

Institution: University of Southampton		
Unit of Assessment: 02 Public Health, Health Services and Primary Care		
Title of case study: 02-01 Antimicrobial stewardship: targeting antibiotics, delayed prescribing, and communication skills training for acute upper and lower respiratory tract infections		
Period when the underpinning research was undertaken: 2000 – 2015		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Paul Little	Professor of Primary Care Research	February 1993 – present
Michael Moore	Professor of Primary Care Research	September 2004 – present
Hazel Everitt	Professor of Primary Care Research	February 1999 – present
Miriam Santer	Professor of Primary Care Research	January 2010 – present
Beth Stuart	Associate Professor of Primary Care Research	August 2010 – present
Mark Lown	Clinical Lecturer	January 2015 – present
Period when the claimed impact occurred: August 2013 – December 2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact</p> <p>The Chief Medical Officer (2011) and O'Neill (2016) reports on antimicrobial resistance (AMR) emphasise the urgency of curbing antibiotic use for acute respiratory tract infections (RTIs), the source of 60% of all antibiotic prescriptions, to reduce the global threat of AMR. Major contributions by the University of Southampton in trials and cohorts have demonstrated reductions in antibiotic use in RTIs using: delayed antibiotic prescriptions; a clinical score for pharyngitis (FeverPAIN); communication skills training; C-reactive protein (CRP) point-of-care tests; and a digital intervention to support handwashing. Over the impact period, the research has formed a key part of 9 national and 4 international guidelines, two UK 5-year AMR strategies and a successful intervention by the CMO for overprescribing GPs. FeverPAIN has been used 100,000 times, the communication skills modules are used internationally, and delayed prescription is proven to be used in everyday practice internationally.</p>		
<p>2. Underpinning research</p> <p>A research group within the University of Southampton's School of Primary Care, Population Sciences and Medical Education, led by Professor Paul Little, has undertaken most of the key studies of delayed antibiotic prescription. Since 2000 the group has performed a series of major cohorts and trials addressing: delayed prescription; clinical scores for sore throat; communication skills and CRP point-of-care tests for lower RTIs (LRTIs); and a digital intervention to support handwashing. Research funding has come from the Department of Health, the Medical Research Council, and the EU.</p> <p>The first randomised trial of delayed prescription for otitis media (1996-2000) [3.1] built on the novel open design used in the first sore throat trial (1997) to assess 'medicalisation' – the effect on beliefs and re-consultations – in addition to the impact on illness. A delayed prescription didn't result in more pain or distress than an immediate antibiotic, and reduced parents' belief in antibiotics and their intention to re-consult.</p> <p>A subsequent international individual participant data meta-analysis using the otitis trial data, working with colleagues in the Netherlands, demonstrated that if an immediate antibiotic is to be used in otitis, key sub-groups (young children, bilateral infections, discharge) can be appropriately targeted. The limited benefit and medicalisation with an immediate prescription was confirmed in the group's trials of: sinusitis; LRTIs; conjunctivitis; and in two trials using different methods of delayed prescription – one in the UK and one with colleagues in Spain [3.2]. For LRTIs, the trial findings that delayed prescribing is preferable to no offer of a prescription in limiting re-consultations was confirmed in large prospective cohorts in both upper RTIs (URTIs) and LRTIs [3.3], which also demonstrated that delayed prescription reduced the progression of illness more effectively than immediate antibiotics.</p> <p>In two large EU-funded trials – GRACE (2007-2010): antibiotics versus placebo for LRTI [3.4] and GRACE INTRO (2010-2011): communication skills training in reducing antibiotic</p>		

prescriptions [3.5] – Little’s group provided definitive evidence for the limited benefit of immediate antibiotics and the potential in using CRP point-of-care tests and communication skills training in reducing antibiotic prescriptions.

A new clinical score (FeverPAIN) was developed by the group to target the use of immediate, delayed and no antibiotics for pharyngitis, and has been shown to both reduce antibiotic use and improve symptom control [3.6].

These trials and cohort studies have resulted in the consistent key recommendation to GPs – **avoid** or **delay** prescribing of antibiotics – as part of a national strategy to reduce the risk of antibiotic resistance.

In order to minimise the spread of RTIs, particularly in winter seasons and pandemics, Little’s group collaborated with colleagues in the School of Psychology to develop an internet-based behavioural intervention, *Germ Defence*, to support the prevention of infection by handwashing. This was assessed in the MRC-funded PRIMIT trial (2008-2013) [3.7] involving 20,066 participants, which demonstrated a 15% reduction in episodes of infection, reduced transmission of infection to family members, and reduced attendance in primary care. The group also developed and trialled (n=3044) a self-management website, *InternetDr*, that demonstrated a reduction of 30% in GP consultations for respiratory infections.

3. References to the research

- 3.1** Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavy J. A pragmatic randomised controlled trial of two prescribing strategies for AOM (acute otitis media). *Bmj* 2001;322:336-42. <https://doi.org/10.1136/bmj.322.7282.336>
Funding: NHS South and West Region R&D, PI: Little, 1996-2000, GBP94,000
- 3.2** de la Poza Abad M, Mas Dalmau G, Moreno Bakedano M... Little P et al. Prescription Strategies in Acute Uncomplicated Respiratory Infections: A Randomized Clinical Trial. *JAMA Intern Med* 2016;176(1):21-29. <https://doi.org/10.1001/jamainternmed.2015.7088>
- 3.3** Little P, Stuart B, Smith S, Thompson M, Knox K, van den Bruel A, Lown M, Moore M, Mant D. Antibiotic prescription strategies and adverse outcome for uncomplicated lower respiratory tract infections: cough complication cohort (3C) study. *Bmj* 2017;357: <https://doi.org/10.1136/bmj.j2148>
- 3.4** Little P, Stuart B, Moore M, et al. Amoxicillin for acute lower respiratory tract infection where pneumonia is not suspected clinically: a 12 country randomised placebo controlled trial in primary care. *Lancet Infectious Disease* 2013;Feb;13(2):123-9. [https://doi.org/10.1016/s1473-3099\(12\)70300-6](https://doi.org/10.1016/s1473-3099(12)70300-6)
Funding: EU FP6 GRACE (EUR11.5m over 35 institutions), PI at Southampton: Little
- 3.5** Little P, Stuart B, Moore M, et al. Effects of internet-based training on antibiotic prescribing rates for acute RTIs: multinational trial. *Lancet* 2013;382(9899):1175-82. [https://doi.org/10.1016/s0140-6736\(13\)60994-0](https://doi.org/10.1016/s0140-6736(13)60994-0)
Funding: EU FP6 GRACE INTRO. PI at Southampton: Dr Gillian O’Reilly, Trial Manager
- 3.6** Little P, Hobbs FDR, Moore M, et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). *Bmj* 2013;347:f5806. <https://doi.org/10.1136/bmj.f5806>
- 3.7** Little P, Stuart B, Hobbs FDR, Moore M et al. An internet-delivered handwashing intervention to modify influenza-like illness and respiratory infection transmission (PRIMIT): a primary care randomised trial. *Lancet* 2015;386(10004):1631-9. [https://doi.org/10.1016/S0140-6736\(15\)60127-1](https://doi.org/10.1016/S0140-6736(15)60127-1)
Funding: MRC PRIMIT trial, PI: Little, 2007-2013, GBP1,282,000

4. Details of the impact

The WHO predicts a global additional annual health expenditure of USD1.2 trillion by 2050 due to the rise of AMR. Reducing antibiotic use is a key strategy for the long-term reduction in the risk of AMR, and additionally creates short-term cost and time savings for health services due to fewer antibiotics dispensed and fewer repeat consultations. More than a quarter of the UK population visit their GP with RTIs annually – the source of 60% of all antibiotic prescribing. In 2017 NICE estimated the costs of non-elective admissions for LRTIs alone to be

GBP147million/year, with a saving of GBP1.4million/year if a conservative 1% of these were prevented by the effective implementation of guidance on prescribing [5.1]. The research at Southampton has made major contributions to such guidance in the UK and internationally.

4.1 UK guidance on antibiotic prescribing

4.1.1 NICE guidance covering specific RTIs and incorporating new research

Southampton's central role in the early studies led to Little being invited to chair the original, overarching 2008 NICE clinical guideline *CG69 Respiratory tract infections (self-limiting): prescribing antibiotics* [5.2]. Integral to the guidance are the key endorsements from the Southampton trials of delayed prescribing or no offer of antibiotics for all acute RTIs.

The endorsements in CG69, together with more recent research by the Southampton group, form the basis of new NICE guidelines released 2017-2019 covering specific RTIs. While CG69 remains in force, it was decided in September 2019 that CG69 would be wholly integrated into the more recent guidelines [5.3]:

- **NG79 for acute sinusitis** (October 2017) cites 3.2, showing that delayed prescribing or no offer of antibiotics is as effective as immediate antibiotic prescription for managing URTIs such as sinusitis.
- **NG84 for acute sore throat** (January 2018) endorses the use of FeverPAIN for assessing symptoms.
- **NG91 for acute otitis media** (March 2018) refers to two meta-analyses that used 3.1 to determine effects of antibiotics in special cases of children with acute otitis media.
- **NG120 for acute cough** (February 2019) includes results of GRACE in a meta-analysis of the effects of antibiotics for acute bronchitis.

Additionally, **CG191 for pneumonia** (December 2014; withdrawn during the COVID pandemic) refers to the GRACE INTRO trial. [5.4]

The above guidelines have fed into NICE's online **Clinical Knowledge Summaries** on sinusitis, sore throat, otitis media, cough and chest infections. [5.5]

4.1.2 NICE guidance on antimicrobial stewardship [5.1]

NICE guideline *NG15 Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use* (August 2015) includes results of the otitis media and LRTI trials in a meta-analysis to support delayed antibiotic prescribing in acute RTIs.

NICE guideline *NG63 Antimicrobial stewardship: changing risk-related behaviours in the general population* (January 2017) supports delayed antibiotic prescribing and the use of the PRIMIT intervention, *Germ Defence*.

4.1.3 Royal College of GPs (RCGP)

Professor Michael Moore was the RCGP National Clinical Champion for Antimicrobial Stewardship in 2012-2015. Together with Little, he developed 'TARGET' (Treat Antibiotics Responsibly, Guidance, Education, Tools) website modules for RTIs - which incorporate both FeverPAIN and a module based on delayed prescribing [5.6]. As noted in the UK's 2019 five-year AMR strategy, TARGET is the most accessed part of the RCGP website, attracting 69,000 views during 2017/18 [5.7].

4.1.4 UK Government initiatives

In November 2014 Moore was appointed to the UK government's Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHA). The TARGET toolkit was recommended in the UK government's 5-year strategies published September 2013 and January 2019 [5.7]. The O'Neill report on AMR (2016) referenced the GRACE INTRO study and supported delayed prescription in reducing antibiotic use [5.8].

Building on the NICE guidance, Public Health England published its *Summary of antimicrobial prescribing guidance: managing common infections*, updated in 2020, which targets all primary care providers in the UK. Referencing the Southampton trials, the guidance advises delayed prescription for otitis media, sinusitis and bronchitis, and FeverPAIN for sore throat. [5.9]

4.2 International guidance on antibiotic prescribing

4.2.1 US Centers for Disease Control and Prevention (CDC)

The CDC's Core Elements of Outpatient Antibiotic Stewardship (2016) [5.10] advised delayed prescribing – termed *watchful waiting* – for selected RTIs. It referenced the American Academy of Paediatrics' (AAP) 2013 guidance for Acute Otitis Media, which cites [3.1] multiple times in advising delayed prescribing – termed *wait-and-see* – for selected children.

4.2.2 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Centre for Disease Prevention and Control (ECDC)

The ESCMID guidance for sore throat (2012) is still in force, as is the ECDC guideline (2017) on antimicrobial stewardship. Both refer to reviews and NICE guidance that relied heavily on Southampton studies [5.11].

4.2.3 Guidelines for acute otitis media (AOM) in developed and developing countries

A 2016 review [5.12] studied guidelines in 5 developed countries (USA, Italy, Japan, South Africa, Australia) and 7 developing countries (Tanzania, Ethiopia, Moldova, Argentina, Fiji, Afghanistan, Sri Lanka) across 5 continents. The review found that watchful waiting in mild–moderate acute otitis media scenarios is now the standard of care in all guidelines from the developed countries, where follow-up is possible. Watchful waiting is an option in 3 out of 7 guidelines from the developing countries (Sri Lanka, Argentina and Moldova).

4.3 Evidence of use of guidelines in practice

4.3.1 Delayed prescriptions A series of studies [5.13] found that 38% of Israeli otolaryngologists in 2016 used delayed prescriptions, 7% of Danish GPs in 2015 - particularly younger GPs - as did 22% of German GPs often or very often in 2015. A national survey in the UK in 2014 [5.14], which referenced several Southampton studies of delayed prescription (both trials and cohorts) demonstrated that more than a third of patients supported clinicians offering a delayed prescription, and that 15% of the population who had been offered an antibiotic had been offered a delayed prescription.

4.3.2 FeverPAIN: The FeverPAIN app was initially hosted on Oxford CTU's website. As of December 2020 it had been used around 100,000 times and is now incorporated into GP clinical systems. [5.15]

4.3.3 Communication skills training: Belgium's most recent antibiotic stewardship campaign and an intervention module for Australian GPs in training (which reduced prescribing for chest infections by 16%) referenced and used the GRACE INTRO communication modules. [5.16]

4.3.4 CMO intervention trial: In 2014 a short letter from England's Chief Medical Officer encouraging delayed prescribing and the use of TARGET was sent to the top 20% prescribing GP practices in all NHS local areas. This was a trial intervention, which was shown to reduce prescribing by 3.3% during the 2014-15 season, equating to 73,406 fewer prescriptions. [5.17]

4.3.5 Germ Defence in COVID-19: In March 2020 Germ Defence was updated for the prevention of COVID-19 by including all methods of reducing infection in the home and rapidly translated into 22 languages. It was also the subject of a clinical trial selected for national prioritisation as an NIHR Urgent Public Health COVID-19 Study to help prevent a second wave of infections in autumn 2020. Half the practices in England have been randomised to endorse the use of the website in autumn (the other half in 2021). [5.18]

5. Sources to corroborate the impact

5.1 NICE Guidelines on antimicrobial stewardship:

- NG15 <https://www.nice.org.uk/guidance/ng15> cites *Spurling et al.* 2013 <https://doi.org/10.1002/14651858.CD004417.pub4> which only uses Southampton trials for sore throat, i.e. otitis media [3.1] and LRTI <https://doi.org/10.1001/jama.293.24.3029>
- NG63 <https://www.nice.org.uk/guidance/ng63> supports delayed antibiotics and the use of PRIMIT intervention *Germ Defence* <https://germdefence.org>. The NG63 impact report estimates the annual costs of costs of non-elective admissions for LRTIs at GBP147million <https://www.nice.org.uk/guidance/ng63/resources/resource-impact-report-pdf-4359024685>

- 5.2** NICE clinical guideline *CG69 Respiratory tract infections (self-limiting): prescribing antibiotics*, 2008 <https://www.nice.org.uk/guidance/cg69>
- 5.3** NICE guidelines for specific RTIs 2017-2019:
- *NG79 for acute sinusitis* <https://www.nice.org.uk/guidance/ng79> cites **3.2**.
 - *NG84 for acute sore throat* <https://www.nice.org.uk/guidance/ng84> endorses FeverPAIN.
 - *NG91 for acute otitis media* <https://www.nice.org.uk/guidance/ng91> refers to *Rovers et al.* 2006 [https://doi.org/10.1016/S0140-6736\(06\)69606-2](https://doi.org/10.1016/S0140-6736(06)69606-2) and *Spurling et al.* 2013 <https://doi.org/10.1002/14651858.CD004417.pub4> which both use **3.1**.
 - *NG120 for acute cough* <https://www.nice.org.uk/guidance/ng120> refers to *Smith et al.* 2017 <https://doi.org/10.1002/14651858.CD000245.pub4>, which uses GRACE results.
- 5.4** *CG191* is offline during COVID pandemic – PDF supplied. Cites GRACE INTRO as ref 122.
- 5.5** NICE Clinical Knowledge Summaries: <https://cks.nice.org.uk/topics/sinusitis> (NG79), <https://cks.nice.org.uk/topics/sore-throat-acute> (NG84), <https://cks.nice.org.uk/topics/otitis-media-acute> (NG91), <https://cks.nice.org.uk/topics/cough> (NG120), <https://cks.nice.org.uk/topics/chest-infections-adult> (CG191)
- 5.6** <https://www.rcgp.org.uk/TARGETantibiotics>
- 5.7** UK government's 5-year strategies for AMR (both recommend the TARGET toolkit):
- September 2013: <https://www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018>
 - January 2019: <https://www.gov.uk/government/publications/uk-5-year-action-plan-for-antimicrobial-resistance-2019-to-2024>
- 5.8** O'Neill review (May 2016): <https://amr-review.org>
- 5.9** PHE guidance: <https://www.gov.uk/government/publications/managing-common-infections-guidance-for-primary-care> (references the diagnostic PRISM cohorts to develop FeverPAIN, FeverPAIN trial; DESCARTE observational data that 5 days of Pen V is justified NICE guidelines (CG69); the OM study; and IPD meta-analyses)
- 5.10** CDC USA 2013: <https://www.cdc.gov/antibiotic-use/community/improving-prescribing/core-elements/core-outpatient-stewardship.html> advises watchful waiting for selected RTIs and references the American Academy of Pediatrics (AAP) guidance for otitis (2013), which references **3.1** and advises wait and see for selected children (<http://pediatrics.aappublications.org/content/early/2013/02/20/peds.2012-3488>)
- 5.11** European guidance: The ESCMID European guidance for sore throat https://www.escmid.org/fileadmin/src/media/PDFs/4ESCMID_Library/2Medical_Guidelines/ESCMID_Guidelines/ESCMID_Sore_Throat_GL_CMI_Mar2012.pdf advocates delayed prescription, references *Spurling et al.* 2013 (see notes in **5.1**). The 2017 ECDC guidance on antimicrobial stewardship advocates delayed prescription, referencing NICE guideline NG63 (see notes in **5.1**) <https://ecdc.europa.eu/en/publications-datadirectory-guidance-prevention-and-controlprudent-use-antibiotics/antimicrobial>
- 5.12** Tamir et al. 2017 <https://adc.bmj.com/content/102/5/450.long>
- 5.13** 38% of Israeli otolaryngologists use delayed prescription in 2016 <https://doi.org/10.1016/j.ijporl.2017.02.003> following initial guidance to GPs in Israel (<https://doi.org/10.1097/INF.0b013e3181d7625e>)
7% of Danish GPs (more in younger GPs) used delayed prescription in 2015 <https://doi.org/10.1080/13814788.2017.1347628>
22% of German GPs in 2015 used delayed prescriptions often or very often <https://doi.org/10.1186/s12879-018-3120-y>
- 5.14** Survey <https://bmjopen.bmj.com/content/5/11/e009748>
- 5.15** Evidence of usage of FeverPAIN (PDF supplied) at <https://ctu1.phc.ox.ac.uk/feverpain>
- 5.16** GRACE INTRO modules referenced in two interventions: Belgium's current AMR campaign (<https://doi.org/10.1080/17843286.2020.1721135>) and GP training in Australia (<https://doi.org/10.1093/fampra/cmz07>) which lowered prescribing for LRTIs.
- 5.17** Hallsworth et al. 2016 [https://doi.org/10.1016/S0140-6736\(16\)00215-4](https://doi.org/10.1016/S0140-6736(16)00215-4)
- 5.18** <http://lang.germdefence.org> selected as urgent COVID-19 study: <https://www.nihr.ac.uk/covid-studies/study-detail.htm?entryId=287978>