**European research has shown that amoxicillin use is a crucial driver of resistance to amoxicillin, a penicillin-like antibiotic. Whereas use of macrolide antibiotics leads to a major increase in macrolide-resistant streptococci that persists for at least 6 months after therapy, changes effected by amoxicillin in the oro-pharyngeal flora are rather short-lived. Specifically, the majority of the streptococci exhibiting high-level resistance to amoxicillin that had emerged immediately after amoxicillin therapy had disappeared within a month.**

Antibiotic use is widely associated with antibiotic resistance, but demonstrating causality is challenging. Research funded by the European Union and the Flanders Research Foundation (FWO-F, Belgium) has succeeded in providing definitive *in vivo* proof of the impact of antibiotic use on emergence and persistence of antibiotic resistance in the human microbial flora.

These studies, led by Profs. Surbhi Malhotra-Kumar, Herman Goossens and Samuel Coenen at the University of Antwerp, Belgium, have clearly shown increased proportions of resistant bacteria in the oropharyngeal flora of individuals receiving the macrolide group of antibiotics (azithromycin and clarithromycin) compared to those treated with a placebo. Furthermore, increased resistance in the macrolide-treated individuals persisted for at least six months following use. In contrast, the increase in resistant bacteria following a course of amoxicillin lasted for a much shorter duration, i.e., a month.

Amoxicillin, a penicillin-like antibiotic, is recommended as first-line therapy by the European Respiratory Society for treatment of community-acquired lower respiratory tract infections (CA-LRTI), the commonest reason for patient consultations in the community. Amoxicillin is therefore also the most commonly prescribed antibiotic in European primary care, accounting for an average 40% of the total outpatient antibiotic use in European countries. Despite this, its potential for selection of resistance in *Streptococcus pneumoniae*, the most common bacterial pathogen causing CA-LRTI, and its persistence in vivo is not yet known. ‘We found commensal oropharyngeal streptococci as ideal model organisms to study resistance selection in *S. pneumoniae* *in vivo* as they are genetically very similar bacteria’ said Surbhi Malhotra–Kumar, lead author of the study. Samples were collected from patients with confirmed CA-LRTI as part of a randomized, placebo-controlled trial (RCT) in several European primary care centres (GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe;[www.grace-lrti.org](http://www.grace-lrti.org/)).

‘We could attribute the observed differences in the resistance trajectories to the distinct mechanisms of action of amoxicillin and the macrolides, and how bacteria acquire resistance to them’ explains Surbhi Malhotra–Kumar. As with other penicillins, amoxicillin affects bacterial cell wall synthesis. Resistance in streptococci, including *S. pneumoniae*, occurs by chromosomal alterations in cell wall synthesizing enzymes, the so-called penicillin-binding proteins (PBPs). This study also analyzed the ‘fitness’ levels of amoxicillin resistant streptococci by competing them with sensitive streptococci and showed that some of the PBP mutations were associated with decreased fitness of the bacteria potentially explaining the shorter duration of high-level resistance selection following amoxicillin use.

Taken together, these findings provide a strong evidence base supporting: (i) European clinical guidelines that recommend prescribing amoxicillin when an antibiotic is indicated for CA-LRTI; (ii) clinical prescribing of an antibiotic with a lower ecological impact such as amoxicillin when an antibiotic needs to be prescribed; and (iii) future antibiotic policy making for respiratory tract infections.

An article on the study appears on November 18 in the Journal of Antimicrobial Chemotherapy to coincide with the European Antibiotic Awareness Day.

<http://jac.oxfordjournals.org/content/71/11/3258.full.pdf>

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