Correspondence

Over-the-counter antimicrobials: the hidden costs of resistance

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Sir,

Concern with rising healthcare costs has led to interest in reclassifying a wide range of pharmaceuticals from prescription to over-the-counter (OTC) status. This, it is argued, will both reduce costs to the public sector purse (currently some £4.25 billion, with antimicrobials comprising some £419 million (Anonymous, 1994; Wiggins, 1995)) and provide greater patient access to medications (Editorial, 1994). In a recent issue of this journal, Pringle (1995) and Reeves & Lewis (1995) provide an excellent introduction to the debate concerning the reclassification of antimicrobial drugs for provision on an OTC basis.

However, although this discussion covers many issues of importance to this decision, neither author considers the very real prospect that increased antimicrobial resistance will have economic effects of sufficient magnitude to negate any short term gains from the move to OTC status. Patients who are infected with a resistant micro-organism will not necessarily recover from their infection with the first antimicrobial they receive. Extra investigation and treatment will be required: this will usually be another, more expensive, form of antimicrobial. For some, a cascade of antimicrobials will be tried before one is found that treats the infection successfully. Patients may additionally have longer stays in hospital and/or more sickness absence from work. Incorrect self-diagnosis, and mistreatment, of infection may mean considerable extra treatment is required to restore the patient to health. Ultimately there may be increased surveillance costs and an increasing requirement for investment to develop novel treatments for infection. There could even be costs associated with restrictions on travel and work in an attempt to control dissemination of antimicrobial resistant bacteria.

Research quantifying such costs is scarce, but what evidence exists suggests such costs may be significant. For instance, a recent literature review covering 87 papers concerning mortality and morbidity associated with antimicrobial resistant and susceptible strains of selected bacteria found that “the mortality, the likelihood of hospitalisation, and the length of hospital stay were usually twice as great for patients infected with drug-resistant strains as for those infected with drug-susceptible strains of the same bacteria” (Holmberg, Solomon & Blake, 1987).

The potential for these effects must lead on to a consideration of possible policy responses. Although this is a complex area it is clear that there is both a greater availability of policies and a greater chance that these policies will be successful where the choice about who should receive antimicrobial treatments is left with those financing and providing healthcare. Following a move to OTC there would really be only one available policy response—to increase prices such that, where demand is less, antimicrobial treatments are not purchased. Such a policy, however, is unlikely to be as efficient as restricting antimicrobial use through physicians, given that patients are not generally as knowledgeable about the potential seriousness of different illnesses as those clinically qualified. Such a policy would also have serious implications for equity, thus conflicting with other objectives of health care policy in the UK.

The alternative of restricting antimicrobial use through physicians would not result in such difficulties. Restriction could potentially be achieved by a number of means, such as clinical guidelines or permits (essentially, perhaps, a budget for antimicrobial treatment). Unfortunately, however, there are likely to be interactions between such policies and the very particular type of market that exists in healthcare, and considerable research in this area is undoubtedly required. A much greater range of policy options is, however, available where antimicrobials remain on prescription and are not converted to OTC.

Moving antimicrobials to OTC status may generate short term benefits for the government...
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A reduced drugs bill and pharmaceutical industry (in wind-fall profits) but will result in considerably increased health service costs in the long term.

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References

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Sir,
The battle against the re-emergence of tuberculosis which the United States and other developed countries are presently experiencing is vastly complicated by the concurrent emergence of multidrug-resistant strains of Mycobacterium tuberculosis (MDR-TB). MDR-TB strains are occurring with increasing frequency and can be resistant to almost all first- and second-line anti-tuberculosis drugs (Takiff et al., 1994). The appearance of such MDR-TB strains has resulted in much attention being focused on the therapeutic potential of the fluoroquinolones as anti-tuberculosis agents (Takiff et al., 1994).

Fluoroquinolones, especially ofloxacin, are relatively new drugs which can be incorporated into short-course anti-tuberculosis chemotherapy regimens (Tsukamura et al., 1985). However, treatment failure has already been reported due to the rapid selection of fluoroquinolone-resistant mutants during treatment (Cambau et al., 1994). In the laboratory, fluoroquinolone-resistant mutants of M. tuberculosis appear at a frequency of $2 \times 10^5$ to $1 \times 10^6$ (Takiff et al., 1994).

Mutations giving rise to fluoroquinolone resistance in mycobacteria, and many other bacterial species, have been attributed to mutations in the quinolone-resistance determining region (QRDR) of their gyrA gene (Piddock, 1995). In this study we sought to identify and characterise gyrA mutations in clinical isolates of M. tuberculosis from Hong Kong that showed decreased susceptibility to ofloxacin.

Antimicrobial susceptibilities were determined by the absolute concentration method using Löwenstein-Jensen medium. The ofloxacin-resistant strains of M. tuberculosis were identified through routine screening of clinical isolates and, once identified, the macrobroth dilution method was used to obtain the MIC values of each agent and to double-check the screening results. No strains of indeterminate susceptibility were isolated. The breakpoint concentrations used in this study, to determine whether a bacterial strain was resistant were $\geq 2$ mg/L for ofloxacin, $\geq 16$ mg/L for streptomycin, $\geq 0.2$ mg/L for isoniazid and $\geq 32$ mg/L for rifampicin.

Chromosomal DNA of the clinical isolates and reference strain, H37Rv, was isolated as described previously by van Soolingen et al. (1991). To amplify the desired region of the gyrA gene encompassing the proposed QRDR, nucleotide 2383 to nucleotide 2667, a biotinylated primer TBGyrA1 (5’TTCCTGGCGAGCGCAAGTT) and the primer TBGyrA2 (5’CAGCTACATCGACTATGCGA) were synthesized. The PCR mixture (50 μL) contained 67 mM Tris-HCl (pH 8.8), 5 mM MgCl₂, 0.01 mM Tween 20, 10 ng chromosomal DNA, 0.2 mM deoxynucleotides, 0.25 μM (each) primer and 1 U of Taq DNA polymerase (Bioline). Amplification was performed for 30 cycles (1 min at 94°C, 1 min at 55°C, 1 min to 72°C) followed by a 3 min extension at 72°C to generate a 285 bp product. For sequencing, PCR products were converted to single strands with alkaline denaturation and separated with streptavidin coated magnetic beads (Dynabeads M-280, Dynal, Oslo, Norway). An internal primer TBGyr A3 (5’AATGTTCGATTCCGGCT-