

## Balancing benefits and risks of antibiotic use

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Guidelines for antibiotic usage are among those public health conundrums with the highest stakes in modern medicine. Antibiotics remain our main treatment response against potentially fatal bacterial diseases, preventing millions of deaths every year, and there is emerging evidence for the benefits of preventative antibiotic administration. For example, pre-emptive azithromycin use in healthy children in regions with high child mortality can increase survival well beyond the capacity of the majority of other targeted interventions [1,2]. Conversely, there is compelling evidence that antibiotic use leads to increased antibiotic resistance prevalence in the community [3,4], an increasing proportion of no longer treatable multidrug resistant infections and eventually to a blunting of our antimicrobial arsenal [5,6]. Appropriate antibiotic use is thus a trade-off between medical best practice for improving patient outcomes and the wider public health implications of antibiotic use at the community level. Balancing this trade-off is particularly challenging in those instances where a substantial increase in antibiotic use in the community offers somewhat marginal health benefits; as is the case for the immediate treatment of otitis media if compared to a 'reactive' prescribing strategy triggered only by the worsening of symptoms [7]. Proposing an evidence-based solution to this issue requires understanding and quantifying the mechanisms underpinning transmission of bacterial carriage and the selection pressures governing the introduction and maintenance of non-susceptible strains.

To elucidate these mechanisms, Lewnard et al. investigated the individual-level effect of antibiotic prescription on pneumococcal penicillin non-susceptible carriage [8]. In a secondary analysis of a randomised double-blind placebo-controlled trial, the authors studied the effects of immediate vs reactive amoxicillin-clavulanate prescription to children attending primary care for acute otitis media over a two-month follow-up period. As otitis media is the main reason for antibiotic prescribing in children in high income settings and contributes substantially to overall antibiotic use [9,10], understanding both the clinical impact and the selective pressure of antibiotic prescribing for otitis media is a key part in the optimisation of antibiotic prescription strategies.

This reanalysis shows clear evidence that a strategy of immediate prescribing following diagnosis confers a fitness advantage on non-susceptible strains. Namely, that amoxicillin-clavulanate based treatment substantially reduces penicillin susceptible pneumococcal carriage prevalence but not that of its non-susceptible counterpart. The largest effect, an 88% reduction in susceptible carriage vs the placebo arm, was seen at the first follow up which was a week after enrolment and the end of the treatment course. Moreover, two months after enrolment, the prevalence of penicillin susceptible pneumococcal carriage in the treatment arm had rebounded but to a much lower level than it had been pre-treatment (52% vs 30%) and to a slightly lower level than in the control arm (41% vs 30%). Furthermore, the study provides evidence that that this fitness advantage is conferred by two mechanisms. First, treatment preferentially clears resident susceptible strains from the nasopharynx (7% vs 61% carriage prevalence immediately after treatment), with lower carriage prevalence of penicillin susceptible strains observed seven weeks after ending treatment (35% vs 64%). Second, treatment may actively block recolonisation by susceptible strains (2% vs 9% prevalence at end of treatment in participants uncolonized at enrolment)—possibly even during the

days, or weeks, after the course is complete (2 vs 12% carriage prevalence one week after treatment has ended). These two mechanisms result in a vacated niche in the treatment arm, cleared of susceptible strains.

One would expect that in the treated patients, the vacated niche would be filled, in part, by penicillin non-susceptible pneumococci, yet there was no evidence for this. While this finding is somewhat reassuring it is important to note that the study was only powered to detect roughly a doubling of penicillin non-susceptible pneumococcal carriage prevalence. For comparison, a prospective observational study in Malawi detected an increase in the prevalence of cotrimoxazole non-susceptible pneumococci of about 20% in the weeks following treatment. However, mass administration of azithromycin in a cluster randomised trial led to almost a 5-fold increase in carriage of azithromycin resistant pneumococci compared with control clusters [5], hinting at a likely non-linear relationship between individual level and population level effects of antimicrobial resistance.

The reanalysis elegantly highlights the complex carriage-treatment dynamics that underlie the deceptively simple linear relationship between antibiotic use and resistance across commensal bacteria–drug combinations that has been reported across Europe [3]. The explicit dynamics of increased antimicrobial use and a subsequent rise in resistance are poorly understood but are likely governed by a highly non-linear combination of factors with competition between susceptible and non-susceptible strains as the balancing mechanism at its core [11–13]. This gap in our knowledge implies that to date it remains impossible to adequately quantify the trade-off between the benefits of a specific antibiotic use recommendation and its implications for increased resistance and associated health losses. In particular, assessing population resistance levels may be complicated both by a delayed effect of changes in prescribing rates and by the uncertainty associated with inferring population level effects from individual level observations. Although we are yet to fully grasp an intuitive and mechanistic understanding of this antibiotic use–resistance relationship [14–16] it is clear that results such as those from Lewnard et al. will be essential to empirically parameterise the selective pressures on pneumococcal transmission. Encouragingly, transmission models of resistant pathogens have routinely relied on calibrating their output using the two fitness advantages reported in by Lewnard et al. [12] and hence this study will help better equip future endeavours that aim to quantify the impact of competition on observed resistance levels.

Ultimately, we have to work towards a mechanistic understanding of resistance transmission if our goal is to inform public health decision making for antibiotic use guidelines. With similar work on other bacteria-treatment combinations, we will build a comprehensive understanding of resistance acquisition and transmission across pathogens. Finally, we anticipate that strengthened evidence of antibiotic use–resistance relationships from countries outside Europe, especially those with higher antibiotic usage, will guide and corroborate our mechanistic understanding of resistance evolution.

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#### *Conflicts of interest*

SF and KEA have no conflicts of interest

#### Literature

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