

## Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study

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### ABSTRACT

**Objective** To assess the effect of community prescribing of an antibiotic for acute respiratory infection on the prevalence of antibiotic resistant bacteria in an individual child.

**Study design** Observational cohort study with follow-up at two and 12 weeks.

**Setting** General practices in Oxfordshire.

**Participants** 119 children with acute respiratory tract infection, of whom 71 received a  $\beta$  lactam antibiotic.

**Main outcome measures** Antibiotic resistance was assessed by the geometric mean minimum inhibitory concentration (MIC) for ampicillin and presence of the *ICEHin1056* resistance element in up to four isolates of *Haemophilus* species recovered from throat swabs at recruitment, two weeks, and 12 weeks.

**Results** Prescribing amoxicillin to a child in general practice more than triples the mean minimum inhibitory concentration for ampicillin (9.2  $\mu$ g/ml v 2.7  $\mu$ g/ml,  $P=0.005$ ) and doubles the risk of isolation of *Haemophilus* isolates possessing homologues of *ICEHin1056* (67% v 36%; relative risk 1.9, 95% confidence interval 1.2 to 2.9) two weeks later. Although this increase is transient (by 12 weeks ampicillin resistance had fallen close to baseline), it is in the context of recovery of the element from 35% of children with *Haemophilus* isolates at recruitment and from 83% (76% to 89%) at some point in the study.

**Conclusion** The short term effect of amoxicillin prescribed in primary care is transitory in the individual child but sufficient to sustain a high level of antibiotic resistance in the population.

### INTRODUCTION

The relation between antibiotic prescribing and resistance is complex.<sup>1</sup> Resistance levels will depend on the pattern of antibiotic use, the specific interaction between bacterium and drug, the potential for transmission, and the stage the country is at in the evolution of resistance. For example, Sweden and Denmark have higher rates of penicillin prescribing than the UK but lower resistance, while Finland has lower prescribing but higher resistance.<sup>2</sup> To develop an effective strategy to manage antibiotic resistance in the community we need to understand what is happening at the level of the individual patient, not just to inform care of

patients but also to provide firm estimates for the population models that should inform policy on antibiotic prescribing.

The highest rates of antibiotic prescribing in primary care are to children with respiratory illness. There have been few prospective controlled studies of the impact of such prescribing on resistance in a community setting. We report a prospective study in children from UK general practice with new methods for identifying a highly mobile integrative and conjugative element that encodes  $\beta$  lactamase and circulates among nasopharyngeal *Haemophilus* species.<sup>3-5</sup>

### METHODS

**Participants**—General practitioners initially recruited 150 children aged 6 months to 12 years presenting with either otitis media or a suspected respiratory infection. After exclusions 119 children took part, of whom 71 were prescribed a  $\beta$  lactam antibiotic (amoxicillin 70, cephadrine 1) at presentation and 48 received no antibiotic.

**Data collection and follow-up**—A research nurse collected information on sociodemographic details, type of infection, child's past antibiotic use, and treatment for current illness. Information on antibiotic prescribing was confirmed from medical records. Children were followed up at two weeks and 12 weeks after recruitment.

**Microbiology**—Throat swabs were inoculated onto two *Haemophilus* selective media: Columbia agar (enriched with haemin and nicotinamide adenine dinucleotide) plus bacitracin, and the same agar with the addition of 2  $\mu$ g/ml ampicillin. Up to four morphologically different colonies were picked from the bacitracin plate and two morphologically different colonies from the ampicillin plate. We estimated the minimum inhibitory concentration for ampicillin from isolates selected from the ampicillin agar plate. We looked for the presence of the integrative and conjugative element homologous to *ICEHin1056* in *Haemophilus* species isolated from the bacitracin agar plate (which selects for *Haemophilus* species and against other bacterial genera). See [bmj.com](http://bmj.com) for further details.

**Analysis**—We compared data between groups at each visit. We applied a log transformation to the

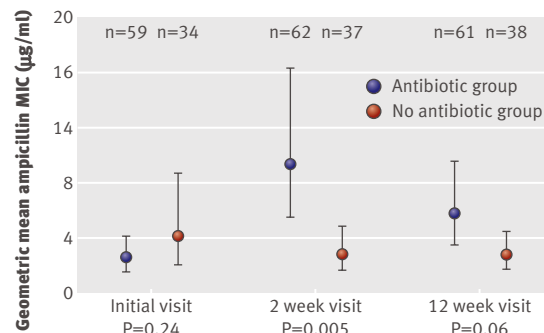
minimum inhibitory concentration for ampicillin and used geometric means to summarise this measure. We used *t* tests to compare the means between groups at each visit and paired *t* tests to compare the means within groups. Where data are reported in relation to individual children rather than individual isolates, the denominator is limited to children in whom *Haemophilus* species were isolated—which was nearly all children.

**RESULTS**

*Completeness of follow-up and recovery of target bacterium*—Loss to follow-up was small: nine children (8%) at two weeks, 10 children (9%) at 12 weeks. Recovery of *Haemophilus* species was high and increased with each visit: 101/119 (85%) children at baseline, 101/110 (92%) at two weeks, and 106/109 (97%) at 12 weeks, with little difference between the antibiotic and no antibiotic groups.

*Initial differences between children*—Mean age (both 5.4 years), mean number of children in household (1.16 *v* 1.13), and previous exposure to antibiotics (87% *v* 85%) were similar in children prescribed and not prescribed an antibiotic. Day care or school attendance was more common in the children who received an antibiotic (66/69 (95%) *v* 40/47 (85%), *P*=0.05). The geometric mean of the minimum inhibitory concentration for ampicillin of the *Haemophilus* species isolates was 2.4 µg/ml in the antibiotic group and 4.1 µg/ml in the no antibiotic group (*P*=0.24). The proportion of children with an isolate carrying an integrative and conjugative element was 32% and 38%, respectively (*P*=0.52). Carriage of the element was common even in children who had never received an antibiotic (8/15, 53%).

*Effect of antibiotics on ampicillin minimum inhibitory concentration*—The figure shows that in children who did not receive an antibiotic, the geometric mean



Geometric mean minimum inhibitory concentration (MIC) for ampicillin of isolates from children according to whether or not they received antibiotics (error bars show 95% confidence intervals; *P* values based on *t* test)

minimum inhibitory concentration for ampicillin was the same (2.7 µg/ml) at both follow-up points, with no significant change from the initial level of 4.1 µg/ml. In contrast, in children who received an antibiotic, the minimum inhibitory concentration increased about fourfold to 9.2 µg/ml at the two week follow-up (ratio to no antibiotic group 3.5, *P*=0.005). At the 12 week follow-up, it fell back to 5.7 µg/ml (ratio to no antibiotic group 2.1, *P*=0.06). We were able to calculate a measure of change between the initial visit and 12 week follow-up in 86 children (54 in antibiotic group, 32 in no antibiotic group). The ratio of geometric mean minimum inhibitory concentration at 12 weeks compared with initial visit was 2.33 in children who received an antibiotic and 0.71 in those who did not (*P*=0.05).

*Effect of antibiotics on carriage of an integrative and conjugative element*—The table shows the proportion of children from whom we recovered an integrative and conjugative element at each visit. As with the minimum inhibitory concentration for ampicillin, there was little change in recovery from children who did not receive an antibiotic at the two week (36%) and 12 week (37%) follow-up visits. In the antibiotic group, however, recovery doubled to 67% at two weeks (*P*=0.002) before falling back to 36% (close to the baseline level of 32%) at 12 weeks. The approximate doubling of risk of carriage at two weeks and the fall close to baseline by 12 weeks were consistent whether or not a resistant element had been recovered from the child at the initial visit. An integrative and conjugative element was recovered from most children from whom *Haemophilus* species were isolated (83%, 95% confidence interval 76% to 89%) at some point in the study, irrespective of whether they received an antibiotic.

**DISCUSSION**

The short term effect of amoxicillin prescribed in primary care is transitory in the individual child but

Isolation of integrative and conjugative resistance element (ICEHin1056) at follow-up according to antibiotic prescribing and whether element was isolated at initial visit. Figures are numbers (percentages) of children unless stated otherwise

	Children prescribed antibiotic (n=71)	Children not prescribed antibiotic (n=48)	Risk (risk ratio) of isolation of resistance element at follow-up if antibiotic prescribed (95% CI)
ICEHin1056 isolated at initial visit	20/62 (32)	15/39 (38)	—
ICEHin1056 isolated at 2 week visit:			
Total	42/63 (67)	14/39 (36)	1.9 (1.3 to 2.7)
Isolated at initial visit*	15/20 (75)	6/15 (40)	1.9
Not isolated at initial visit*	25/42 (60)	7/24 (29)	2.0
ICEHin1056 isolated at 12 week visit:			
Total	24/66 (36)	15/40 (37)	1.0 (0.5 to 1.7)
Isolated at initial visit*	10/20 (50)	7/15 (47)	1.1
Not isolated at initial visit*	12/42 (29)	8/24 (33)	0.9

\*Do not sum to total for all children because *Haemophilus* species were not isolated from every child at every visit (see text).

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

UK general practitioners are strongly encouraged to reduce antibiotic prescribing to minimise the risk of antibiotic resistance

Epidemiological studies of the likely effect of reducing antibiotic prescribing outside hospital on antibiotic resistance have reported inconsistent results

**WHAT THIS STUDY ADDS**

Prescribing amoxicillin to a child in general practice doubles the risk of recovering a  $\beta$  lactamase encoding resistance element from that child's throat two weeks later

This risk falls back to the level seen before treatment within 12 weeks, but a  $\beta$  lactamase inhibitor combination antibiotic should probably be prescribed during this period

The ICEHin1056 resistance element is endemic in UK children, but reversal of this will require further substantial and sustained changes in antibiotic prescribing in the community

sufficient to sustain a high level of antibiotic resistance in the population. The inclusion of commensal as well as pathogenic *Haemophilus* species and the focus on mobile resistance elements allowed us to avoid bias inherent in previous studies. It also allowed us to characterise the bacterial flora from more than a single isolate even when we sampled by throat swab. The similarity of baseline characteristics and levels of initial resistance, plus the lack of any suggestion that the integrative and conjugative element is associated with disease virulence or a pathogenic factor,<sup>4,5</sup> makes serious confounding unlikely.

The integrative and conjugative element can be isolated from both pathogenic *H influenzae* and commensal *H parainfluenzae* and like a plasmid moves freely between them by horizontal transfer.<sup>5-7</sup> It is this global gene pool of transferable antibiotic resistance elements that maintains antibiotic resistance in the community. Our results, however, are consistent with the report of a doubling of odds of isolation of penicillin resistant pneumococci from children who had received a  $\beta$  lactam antibiotic within two months but not six months.<sup>8</sup>

If our ability to recover an integrative and conjugative element mirrors the change in transmission potential, the marginal effect of community prescribing on the proportion of children in the UK who are able to transmit an integrative and conjugative element at any one time is perhaps 2-3%. However, this does not imply a marginal 2-3% impact on resistance because this is not a static system. For example, applying a transmission dynamics model to data from Finland, showed that a paediatric prescribing rate of 14 days of antibiotics each year, and an estimated duration of carriage of a  $\beta$  lactamase producing strain of *Moraxella catarrhalis* of just over one month, was consistent with an increase in community prevalence of these strains

by about 10% a year to an equilibrium level of about 50%.<sup>9</sup> These parameter estimates are not dissimilar to ours.

**Clinical implications**

In the few cases where it is appropriate to repeat the prescription of an antibiotic within under three months, it may be sensible to choose one (for example, co-amoxiclav) that has activity against  $\beta$  lactamase producing strains.

From a population perspective, of concern is the high (about 35%) equilibrium level of recovery of resistant *Haemophilus* species to which the children receiving antibiotics returned after 12 weeks and the endemic carriage of the integrative and conjugative element by nasopharyngeal *Haemophilus* species. This may indicate that bacteria can adapt to carry the resistance element with minimal metabolic cost and therefore without much biological disadvantage in the absence of antibiotic selection. Any reduction in community resistance is likely to need a substantial and sustained reduction in community prescribing.<sup>9</sup> One option is to reduce the duration of each course of antibiotics prescribed in the community.<sup>8</sup> A more radical option is to advise stopping prescribing antibiotics to any child with respiratory infection in the community except in well defined and exceptional circumstances.

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- 1 Turnidge J, Christiansen K. Antibiotic use and resistance—proving the obvious. *Lancet* 2005;365:548-9.
- 2 Goosens H, Ferech M, Stichele RV, Elseviers M. Outpatient antibiotic uses in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579-87.
- 3 Mohd-Zain Z, Turner SL, Cerdeno-Tarraga AM, Lilley AK, Inzana TJ, Duncan AJ, et al. Transferable antibiotic resistance elements in *Haemophilus influenzae* share a common evolutionary origin with a diverse family of syntenic genomic islands. *J Bacteriol* 2004;186:8114-22.
- 4 Dimopoulou I, Russell J, Mohd-Zain Z, Herbert R, Crook DW. Site-specific recombination with the chromosomal tRNA(Leu) gene by the large conjugative *Haemophilus* resistance plasmid. *Antimicrob Agents Chemother* 2002;46:1602-3.
- 5 Leaves N, Dimopoulou I, Hayes I, Kerridge S, Falla T, Secka O, et al. Epidemiological studies of large resistance plasmids in *Haemophilus*. *J Antimicrob Chemother* 2000;45:599-604.
- 6 Dimopoulou I, Kartali S, Harding R, Peto T, Crook D. Diversity of antibiotic resistance integrative and conjugative elements among haemophili. *J Med Microbiol* 2007;56:838-46.
- 7 Nasrin D, Collignon P, Roberts L, Wilson E, Pilotto S, Douglas M. Effect of beta lactam antibiotic uses in children on resistance to penicillin: prospective cohort study. *BMJ* 2002;324:1-4.
- 8 Scheifele DW, Fussell SJ, Roberts MC. Characterization of ampicillin-resistant *Haemophilus parainfluenzae*. *Antimicrob Agents Chemother* 1982;21:734-9.
- 9 Austin D, Kristinsson K, Anderson R. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proc Natl Acad Sci USA* 1999;96:1152-6.

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