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# A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance

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## Abstract

**Background:** Greater use of antibiotics during the past 50 years has exerted selective pressure on susceptible bacteria and may have favoured the survival of resistant strains. Existing information on antibiotic resistance patterns from pathogens circulating among community-based patients is substantially less than from hospitalized patients on whom guidelines are often based. We therefore chose to assess the relationship between the antibiotic resistance pattern of bacteria circulating in the community and the consumption of antibiotics in the community.

**Methods:** Both gray literature and published scientific literature in English and other European languages was examined. Multiple regression analysis was used to analyse whether studies found a positive relationship between antibiotic consumption and resistance. A subsequent meta-analysis and meta-regression was conducted for studies for which a common effect size measure (odds ratio) could be calculated.

**Results:** Electronic searches identified 974 studies but only 243 studies were considered eligible for inclusion by the two independent reviewers who extracted the data. A binomial test revealed a positive relationship between antibiotic consumption and resistance ($p < .001$) but multiple regression modelling did not produce any significant predictors of study outcome. The meta-analysis generated a significant pooled odds ratio of 2.3 (95% confidence interval 2.2 to 2.5) with a meta-regression producing several significant predictors ($F(10,77) = 5.82$, $p < .01$). Countries in southern Europe produced a stronger link between consumption and resistance than other regions.

**Conclusions:** Using a large set of studies we found that antibiotic consumption is associated with the development of antibiotic resistance. A subsequent meta-analysis, with a subsample of the studies, generated several significant predictors. Countries in southern Europe produced a stronger link between consumption and resistance than other regions so efforts at reducing antibiotic consumption may need to be strengthened in this area. Increased consumption of antibiotics may not only produce greater resistance at the individual patient level but may also produce greater resistance at the community, country, and regional levels, which can harm individual patients.

**Keywords:** Antibiotic resistance, Antibiotic usage, Community-acquired infections, Meta-analysis

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## Background

In the absence of the development of new generations of antibiotic drugs, appropriate use of existing antibiotics is needed to ensure the long term availability of effective treatment for bacterial infections [1]. If antibiotics become ineffective, then established and newly emerging infectious diseases, which are becoming an increasing threat, may lead to increased morbidity, health care utilisation and premature mortality [2-4].

Unfortunately, greater use of antibiotics during the past 50 years has exerted selective pressure on susceptible bacteria and may have favoured the survival of resistant strains [5], some of which are resistant to more than one antibiotic. If excessive antibiotic use can be reduced, the expectation is that resistant bacteria may be replaced by susceptible bacteria because resistant bacteria may be less 'fit' than susceptible bacteria [6].

More than 90% of antibiotics for medical use in Europe are prescribed to non-hospitalized patients [7]. However, existing information on antibiotic resistance patterns from pathogens circulating among community-based patients is substantially less than from hospitalized patients on whom guidelines are often based. We therefore chose to assess the relationship between the antibiotic resistance pattern of bacteria circulating in the community and the consumption of antibiotics in the community. Although Costelloe [8] et al. studied the relationship between consumption and resistance in primary care, they examined studies at the individual patient level only, omitting ecological studies (those conducted at the supra-individual level) which are included in this review. In this paper, we present a systematic review and meta-analysis of the literature on the relationship between antibiotic consumption in outpatient settings and antibiotic resistance of pathogens circulating in the community.

## Methods

### Search strategy

We searched both the English and non-English language literature for studies that looked at the relationship between antibiotic resistance and human antibiotic consumption in the community. An attempt was made to find the grey literature and published scientific literature in English, Spanish, French, German, Hungarian, Dutch, Swedish, and Croatian. These languages were chosen because the corresponding European countries were involved in the current project (Appropriateness of Prescribing Antibiotics in Primary Health Care with respect to Antibiotic Resistance). Search engines, such as Google Scholar, Embase, and Medline, were used to find published literature with reference lists of relevant articles searched by hand. Medline was searched from 1950 to late 2010 while Embase was searched from 1980 to late 2010. A list of search terms and connectors, which were used for both the English and non-English searches, can be found in Appendix 1.

### Study selection

We selected studies where a) the bacteria were acquired, and antibiotic consumption was measured, in the community b) the majority of the participants did not have a serious illness such as HIV or cancer c) the interval between consumption and resistance was one month or greater because we wanted to examine whether there was an enduring association between consumption and resistance and d) a statistical link between consumption and resistance was tested. Studies that presented descriptive information and made no attempt to establish a statistical connection between consumption and resistance were not included in the analysis. No limits were placed on when the study was published and few restrictions were placed on the type of study methodology, so both observational and experimental studies were included.

The level of analysis for any given study ranged from the individual patient (or individual bacterial isolate) level to the country (or groups of countries) level. Studies examined either children or adults or both, there were no restrictions on which body sites were sampled for establishing bacterial resistance or how antibiotic consumption was measured, and all bacteria and all antibiotics were considered relevant. Studies undertaken anywhere in the world were included with both English and non-English articles retrieved for our review. The list of the criteria we used to exclude studies is provided in Appendix 2.

To minimise the tendency to include studies that only reported significant results, we systematically searched the grey literature and included studies in which the primary focus of the article was not on the relationship between antibiotic consumption and antibiotic resistance. Abstracts were examined with full articles obtained and translated if the study looked relevant. When questions arose in applying the exclusion criteria, the authors resolved any disagreements through discussion.

### Data extraction

Full articles were examined for quality and data were independently extracted by the authors using purpose-built forms that listed the relevant variables. Any disagreements were resolved by discussing the articles and reaching consensus. Explanatory variables that were extracted from the studies are listed in Table 1.

The main dependent variable was a dichotomous coding of study outcome based on whether or not the article supported a positive relationship between antibiotic consumption and antibiotic resistance. A positive

**Table 1 Explanatory variables**

| Variable | Number (percentages in parenthesis) total sample = 243 | |
|---|---|---|
| Outcome | Positive | 164 (67%) |
| | Negative or equivocal | 79 (33%) |
| Level of sampling | Individual | 72 (30%) |
| | Region/Country | 124 (51%) |
| | Other | 47 (19%) |
| Level of analysis | Individual | 178 (73%) |
| | Region/Country | 53 (22%) |
| | Other | 12 (5%) |
| Children/Adults | Children | 88 (36%) |
| | Adults | 62 (26%) |
| | Both | 93 (38%) |
| Bacteria* | *Streptococcus* | 132 (54%) |
| | *Staphylococcus* | 50 (21%) |
| | Enteric Bacteria | 69 (28%) |
| | *Haemophilus* | 24 (10%) |
| | Other | 17 (7%) |
| Most common bacteria/Drug combinations** | *B*-lactam resistant *S pneumonia* | 104 (43%) |
| | Macrolide resistant *S pneumonia* | 56 (23%) |
| | Quinolone resistant *E coli* | 41 (17%) |
| | *B*-lactam resistant *E coli* | 35 (14%) |
| | Sulphonamide resistant *E coli* | 31 (13%) |
| | Methicillin-resistant *S aureus* | 38 (16%) |
| Most common antibiotics consumed*** | *B*-lactams | 132 (54%) |
| | Macrolides | 93 (38%) |
| | Sulphonamides | 59 (24%) |
| | Quinolones | 52 (21%) |
| | Antibiotic not specified | 65 (27%) |
| Time between consumption and resistance^ | Six months or less | 129 (53%) |
| | More than 6 months | 57 (23%) |
| | Same time | 43 (18%) |
| | Not specified | 14 (6%) |
| How antibiotic consumption was assessed# | Self report | 99 (41%) |
| | Medical records | 92 (38%) |
| | Sales/Prescriptions | 65 (27%) |
| | Direct application of antibiotic | 14 (6%) |
| Region where study was conducted## | Northern Europe | 66 (27%) |
| | Southern Europe | 45 (18%) |
| | US | 67 (28%) |
| | Other | 61 (25%) |

**Table 1 Explanatory variables** *(Continued)*

| | | |
|---|---|---|
| Type of study | Cross-sectional | 101 (42%) |
| | Ecological | 56 (23%) |
| | Case–control | 35 (14%) |
| | Quasi-experiment | 21 (9%) |
| | Other | 30 (12%) |

*Percentages do not equal 100% as any given study may have examined more than one type of bacteria.
**Percentage do not equal 100% as any given study may have examined more than one combination; resistant and non-susceptible strains of *S pneumonia* are combined under the resistant label for this bacterium.
***Percentages do not equal 100% as any given study may have examined more than one antibiotic.
^This variable represents the maximum time interval in any given study between when consumption occurred and resistance was measured. Studies classified as 'same time' tended to be ecological studies where the precise interval separating consumption and resistance could not be determined, these studies often simply reported consumption and resistance occurring together over some multi-year interval.
#Percentages do not equal 100% as any given study may have used more than one method.
##The total equals 239 as three studies were conducted in both southern Europe and northern Europe and one study was coded as not applicable.

relationship could be represented by either increased consumption associated with increased resistance or decreased consumption associated with decreased resistance. A negative relationship could be represented by either the absence of a significant relationship between consumption and resistance or, in rare instances, a truly negative relationship, such as increased consumption associated with decreased resistance. Studies that did not clearly provide either positive or negative evidence were combined with studies that produced a negative relationship to form a not-positive category which was compared with the positive studies in the data analysis. Studies were classified as positive or negative based on a preponderance of the evidence with a positive outcome recorded when an increase in antibiotic consumption was associated with either an increase in resistant bacteria or a decrease in susceptible bacteria. For the meta-analysis the dependent variable was the odds ratio for the study based on the standardized effect size.

### Data analysis

We wanted to use all of the studies in our analysis in order to improve power and examine whether a relationship between antibiotic consumption and antibiotic resistance existed for the complete set of data, so we first ran simple correlations and a logistic regression because the data did not generally lend themselves to a meta-analytic approach. The studies were heterogeneous with study design and effect size measures varying greatly between studies. Furthermore, a single effect size could not be calculated for many studies because numerous associations between consumption and resistance were reported and simple averaging of effect sizes for any given study was not appropriate. For those studies (N = 88) for which a single effect size measure could be obtained a meta-analysis and meta-regression analysis were conducted.

We ran a series of correlations between each of the explanatory variables and the dichotomous outcome variable in order to reduce the number of predictors in the subsequent regression and ensure that the number of cases (studies) relative to the number of predictors was adequate. Variables that were significantly correlated at this level were used in a logistic regression and entered in a single step to predict whether a positive or negative relationship was found between consumption and resistance. A binomial test was also run to see whether a significantly greater number of positive associations between consumption and resistance were found in the studies. The binomial test examined whether the proportion of studies with a positive association between consumption and resistance significantly differed from the proportion of studies with a positive association that would be expected under the null hypothesis. The proportion under the null hypothesis (no association between resistance and consumption) was 50% (i.e., the probability of a positive association was equal to the probability of a non-positive association). For a subset of the studies, a meta-analysis and subsequent meta-regression analysis were run. Analyses were conducted in SPSS version 16 and Stata version 11.2.

## Results

### Application of exclusion criteria

To arrive at the studies that formed the basis of our analysis (see Figure 1), we searched the English language literature and identified 745 studies that appeared relevant. However, 503 studies (68%) did not meet our inclusion criteria. Most of the excluded studies (over 95%) were eliminated for one of the following five reasons: methodological weaknesses (N = 213) such as no attempt to statistically analyse the data, review article or editorial (N = 82), study did not measure either resistance or consumption (N = 62), hospital study or the patients were too ill (N = 80), and short interval (less than a month) between the measurement of consumption and resistance (N = 54). Altogether 242 English-language studies or 32% (239 published studies and 3 grey literature

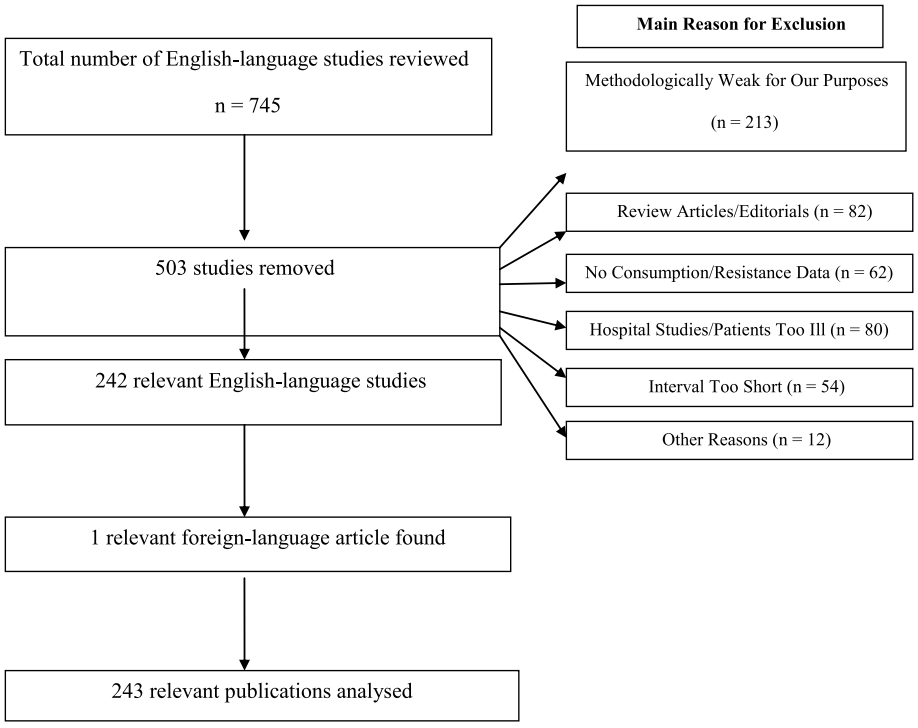


**Figure 1 How studies were selected.**

documents) of the 745 originally identified studies were considered relevant. A list of excluded studies is available from the authors upon request.

Searches conducted by colleagues in other countries revealed 229 studies that appeared relevant, but only one of these studies was included in our analysis. Non-English articles were excluded, with three exceptions, because either a version of the study had already been obtained in English or the study did not provide statistical analysis of a link between antibiotic consumption and resistance in the community. The relevant non-English language article (Appendix 3: Dellamonica et al 2002) along with the 242 English language articles provided us with a total of 243 studies that formed the basis of our analysis.

### Study characteristics

Table 1 shows the number of studies that fell into various categories for the 243 studies included in the final analysis. More than two-thirds of the studies found a positive relationship between antibiotic resistance and antibiotic consumption. Most of the studies (51%) sampled data at the regional or country level but analysed data at the individual level (73%) which means that data from individual participants were often sampled from some larger unit, such as an entire country.

With few exceptions, the bacteria that were studied fell into one of three classes (*Streptococcus*, *Staphylococcus*, or Enteric bacteria, such as *E coli*). The most common classes of antibiotics for which consumption was measured included *B*-lactams, macrolides, sulphonamides, and quinolones although more than a quarter of the studies did not specify which antibiotics had been consumed.

The studies in our sample were usually conducted in either Europe or the US. More studies took place in northern Europe than in southern Europe although both regions were well represented. Almost 80% of the studies used one of three study designs: cross-sectional, ecological, or case–control.

### Predicting study outcome

We used the binomial test to examine whether there were more studies that produced a positive outcome in which either increased consumption was associated with increased resistance or decreased consumption associated with decreased resistance. The binomial test revealed that the probability of a positive outcome was significantly greater than the probability of an outcome that was not positive ($p < .001$).

We next examined the correlations between the predictor variables listed in Table 1 and our dichotomous outcome measure. Each of the categorical variables listed in Table 1 was turned into a set of dichotomous variables for this purpose. For example, the adult/child variable was recoded into three dichotomous variables, one

representing children, another representing adults, and a third representing both children and adults.

Three positive correlations were found: studies that included both adults and children were more likely to find a positive association between antibiotic consumption and resistance ($r = 0.17$, $p < .01$) as were studies that examined tetracycline-resistant *S pneumonia* ($r = 0.14$, $p < .05$) and those that looked at quinolone consumption ($r = 0.15$, $P < .05$). Three negative correlations were also produced: for studies that only contained children ($r = -0.13$, $p < .05$), those conducted in the US ($r = -0.16$, $p < .05$) and cross-sectional studies ($r = -0.15$, $p < .05$). Studies which contained children, those conducted in the US, and cross-sectional studies were more likely to find a small, either negative or not positive, association between antibiotic consumption and antibiotic resistance.

All of the variables for which significant correlations were found were simultaneously entered into a logistic regression equation to predict study outcome. None of the variables that produced significant bivariate correlations were significant predictors in the logistic regression equation, although as a set, they did significantly predict the outcome variable (chi-square = 22.81, $df = 6$, $p < .01$) thereby distinguishing between studies with a positive association and other studies. However, only a little more than 10% of the variance in the outcome variable was explained by these predictors (Nagelkerke $R^2 = 0.12$).

We noticed that the relationship between consumption and resistance often varied within a study depending on which bacteria were being considered. So, a study that looked at multiple types of bacteria may have found a positive relationship between consumption and resistance for one but a negative relationship for another. Our global outcome measure did not allow us to investigate these differences because it was based on the preponderance of evidence across bacterial classes for any given study. Therefore, we decided to conduct a separate analysis for each bacterial category (Streptococcus, Staphylococcus, Enteric Bacteria, and Haemophilus/Other). We recoded the outcome measure for those studies that contained more than one type of bacteria so that the outcome measure in any given analysis was based on the relationship between consumption and resistance for a single type of bacteria.

First, looking at the results from the binomial tests, we found that only enteric bacteria and streptococcus produced significantly more positive outcomes than negative outcomes ($p < .01$ for enteric bacteria and $p < .001$ for streptococcus). For Staphylococcus and Haemophilus/Other, the results from the binomial tests were not significant. Therefore, we decided to focus on enteric bacteria and streptococcus in subsequent analyses.

When correlations were run for the streptococcus bacteria, only two variables out of 48 were significantly correlated with outcome. Tetracycline resistant S pneumonia was significantly correlated with the outcome variable ($r = 0.19$, $p < .05$) and so was trimethoprim consumption ($r = -0.23$, $p < .01$). However, this is probably due to chance as the number of significant correlations was less than 5% of the total number of correlations that were run, so a logistic regression was not conducted. In a similar vein, only two correlations were significant for enteric bacteria. Patients who were children ($r = -0.28$, $p < .05$) and quinolone consumption ($r = 0.33$, $p < .01$) were significantly correlated with outcome. Again, with only two significant correlations, we can conclude that the results are probably due to chance, so a logistic regression was not run.

### Meta-analysis

We conducted a fixed-effects meta-analysis of a subset of studies for which a common effect size could be obtained. A fixed effects meta-analysis was more appropriate than a random effects meta-analysis because we wanted to determine whether heterogeneity between the studies could be explained by our predictors [9]. Our meta-analysis focused on the most common study designs and included articles that used cross-sectional, case–control, cohort, non-randomised quasi-experimental and randomized controlled trial designs. We ran a separate meta-analysis for each of the most common study designs (53 cross-sectional studies, 21 case–control studies, and 8 cohort studies) to see whether the results varied by study design. Ecological studies, which were conducted at the regional or country level, were excluded due to much larger sample sizes that would not allow comparisons with the much smaller studies that were used in this analysis. We decided against conducting a separate meta-analysis of the ecological studies because there were only 17 such studies for which a common effect size measure could be calculated. More studies than this would have been needed to explore relationships between predictors and effect size in any subsequent meta-regression. For the 88 studies that were included we were able to either use the odds ratio that was reported in the study or calculate one from the available data.

Our meta-analysis revealed that there was a significant positive relationship between antibiotic consumption and resistance with a pooled effect size (odds ratio) of 2.33 ($z = 25.71$, $p < .01$, 95% confidence interval 2.19 to 2.49). The results were similar for each of the most common study designs including cross-sectional (OR = 2.46, $z = 17.06$, $p < .01$, 95% CI = 2.22 to 2.73), cohort (OR = 2.93, $z = 7.02$, $p < .01$, 95% CI = 2.17 to 3.96) and case–control studies (OR = 2.26, $z = 17.41$, $p < .01$, 95% CI =

2.07 to 2.48) so further analyses were conducted with all 88 studies. The forest plot in Figure 2 displays the odds ratio and weight for each study. One of the studies (Appendix 3: Schneider-Lindner et al 2007) was weighted more heavily than the other studies due to a very small standard error for the odds ratio but removing this study did not change our findings (OR = 2.74, z = 25.86, p < .01).

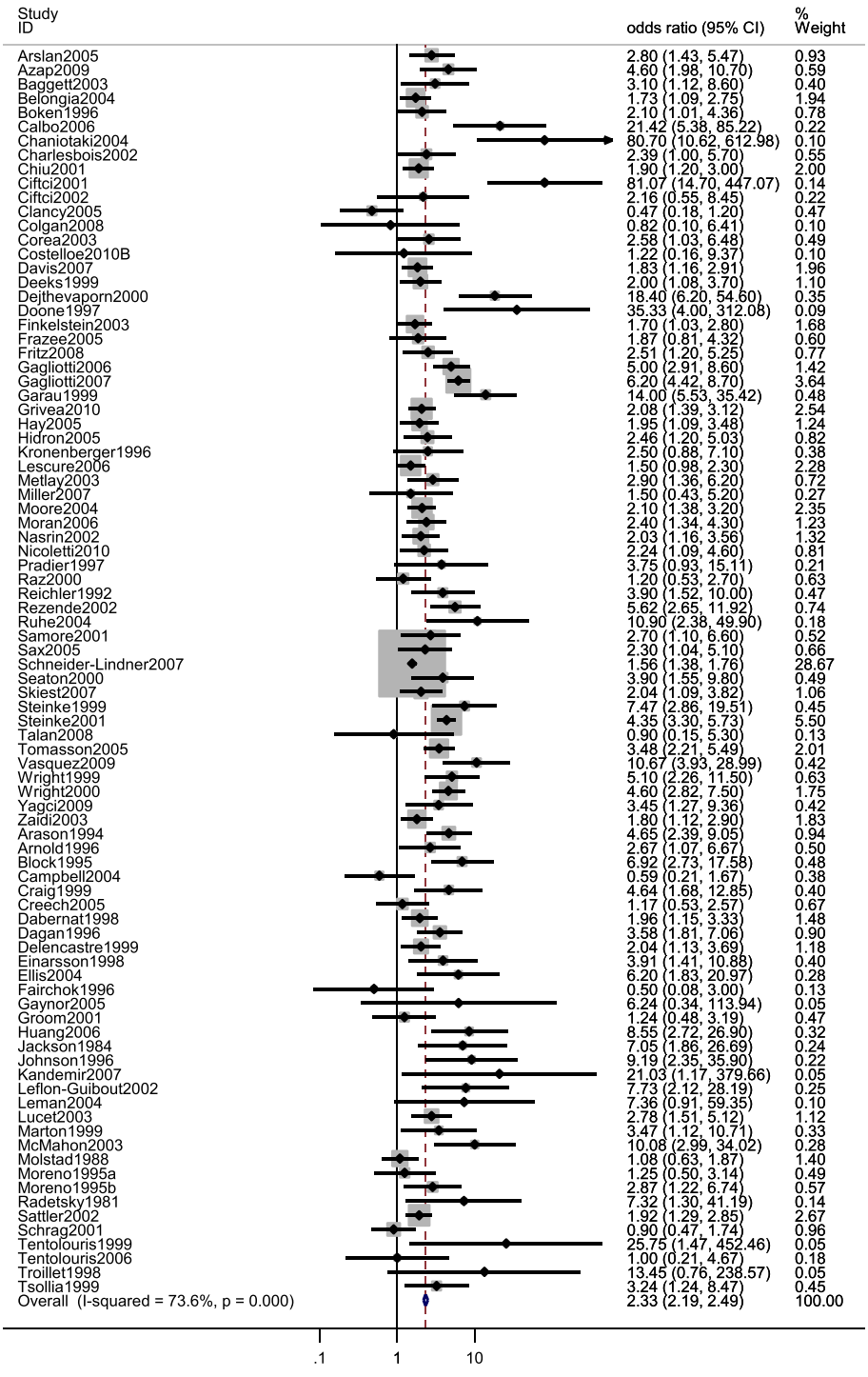


**Figure 2** Forest plot showing odds ratio and 95% confidence interval for each study along with study weight.

We should also mention, as can be seen from the funnel plot in Figure 3, that there was some evidence of potential publication bias in our sample of studies. The absence of small studies in the lower left hand side of the plot suggests that small studies that did not find a strong association between antibiotic consumption and resistance may not have been published, although as Moller and Jennions [10] note, publication bias is not the only explanation for a skewed funnel plot.

Significant heterogeneity was observed with a heterogeneity chi-squared value of 329.75 ($p < .01$). The percentage of variation between studies due to heterogeneity was high (73.6%) so we decided to examine whether our independent variables could explain differences between studies in the odds ratios. Using weighted correlations, in which the correlation between the independent variable and the odds ratio was weighted by the corresponding standard error, we found 11 significant correlations (see Table 2) and then conducted a meta-regression to determine the independent effect of each variable on the odds ratio. We excluded the variable staphylococcus because it was highly correlated with Methicillin-Resistant *S aureus* (MRSA ($r = 0.97$)).

The meta-regression showed that our set of independent variables significantly predicted the odds ratios ($F\ (10,\ 77) = 5.82\ p < .01$) although significant residual variability remained (residual sum of squares = 187.78, $df = 77$, $p < .01$). Five variables were significant independent predictors: 'both children and adults' $z = 3.90 < .01$, 'southern Europe' $z = 2.25\ p < .05$, '*B*-lactam consumption' $z = -3.15\ p < .01$, 'MRSA' $z = -4.58\ p < .01$, and 'quinolone-resistant *E coli*' (QREC) $z = 2.57\ p < .05$. We can conclude that studies which contained both adults and children, those conducted in southern Europe, and studies that looked at QREC were more likely to find a strong positive relationship between antibiotic consumption and resistance. Studies that examined *B*-lactam consumption or MRSA tended to find a weaker relationship between consumption and resistance. The finding that southern European countries produced a much stronger link between resistance and consumption confirms previous observations that antibiotic resistance due to the consumption of antibiotics may be a greater problem in southern Europe than in northern Europe (Appendix 3: Goossens et al 2005).

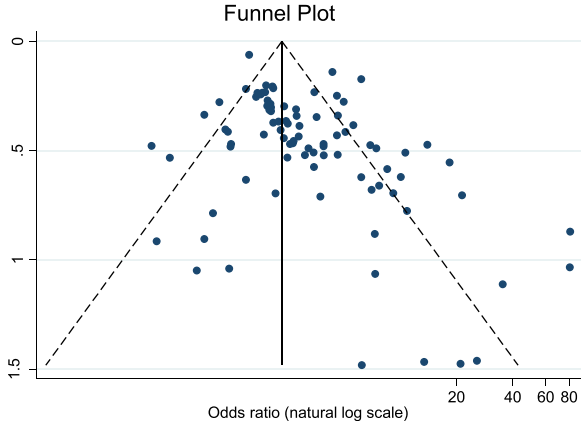


**Figure 3 Funnel plot showing effect size (odds ratio) as a function of sample size (natural log of standard error).**

### Publication bias

As noted earlier, there was some evidence of publication bias in the subsample of studies that formed our meta-analysis. Turning to the issue of publication bias for the full set of 243 studies, a large number of these studies (a third of our sample) did not find a positive association between antibiotic consumption and antibiotic resistance, which reduces the likelihood of publication bias and lessens concerns that we chose studies for inclusion simply because they supported our hypothesis. Concerns with publication bias are also reduced by our contention that studies which reported negative evidence probably would be published since studies that found no relationship between consumption and resistance would still generate a great deal of interest. To examine potential publication bias further, we looked at 92 studies that were primarily concerned with something other than the relationship between consumption and resistance. These studies, which should be less prone to the publication bias that we are concerned with, found a roughly similar split in the ratio of positive to not positive outcomes that we found with the larger sample, 60% of the studies found a positive relationship and 40% did not find a positive association.

## Discussion

Our initial analysis with the entire sample of 243 studies revealed that there was a positive association between bacterial resistance and antibiotic consumption in the community, which means that either increased consumption was associated with increased resistance or decreased consumption was associated with decreased resistance. Using a much larger sample of studies we found support for Costelloe's [8] conclusion that antibiotic prescribing is associated with the development of antibiotic resistance. We also extended Costelloe's work by including studies that were conducted at both the ecological level and the individual level and finding that level of analysis did not affect the relationship between consumption and resistance.

Although several study variables were significantly correlated with study outcome (whether or not a positive association was obtained between resistance and consumption), all of the correlation coefficients were small

**Table 2 Weighted correlations between odds ratios and independent variables**

| Variable | Correlation | Significance | Sample size* |
|---|---|---|---|
| Both children and adults | 0.32 | $p < .01$ | 20 |
| Enteric bacteria | 0.45 | $p < .01$ | 20 |
| *Staphylococcus* | −0.44 | $p < .01$ | 30 |
| MRSA | −0.48 | $p < .01$ | 29 |
| QREC | 0.37 | $p < .01$ | 10 |
| *B*-lactam consumption | −0.31 | $p < .01$ | 41 |
| Sulphonamides consumption | −0.28 | $p < .01$ | 20 |
| Macrolide consumption | −0.24 | $p < .05$ | 16 |
| Quinolones consumption | −0.22 | $p < .05$ | 12 |
| Northern Europe | −0.22 | $p < .05$ | 14 |
| Southern Europe | 0.24 | $p < .05$ | 15 |

*Number of cases in each category out of 88 cases total.

(0.20 or less), and none of these variables were significant predictors of study outcome when they were entered into a logistic regression equation. A lack of significant predictors means that the association between antibiotic consumption and bacterial resistance does not depend on any of the demographic variables that we investigated or on other variables of interest, such as the level at which the data were sampled or analysed. Although no significant predictors were found when individual classes of bacteria were examined either, the binomial test showed that the positive relationship between consumption and resistance was only obtained for enteric bacteria and streptococcus so efforts at controlling resistance needs to focus on these bacteria.

When the 88 studies in our meta-analysis were examined, we found that there was a significant positive relationship between consumption and resistance and several variables that were significant predictors. Studies that contained both adults and children, those conducted in southern Europe, and studies that looked at QREC were more likely to find a strong positive relationship between antibiotic consumption and resistance whereas studies that examined *B*-lactam consumption or MRSA tended to find a weaker relationship between consumption and resistance. The finding that southern European countries produced a much stronger link between resistance and consumption confirms previous observations that antibiotic resistance due to the consumption of antibiotics may be a greater problem in southern Europe than in northern Europe (Appendix 3: Goossens et al 2005). Also, the results from the meta-analysis indicate that the use of quinolones may need to be reduced when treating *E Coli* infections.

One of the major strengths of our review is the large number of studies that contributed to our analysis, which means that we had plenty of power to detect an effect. We placed few restrictions on the types of studies that we considered relevant, which make our findings applicable to a wide range of settings thereby increasing ecological validity and also reducing publication bias in which non-published studies that do not produce significant findings are overlooked. Our review included English-language studies and studies published in other languages, observational and experimental studies, grey literature as well as published scientific literature, with no geographical restrictions placed on where the study was conducted. For any given study the level of analysis ranged from the individual patient (or individual isolate) level to the country (or groups of countries) level and both children and adults were well represented. There were no restrictions on which body sites were sampled for establishing bacterial resistance, how antibiotic consumption was measured, which bacteria were isolated, or which antibiotics were consumed. In spite of the comprehensive nature of our review, a final strength is our targeted approach to answering the primary question, is there a relationship between antibiotic consumption and antibiotic resistance in the community, by the use of a clear set of exclusion criteria.

Potential limitations should also be noted with our review. First, our primary outcome measure was based on a dichotomous coding of whether or not a study supported a positive relationship between antibiotic consumption and antibiotic resistance so it ignored possible differences within studies because it was based on the preponderance of evidence for any given study. However, we believe that using a global measure of outcome to represent the relationship between antibiotic consumption and resistance was justified as a common effect size measure could not be calculated for most of the studies that were used in our review. Another limitation concerns poor reporting of important information and the use of weak measures in many studies. More than a quarter of the included studies did not specify which

antibiotic had been consumed and almost half (41%) of the studies used self-reports, which may be unreliable, to assess antibiotic consumption. The most serious limitation in this regard concerned inadequate reporting of how much time had elapsed between antibiotic consumption and the measurement of bacterial resistance. Most studies did not provide the precise interval between when antibiotics were consumed and when resistance was measured, which hindered our attempts to determine whether resistance endured over time as Costelloe [8] had done. A final limitation concerns some evidence of potential publication bias in our meta-analysis in which smaller studies that did not find a strong positive association between antibiotic consumption and resistance may not have been published.

## Conclusions

To conclude, our literature review reveals the following. First, there is an association between antibiotic consumption and the subsequent development of bacterial resistance at both the individual and community level. For clinicians this is important because our findings do not just apply at the individual patient level but also at the community, country and regional levels. As Bergman (Appendix 3: Bergman et al 2006) noted, antibiotic pressure at the population level may be more important than the individual's use of antibiotics in determining that individual's risk of harbouring resistant bacteria. Both responsible prescribing at the individual level as well as public policy that addresses the problem at the national or regional level are critical components of any strategy to reduce bacterial resistance, which supports the current efforts of many countries, including the UK, to ensure that antibiotics are only used when indicated and that the most appropriate antibiotic (often an older established antibiotic) is used. We also found that the link between antibiotic consumption and resistance does not depend on any of the demographic variables that we investigated which means that antibiotic consumption may lead to resistance for diverse groups of people in various settings, although we would hasten to add that several important predictors were identified in the meta-analysis including a stronger link between resistance and consumption in southern Europe than in other regions. This discrepancy may have been due to the outcome measure that was used or the particular mix of studies that was examined in the meta-analysis. More work needs to be done because significant residual variability remained that could not be accounted for by the variables that were used in our meta-analysis.

Future work should also address the issue of co-selection in which the use of one antibiotic produces resistance to another antibiotic. If co-selection is widespread, then resistance to one antibiotic could be due to the use of another antibiotic that was not measured in the study under investigation, in which case the conclusion that there was no association between consumption and resistance would be misleading. Unfortunately, the studies that we examined rarely looked at this issue. More thought also needs to be given to improving measures of antibiotic consumption. Proxy measures, such as patient self-report of antibiotic use, do not directly assess consumption and therefore may be of limited utility.

## Appendix 1 Search terms and connectors (AND/OR) for literature search

'Drug Resistance, Microbial'
OR
'Drug Resistance, Bacterial'
OR
'Bacterial Resistan*' (which captures terms such as 'Resistant' and 'Resistance')
OR
'Antimicrobial Resistan*'
OR
'Antibiotic Resistan*'
AND
'Consumption'
OR
'Antibiotic Consumption'
OR
'Antibiotic Prescri*' which includes terms such as 'Prescribing' and 'Prescription'
OR
'Antibiotic Utilization'
OR
Antibiotic Use'
OR
'Antibiotic Sales'
AND
'Community'
OR
'Primary Care'
OR
'Primary Health Care'
OR
'General Practice'
OR
'Family Practice'
OR
'Ambulatory Care'

## Appendix 2 Exclusion criteria

A). Some studies were excluded because the infection was not community acquired or the setting was not appropriate:

1) Studies where more than half of the resistant bacteria were acquired in a hospital setting or

in another institutional setting such as a nursing home.

2) Studies where antibiotic consumption was only measured in a hospital or nursing home, not in the community
3) In vitro studies unless in vivo resistance was also examined
4) Studies that examined the topical use of antibiotics for skin infections, dental use of antibiotics, veterinary studies, and those that looked at the use of antibiotics in agriculture or as antiseptics
5) Studies that looked at the effects of bacteria from waste or industry on soil, air and water
6) Studies that looked at viruses, parasites or fungi
7) Studies that only looked at treatment failure or eradication of bacteria unless resistance was also measured
8) Studies where most of the patients were seriously ill (such as, when over half the patients were on immunosuppressive therapy, were HIV positive, had meningitis or end-stage cancer, were using catheters, or were recruited in tertiary centres). Those studies that looked at urinary tract infection were only included when at least 2/3 of the sample contained women (not girls) with an uncomplicated urinary tract infection.

B) Some studies conducted at the level of the individual patient (as opposed to country or region) were excluded because the temporal relationship between consumption and resistance was not clear or the interval between consumption and resistance was too short (we wanted evidence of an enduring effect):

9) Studies in which consumption was measured after resistance or where the time between consumption and resistance was exclusively less than one month. Patients could be currently taking antibiotics at the time that resistance was measured if the long term use of antibiotics was investigated (such as the effect of antibiotics received in the past 6 months on resistance to current treatment with antibiotics)

C) Some studies were given less weight than others:

10) We focused on newer studies (those conducted since 1990) although some older studies from the 1970s and 1980s were also included. [Older studies tended to be methodologically inferior (in reporting of statistics) and resistance tends to be greater in newer studies, which is an important consideration as the current relationship between resistance and consumption is more important than the relationship from 40 or 50 years ago].
11) Review articles were not included (except as a source of references) unless the study combined previous work in a meta-analysis or systematic review.
12) Studies that simply looked at the biological mechanisms which produced resistance were excluded (However, some studies examined bacteria that produced resistance in a particular way, such as b-lactamase-producing bacteria. These studies were included because they looked at the effects of antibiotic consumption on the production of a particular type of resistant bacteria).
13) Studies that looked at treatment failure or bacterial eradication were excluded unless resistance was also measured. For example, some studies examined C Difficile, which is difficult to eradicate, but these articles were excluded unless resistance was also measured.

D) Studies were generally classified as weak, and therefore excluded, when:

14) The authors acknowledged that there was insufficient power to detect an effect
15) No statistical analysis was conducted. In some cases, conclusions were based on graphs and figures with no statistical results provided, for other studies a single participant or a handful of participants was studied so no statistical tests were conducted.
16) Poor measures were used, usually poor consumption measures (such as relying on participant self-report when recall was poor).

## Appendix 3 Included studies

1. Albrich, W.C., Monnett, D.L., & Harbarth, S., *Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes.* Emerging Infectious Diseases, 2004. **10**(3): p. 514–517.
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#### Competing interests
The authors declare that they have no competing interests.

#### Authors' contribution
BB performed the searches, analysed the data, and drafted first sections of the text. MP designed the study and formulated the hypotheses. FS led the APRES team. HG and ES provided their expertise in microbiology. MP and BB are the guarantors. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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#### Data sharing
Limited to other researchers on personal request.

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