Moreover, by reporting an average 32% erythromycin-resistant Streptococcus pneumoniae for Europe, the meta-analysis gives a biased view of macrolide resistance on this continent. EARSS data show that, in many European countries, resistance to macrolides is still below 10%. In 2004, erythromycin resistance in S. pneumoniae isolates from sterile body sites was only 3.7% in Denmark. However, it showed an increase from 0.5% in 1994 to a maximum of 5.2% in 2003 (Figure 1). Despite the low prevalence, this 10-fold increase prompted us to remind prescribers about the few indications for use of macrolides in a country with low penicillin resistance. Moreover, by reporting an average 32% erythromycin-resistant Streptococcus pneumoniae for Europe, the meta-analysis gives a biased view of macrolide resistance on this continent. EARSS data show that, in many European countries, resistance to macrolides is still below 10%.

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For most European countries, data on antimicrobial consumption are now available from the European Surveillance of Antimicrobial Consumption (ESAC) system (http://www.ua.ac.be/esc). Differences in macrolide consumption are the most likely causes for the observed differences in macrolide resistance among countries. In 2005, it does not make sense to report consumption and resistance by continent. Moreover, there is now a consensus in Europe that both should be reported not only by country, but also by region for community microorganisms, or by hospital for nosocomial microorganisms. Rather than providing new information, the meta-analysis by Halpern et al. underscores the importance and need for ongoing surveillance of the local antimicrobial resistance combined with surveillance of antimicrobial consumption.

Figure 1. Community consumption of macrolides and erythromycin-resistant S. pneumoniae from blood and spinal fluid, Denmark, 1994–2004. Lines, community consumption of macrolides [defined daily doses (DDD)/1000 inhabitant-days]: filled squares, total macrolide consumption; open diamonds, erythromycin consumption; open triangles, roxithromycin consumption; open circles, clarithromycin consumption; open squares, azithromycin consumption. Bars, erythromycin-resistant S. pneumoniae from blood and spinal fluid (%). Isolates with an MIC \( \geq 1 \text{mg/L} \) were considered resistant to erythromycin.

### Meta-analysis of bacterial resistance to macrolides—providing generalizable results: authors’ response

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Sir,

Thank you for the letter from Monnet et al. regarding our manuscript, ‘Meta-analysis of bacterial resistance to macrolides’. These investigators raise a number of important points. First is the issue of local factors affecting bacterial resistance. Clearly, local factors can affect resistance, although we do not believe it has been documented, as Monnet et al. state, that levels of resistance ‘depend almost solely on local factors’. With the ever increasing rates of travel and global interactions, spread of resistance between different locales will probably continue to be an important issue. For example, a study by other researchers at Monnet’s institute in Denmark reported that foreign travel was a risk factor for quinolone-resistant Campylobacter jejuni infections. A recent report also indicated that bacteria collected from international

### References


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travellers to the same geographic region may not share the same DNA restriction patterns. Regardless, our meta-analysis would have been incomplete if we had not explored the potential heterogeneity of the included studies. All of the included studies involved similar criteria in assessing resistance: isolates of *Streptococcus pneumoniae* and/or *Streptococcus pyogenes* obtained from community or outpatient settings in 1997–2003 with specified MIC levels. Further, statistical analyses were performed (using the Q-statistic) to evaluate potential heterogeneity between studies. Thus, despite the potential effects of local factors, we were able to identify a statistically homogenous group of studies for pooling in the meta-analysis.

Monnet *et al.* also question the exclusion of a number of surveillance studies. As discussed in our paper, reports from a number of broad surveillance studies (e.g. PROTEKT) were excluded from this meta-analysis as they did not provide resistance information separately for each macrolide (i.e. they presented pooled results across different macrolides) and/or they did not provide resistance information for patients with only the selected disease conditions (e.g. lower respiratory tract infections). Both of these study characteristics (resistance information for individual macrolides and from patients with selected infectious diseases) were important in enhancing the specificity of the included resistance data and the pooled results. We did attempt to contact authors regarding unpublished work and for additional information when data in an abstract or article were unclear. A number of the resistance studies mentioned by Monnet *et al.* did not appear in MEDLINE or EMBASE and/or did not meet the meta-analysis inclusion criteria. For example, the DANMAP 2003 study presents resistance data for all macrolides combined and does not specify the infectious condition or conditions of individuals from whom isolates were collected. Thus, the studies mentioned by Monnet *et al.* would have been specifically excluded from the meta-analysis.

Monnet *et al.* comment that the meta-analysis results are out of date as soon as they are published, with national surveillance reports and meeting abstracts presenting more recent information. This is a clear limitation to any meta-analysis, that it can provide results that are only as current as the data available when it was performed. Further, data that are publicly unavailable are difficult to consider. However, this concern ignores the principal reason for performing a meta-analysis: to pool data across multiple studies in order to assess specific outcomes more accurately and with greater statistical power. Individual studies and meeting abstracts do present more current resistance data, but these reports are limited in their sample size, scope and generalizability. The comments by Monnet *et al.* that erythromycin resistance is much lower in Denmark illustrate this point; while the resistance figure quoted provides one data point, its relevance to overall erythromycin resistance is uncertain. By combining resistance data across multiple studies in a systematic manner, we were able to evaluate resistance more broadly, without the limitations of any individual study (which, as Monnet *et al.* point out, may be influenced by local factors).

We are puzzled by the comment from Monnet *et al.* that the money spent on the meta-analysis would have been better spent collecting resistance data from regions where such data are missing. We are unaware of criteria being used to assess the best global expenditures of research monies. While there are many worthy uses of research funds, we believe that this meta-analysis is an important contribution to the literature, providing broadly generalizable data regarding macrolide resistance in community and outpatient settings. To our knowledge, such an analysis has not been previously performed.

We agree with the conclusion by Monnet *et al.* that our meta-analysis ‘underscores the importance and need for ongoing surveillance of the local antimicrobial resistance combined with surveillance of antimicrobial consumption’. Collection of local data will continue to be crucial in evaluating trends in bacterial resistance. However, local data provide only isolated pictures of bacterial resistance. In this era with global interactions being increasingly common, combining data in a consistent and robust manner, with the appropriate methods of a meta-analysis, provides broader and more generalizable information for the development of national and multi-national health policy.

**References**


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Sir,

We read with interest the report of increasing erythromycin resistance in *Campylobacter* isolated from humans in Northern Ireland.1 We have been monitoring antimicrobial resistance in *Campylobacter* of human origin in Oxfordshire since