**Institution:** University of Southampton

**Unit of Assessment:** 02 Public Health, Health Services and Primary Care

**Title of case study:** 02-11 Fighting Antibiotic Resistance: Changing International Prescribing Policies

## 1. Summary of the impact

Research by the University of Southampton has contributed significantly to reducing the global threat of antibiotic resistance. A series of both conventional placebo-controlled and novel open design trials has influenced a number of important national clinical guidelines for Respiratory Tract Infections (RTIs) and the implementation of novel prescribing strategies that discourage unnecessary antibiotic prescription. As a direct result of the research, delayed prescribing for all acute respiratory infections is a tool in the everyday practice of the UK's GPs. Southampton's work in this field has informed international guidelines currently in place in the United States, Israel and the European Union.

## 2. Underpinning research

Unnecessary antibiotic prescriptions in primary care are a key driver for antibiotic resistance, which is recognised as a global health threat. Several campaigns by the UK Department of Health (DH) have discouraged overuse and overprescription of antibiotics by patients and doctors. A recent major effort to raise awareness of antibiotic resistance commenced with a 1998 report *The Path of Least Resistance* by the Standing Medical Advisory Committee, which advised DH. Highlighting that 80% of UK human prescribing occurs in primary care, the report recommended the National Institute for Health and Clinical Excellence (NICE) develop new guidelines on antibiotic prescribing by medical practitioners. In 2008 NICE reported that 25% of the UK population visited their GP with RTIs each year, costing £24.3 million and accounting for 60% of GP antibiotic prescribing.

Starting in the mid-1990s, and continuing currently, a research group at the University of Southampton's Faculty of Medicine embarked on a series of trials to assess the effectiveness of different antibiotic prescribing strategies for acute infections. The key team members are Paul Little, Professor of Primary Care Research (employed at Southampton since 1993), Ian Williamson, Senior Lecturer in Primary Care (since 1987), Michael Moore, Reader in Primary Care Research (since 2004), and Hazel Everitt, Clinical Lecturer in General Practice (since 1999).

In the first trial, funded by DH and published in the *British Medical Journal* in 1997 **[3.1]**, 700 patients with sore throats received one of three antibiotic prescribing strategies: immediate prescription, no prescription and, if symptoms did not settle after three days, delayed prescription. The research represented a novel approach in developing open designs, allowing them to assess not only the effectiveness of the different strategies but, crucially, the 'medicalisation' of illness – that is, the effect of prescription on patients' belief in the power of antibiotics and their intention to reconsult their GP.

The research found that prescribing antibiotics for sore throats – one of the most common respiratory illnesses for which people consult GPs – does not reduce the extent and duration of symptoms. However, the strategies of offering no antibiotics or delayed prescribing significantly reduce patients' use of antibiotics, their belief in antibiotics and their intention to consult and reconsult their GP in future.

Similar findings of the limited benefit and medicalising effect of immediate prescriptions followed in DH-funded studies of antibiotic prescribing strategies for acute otitis media (2001) and sinusitis (2007) and Medical Research Council-funded studies of lower respiratory tract infections (RTIs) (2005) and conjunctivitis (2006) **[3.2-3.5]**.This led to substantial further funding to the group for RTI research, including the NIHR-funded PRIME Programme (2008-13, £1,999,000) and the MRC PRIMIT trial (2007-2013, £1,282,000).

In the case of lower RTIs, the academics showed a delayed prescribing strategy is preferable to no offer of a prescription in limiting reconsultations **[3.3]**. In further DH-funded research, similar trials involving urinary tract infection (UTI) concluded antibiotic use can be reduced by either a 48-hour delayed prescription or by offering delayed prescription if results of diagnostic dipsticks are negative **[3.6]**. All the trials resulted in the same key recommendation to GPs: avoid or delay prescribing antibiotics as part of a national strategy to reduce the risk of antibiotic resistance.

## 3. References to the research

**3.1** Little PS, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. An open randomised trial of prescribing strategies for sore throat. *BMJ* 1997; 314:722-727.

Funded by NHS South and West Region Research and Development, to Little and Williamson, 1993-5, £49,000)

**3.2** Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001; 322:336-342.

Funded by NHS South and West Region Reseach and Development, to Little, Williamson and Moore, 1996-2000, £94,000

**3.3** Little P, Rumsby K, Kelly J, Watson L, Moore M, Warner G et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomised controlled trial. *JAMA* 2005; 293:3029-3035.

Funded by MRC, Clinician Scientist Fellowship for Little, 1998-2003, £416,000

**3.4** Williamson IG, Rumsby K, Benge S, Moore M, Smith PW, Cross M, Little P. Antibiotics and Topical Nasal Steroid for Treatment of Acute Maxillary Sinusitis: A Randomized Controlled Trial. *JAMA* 2007; 298(21): 2487-2496.

Funded by NHS South and West Region Research and Development, to Little, Williamson and Moore, 2001-2006, £140,000

**3.5** Everitt HA, Little PS, Smith PWF. A randomised controlled trial of management strategies for acute infective conjunctivitis in general practice. *BMJ* 2006; 333:321.

Funded as part of MRC HSR training fellowship for Everitt, 2003-2006 £87,000

**3.6** Little P, Turner S, Rumsby K, Warner G, Moore M, Lowes JA et al. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study. *Health Technol Assess* 2009; 13: No 19.

Funded by NHS Health Technology Assessment Board, 2001-2007 £326,000

## 4. Details of the impact

UK antibiotic prescribing rose progressively until 1997 then fell markedly until 2000 since when it has risen slowly. There is a link between the use of delayed prescriptions and the fall in prescriptions that can be traced to the first Southampton study (1997) of delayed prescribing for acute infections. Sharland et al reported (in 2005) an 18% reduction in national antibiotic prescribing for children in the five years after 1997 due to a progressive divergence between antibiotics prescribed and antibiotics used. The authors concluded that GPs were adopting delayed prescribing, “introduced after widespread dissemination of trial results supporting this practice”. This impact continued through the REF assessment period, demonstrated by an Ipsos MORI household questionnaire survey in January 2011 which showed that 14.2% of adults in England had been offered a delayed prescription for antibiotics **[5.1],** and the recent national MRC-funded DESCARTE study – that showed delayed prescribing was used in 18% of sore throat consultations, reducing complications and reconsultations as effectively as immediate antibiotics.

The rise in antibiotic prescribing highlights the importance of guidelines for primary care that, influenced by our research, discourage the immediate prescription of antibiotics and advocate delayed prescribing. The long-term impact is in reducing the risk of antibiotic resistance and saving NHS resources due to fewer antibiotic prescriptions and repeat consultations.

The wealth of research, and recognition of antibiotic resistance as a public health priority, spurred NICE to commission guidance for managing RTIs focusing on novel prescribing strategies. The recognition of Southampton's central role in generating the evidence led to Little being invited to chair the NICE guideline group **[5.2]**. Integral to the formulation of this guidance - and referenced in it - were the Southampton trials for sore throat, chest infection and otitis media. The guidance (CG69, 2008) endorsed delayed prescribing or no offer of antibiotics for all acute RTIs by GPs, emergency departments and walk-in centres. NICE made conservative assumptions that the guidance would save £3.7 million annually **[5.2]**.

Building on the NICE guidance, the Health Protection Agency published its Management of Infection Guidance for Primary Care in the UK (2010) **[5.3]**. Referencing the Southampton trials, the guidance advises delayed prescription for otitis media, sinusitis and bronchitis and also uses and references Southampton's UTI diagnostic work. Williamson and Everitt, on the strength of their research, were asked to draft two Drug and Therapeutics Bulletins (DTB) for sinusitis (2009) **[5.4]** and conjunctivitis (2011) **[5.5]**. DTB is owned by BMJ Group, provides independent advice for doctors, pharmacists and healthcare professionals, and is described as essential reading for practising doctors by the House of Commons Health Select Committee.

The research also informed Scottish Intercollegiate Guidelines Network (SIGN) guidance on sore throats (guideline 117, 2010) for the NHS in Scotland **[5.6],** and has been central to guidance bulletins published by the Medicine Resource Centre, which is attached to the National Prescribing Centre, and read by GPs across the UK. It is also forming the basis of online training for existing and future GPs. The Royal College of General Practitioners appointed Moore as its Antibiotic Resistance champion in 2011, and has developed online modules on treatment of RTIs and UTIs (with input from Little and Moore), with one module based on delayed prescribing **[5.7]**.

The impact is felt internationally with guidelines that remain in force. Southampton studies laid the foundations for a change in policy of the American Academy of Paediatrics which updated its Guideline for the Diagnosis and Management of Acute Otitis Media in 2013 **[5.8]**. It generated controversy in the United States, representing the first time a US health organisation had advised a wait-and-see approach in the form of delayed prescription.

The European Society of Clinical Microbiology and Infectious Diseases issued guidance on the management of sore throats (2012), referencing the Southampton trials and the University's research on sore throats **[5.9]**. The guidelines are read by GPs and doctors in emergency departments around the EU. The research on delayed prescribing has also been used as the central recommendation in Israeli guidance on managing otitis media in Israel, in force throughout the REF assessment period **[5.10]**.

## 5. Sources to corroborate the impact

**Examples of national and international Guidelines that have been in force throughout the REF assessment period, that have provided recommendations based on our research and which advocate delayed prescribing as a strategy [5.2-5.10].**

**5.1** McNulty CAM, Nichols T, French DP, Joshi P, Butler CC. Expectations for consultations and antibiotics for respiratory tract infection in primary care: the RTI clinical iceberg. *Br J Gen Pract* 2013; 63(612):e429-36.

**5.2** NICE guidance 2008. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. http://guidance.nice.org.uk/CG69/NICEGuidance/pdf/English *Central to the formulation of this guidance (chaired by Little) were our trials for acute sore throat,*

*acute cough and otitis media. The guidance advocates delayed prescribing as one option,and references the respiratory trials. The sore throat trial was the basis of NICE's economic modelling.*

**5.3** Health Protection Agency. Management of Infection Guidance for Primary Care. HPA 2010; http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/PrimaryCareGuidance/ *This guidance advises delayed prescription for otitis media, sinusitis, bronchitis, references the NICE guidance above which our group was formative in developing, and also directly references our trials. The guidance on diagnosis also uses and references our diagnostic work in UTI.*

**5.4** Drug and Therapeutics Bulletin. The management of acute sinusitis. *DTB* 2009 47: 26-30. *This guidance was drafted by Williamson and references both the JAMA trial **[3.4]** and the Lancet individual patient data meta-analysis by Young et al., co-authored by Williamson*

**5.5** Drug and Therapeutics Bulletin The management of acute infective conjunctivitis *DTB* 2011 49: 78-81. *This guidance was drafted by Everitt and both references her research **[3.5]** and advises delayed prescribing as a reasonable option.*

**5.6** SIGN guidance on sore throat (guideline 117, 2010). http://www.sign.ac.uk/pdf/sign117.pdf *This refers to our trials and provides guidance about antibiotic prescribing strategies.*

**5.7** The Royal College of General Practitioners' (RCGP, 2011) e-learning modules on respiratory tract infections: Managing Acute Respiratory Tract Infections – www.elearning.rcgp.org.uk

**5.8** American Academy of Paediatrics Guideline in the Diagnosis and Management of Acute Otitis Media. *Pediatrics* 2004; 113:1451-65, updated 2013 (*Pediatrics* 2013;131:e964–e999). *This guidance was very controversial and, for the first time in the US, advocates a wait and see approach trialled by Little, Williamson, Moore, Everitt and team*.

**5.9** European Society of Clinical Microbiology and Infectious Diseases Sore Throat Guideline Group, Pelucchi C, Grigoryan L, Galeone C, Esposito S, Huovinen P, Little P, Verheij T. *Clin Microbiol Infect* 2012; Apr; 18 Suppl 1:1-28. Doi: 10.1111/j.1469-0691.2012.03766. *This guidance uses and references our trials and other research on sore throat.*

**5.10** Clinical guidelines: diagnosis and treatment of acute otitis media in children. Israel Medical Association 2004, updated in a new edition in 2010. *This guideline references our trial **[3.2]**, and provides guidance on using the delayed prescribing approach. N.B. Document available from Southampton (in Hebrew).*