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## Antibiotics, resistance, and clinical outcomes

### *Data at the individual level are needed to direct policies*

Concern exists worldwide about the threat posed to human health by antibiotic resistance in common microbial pathogens. In response the World Health Organization has launched a global strategy for containment of antimicrobial resistance and the United Kingdom has an antimicrobial resistance strategy and action plan.<sup>1 2</sup> Fundamental to any action is an accurate understanding of the relation between prescribing and resistance. This is especially important where most prescribing occurs—in the community.

At the level of individual patients a link between prescribing and resistance has been found for many bacteria.<sup>3</sup> In the United Kingdom, data about antibiotic prescribing are usually available only at the practice level. These have been investigated in relation to bacterial resistance to antibiotics, with only a weak association found.<sup>4</sup> The validity of such analysis can be questioned, however, because exposure and outcome in any one individual are not linked and controls are not available. These potential flaws can be overcome by use of individual patient data; however, this raises important issues of confidentiality. For such data to be collected and used it needs to be shown that this approach has added value. Few studies have compared these methods directly.

A North American study showed only a weak association between data for group level prescribing and resistance to a number of antibiotics in gram negative bacilli, whereas when data were analysed at the level of the individual patient, exposure to antibiotics was strongly related to resistance.<sup>5</sup> In this issue Donnan et al have performed a similar analysis comparing the frequency of resistance to trimethoprim in gram negative bacilli in urine samples with trimethoprim prescribing.<sup>6</sup> (p 1297) At a practice level, trimethoprim prescribing was not related to trimethoprim resistance, but at an individual level a strong association existed between the two. These studies, therefore, confirm the association between the use of antibiotics and the development of resistance, but also show that the ecological fallacy introduced by using group level data may mislead strategies to combat antibiotic resistance. Analyses of data of individual patients appear to be essential. Similar studies in other common infection groups (for example, the respiratory tract) are required.

Reduced prescribing is an essential component of strategies to combat antibiotic resistance. Cost analysis data for prescriptions in England (based on prescriptions dispensed) showed a rise in antibiotic prescriptions from 43.7 million items in 1991 to 49.4 million items in 1995, since which time there has been a 25% decrease to 36.9 million prescriptions in 2000.<sup>7</sup> In paediatrics this reduction has been more dramatic at 47%.<sup>8</sup>

Reduced prescribing should mean the cessation of such prescribing where inappropriate, but the continuation of prescribing where appropriate. Reduced prescribing for the latter group might be followed by harm. Unnecessary alarm may have been caused by three studies suggesting that harm might be occurring from reduced prescribing in respiratory tract infections. Two of these studies in children have found an association between a higher incidence of mastoiditis and low rates of antibiotic prescription,<sup>9</sup> and higher rates for hospital admission for mastoiditis and quinsy with lower use of penicillin in primary care.<sup>10</sup> However, the differences were small, and the authors did not conclude that an increase in antibiotic prescription was warranted. The third study was in adults and found an association between a rise in mortality due to pneumonia and reduced prescribing for respiratory infection.<sup>11</sup> All three studies may suffer from the ecological fallacy described above for population studies relating prescribing and resistance, and the method of the latter paper has been heavily criticised.<sup>12</sup> Analysis of outcomes related to prescribing at an individual level was not performed. Comparisons of individual linked data with group data for prescribing and outcome are required to clarify relations that may be obscured by group level analysis.

We must approach data about reductions in antibiotic prescription with caution when the reason for this reduction is unknown. Some 50% of antibiotic prescription in the community is for presumptive respiratory tract infection. Presentations for such respiratory infections to general practitioners declined between 1995 and 2000.<sup>13</sup> The reduction in antibiotic prescription might be for reasons other than altered prescribing behaviour.

Weak and potentially inaccurate data about antibiotic prescription and either resistance or outcome should be recognised for what it is and not used to

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diminish the drive for more prudent antibiotic prescription. Group level studies may be helpful, but only if known to produce convergent data with individual linked studies. Donnan et al have shown that data can be analysed at an individual level without compromising confidentiality issues. Further clarification of when and where such data provide added benefit is required.

We ignore the risks from increasing antibiotic resistance at our peril. Reduced antibiotic prescribing is beginning to occur and may be leading to reduced resistance in *Streptococcus pneumoniae*. No good evidence of harm has been produced. The drive for more appropriate prescribing of antibiotics in the community should continue.

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## The free trade agreement between Australia and the United States

*Undermines Australian public health and protects US interests in pharmaceuticals*

On 4 March 2004 Australia and the United States released the text of a bilateral trade agreement designed to reduce trade barriers between the countries.<sup>1</sup> Surprisingly, the Australian pharmaceutical benefits scheme (the national drug subsidy programme operated by the federal government of Australia) was part of the deal, with Australian negotiators conceding to several US demands. These included the creation of an independent review body to examine drugs rejected by the Pharmaceutical Benefits Advisory Committee. Under existing legislation only the advisory committee can recommend listing of drugs for subsidy. However, the dissenting views of another review body, supported by publicity and lobbying, may undermine the famously tough stance of this committee concerning the cost effectiveness and prices of pharmaceutical products. In addition, Australia has agreed to changes in intellectual property protection that, among other things, increase the risk of delayed entry of generic drugs on to the Australian market. The use of the trade agreement to push the interests of US pharmaceutical companies is one in a long list of hostile moves that have included legal challenges to the decisions of the Pharmaceutical Benefits Advisory Committee to reject drugs for subsidy and political lobbying for removal of committee members.<sup>2</sup>

This trade agreement, however, is of wider importance. It follows a pattern of trade agreements by the

United States (with Jordan, Chile, and Singapore) that contain long chapters on intellectual property. These represent a retreat from the principles espoused in the Doha declaration of the World Trade Organisation (WTO), which stated that the agreement on trade related aspects of intellectual property rights (TRIPS) should be interpreted and implemented so as "to protect public health and, in particular, to promote access to medicines for all."<sup>3</sup> This was a major step forward for public health and access to medicines. The bilateral trade agreements now being negotiated by the United States seem to be designed to undermine the Doha agreement and promote a particular business model for the production of medicines that is based on ever stronger patent protection.

TRIPS forms one of the pillars of the WTO. One of the most important obligations in TRIPS is the recognition of patents in any field of technology for both products and processes. This in effect globalises the patenting of pharmaceutical technologies. As the HIV/AIDS epidemic grew, and patented (but expensive) antiretroviral drugs became available in rich countries, the full implications of TRIPS for access to long term treatment by poor people became clear. The adoption of the Doha declaration in 2001 to address this problem was crucial. The declaration is really a bill for rights for the public health regulation of medicines. Lying at its core is the recognition that WTO members