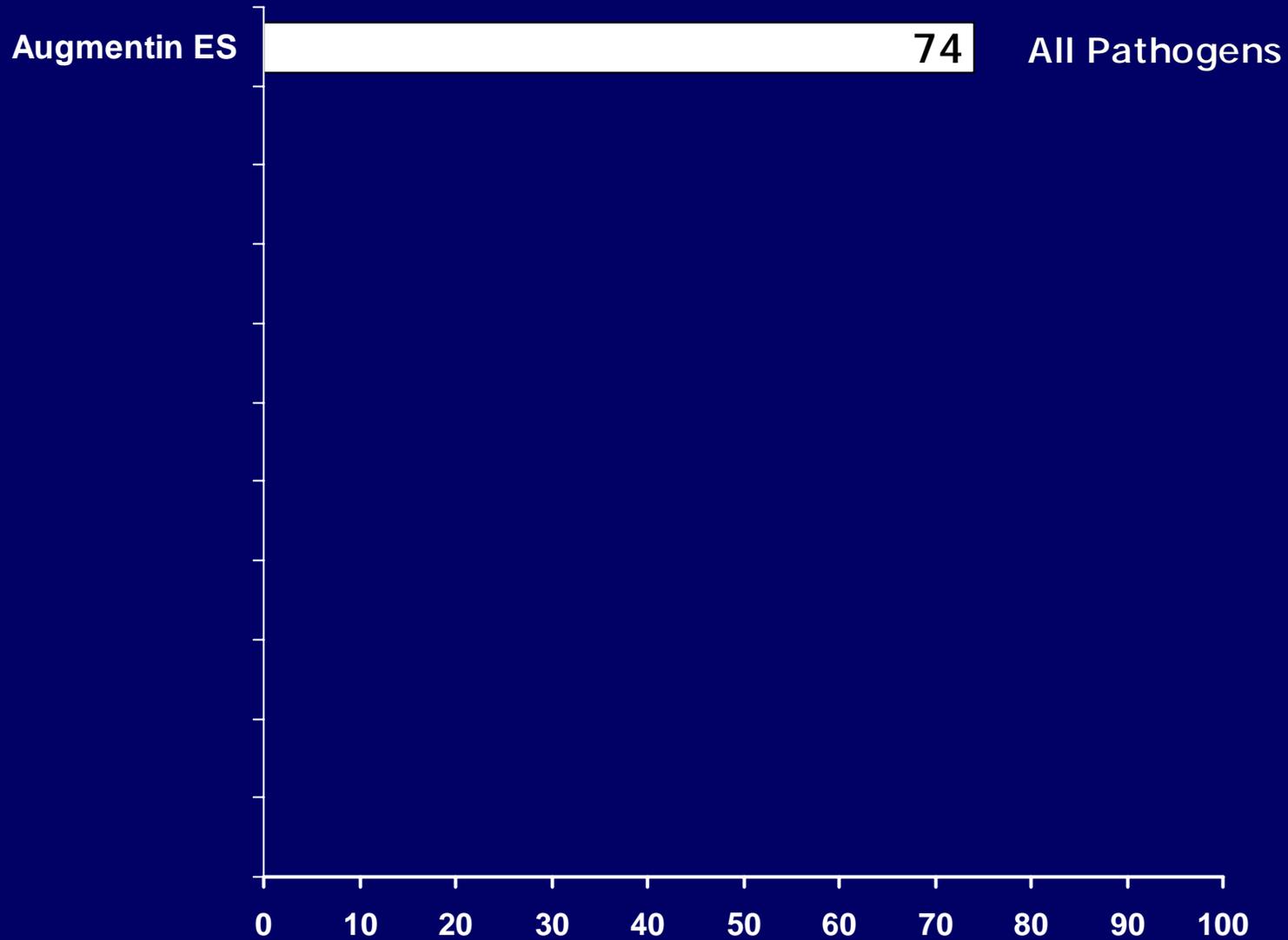
Retrospective Comparison of Known AOM Risk Factors in PRSP vs PSSP* Patients

| Risk Factor for Recurrent AOM | PRSP Patients N=34 | PSSP Patients N=97 | p-Value |
|---|-----------------------|-----------------------|---------|
| Age in Months (mean) | 13.4 | 18.8 | 0.0063 |
| Prior History of AOM | 59% | 36% | 0.027 |
| Received Antibiotics in Previous 3 mos. | 77% | 42% | 0.004 |
| Attended Daycare | 41% | 36% | NS |
| Male | 59% | 51% | NS |
| Siblings | 73% | 68% | NS |

* Penicillin MIC < 2 mcg/mL

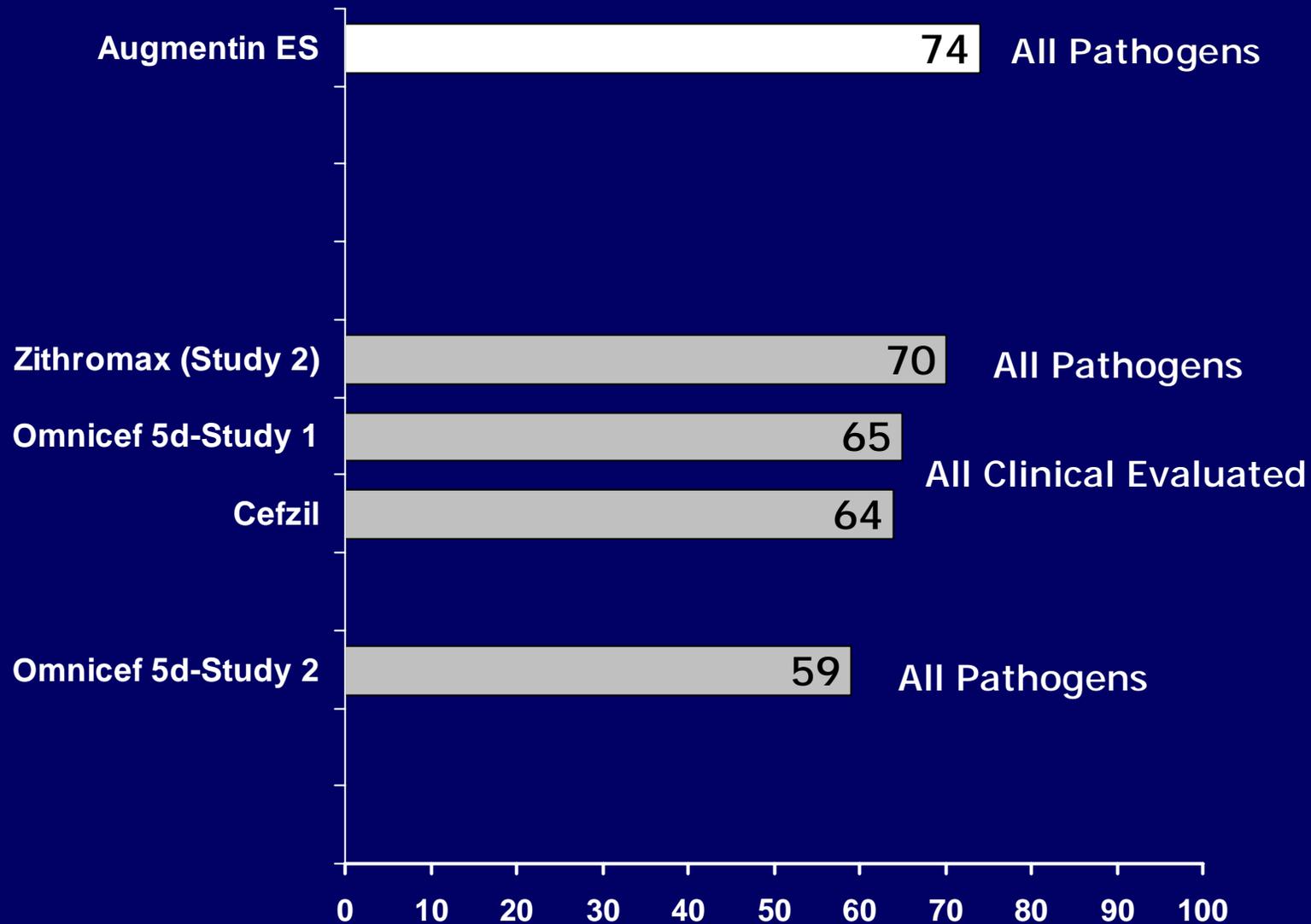
How does the TOC clinical efficacy of *Augmentin ES* compare to currently approved drugs?

Clinical Success at TOC for *Augmentin ES*



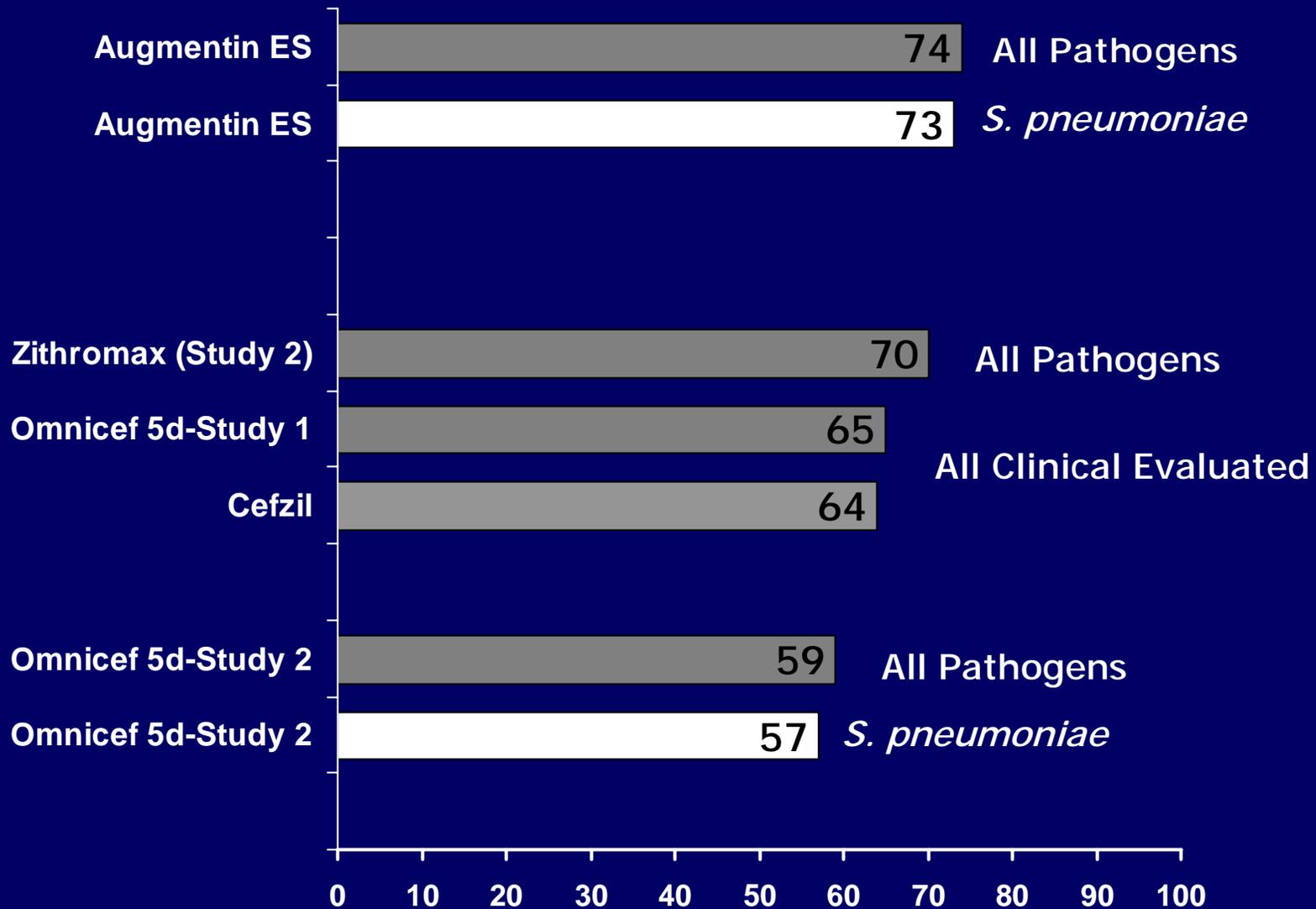
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Clinical Success at TOC for *Augmentin* ES and Other Drugs (Studies w/Bacteriology)



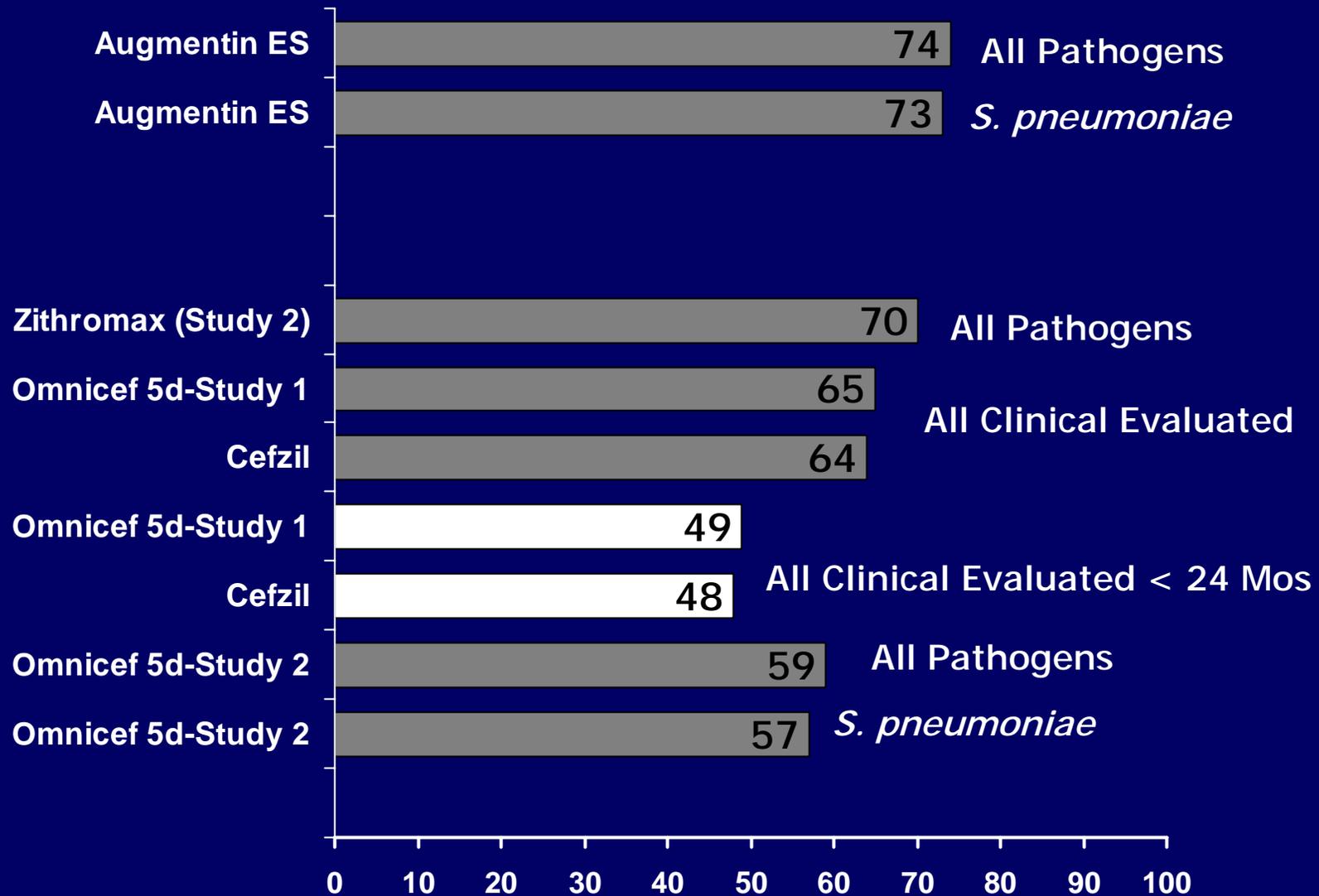
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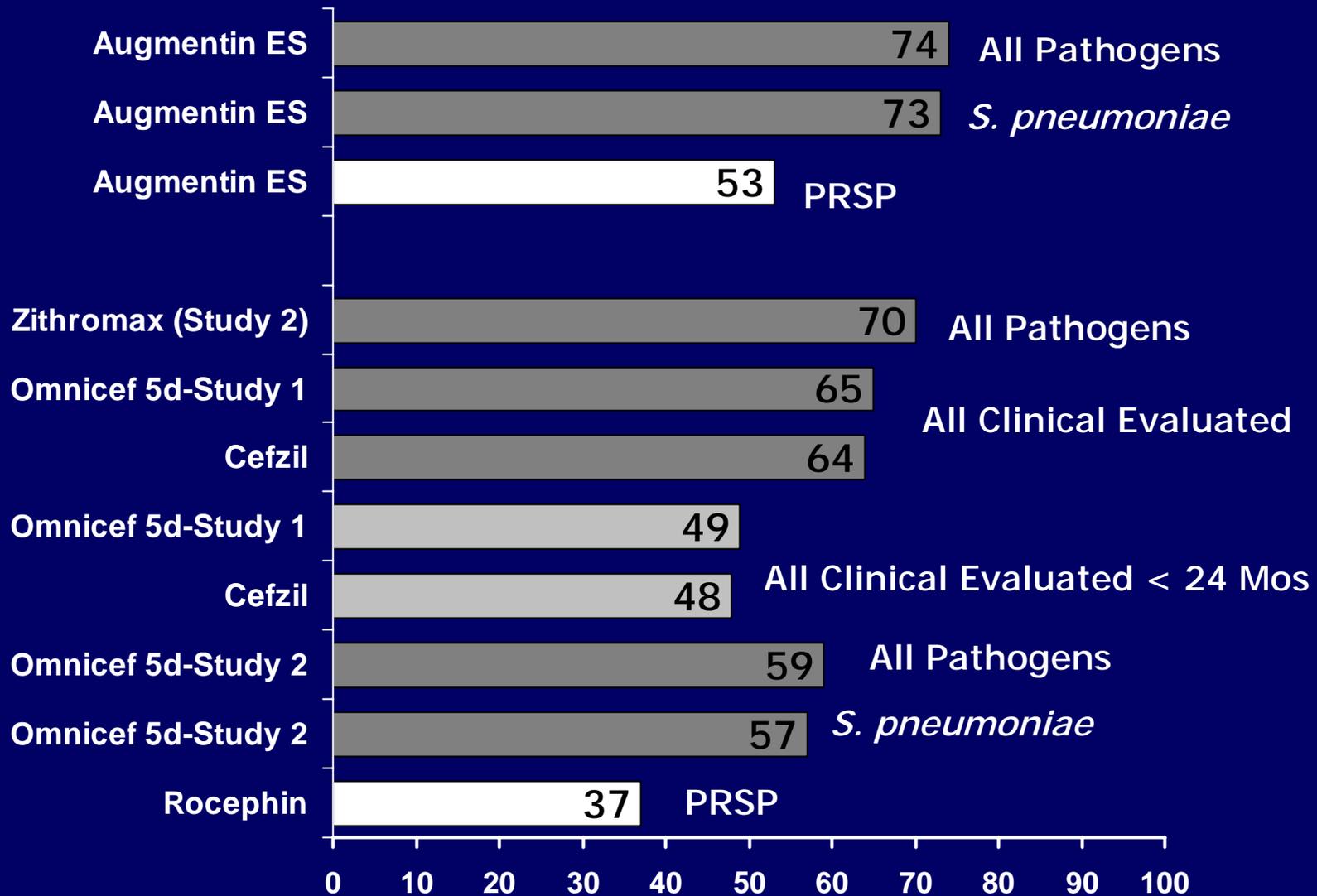
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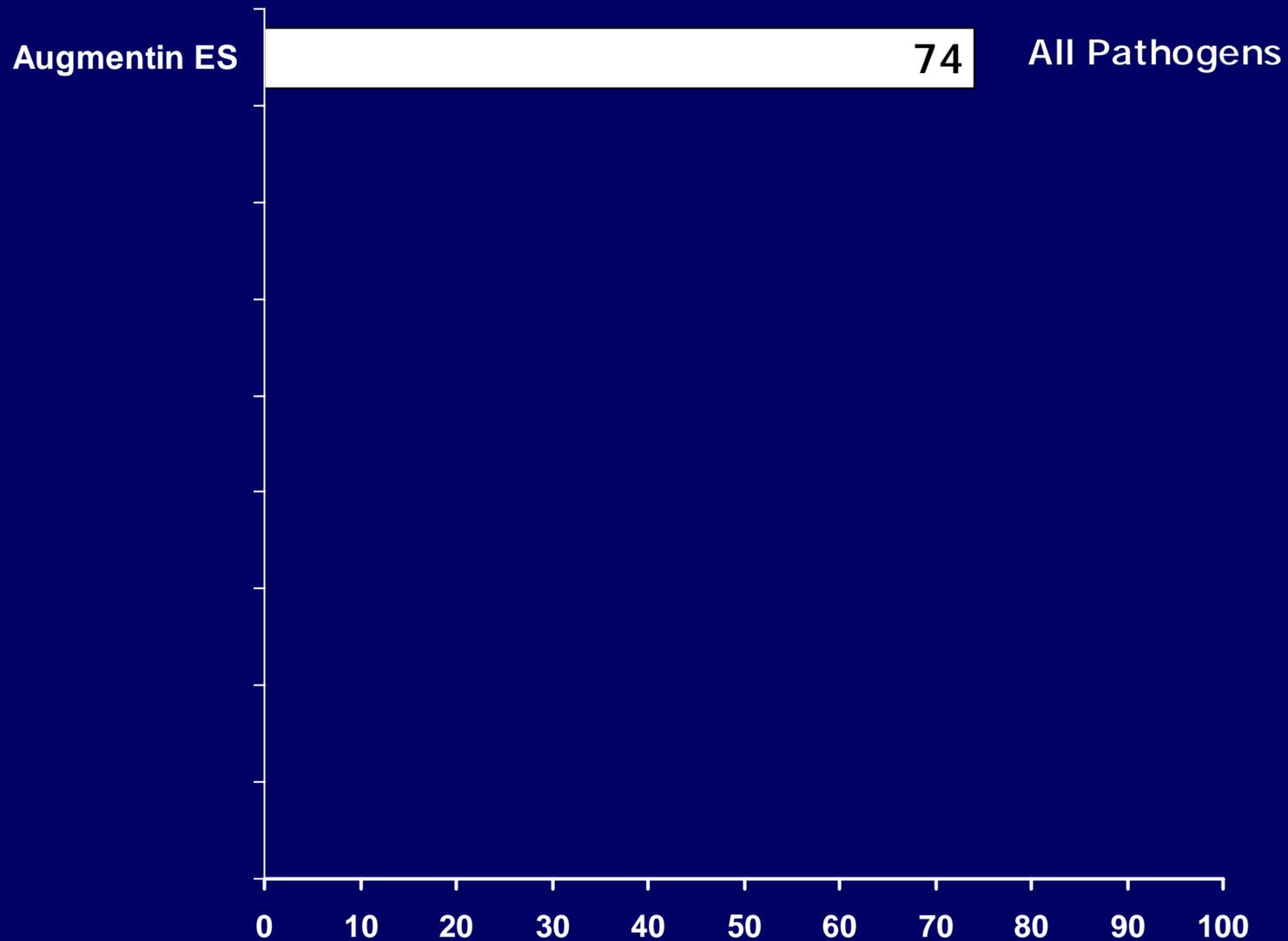
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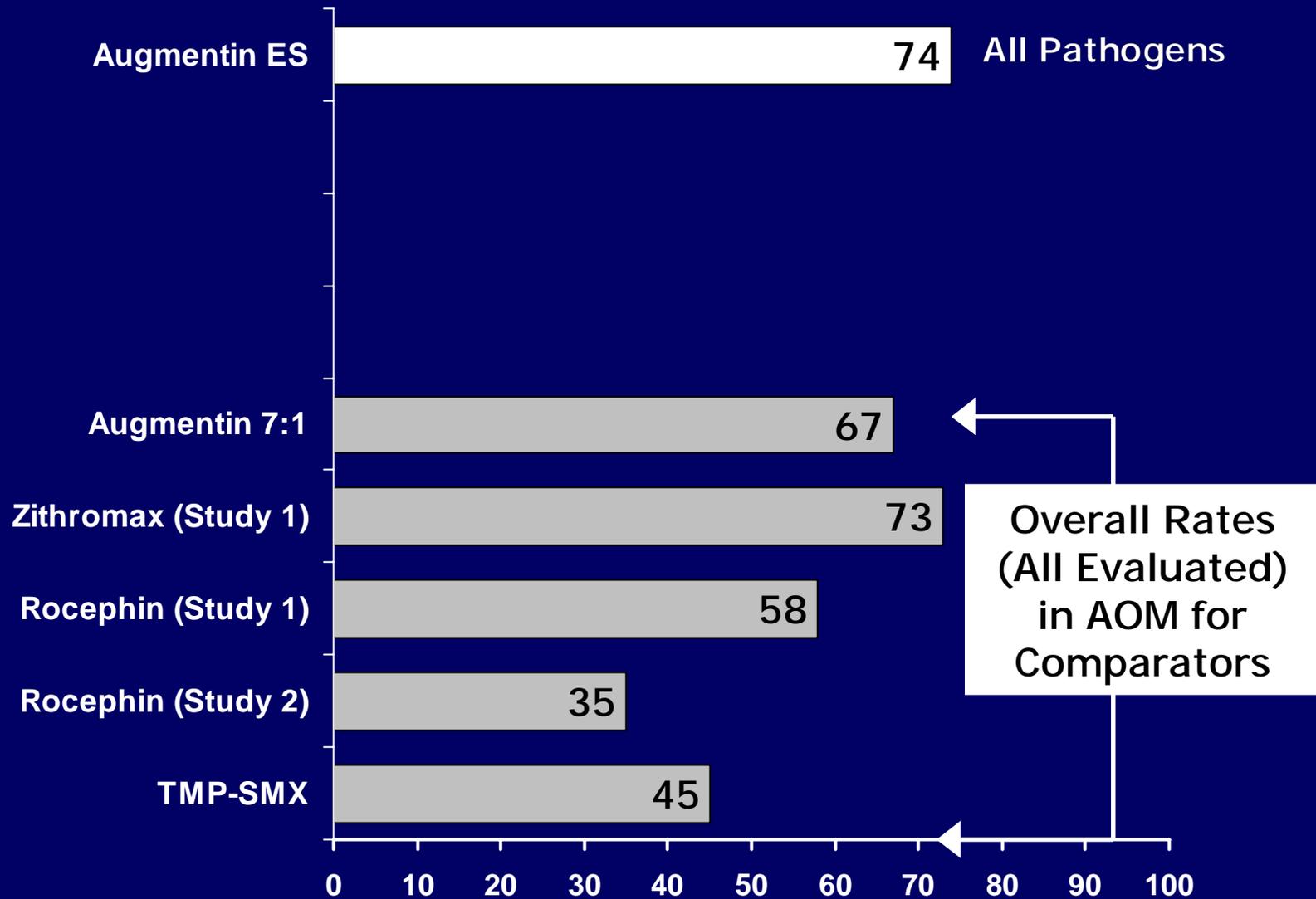
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Clinical Success at TOC for *Augmentin ES*



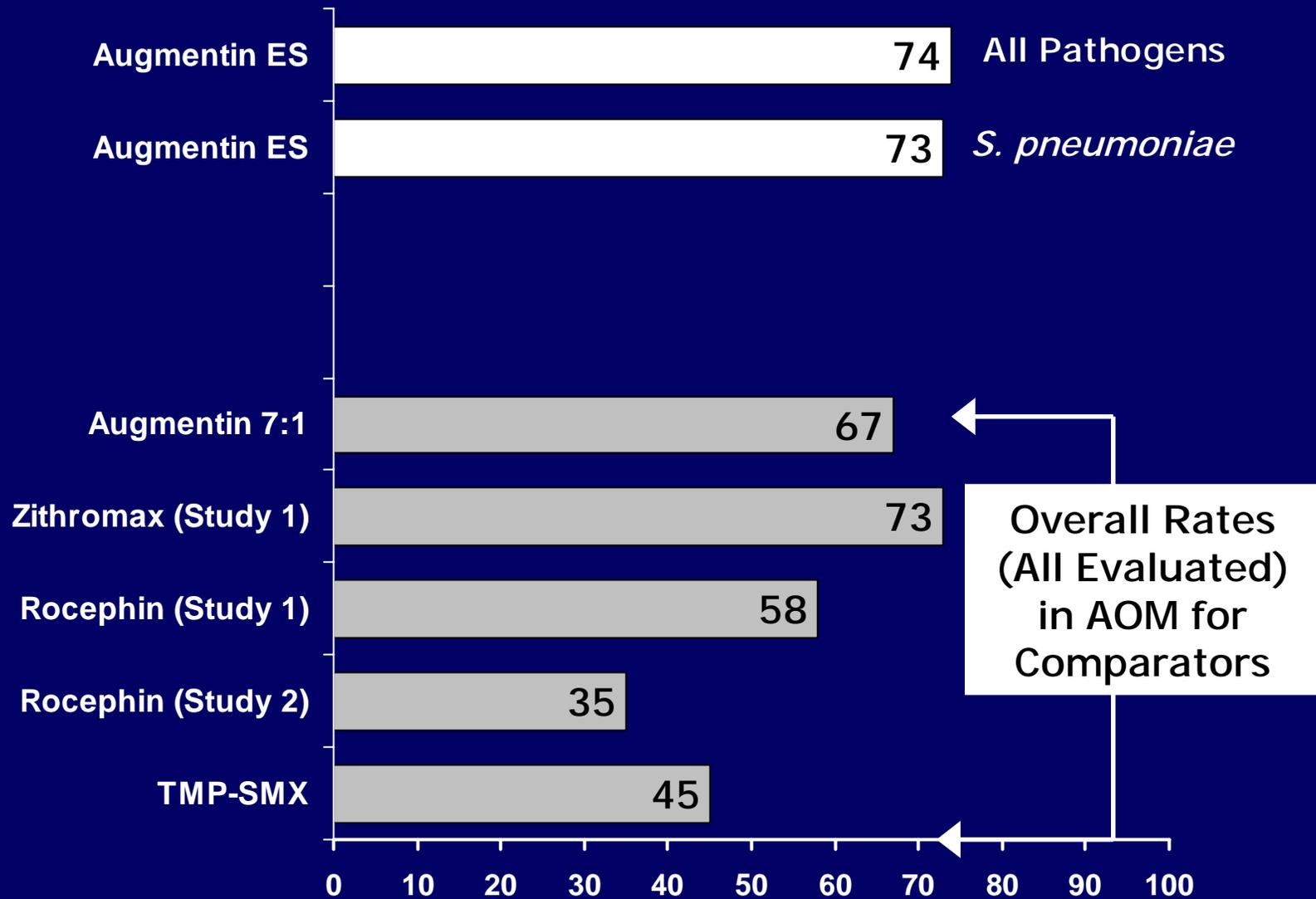
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Clinical Success at TOC for *Augmentin* ES and Other Drugs (Clinical Studies)



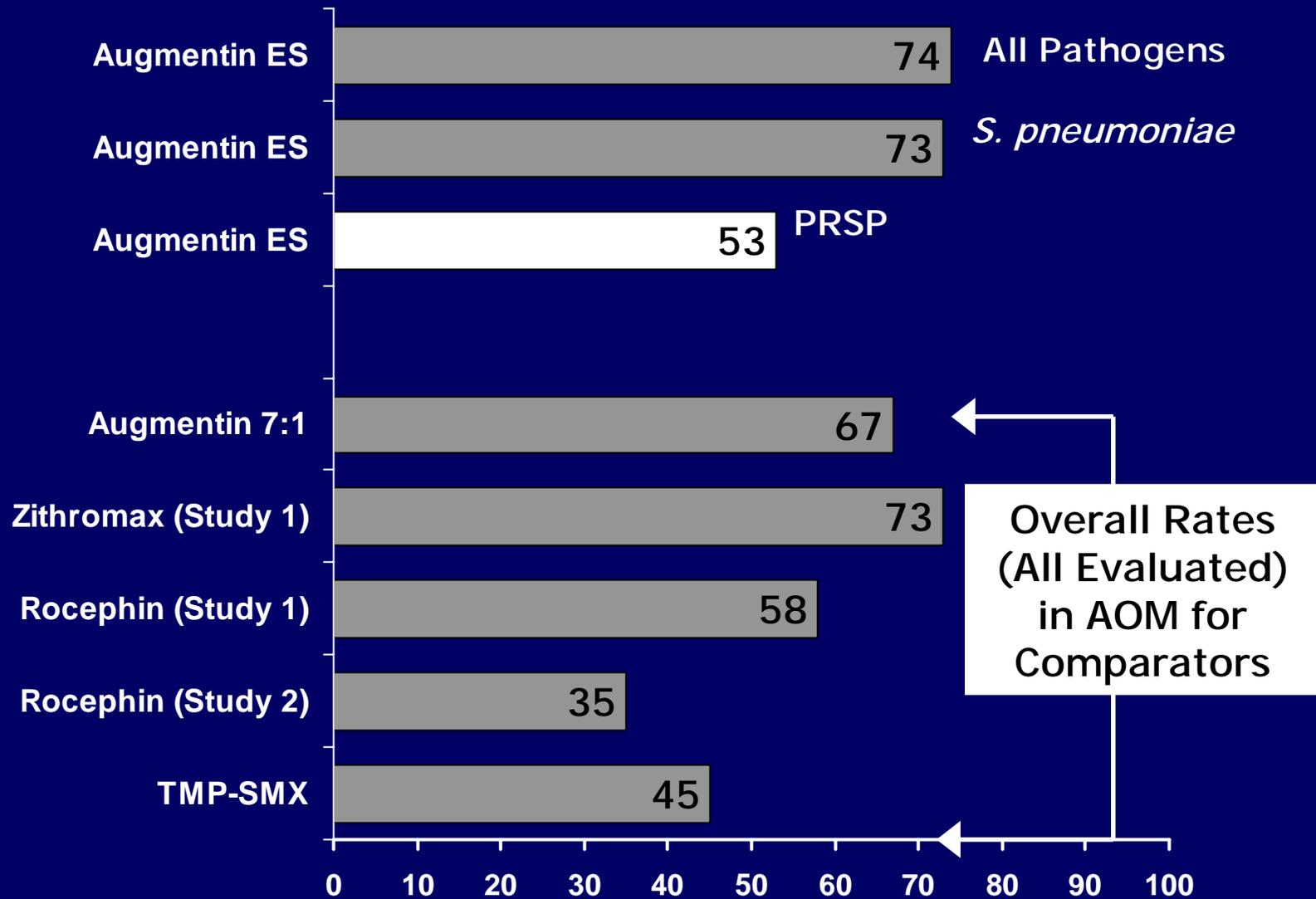
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Clinical Success at TOC for *Augmentin* ES and Other Drugs (Clinical Studies)



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Clinical Success at TOC for *Augmentin* ES and Other Drugs (Clinical Studies)



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PRSP Conclusion

- Excellent bacteriological and clinical efficacy in AOM caused by *S. pneumoniae*, including PRSP

**Efficacy vs. *S. pneumoniae* with
Amoxicillin/Clavulanic Acid
MIC = 4 mcg/mL**

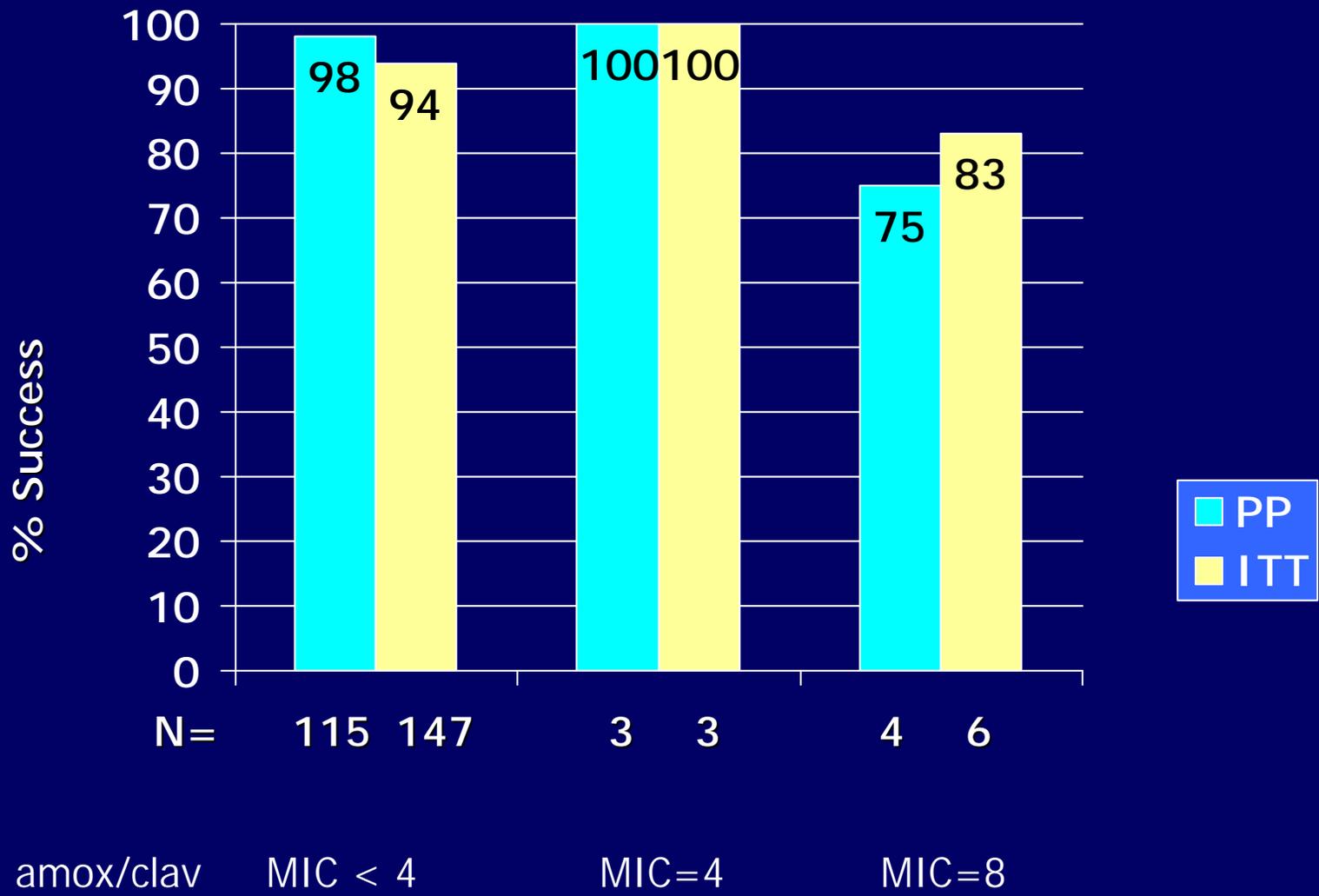
November 1999 Analysis

- 41 PRSP Isolates (PCN MIC_≥ 2 mcg/mL)

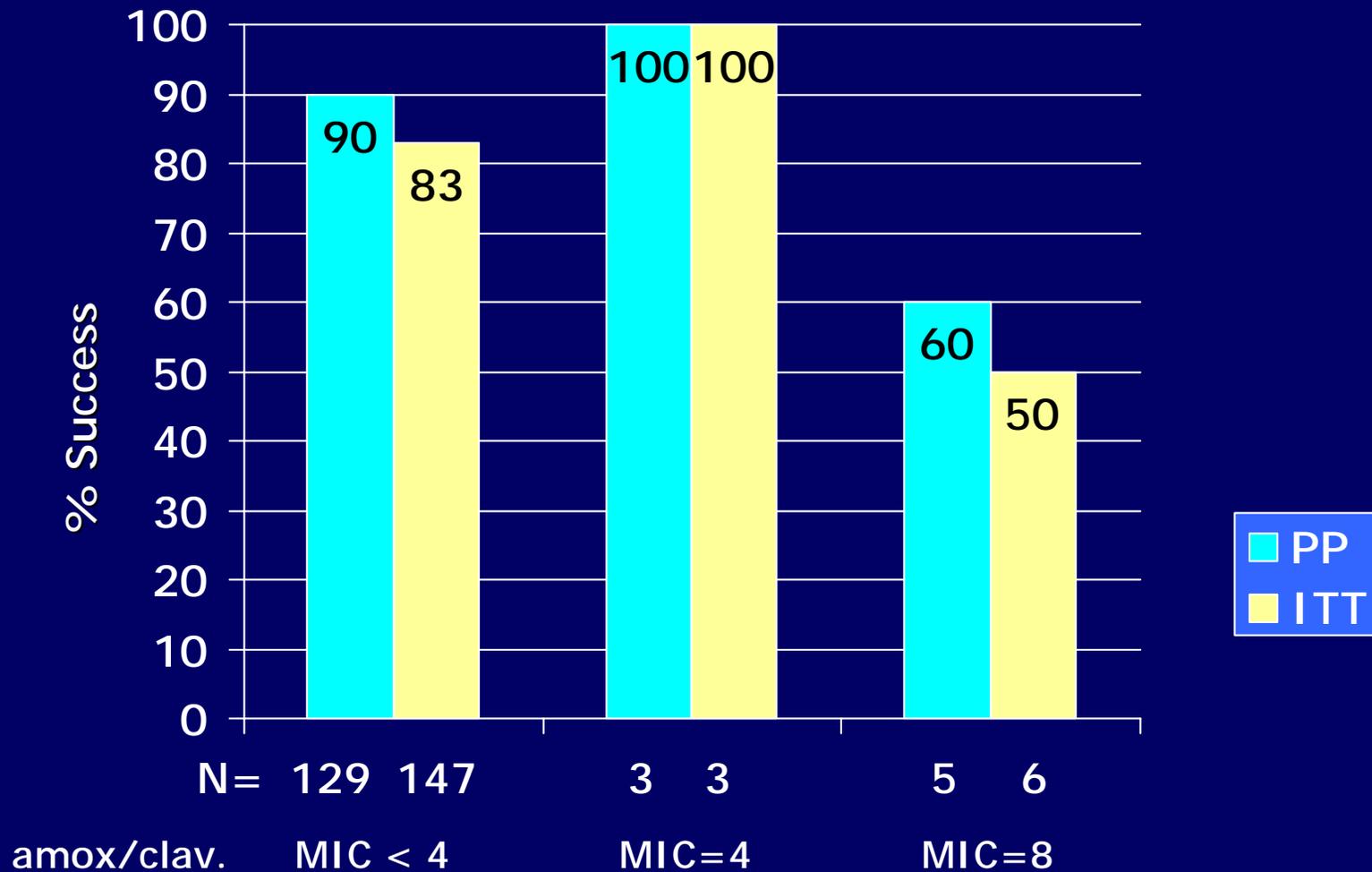
- Amox/Clav MIC Bact. PP (ITT)
 4 mcg/mL 3 (3)
 8 mcg/mL 4 (6)

- Reviewed by Agency

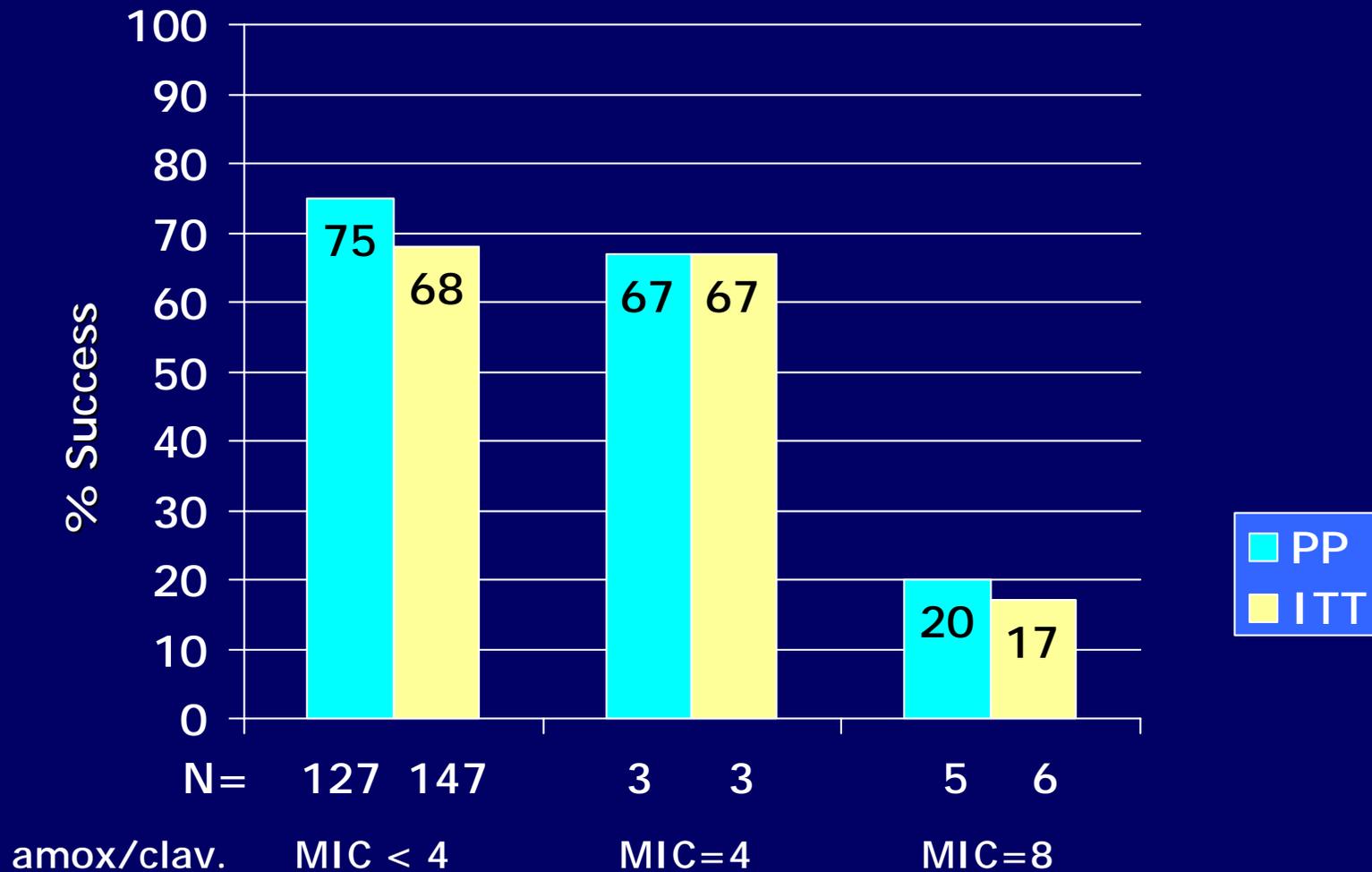
High Bacteriological Success *S. pneumoniae* with Amox/Clav MIC = 4 mcg/mL (November 1999)



High Clinical Success at EOT
S. pneumoniae Amox/Clav. MIC = 4 mcg/mL
(November 1999)



High Clinical Success at TOC
S. pneumoniae Amox/Clav. MIC = 4 mcg/mL
(November 1999)



Patients with *S. pneumoniae* with Amox/Clav MICs = 4 mcg/mL June 2000 Analysis

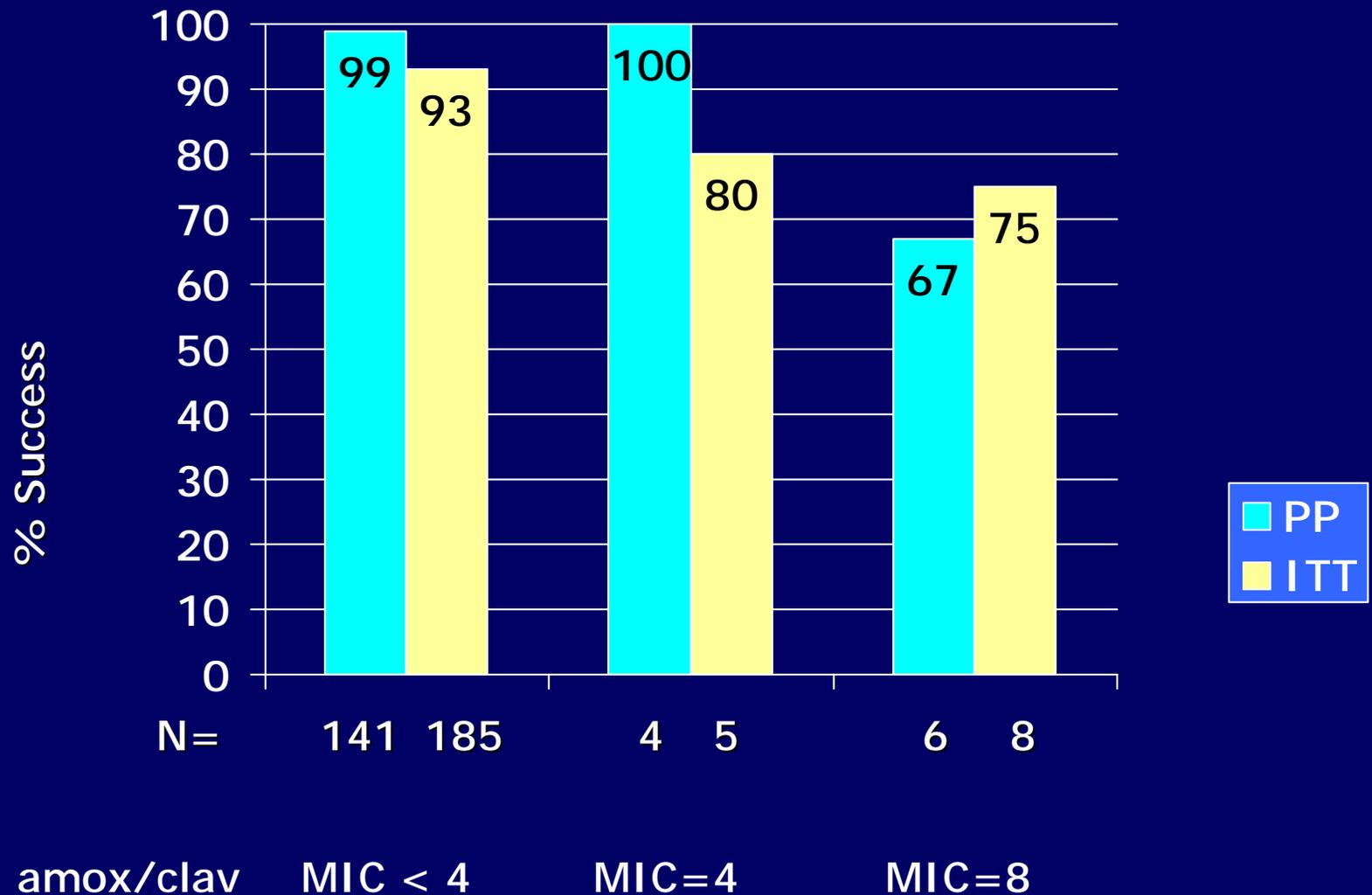
- Investigators instructed to continue to enroll patients until June 2000 in order to attain additional patients with amox/clav MIC=4 mcg/mL for the final analysis
- Two additional *S. pneumoniae* isolates at MIC of 4 and 2 at an MIC of 8 mcg/mL

**Patients with *S. pneumoniae* with
Amox/Clav MICs = 4 and 8 mcg/mL
June Analysis**

| Amox/Clav MIC | Bact. PP (ITT) |
|----------------------|-----------------------|
| 4 mcg/mL | 4 (5) |
| 8 mcg/mL | 6 (8) |

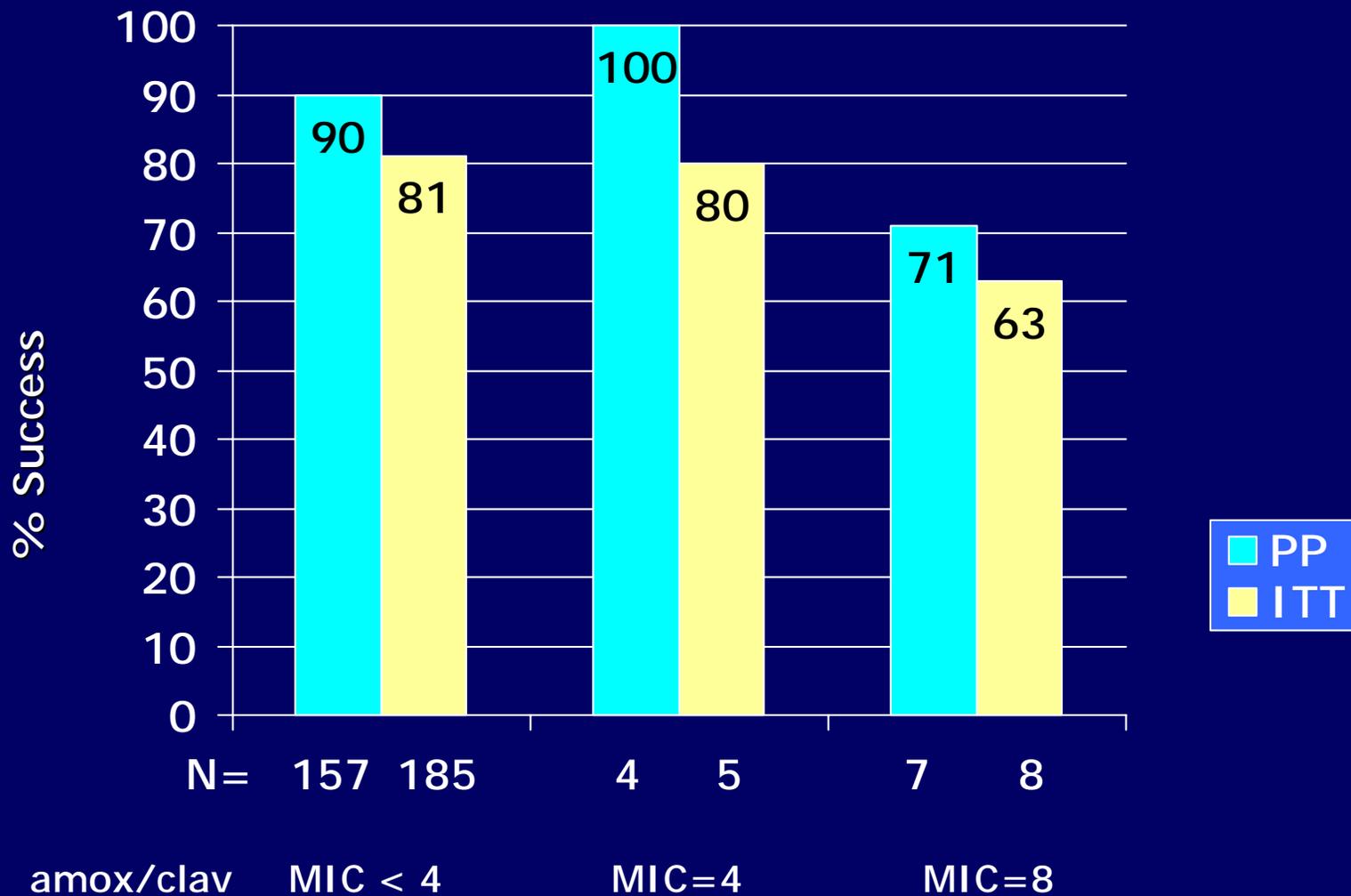
2 additional patients at amox/clav MIC = 4, 8

High Bacteriological Success *S. pneumoniae* with Amox/Clav MIC = 4 mcg/mL (June 2000)

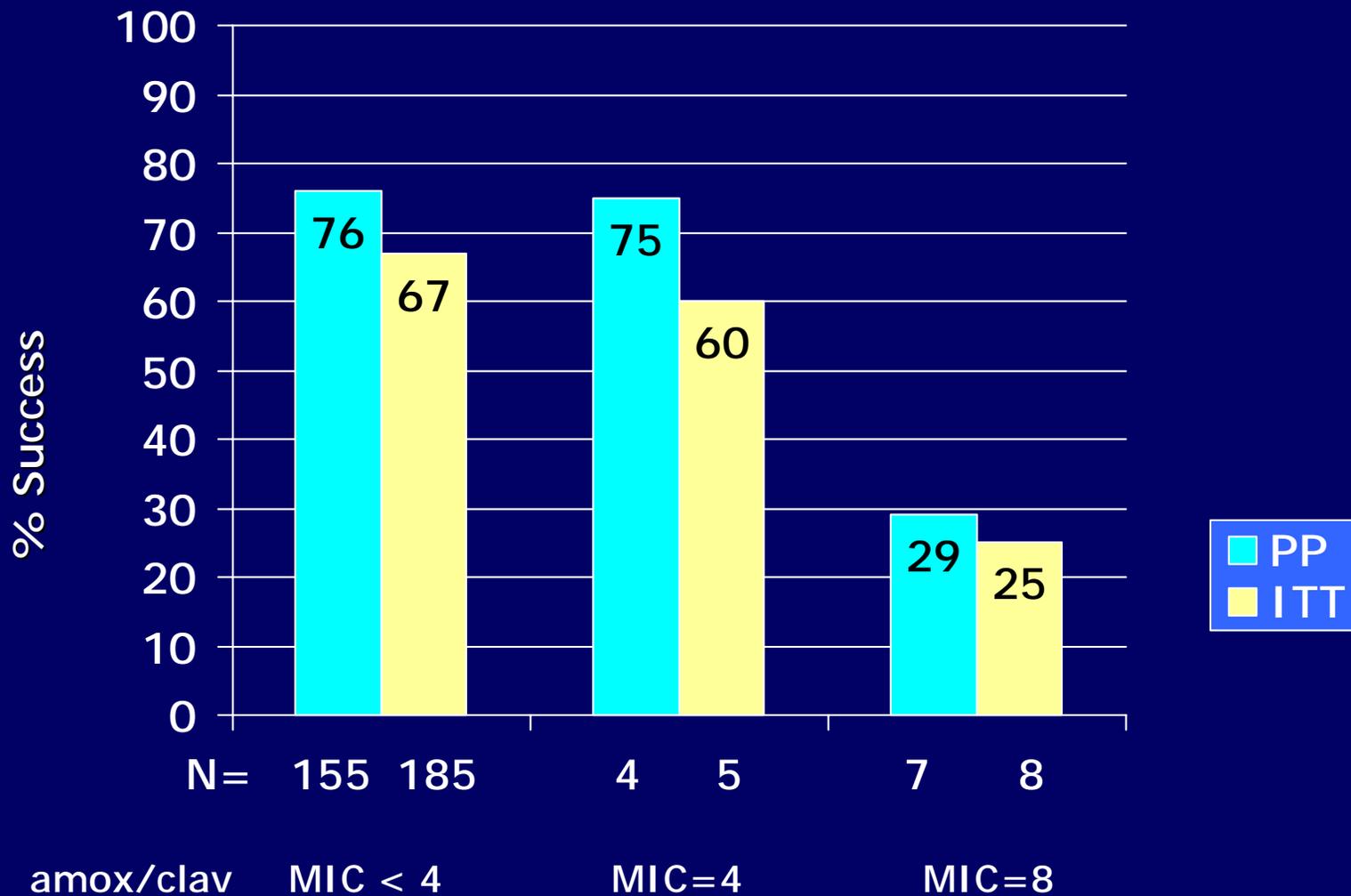


High Clinical Success at EOT

S. pneumoniae with Amox/Clav MIC = 4 mcg/mL
(June 2000)



High Clinical Success at TOC *S. pneumoniae* with Amox/Clav MIC = 4 mcg/mL (June 2000)



**Summary of High Bacteriological (OT)
and Clinical Response (EOT&TOC) Rates
S. pneumoniae with Amox/Clav MIC 4 mcg/mL
(June 2000)**

| Amox/clav MIC = 4 | PP, % success | | ITT, % success | |
|-----------------------------|---------------|-------|----------------|------|
| Bacteriological Response OT | 4/4 | (100) | 4/5 | (80) |
| Clinical Response EOT | 4/4 | (100) | 4/5 | (80) |
| Clinical Response TOC | 3/4 | (75) | 3/5 | (60) |
| Amox/clav MIC=8 | PP, % success | | ITT, % success | |
| Bacteriological Response OT | 4/6 | (67) | 6/8 | (75) |
| Clinical Response EOT | 5/7 | (71) | 5/8 | (63) |
| Clinical Response TOC | 2/7 | (29) | 2/8 | (25) |

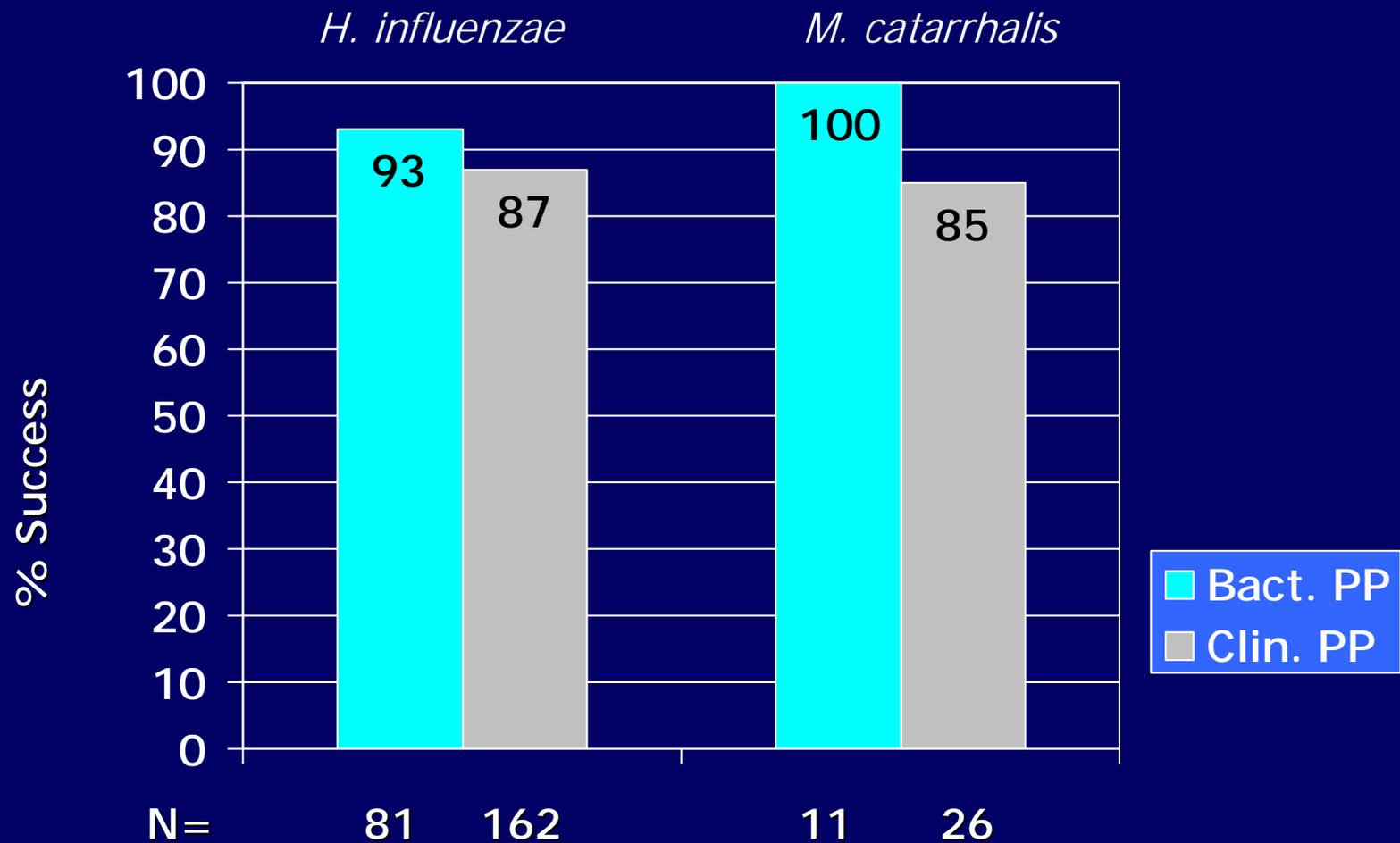
Efficacy Conclusions

Amox/Clav MIC \leq 4 mcg/mL

- Clinical trial data support the efficacy of *Augmentin* ES against *S. pneumoniae* with amox/clav MIC \leq 4 mcg/mL
- Lesser efficacy at amox/clav MIC = 8 mcg/mL
- Both results consistent with predictions from the PK/PD model

**Efficacy in Patients with
 β -Lactamase Producing
Organisms**

High On-Therapy Bacteriological Success & Clinical Success at EOT by Baseline Pathogen



Safety Summary of *Augmentin* ES

- Overall, excellent safety profile
- Similar to that of the currently marketed 7:1 formulation in a comparative study trial
- Builds on 20+ years of *Augmentin* in children & adults worldwide

Conclusions

Augmentin ES Conclusions

- Excellent clinical and bacteriologic efficacy in children with AOM caused by key pathogens, including PRSP
- PK/PD (46% T>MIC at 4 mcg/mL), *in vivo* and clinical data all support efficacy against isolates of *S. pneumoniae* with amox/clav MIC \leq 4 mcg/mL

Augmentin ES Conclusions

- Maintains excellent clinical and bacteriologic efficacy against β -lactamase producing organisms that cause AOM, including *H. influenzae* and *M. catarrhalis*
- Maintains the safety profile of the currently marketed formulation