Early oral step-down to amoxicillin is safe and effective for children hospitalised with severe community-acquired pneumonia: the PediCAP trial

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Conflict of Interest to declare

- Study drugs were donated by Sandoz. Sandoz did not participate in the design of the trial or analysis of the data

- No other conflicts to declare

PediCAP background

- Recent trials in non-severe (mild-moderate) pneumonia have demonstrated shorter antibiotic courses are safe and effective
- Recommendations for IV to oral stepdown supported by limited trial evidence and safe overall duration unknown
- High uptake of PCV resulting in uncertainty about optimal antibiotic for oral stepdown

- Shorter treatment with oral stepdown for children initially admitted for treatment of severe pneumonia in sub-Saharan Africa could reduce:
  - Exposure to hospital and associated risk of nosocomial infection
  - Acquisition of resistant bacteria typical of hospital
  - Costs to healthcare system, families and society

PediCAP questions

1. Is oral step-down therapy safe (non-inferior) compared to WHO-recommended 5 days IV?

2. Is the rate of clinical cure superior with co-amoxiclav versus amoxicillin oral step-down therapy?

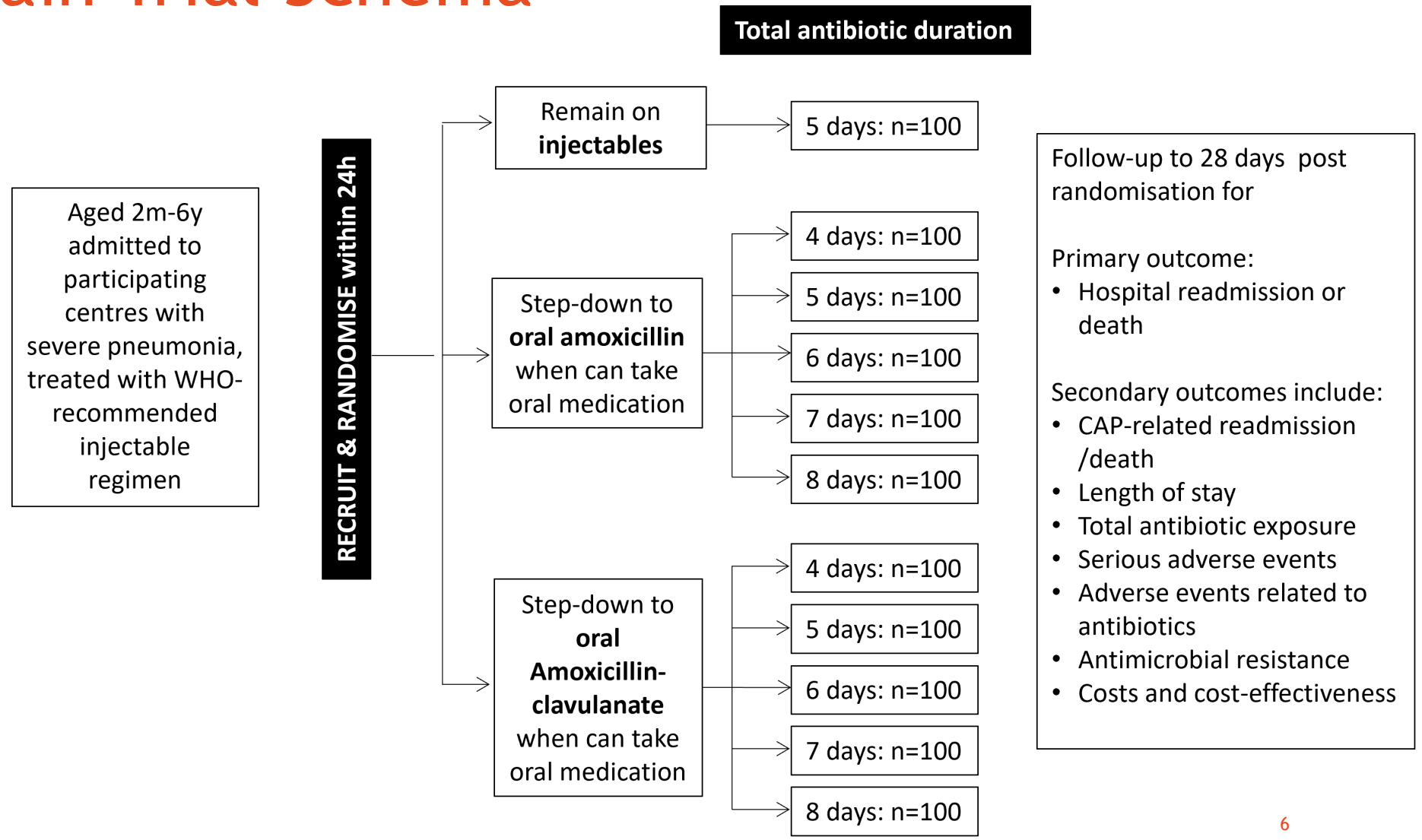
3. What is the **optimal total antibiotic treatment duration (iv+oral)** that achieves good rates of clinical cure whilst minimising length of hospital stay?

PediCAP trial: design and setting

- An open-label, parallel group, 2x5 factorial + 1 (IV only) randomised trial
  - Novel ‘MAMS-ROCI’ design*
- Children hospitalised with severe community acquired pneumonia in 13 African district and tertiary hospitals
  - Age 2m – 6y
  - Weight 3 – 30kg
  - CRP >10mg/L (point of care (POC) test)
  - Received <24 hours of antibiotics
- Recruitment Dec 2020 - Aug 2023
- COVID 19 precautions taken
- Participants received new dispersible tablet formulations

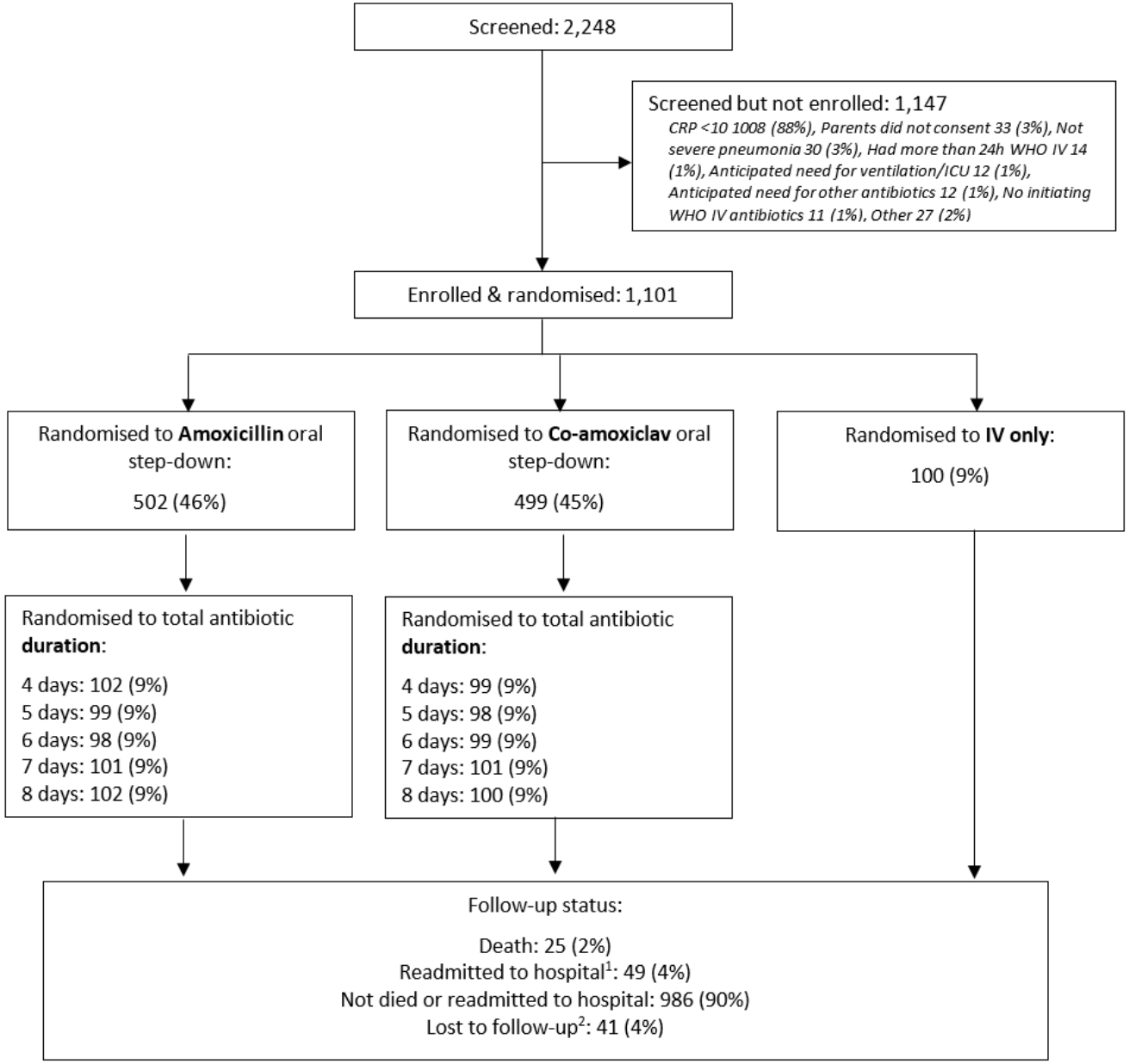
* Quartagno, Matteo, et al. "The DURATIONS randomised trial design: Estimation targets, analysis methods and operating characteristics." *Clinical Trials* 17.6 (2020): 644-653.

Main Trial Schema



Note: amoxicillin-clavulanate formulation 7:1

PediCAP – participant flow



Baseline

- 1,101 children randomised
- Mean age 19 months; median age 13 months
- 49% in weight band 6-10kg; 15% lower; 36% higher
- 1% known to be HIV positive
- 91% known to have had at least 1 PCV vaccine
- CRP (POC): 19% 10-40, 37% 40-80, 45% 80+ mg/L
- 62% on oxygen at baseline
- Differences between arms consistent with chance

Treatment – step-down to oral antibiotics

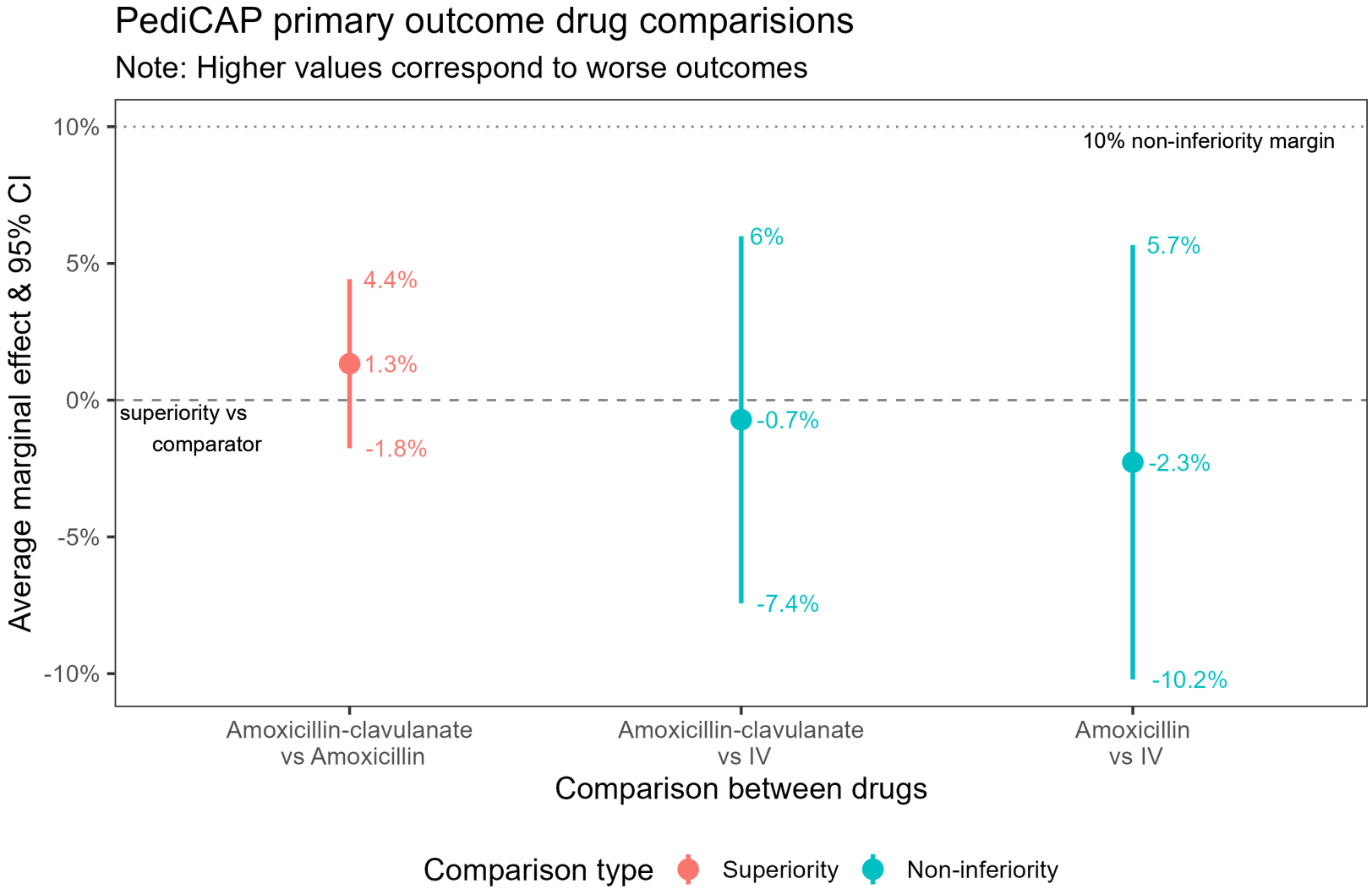
- Good compliance with protocol
- Children were stepped-down to their randomised oral formulation when clinicians judged them well enough to take dispersible tablets
- No evidence of differences in stepdown time between randomised oral arms
  - 68% stepped down on day 1-3; 18% did not step-down and only received IV antibiotics
- More children randomised to longer total duration arms were able to step-down within their randomised duration
  - 4 days: 69%
  - 5 days: 76%
  - 6 days: 85%
  - 7 days: 90%
  - 8 days: 92%

Treatment – total duration of IV+oral antibiotics

- Good compliance with protocol
- Slightly fewer children randomised to shorter total duration arms stepped-down, but most received their randomised total duration: mean antibiotic days was
  - 4 days: 4.4 days 86% within ±1 day
  - 5 days: 5.0 days 86% within ±1 day
  - 6 days: 6.2 days 93% within ±1 day
  - 7 days: 7.0 days 92% within ±1 day
  - 8 days: 8.0 days 96% within ±1 day
  - IV only: 5.4 days 87% within ±1 day

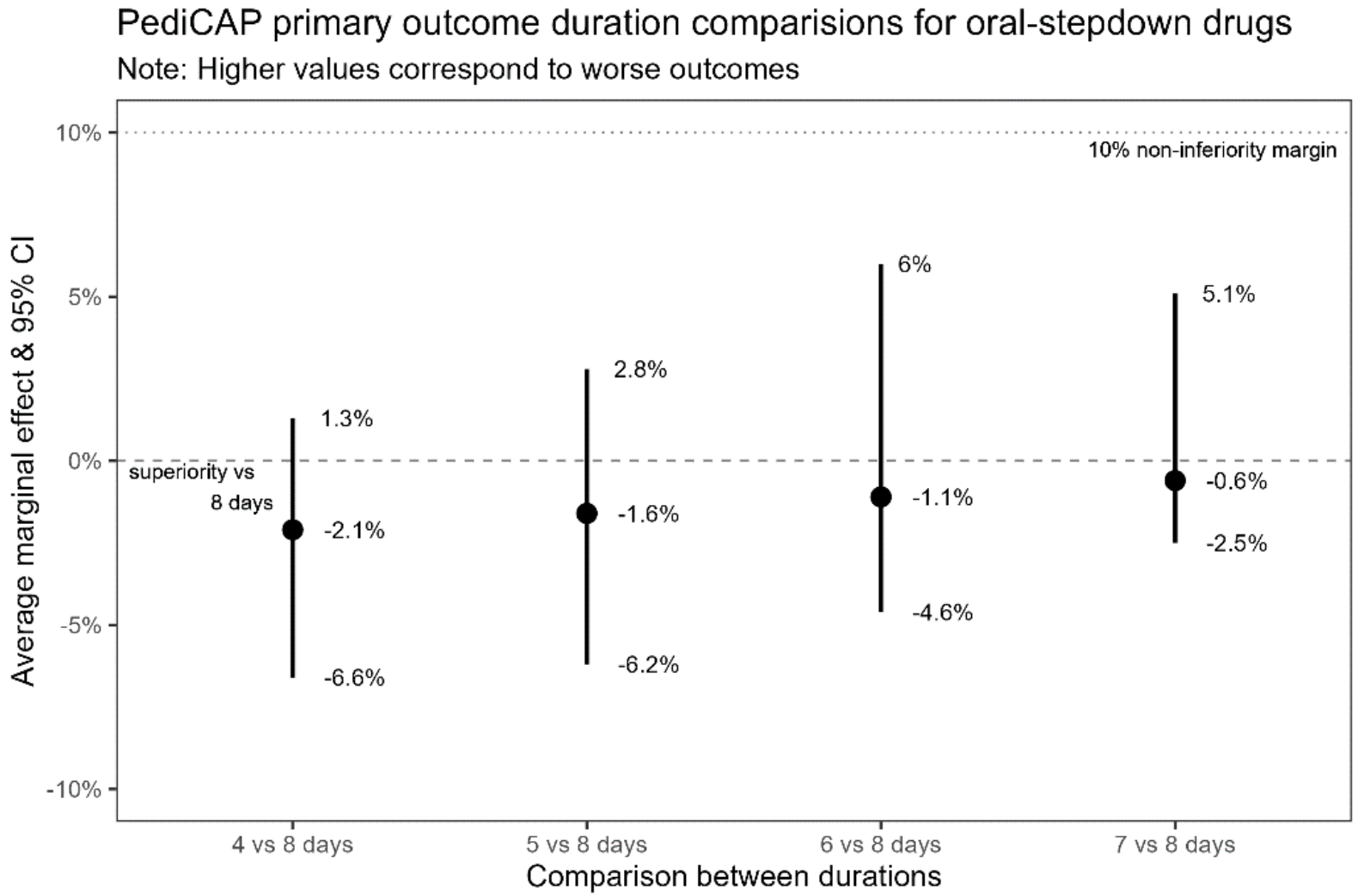
Impact of randomised drug on readmission /death within 28 days

- Event rates:
  - 6% amoxicillin arm,
  - 7% amoxicillin-clavulanate arm
  - 6% IV only arm
- No evidence coamox 7:1 superior to amoxicillin
- Co-amox 7:1 non-inferior to IV
- Amoxicillin non-inferior to IV



Impact of total IV+oral duration in oral stepdown arms on readmission / death within 28 days

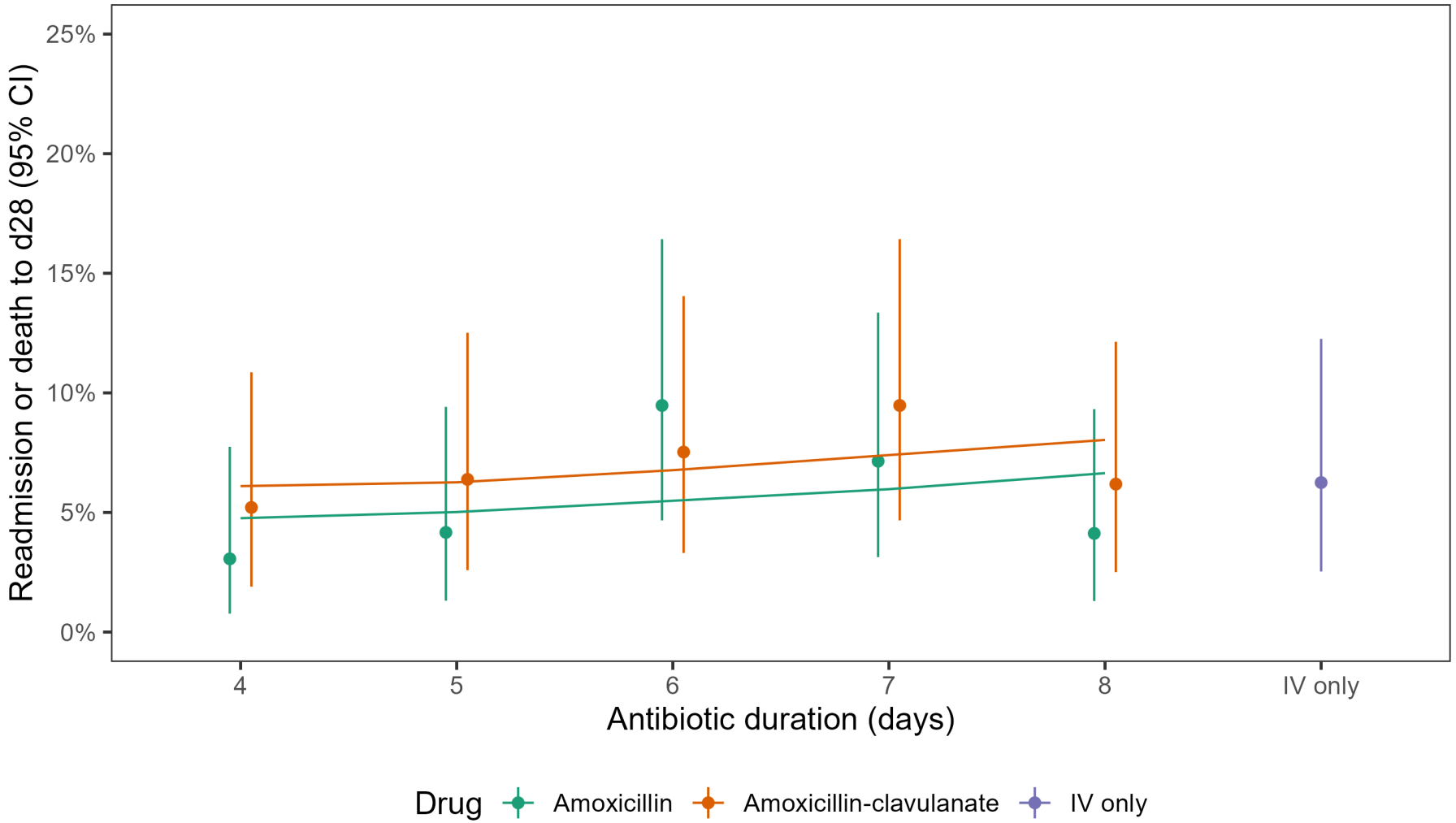
- Event rates:
  - 4%: 4 days
  - 5%: 5 days
  - 9%: 6 days
  - 8%: 7 days
  - 5%: 8 days
- All durations non-inferior to 8 days oral



Duration-response effect

PediCAP observed (dots) and fitted (line) primary outcome by antibiotic duration

Note: higher values correspond to worse outcomes



Secondary outcomes

- Drug effects:
  - Children randomised to the IV only arm had more line complications
  - Length of hospital stay to day 28 was longer in the IV only arm than the oral stepdown arms (estimate: +1.1 days [95% CI: +0.1,+2.0])
  - No evidence of differences between drugs in other secondary endpoints including SAEs
- Duration effects:
  - Children randomised to longer durations of antibiotics received more days of antibiotics (average daily linear effect: +0.8 [95% CI: +0.6,+0.9])
  - No evidence of consistent differences between durations in other secondary endpoints including SAEs and length of hospital stay

Key findings

Switching children to oral antibiotics when their health improves is safe, and works just as well as 5 days of injectable antibiotics.

Both oral antibiotics are equally effective.

But **amoxicillin** is more affordable and readily available.

4 days' total antibiotic treatment is generally enough.

All shorter durations were just as good as 8 days.

This means children could come home from hospital sooner.

Acknowledgments

- Participants and their families
- Study personnel

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