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EDITORIAL COMMENTARY

Balancing Benefits and Risks of Antibiotic Use

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(See the Major Article Lewnard et al, on pages 1356–66.)

Guidelines for antibiotic use are among those public health conundrums with the highest stakes in modern medicine. Antibiotics remain our main treatment response to potentially fatal bacterial diseases, preventing millions of deaths every year, and there is emerging evidence for the benefits of preventive antibiotic administration. For example, preemptive azithromycin use in healthy children in regions with a high child mortality rate 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 an increased prevalence of antibiotic resistance in the community [3, 4], to an increasing proportion of multidrug-resistant infections that are no longer treatable, 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 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 as 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 nonsusceptible strains.

To elucidate these mechanisms, Lewnard et al, in this issue of *The Journal of Infectious Diseases*, investigated the individual-level effect of antibiotic prescription on carriage of penicillin-nonsusceptible pneumococci [8]. In a secondary analysis of a randomized, double-blinded, placebo-controlled trial, the authors studied the effects of immediate versus reactive administration of amoxicillin-clavulanate therapy to children attending primary care for acute otitis media, over a 2-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 optimization of antibiotic prescription strategies.

This reanalysis shows clear evidence that a strategy of immediate prescribing following diagnosis confers a fitness advantage on nonsusceptible strains: amoxicillin-clavulanate–based treatment substantially reduces carriage prevalence of penicillin-susceptible pneumococci but that of not their nonsusceptible counterparts. The largest effect, an 88% reduction in carriage of susceptible strains versus the placebo arm, was seen at the first follow-up visit, which was a week after enrollment and the end of the treatment course. Moreover, 2 months after enrollment, the prevalence of penicillin-susceptible pneumococcal carriage in the treatment arm had rebounded but to a much lower level than it had been before 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 recolonization by susceptible strains (2% vs 9% prevalence at end of treatment in participants uncolonized at enrollment)—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-nonsusceptible 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 the prevalence of penicillin-nonsusceptible pneumococcal carriage. For comparison, a prospective observational study in Malawi detected an increase of about 20% in the prevalence of cotrimoxazole-nonsusceptible pneumococci in the weeks following treatment. However, mass administration

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of azithromycin in a cluster randomized trial led to almost a 5-fold increase in carriage of azithromycin-resistant pneumococci, compared with control clusters [5], hinting at a likely nonlinear relationship between individual-level and population-level effects of antimicrobial resistance.

The reanalysis by Lewnard et al elegantly highlights the complex dynamics between carriage and treatment that underlie the deceptively simple linear relationship between antibiotic use and resistance across commensal bacteria and 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 nonlinear combination of factors, with competition between susceptible and nonsusceptible 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 relationship between antibiotic use and resistance [14–16], it is clear that results such as those from the study by Lewnard et al will be essential to empirically parameterize the selective pressures on pneumococcal transmission. Encouragingly, transmission models of resistant pathogens have routinely relied on calibrating their output by using the 2 fitness advantages reported by Lewnard et al [12], and, hence, this study will help better equip future endeavors that aim to quantify the impact of competition on observed resistance levels.

Ultimately, we must work toward 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 and treatment combinations, we will build a comprehensive understanding of resistance acquisition and transmission across pathogens. Finally, we anticipate that strengthened evidence of the relationships between antibiotic use and resistance from countries outside Europe, especially those with higher rates of antibiotic use, will guide and corroborate our mechanistic understanding of the evolution of antibiotic-resistant strains.

Notes

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