The impact of azithromycin therapy on antimicrobial resistance

Preliminary results

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Outline

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Introduction and rationale

- Azithromycin has **anti-inflammatory** and **anti-bacterial** properties and shown to be beneficial in other forms chronic lung diseases.
- Long-term use has been associated with **antimicrobial resistance** in common respiratory pathogens.[1,2,3,4,5]
- There are **conflicting reports** on the effect of this therapy on prevalence of respiratory bacteria, extent and persistence of macrolide resistance.[1,2,4,5]
  - ✓ may be explained by pre-treatment antimicrobial resistance levels, dose and duration of therapy and adherence.[4]
  - ✓ necessitate an independent assessment of this phenomenon within the BREATHE trial.
- Development of **resistance** is of concern because of
  - ✓ **transmission of resistant isolates** to community & healthcare centers participants regularly visit.[2,6]
  - ✓ development of **drug-resistant infections** which may be difficult to treat.[6]

[1]Hansen et al, J Cystic Fibrosis (2009) 8, 58–62
[2]Tramper-Stranders et al, J Antimicrob Chemother (2007) 60, 665–668
[3]Samson et al, Respir Med (2016) 117:1e6
[4]Hare et al, Eur J Clin Microbiol Infect Dis (2015) 34(11):2275-85
[5]Phaff et al, J Antimicrob Chemother (2006) 57, 741–746
[6]Serisier D.J, Lancet Respir Med (2013) 1: 262–74

Aim

To determine the effect of long-term azithromycin therapy on the **prevalence** of clinically relevant respiratory bacteria and associated **antimicrobial resistance** in participants within the BREATHE trial.

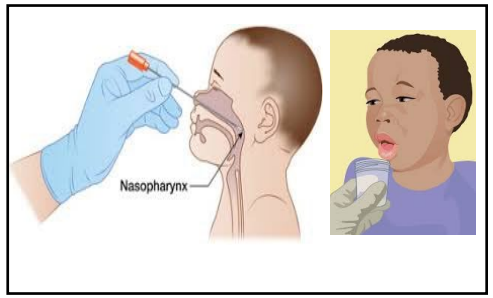
Specific objectives

1. To assess the proportion of participants colonized in the nasopharynx (NP) and sputa by clinically relevant bacteria (*S. pneumoniae, S. aureus, H. influenzae* and *M. catarrhalis)* in each trial arm [azithromycin(AZM) and placebo] at all timepoints.

2. To compare, between the trial arms, the proportion of isolates resistant to macrolides and other relevant antimicrobials at all timepoints.

Laboratory investigation

Specimen collection, storage & transport



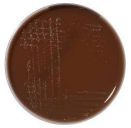
Paired NP & Sputum collection

[1]STGG

Bacteria isolation & identification

S. aureus
Mannitol Salt agar
Dnase test

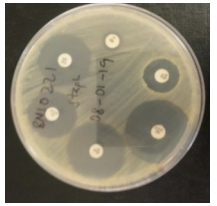
S. pneumoniae
Colgent agar
Optochin disc test

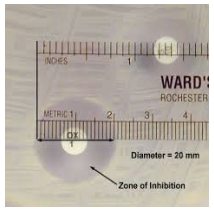


H. influenzae
[2]BHB agar
Factor XV test

M. catarrhalis
Blood agar
Push test

Antimicrobial susceptibility testing (disc diffusion)





All isolates
Azithromycin
Tetracycline
Cotrimoxazole

Bacteria specific
Oxacillin (Strep)
Cefoxitin (Staph)
Penicillin (Staph)
Clindamycin (Staph)
Amox-clav (Morax)
Amox-clav (Haem)
Cefuroxime (Haem)
Ampicillin (Haem)

Objective 1
Bacteria prevalence

Objective 2
Antimicrobial resistance

Figure 1. Flow chart of the laboratory investigations. [1]STGG : Skimmed milk tryptone glucose glycerol, [2]BHB : Bacitracin-heated blood agar

Number of samples collected

Timepoint	Trial arm	No. participants	NP		Sputum	
			No. collected (% of total participants)	No. cultured (% of total collected)	No. collected (% of total participants)	No. cultured (% of total collected)
Baseline	AZM	173	168 (97%)	168 (100%)	167 (97%)	166 (99%)
Baseline	Placebo	174	171 (98%)	171 (100%)	169 (97%)	164 (97%)
12 months	AZM	164	159 (97%)	159 (100%)	157 (96%)	148 (94%)
12 months	Placebo	160	153 (96%)	153 (100%)	149 (93%)	143 (96%)
18 months	AZM	134	128 (96%)	118 (92%)	127 (95%)	117 (92%)
18 months	Placebo	120	115 (96%)	105 (91%)	115 (96%)	107 (93%)
Totals						
All	AZM	471	455 (97%)	445 (98%)	451 (96%)	431 (96%)
All	Placebo	454	439 (97%)	429 (98%)	433 (95%)	414 (96%)
Grand total	Both	925	894 (97%)	874 (98%)	884 (96%)	845 (96%)

Bacteria prevalence in NP

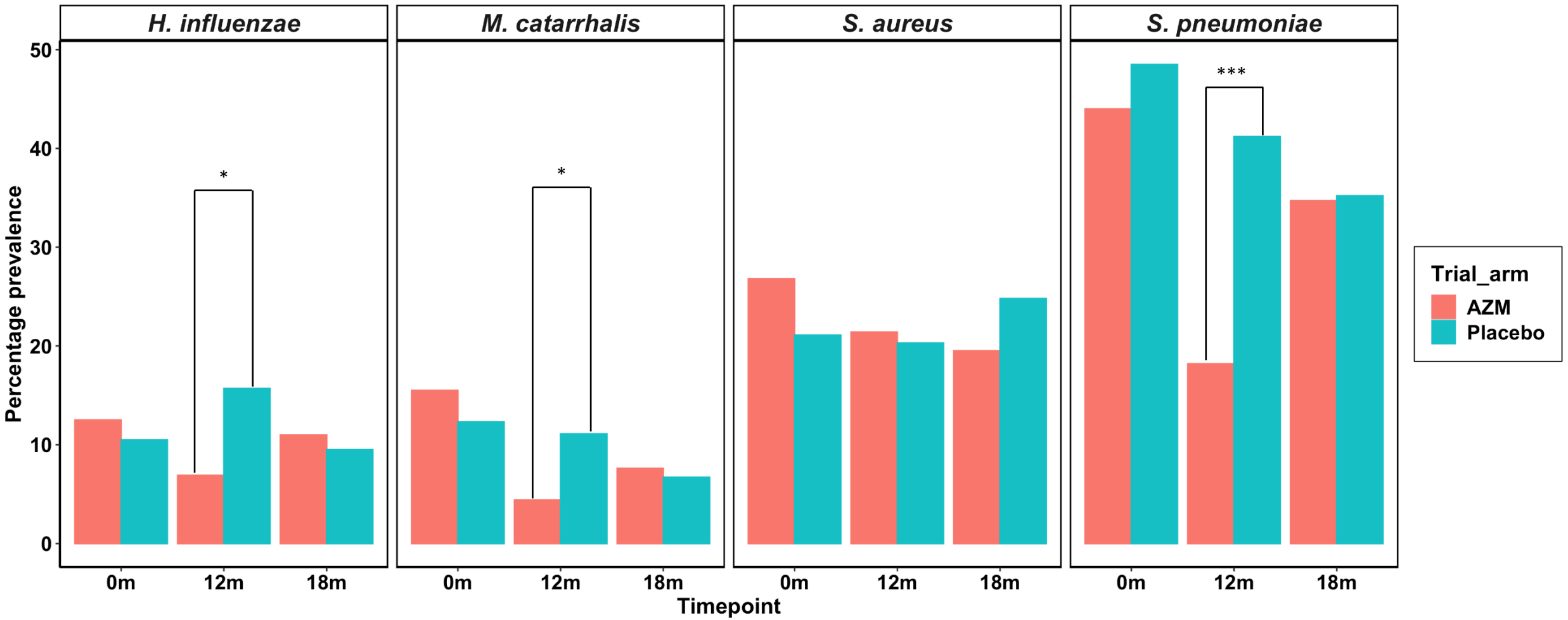


Figure 2. Bar plot of the NP prevalence of respiratory bacteria isolated at all timepoints from **AZM** (baseline; n=168, 12 months; n=159, 18 months; n=118) and **Placebo** (baseline; n=171, 12 months; n=153 , 18 months; n=105) arms of trial. *$p < 0.01$, *** $p < 0.0001$

Bacteria prevalence in sputa

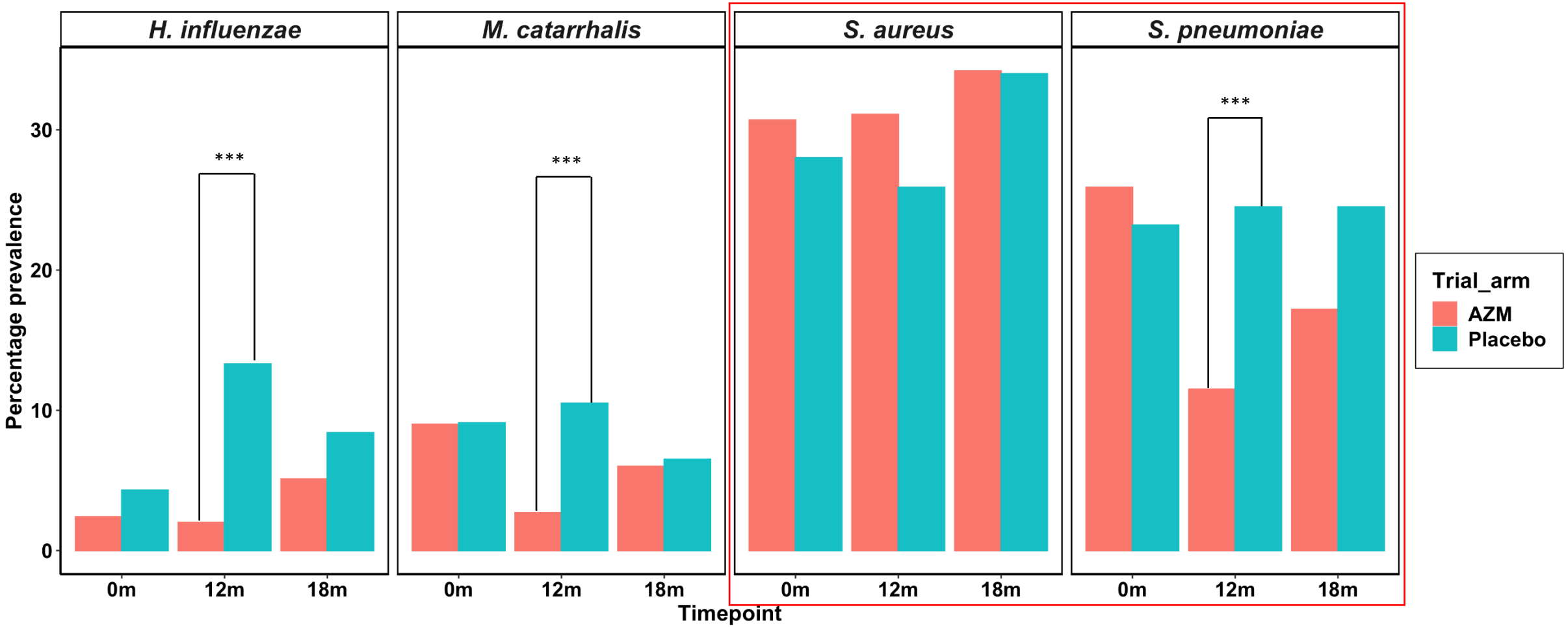


Figure 3. Bar plot of the sputum prevalence of respiratory bacteria isolated at all timepoints from **AZM** [baseline(n=166), 12 months (n=148), 18 months(n=117)] and **Placebo** [baseline(n=164), 12 months (n=143), 18 months (n=107)] arms of trial. *** $p < 0.0001$

Antimicrobial resistance of *S. pneumoniae* from NP

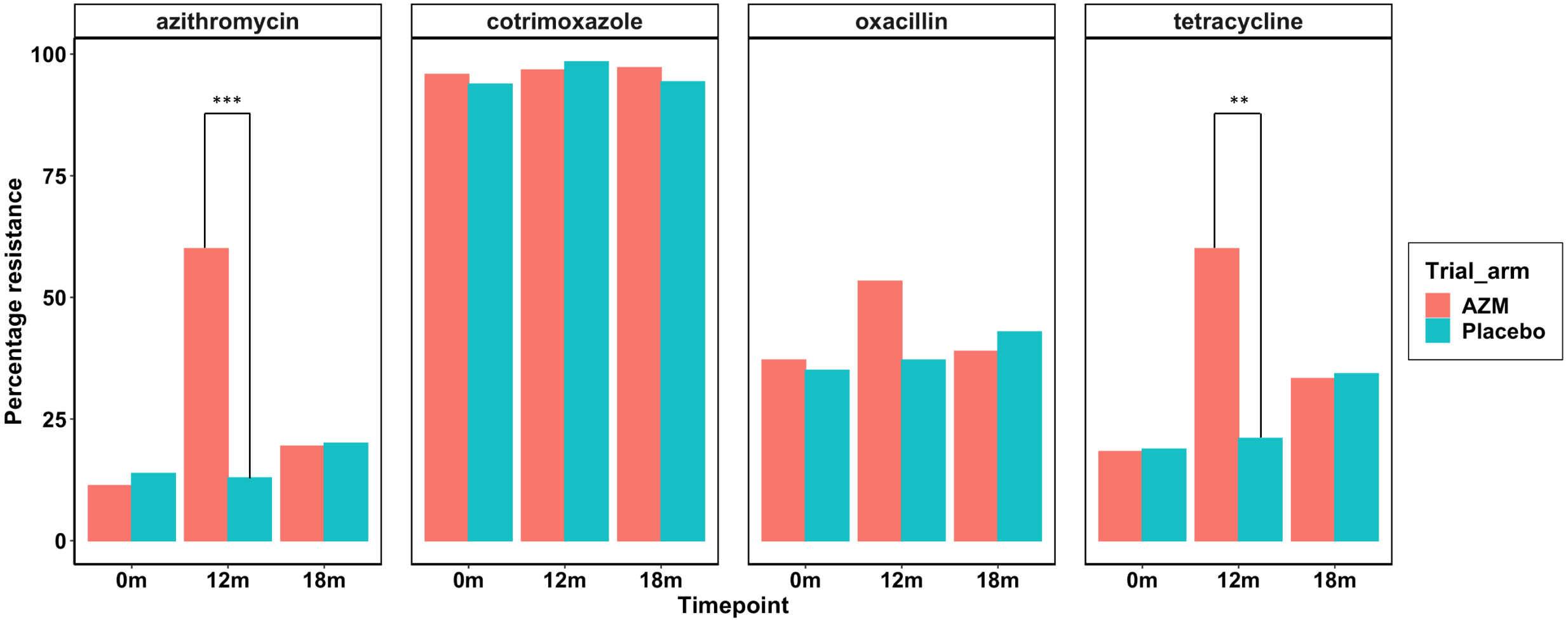


Figure 4. Bar plot of the percentage resistance of *S. pneumoniae* from NP swabs at all timepoints from **AZM** [baseline (n=74), 12 months (n=29), 18 months (n=41)] and **Placebo** [baseline (n=83), 12 months (n=63), 18 months (n=37)] arms of trial. ** $p < 0.001$, *** $p < 0.0001$

Antimicrobial resistance of *S. pneumoniae* from sputa

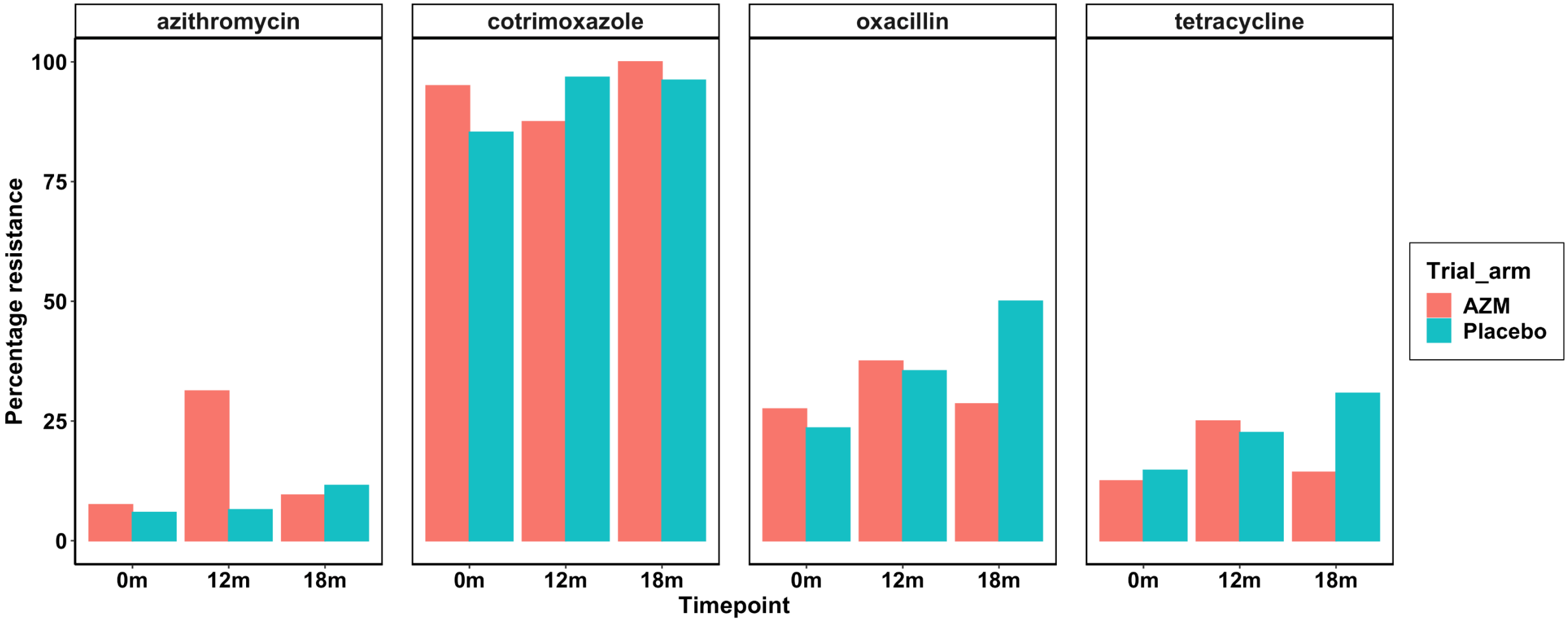


Figure 5. Bar plot of the percentage resistance of *S. pneumoniae* from sputa at all timepoints from **AZM** [baseline (n=43), 12 months (n=17), 18 months (n=20)] and **Placebo** [baseline (n=38), 12 months (n=35), 18 months (n=26)] arms of trial.

Antimicrobial resistance of *S. aureus* from NP

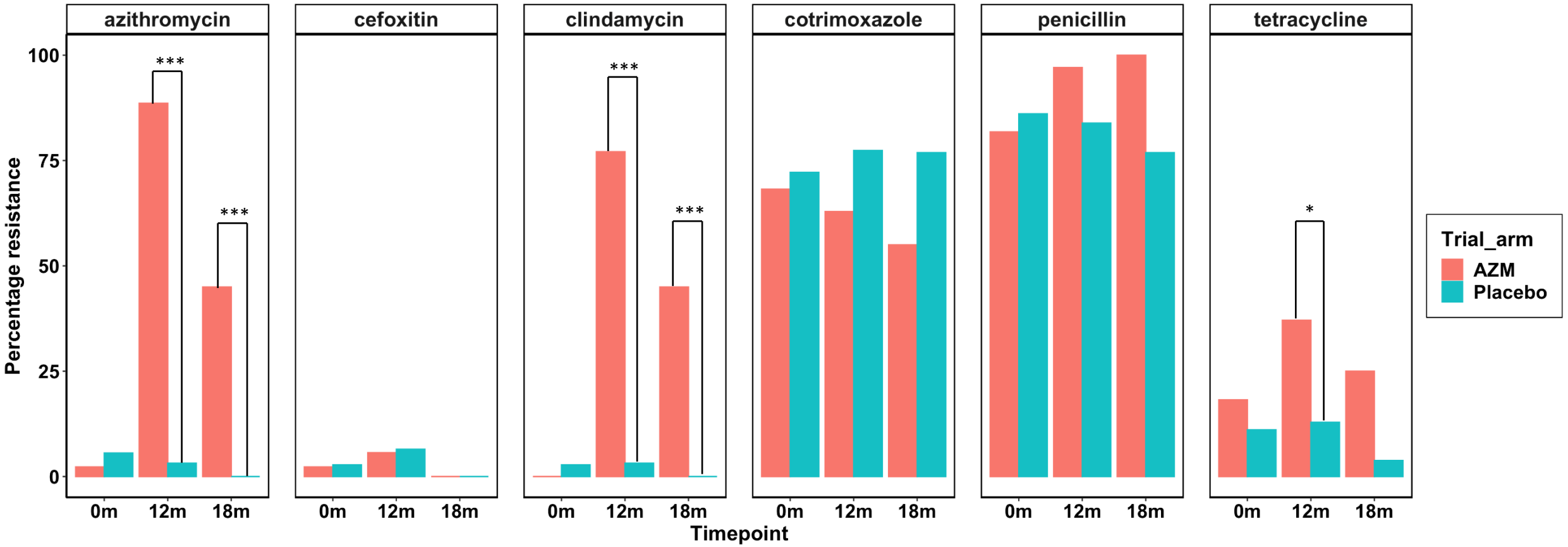


Figure 6. Bar plot of the percentage resistance of *S. aureus* from NP swabs at all timepoints from **AZM** [baseline (n=45), 12 months (n=34), 18 months (n=23)] and **Placebo** [baseline (n=36), 12 months (n=31), 18 months (n=26)] arms of trial. *$p < 0.01$, *** $p < 0.0001$

Antimicrobial resistance of *S. aureus* from sputa

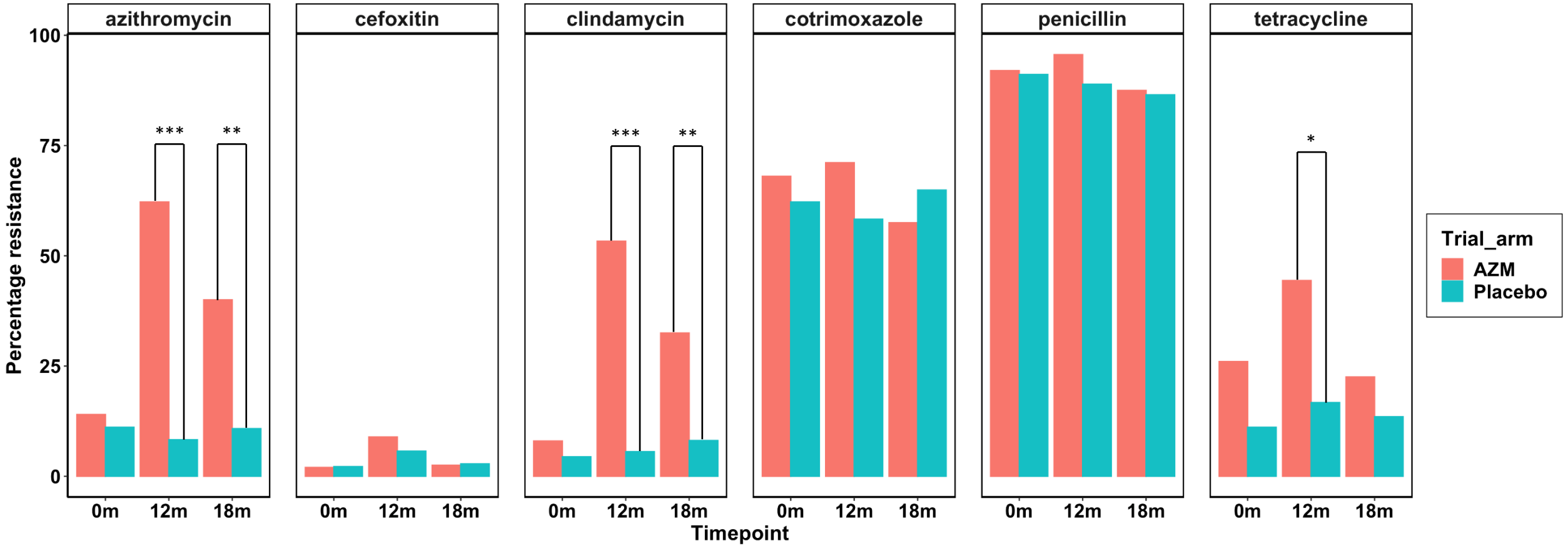


Figure 7. Bar plot of the percentage resistance of *S. aureus* from sputa at all timepoints from **AZM** [baseline (n=51), 12 months (n=46), 18 months (n=40)] and **Placebo** [baseline (n=46), 12 months (n=37), 18 months (n=36)] arms of trial. *$p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$

Conclusions & next steps

In conclusion,

- Long-term azithromycin therapy:
  - ✓ reduce the respiratory carriage of *S. pneumoniae, H. influenzae* and *M. catarrhalis* but not *S. aureus*. This effect did not persist 6 months after therapy cessation.
  - ✓ increased azithromycin and tetracycline resistance in *S. pneumoniae* and *S. aureus* (and clindamycin resistance) but not *H. influenzae* and *M. catarrhalis*. Effect reversed at 6 months in *S. pneumoniae* but not *S. aureus*.

Next steps:

- Whole genome sequencing of *S. pneumoniae* and *S. aureus* to characterise
  - ✓ Mechanisms underlying antimicrobial resistance: Key in understanding transmissibility and treatment strategies
  - ✓ Serotypes and lineages of *S. pneumoniae*: Provide data that will advise vaccine formulation strategies
  - ✓ Population structure: Will improve preparedness and response to future outbreaks of disease caused by Ab-R bacteria

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SEEK WISDOM

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Sida Swedish International Development Cooperation Agency

Organization for Women in Science for the Developing World

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Margaret McNamara Education Grants

NRF National Research Foundation

MPRU NIHR Mucosal Pathogens Research Unit

IDM Institute of Infectious Disease and Molecular Medicine

University of Oxford