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<th>Title</th>
<th>Intervention to improve the quality of antimicrobial prescribing for urinary tract infection: a cluster randomized trial</th>
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<td>Author(s)</td>
<td>Vellinga, Akke; Galvin, Sandra; Duane, Sinead; Callan, Aoife; Bennett, Kathleen; Cormican, Martin; Domegan, Christine; Murphy, Andrew W.</td>
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A wicked problem and a SIMPle solution: results from a cluster randomised intervention to improve the quality of antibiotic prescribing for UTI in Irish General Practice

Background
The recent global report from the World Health Organisation (WHO) on antimicrobial resistance warns that widespread resistance is not a future threat but shows that many of the available treatment options for common infections are becoming ineffective (1, 2). Antibiotic resistance is a wicked problem, meaning that there is not one single solution but a myriad of angles need to be considered to address the increasing spread of antibiotic resistance (3). The WHO’s news release points out that tackling antimicrobial resistance needs a multi-sectorial approach including patients, health workers, policy makers and industry (2).

Antibiotics did not create the problem of antimicrobial resistance but their use and misuse exacerbate it (4). Overuse of antibiotics is associated with increased antibiotic resistance in the community. This societal risk affects the patient as infections resistant to many antibiotics have become more prevalent (5). In addition, previous individual antibiotic use will also increase the risk that a next infection is caused by resistant organisms (5, 6). One important approach to tackle resistance is by improving prescribing, dispensing and consumption of the right antibiotic and only when truly needed (2). Despite the increasing concerns relating to antibiotic resistance, ambulatory antibiotic prescribing in Europe from 2010 showed the largest increase in Ireland (7).

Most antibiotics are prescribed in primary care (8). GPs have shown to be driven by a number of factors when prescribing antibiotics. Patient satisfaction is perceived to be related to (antibiotic) prescribing which is important in the two tiered Irish health care system.

A systematic review of interventions has shown that a complex intervention design is appropriate to take into account the multiple, intricate and sometimes even contradictory issues and interests involved in the decision to prescribe or consume antibiotics (9-11). Such a complex intervention framework aimed at various stakeholders (patients, GP, and wider community) can bring about social change by addressing local barriers and opportunities as the leading systematic review in this area has shown only multifaceted interventions to be successful (10, 12).

The presented study is part of a complex intervention to improve the quality and quantity of antibiotic prescribing for UTI in primary care: the SIMPle study. The SIMPle study includes interactive, multimedia and electronic components with integrated feedback for both GPs and patients (12). The intervention was developed based on explicit theoretical frameworks and following social marketing principles. The results from the intervention include papers on the developmental formative research (ref), process evaluation (ref), economic evaluation (ref) and the evaluation of changes in quality and quantity of prescribing (ref) and its impact on...
subsequent resistance and clonal groups (ref). This paper reports the evaluation of the SIMPle study on the quality of prescribing measured against national antibiotic prescribing guidelines (13).

**Methods**

The protocol of the intervention has been previously reported (12). In short, the Supporting the Improvement and Management of Prescribing for UTI – SIMPle study is a three armed intervention with practice level randomisation.

Based on the formative research, the focus of the intervention aimed to improve the quality of prescribing integrated in an active learning environment for the GP through the use of an audit report. The audit report shows the practice prescribing and practice resistance patterns of antibiotics for UTI in relation to other practices. Because the intervention was integrated into routine care, the changes will not compromise the duration of the consultation but will support better care and the sustainability of changing behaviour.

The aim of the intervention was to improve prescribing according to first line guidelines and in addition to this, in arm B, to consider delayed prescribing. First line treatment for acute uncomplicated UTI in adults is nitrofurantoin or trimethoprim. Due to the high prevalence of resistance to trimethoprim in this area and based on international recommendation (14), the focus for changing prescribing was on nitrofurantoin. Fosfomycin was introduced as first line treatment during the intervention, but no particular emphasis was put on the inclusion of this new first line treatment. As the guidelines outline similar first line treatment for males and females, all adult patients with symptoms suggestive of UTI were included.

Computerised practices with one type of patient management software and member of the Irish Primary Care Research Network (iPCRN), who routinely submit urine samples to the Galway University Hospital laboratory, were eligible for randomisation. A list of practices was generated and ranked according to number of urine samples submitted, to limit potential increase in workload to the laboratory. Of the 31 practices invited by letter to the SIMPle study, 30 confirmed their participation in the follow up phone call. The software of the participating practices was updated to allow remote data collection as well as the integration of a reminder prompt and audit generation. In phase 1 all GPs from each participating practice were invited to the first workshop which explained the SIMPle study and introduced the importance of consultation coding for audit report generation. All participating practices were then randomised following a computer generated randomisation plan into an intervention arm. Phase 2 and the launch of the intervention was initiated by a workshop of which the content differed according to the intervention arm. Practices in intervention arm A received information on the national guidelines and were shown their first practice audit report. Practices in intervention arm B received the same information as in arm A and additional information on delayed prescription of antibiotics for suspected UTI which included a video showing how such a consultation may proceed. Upon coding the consultation as UTI, a reminder prompt which appeared on the computer screen which showed first line recommended treatment and the weblink www.antibioticprescribing.ie. Practices in the control arm were informed of their coding routine to standardise the
intervention. All practices were requested to send in a urine sample from all patients with suspected UTI as well as a mobile phone number of the patient. Information leaflets were made available and a poster informing patients of the practices’ involvement in the SIMPle study was displayed in the waiting room. All patients with a UTI coded consultation were automatically included in the anonymised remote data extraction, unless the patient explicitly requested to be excluded (passive consent).

The practices in intervention arm A and B received a monthly audit report of changes in their prescribing over the duration of the study. Control practices were informed of the intervention at the end, presented with all the supporting materials and given the opportunity to create an audit report over 1 month showing their (potential) change in prescribing. The audit report provided through the intervention met the requirement of GPs to perform a yearly clinical audit to maintain their professional competence.

Patients were supported through multimedia applications in the waiting room. This supportive framework consisted of an app (Bug Run School Days) which included a game for children and a video for adults addressing antibiotic awareness. The app was made available in the waiting room on secured iPads accessible during phase 3 of the intervention. The app is available for free download from the app store.

The coding workshops took place in June/July 2013, the intervention workshop was arranged during September/October 2013 and the iPads were installed at the end of November 2013. A reminder workshop was organised in all practices during January 2014 to improve coding, due to a decline at the end of 2013. The intervention ended the 31st of March 2014. The intervention was reviewed and approved by the Irish Council of General Practitioners (ICGP) Research Ethics Committee prior to study commencement.

Outcome measures
Outcome measures proportions of antibiotic prescribing according to guidelines for first line treatment for suspected UTI in arm A and B compared with equivalent data from the control arm.

Sample size
The sample size was based on the primary outcome to increase the proportion of first line antibiotics for UTI by 10% in the intervention arm A compared to the control. Sample size estimates were inflated due to the clustering of data at the practice level. The estimated intraclass correlation coefficient was 1%. A total number of 920 patients with suspected UTI from 20 practices would give a power of 80% to detect a significant change in the proportion of patient receiving a first line antibiotic treatment in arm A compared to the control arm.
Data collection

Analysis was based on a 9 month period and extracted remotely from the patient management software after an automatic anonymisation. For each practice the number of antibiotic prescriptions per 100 consultations was calculated as a measure of high and low prescribers. Other practice variables included number of GPs (Whole Time Equivalent), practice nurse, number of medical card patients, average age of patients, average age of GPSs. For patients age, gender and medical card status was included. The exact date of each workshop was used for each practice to analyse the results of the intervention.

Statistical analyses are reported according to the CONSORT guidelines. The relative frequency of patients receiving a first line antibiotic for a suspected UTI was calculated for each arm over 2 month periods.

To control for clustering at the practice level and temporal trend a longitudinal logistic mixed model analysis was used to evaluate the effect of the intervention. A population averaged approach was taken using GEE analysis with an exchangeable correlation structure which allows a random intercepts (insert twisk). This approach allows clustering at the practice level and predicts first line antibiotic prescribing for UTI as a function of study arm adjusting for gender, age and insurance status. The resulting odds ratios and their 95% Confidence Interval were calculated. As practices were randomised, the variance between practices is due to chance and differences are due to type I error. Therefore, inclusion of covariates in the model removes only random variance. A exchangeable correlation structure was fitted. The intraclass-correlation coefficients were estimated with the (xtgee) post-estimation function (estat wcorrelation) in STATA 13.

To assess a possible diagnostic shift due to selective coding behaviour, the influence of the January workshop was evaluated, which was organised to emphasise the importance of coding for the purpose of reference.

Overall statistical analysis was performed with IBM SPSS and the GEE analysis was performed using STATA 13.

Results

A total of 30 practices, including xx GPs, were randomised into one of the three study arms. The flowchart of the study participant can be observed in figure 1. Over the 9 month period a total of xx consultations were recorded of which xx were UTI consultations. The numbers were evenly spread between the three arms over the whole intervention period. About xx% of the consultations were recorded in the baseline period (N=xx) and xx after the intervention workshop. An antibiotic was prescribed for xx% of the patients presenting with symptoms of UTI and the microbiological results of xx urine samples was available.

Most patients were women and the mean age of patients was xx (+/- ). XX5 of the patients received free medical care. Table 1 presents an overview of practice and patient characteristics. The total number of patients included in the analysis was 3557, in 30 practices, with a mean of 119 patients per practice ranging from, 42 to 372.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Arm A</th>
<th>Arm B</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practice</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>GPs (mean FTE)</td>
<td>2.2</td>
<td>1.2</td>
<td>2.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Mean years practicing (SD)</td>
<td>16.7</td>
<td>15.1</td>
<td>17.8</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>39</td>
<td>59</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Medical card consultations (mean %)</td>
<td>66.8</td>
<td>15.5</td>
<td>17.3</td>
<td>57.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultations</td>
<td>14810</td>
<td>10169</td>
<td>15464</td>
<td>12950</td>
</tr>
<tr>
<td>Overall nr AB prescriptions/100 consultations (SD)</td>
<td>14.1</td>
<td>4.6</td>
<td>11.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Patients</td>
<td>Total</td>
<td>1124</td>
<td>1047</td>
<td>1143</td>
</tr>
<tr>
<td>N</td>
<td>Pre intervention</td>
<td>381</td>
<td>309</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td>Post intervention</td>
<td>743</td>
<td>738</td>
<td>783</td>
</tr>
<tr>
<td>Mean Age (SD) years</td>
<td>57.3</td>
<td>21.1</td>
<td>56.4</td>
<td>19.7</td>
</tr>
<tr>
<td>Male (%)</td>
<td>12.4</td>
<td>6.5</td>
<td>10.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Medical card (%)</td>
<td>65.7</td>
<td>47.5</td>
<td>67.5</td>
<td>46.8</td>
</tr>
</tbody>
</table>

The difference in prescribing during and after the intervention workshop is shown in 2 month intervals in figure 2. Prescribing did not differ between groups during the baseline period. The percentage of first line prescribing observed over 2 month period intervals (figure 2) showed an increase in first line prescribing after the delivery of the intervention workshop whereas the control arm shows no difference with the baseline period. During the third post period, the control group received the information presented to the intervention arms A and B, and an increase in appropriate prescribing can be observed. The difference between the relative percentage of first line before and after the intervention is shown in figure 3, showing an increase in both arm A and B and equilibrium in the control group. In arm A, a first line antibiotic was prescribed in 45% of the UTI consultations, in arm B 50% and in the control group 46% (Table 2). After the intervention workshop first line prescribing went up to 68% in arm A (23 absolute percentage increase), 67% for arm B (17 absolute percentage) and 44% for the control group (-2 absolute percentage decrease). However, the percentage of
consultations with an antibiotic prescribed went up in the intervention arm A with 15 percentage points, 6 in arm B and went down by 2 in the control arm.

The impact of the intervention was calculated as an odds ratio in a logistic GEE model. The adjusted odds ratio (OR) and 95% confidence interval (CI) was 2.7 (1.7-4.1) for intervention arm A and 1.9 (1.2-3.0) for intervention arm B. The overall impact of the intervention was 2.3 (1.7-3.2) which means that a patient visiting an intervention practice with symptoms suggestive of a UTI is 2.3 times as likely to be prescribed a first line antibiotics compared to a similar patient visiting a control practice.

No other intervention approaches had a significant impact on the outcome, with the exception of the reminder visit, which showed a significant OR of 1.03 (1.00-1.06), which means there is a slight increase in the likelihood of a first line prescription after the reminder visit. The intraclass correlation coefficient was 6%. Power calculations based on this result in a z value of 6.55 or a probability < 0.0001, which translate into a power > 0.9999 (15).

Other measures of the intervention

Internet hits

Google analytics showed that visits to the antibiotics page of the HSE website for the November – March period, increased from 8,675 visits in 2012/2013 to 22,724 visits in 2013/2014.

Delayed

Commented [AV1]: This is higher than originally estimated. How to do power calculations from here for a GEE mixed model?
Commented [AV2]: Is now calculated with 95% CI based on all sample, but can also first calculate average percentages per practice and then calculate differences. The CI is much bigger in that case, obviously, is on N=20.
<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Intervention</th>
<th>Arm B</th>
<th>Intervention</th>
<th>Control</th>
<th>Baseline</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of consultations</td>
<td>381</td>
<td>743</td>
<td>309</td>
<td>738</td>
<td>360</td>
<td>783</td>
<td></td>
</tr>
<tr>
<td>AB % (95% CI)</td>
<td>63.3 (58.4-68.1)</td>
<td>78.6 (75.6-81.6)</td>
<td>69.9 (64.8-75.1)</td>
<td>75.8 (72.7-78.8)</td>
<td>68.6 (63.8-73.4)</td>
<td>66.5 (63.2-68.9)</td>
<td></td>
</tr>
<tr>
<td>Absolute difference baseline-intervention (95% CI)</td>
<td>15.3 (9.4-21.2)</td>
<td>5.9 (-0.3-12.1)</td>
<td>-2.1 (-3.9-8.1)</td>
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<tr>
<td>Difference between difference with control (95% CI)</td>
<td>17.4 (15.1-19.7)</td>
<td>8.0 (3.6-9.7)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>First line % (95% CI)</td>
<td>45.4 (40.4-50.4)</td>
<td>68.2 (64.9-71.6)</td>
<td>49.8 (44.2-55.4)</td>
<td>66.5 (63.1-69.9)</td>
<td>45.8 (40.7-51.0)</td>
<td>44.1 (40.6-47.6)</td>
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<tr>
<td>Absolute difference baseline-intervention (95% CI)</td>
<td>22.8 (16.6-29.0)</td>
<td>16.7 (9.9-23.5)</td>
<td>-1.7 (-4.7-8.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference between difference with control (95% CI)</td>
<td>24.5 (22.0-27.1)</td>
<td>18.4 (16.0-20.8)</td>
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</table>

Commented [AV3]: I have calculated these intervals and differences from an average of the percentage prescribed. Should this be done in a chi square setting or can I consider this as continuous?
*difference between proportions, large sample method, continuity corrected (Fleiss),
‘What is’ in WinPepi
Initial comparison with anova, descriptives
References

15:37:52;348.
3. Kreuter MW, De Rosa C, Howze EH, Baldwin GT. Understanding wicked problems: A key to
5. Stewardson AJ, Huttenb R, Harbarth S. At least it won’t hurt: the personal risks of antibiotic
6. Vellinga A, Cormican M, Hanahoe B, Murphy AW. Predictive value of antimicrobial
susceptibility from previous urinary tract infection in the treatment of re-infection. British Journal
of General Practice. 2010;60:511-3.
7. European Centre for Disease Control. Surveillance of antimicrobial consumption in Europe
primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis.
BMJ. 2010;340:c2086.
Oct 25;337(7676).
10. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory
antibiotic prescribing practices in respiratory tract infections: A meta-analysis. Health Psychology
improvement and management of prescribing for urinary tract infections (SIMPle): protocol for a
13. Health Services Executive H. Guidelines for Antimicrobial Prescribing in Primary Care in
Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women:
A 2010 Update by the Infectious Diseases Society of America and the European Society for
Microbiology and Infectious Diseases. Clinical Infectious Diseases. 2011 March 1, 2011;52(5):e103-
e20.
15. Twisk JWR. Sample size calculations. Applied Longitudinal Data Analysis for Epidemiology: A