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TITLE

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Contributors: AWM, AV, AC, EOS, SD, SG, CD and PG conceived the study and participated in the design of the trial and intervention. PG, AC and EOS undertook the acquisition and analysis of the health economic data. All authors participated in critical revision of the manuscript, and have seen and approved the final version.

ABSTRACT

Background

Antimicrobial resistance is a major public health issue. This study examines the cost effectiveness of the SIMPle (Supporting the Improvement and Management of Prescribing for Urinary Tract Infections (UTI)) intervention to improve antimicrobial prescribing in primary care in Ireland.

Methods

An economic evaluation was conducted alongside a cluster randomised controlled trial of 30 general practices and 2,560 patients with a diagnosis of UTI. Practices were randomised to the usual practice control or the SIMPle intervention (arm A or B). Data at 6 months follow up were used to estimate incremental costs, incremental effectiveness in terms of first line antimicrobial prescribing for UTI, and cost effectiveness acceptability curves.

Results

The SIMPle intervention was, on average, more costly and more effective than the control. The probability of intervention arm A being cost effective was 0.280, 0.995 and 1.000 at threshold values of €50, €150 and €250 per percentage point increase in first line antimicrobial prescribing respectively. The equivalent probabilities for intervention arm B were 0.121, 0.863, and 0.985 respectively.

Conclusion

The cost effectiveness of the SIMPle intervention depends on the value placed on improving antimicrobial prescribing. Future studies should examine the wider and longer term costs and outcomes of improving antimicrobial prescribing.

Keywords: economics, primary care, public health

INTRODUCTION

Overuse of antimicrobials is a major public health problem (1), as the growth of antimicrobial resistance (AMR) reduces the effectiveness of antimicrobial therapy and increases the burden on already resource constrained healthcare systems (2,3). Moreover, the growth of AMR will have direct implications for the availability of effective antimicrobial treatments in the future (3). This has given rise to calls for the development of strategies to improve antimicrobial prescribing, with the recent World Health Organisation (WHO) report suggesting that such strategies should incorporate a multi-sectorial approach including patients, health workers, policy makers and industry (3).

Within this context, and in line with national prescribing guidelines (4) for Ireland, the SIMPle (Supporting the Improvement and Management of Prescribing for Urinary Tract Infections (UTI)) study (5) aimed to design and evaluate an intervention to improve first line antimicrobial prescribing for UTI in general practice (5). UTI is a bacterial infection that affects almost half of women at least once in their lifetime (6) and is one of the most common bacterial infections presenting in primary care (5). It is therefore an important contributor to antimicrobial consumption in primary care. Prescribing of appropriate first line antimicrobial treatment is a key component in the clinical management of UTI (4). This notwithstanding, in a recent study of the management of UTI in Irish general practice, the authors found that while an antimicrobial agent was prescribed in 56% of cases, only 55% of these prescriptions were identified as being appropriate (7). In addition to the implications of the inappropriate antimicrobial UTI prescribing pattern for AMR, there are also the likely implications for patient outcomes, in terms of the reductions in symptom resolution, as well as the increases in healthcare resource usage and cost. Taken together, these go to highlight the scope for improving the quality of antimicrobial prescribing for UTI in Ireland. The SIMPle intervention included interactive, multimedia and electronic components with integrated feedback for both general practices and patients and was evaluated using a cluster randomised controlled trial (RCT)(5). The clinical effectiveness study reported that the intervention improved first line antimicrobial prescribing for UTI relative to the control (8).

In addition to clinical effectiveness, any decision regarding the adoption of a healthcare intervention in clinical practice will depend upon its expected cost effectiveness (9). The technique of economic evaluation is concerned with the estimation of the relative cost effectiveness of alternative treatment strategies by relating their mean differences in cost to their mean differences in effectiveness, and by quantifying the uncertainty surrounding these incremental point estimates. In this study, we report the results of the economic evaluation conducted to examine the cost effectiveness of the SIMPle intervention.

METHODS

THE SIMPle RCT

Full details on the cluster RCT, which was conducted in line with the CONSORT requirements (10), are published elsewhere (5). In brief, the RCT (ClinicalTrials.gov Identifier: ID NCT01913860) identified and recruited eligible practices from the Irish Primary Care Research Network (IPCRN), an established national research network of general practices in Ireland. Of the 32 practices invited to participate by letter, 30 practices confirmed their participation in the follow-up phone call, before practices were sequentially allocated, using a computer generated randomisation schedule, to one of three treatment arms: [1] intervention arm A; [2] intervention arm B; or [3] control. Patients attending participating practices were automatically enrolled by passive consent and were informed of the study through information leaflets and posters displayed in the practice waiting room. The RCT was conducted over a baseline period of 2 months and a follow up of 6 months, with the interventions and control delivered in a phased approach.

During phase 1, all general practitioners (GPs) from participating practices were invited to a coding workshop which explained the SIMPle study and introduced the importance of UTI coding for audit report generation. This initiated the baseline period where antimicrobial prescribing data was collected across the three arms over a period of 2 months, after which practices were randomised to the intervention or control groups. After control practices received the workshop on UTI coding, they continued to provide usual general practice care.

The intervention consisted of two components, arms A and B, which comprised of a multifaceted complex design with interactive, multimedia and electronic components. Phase 2 consisted of an interactive workshop which differed for arms A and B. All intervention practices received information on the national antimicrobial prescribing guidelines for UTI and their first practice audit report was discussed. In addition, practices in arm B received guidance on delayed antimicrobial prescribing for suspected UTI. All intervention practices received reminder prompts outlining the prescribing guidelines upon coding UTI. For practices in arm B, the reminder prompts also urged delayed prescribing. All intervention practices received monthly audits of their antimicrobial prescribing by email. The audit report contributed to the Irish Medical Council requirements with respect to maintaining professional competence. Phase 3 focused on the provision of patient focused information with the introduction of a multimedia application which included a game for children and an infomercial for adults addressing antimicrobial awareness.

Phase 4, the follow-up period, started at the end of the intervention delivery and included a period of data collection up to 6 months. After the 6 month follow up was completed, control practices were offered a workshop in which all the supporting materials to create an audit report was presented.

Descriptive statistics of the 30 participating practices and 2,560 patients participating in the analysis are presented in Table 1. The study took place from June 2013 until March 2014. The intervention was reviewed and approved by the Irish College of General Practitioners Research Ethics Committee.

Economic Evaluation

The economic evaluation was conducted following the methodological guidelines for Ireland (11). It consisted of a trial-based analysis with a time horizon of 6 months, the trial follow up period. The perspective of the primary healthcare provider was adopted with respect to costing and health outcomes were expressed in terms of first line antimicrobial prescribing for UTI. Data was extracted from the IPCRN dataset, at baseline and follow up. Given the length of follow up, neither costs nor outcomes were discounted. The statistical analysis was conducted on an intention to treat basis, and in accordance with guidelines for cluster RCTs (11,12,13,14). The incremental analysis was undertaken using generalised estimating equations (GEE), a multivariate regression framework for the modelling of multiple distributional forms of clustered data (14). Uncertainty in the analysis was addressed by estimating 95% confidence intervals and cost effectiveness acceptability curves (CEACs) (15). All analysis was undertaken in the Stata 13 statistical software package.

Cost Analysis

The focus of the cost analysis was limited to three resource categories within the primary care sector. Resource use data was captured from the IPCRN dataset and a vector of unit costs was applied to calculate the costs associated. Unit cost estimates were obtained from national data sources and were transformed to Euros (€) in 2013 prices using appropriate indices (11, 16). A summary of the unit cost data and their sources are presented in Table 2.

The first cost category related to intervention delivery and in particular, the costs of intervention set-up, audit and feedback. These were calculated using data captured from the study's financial accounts and participant interviews and were allocated per practice and per patient in the intervention arms. The resources considered include those relating to the provision of workshops, including the trainer and participation time input, educational materials and consumables, and fees associated with IPCRN data collection, electronic audit and feedback reports, and electronic reminder software installations. Data on the additional time-input associated with reviewing audit and feedback reports, first line treatments, delayed prescriptions and coding, was captured through interviews with the participating practices. The cost of intervention set-up was estimated at €661.86 per practice, while the costs of audit and feedback were estimated at €886.35 per practice for intervention arm A and €811.64 per practice for intervention arm B. For the purposes of the analysis, the practice-level costs were allocated per patient consultation for all intervention practices.

The second cost category related to GP care and laboratory analysis per patient consultation. Data on resource use relating to GP consultations and urinanalysis were extracted from the IPCRN dataset. Unit costs for consultations were obtained from published national sources and unit costs for laboratory analysis were obtained from the participating study laboratory at Galway University Hospitals (GUH).

The third cost category related to medication prescriptions per patient consultation. Data on antimicrobial prescriptions was obtained from the IPCRN on script type, quantity and duration of the prescription. Unit costs associated with antimicrobial medications were obtained from the Health Service Executive Primary Care Reimbursement Scheme (HSE PCRS) tool (17) and were adjusted to account for pharmacy dispensing and rebate costs.

A total cost per patient consultation variable was constructed for the incremental analysis. To determine the incremental costs, estimation was undertaken using a GEE regression model, assuming a Gaussian variance function, an identity link and exchangeable correlation structure, and controlling for treatment arm, baseline costs, age, gender, medical card status (i.e. entitlement to free primary care and reduced cost medications) and clustering.

Effectiveness Analysis

The health outcome adopted for the cost effectiveness analysis was proportion of prescriptions for recommended first line antimicrobials for UTI. Data extracted for each patient consultation for each practice from the IPCRN dataset at baseline and follow up was analysed. The results are presented in terms of the percentage point increase in first line antimicrobial prescribing. To this end, estimation was undertaken using a GEE model, assuming a binomial variance function, a log link and an exchangeable correlation structure, and controlling for treatment arm, baseline prescriptions, age, gender, medical card status and clustering.

Cost Effectiveness Analysis

In the cost effectiveness analysis, the difference in the mean cost per patient consultation was related to the difference in the proportion of first line antimicrobial prescribing per patient consultation by estimating incremental cost effectiveness ratios (ICERs), which identify the additional cost per percentage point increase in first line antimicrobial prescribing for UTI. Incremental results are reported for the comparison of intervention arm A and intervention arm B relative to the control strategy. In both cases, the intervention may be defined as cost effective if the reported ICER is considered worth paying by decision-makers (9). Uncertainty is examined using CEACs, which report cost effectiveness probabilities for a range of threshold values. In this case, the threshold value refers to the maximum that decision makers may be willing to pay to achieve a percentage point increase in first line prescribing for UTI. The CEACs thereby incorporate both the sampling uncertainty around the mean cost effectiveness point estimates and the uncertainty around the true threshold value (15), which is unknown.

RESULTS

Summary statistics for the levels and types of antimicrobial prescribing, in addition to the number of GP consultations per patient are presented in Table 3. The incremental results are presented in Table 4 and Figure 1. On average, the total cost per patient consultation was €84.20 (SD: 24.57) in intervention arm A, €88.72 (SD: 24.29) in intervention arm B, and €67.00 (26.07) in the control arm. In terms of effectiveness, 68.2% of consultation prescriptions in arm A were recommended first line treatments for UTI, compared to 66.5% in arm B and 44.1% in the control arm.

The results from the incremental analyses indicate that both intervention arm A and arm B were statistically significantly associated with increased costs and increased effectiveness. Relative to the control, mean cost per patient consultation for arm A was €14.70 (95% Confidence Intervals (CI): 5.14, 24.25) higher and for arm B was 17.29 (95% CI: 7.73, 26.86) higher. First line antimicrobial prescribing for UTI was 22.9 (95% CI: 14.1, 31.7) percentage points higher for arm A and 16.4 (95% CI: 7.2, 25.7) percentage points higher for arm B, when compared to the control.

These translated into ICERs of €64.19 (95% CI: 22.03, 121.76) per percentage point increase in first line antimicrobial prescribing for UTI for arm A and €105.43 (95% CI: 46.55, 241.69) for arm B. These are the values that decision makers would have to be willing to pay for the intervention to be cost effective. This is further explored in the probabilistic results summarised in Table 4 and graphically in Figure 1. These indicate that the probability of arm A being cost effective was 0.280, 0.995, and 1.000 at threshold values of €50, €150 and €250 per percentage point increase in first line antimicrobial prescribing for UTI respectively. The equivalent probabilities for arm B were 0.121, 0.863, and 0.985 respectively.

DISCUSSION

Main finding of this study

On the basis of a cluster RCT, the SIMPle intervention, which included interactive, multimedia and electronic components with integrated feedback for both practices and patients, was, on average, more costly and more effective in improving first line antimicrobial prescribing for UTI than usual general practice care. With respect to costs, the observed increases were predominately driven by the set-up and audit and feedback components of the intervention. In terms of outcomes, while we did not capture the effect of the improved antimicrobial prescribing on patient outcomes, previous studies have identified that improved prescribing is associated with improved symptom resolution, including in the case of UTI (18). Moreover, the reported improvements in antimicrobial prescribing may have potentially important and positive implications for levels of AMR.

Taken together, in such cases when an intervention is both more costly and more effective, it will only be judged cost effective if decision makers are willing to pay for the additional health generated (9). Given that there is no formal or informal threshold value per percentage point increase in first line antimicrobial prescribing for UTI, we present results for a series of potential values. For example, if decision makers are willing to pay €100 to increase first line antimicrobial prescribing by one percentage point, there is 90% probability that intervention arm A would be cost effective, which compares to a 59% probability for intervention arm B. Whether or not the threshold values reported are appropriate or acceptable is open to debate given the absence of any such information for citizens or policy makers. That said, our results provide a timely reminder for the need to consider of such questions given concerns over growing level antimicrobial resistance.

Notably, while these results may prove to be supportive of the SIMPLE intervention it is important to note that one of its unintended consequences was an increase in overall prescribing of antimicrobials (8). While this may have been clinically appropriate for the patients who received these prescriptions, and in doing so represented an improvement in the quality of prescribing, it could also contribute to an increase in antimicrobial resistance in the future. Therefore, any improvement in the quality of prescribing must be viewed in the context of its potentially negative effect on outcomes in the long run.

What is already known on this topic

A limited number of studies have evaluated multi-faceted complex interventions targeting improvements in antimicrobial prescribing in primary care. While these studies report on the clinical aspects of various interventions (19,20), few consider costs explicitly and none estimate cost effectiveness. The absence of economic evaluation in this context may in part be due to the difficulty in assessing the scale and scope of the negative externalities associated with over-prescribing and the time horizon associated with these externalities. Indeed, there may be advantages in adopting alternative valuation approaches, in addition to the cost effectiveness approach reported here, for evaluating policies associated with combatting AMR, given the absence of specific information on the impact of over-prescribing on health outcomes in the future. Whatever approach is taken, we do need better estimates on what citizens and policy makers are prepared to pay for changes in consumer and provider behaviour with respect to the use of antimicrobials to treat UTI and other infections

What this study adds

This study makes a significant contribution through the conduct of an economic evaluation of an intervention targeting antimicrobial prescribing based on a RCT. Indeed, the health economic evidence base with respect to both the cost of resistance and the cost effectiveness of interventions to reduce it has been described as poor (21). Furthermore, the analysis was based on the extraction of anonymised electronic patient records provided micro level data from the IPCRN, an established national research network of general practices in Ireland. This novel approach proved to be feasible and effective and should be further explored for the conduct of such evaluations in this context in the future.

Limitations of this study

Given the clinical research question, the unit of measurement for the analysis was patient consultations and not patients. This has important implications for the interpretation of the results. As the cost analysis was conducted from the primary health service perspective, potentially important resource items such as costs of hospital and community care services were not captured. Furthermore, private patient costs such as private health insurance premiums, and broader costs to society such as the external costs of AMR and productivity losses were not captured. The process of conducting cost analysis in Ireland is compromised by the lack of nationally available unit cost data. In estimating unit costs for individual resource activities, we endeavoured at all times to be conservative in any assumptions adopted. Notably, we were unable to estimate a generic health outcome such as quality adjusted life years (QALYs), which are recommended for economic evaluation (9). Finally, the time horizon for analysis was limited to the trial follow up of 6 months. Additional follow up of the trial sample should be conducted to explore the longer term implications of the results presented here.

Conclusion

Depending on the value placed by policy makers on improving antimicrobial prescribing, the SIMPle intervention may be a cost effective means of improving the quality of antimicrobial prescribing for UTI in Irish general practice. Behavioural changes resulted in improved outcomes for relatively low cost. This finding is predicated on the assumption that decision makers are willing for pay the additional costs required to generate the additional effectiveness. In that regard, the threshold values, though arbitrary and not QALY specific or comparable, appear reasonable in comparison to other demands on the healthcare budget. However, further evidence is required on the longer term implications of such interventions; that is, to examine the extent to which improvements in current antimicrobial prescribing impacts upon health outcomes and healthcare expenditures in the future.

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Table 1: Practice and Patient Characteristics by Arm

	Intervention Arm A	Intervention Arm B	Control
Practices			
Number of practices	10	10	10
Median Number of GPs (IQR)	2.3 (1.5)	2.0 (2.5)	2.0 (1.5)
% of full time GPs	76.5	86.7	57.2
Mean years practicing of GPs (SD)	18.7 (12.5)	14.8 (11.4)	16.9 (8.8)
Mean number of practice contacts per year (SD)	14,810 (10,169)	15,464 (12,950)	12,820 (7,661)
Patients			
Mean age in years (SD)	56.3 (3.3)	51.5 (11.43)	54.1 (7.7)
% Male	12.0	12.4	8.3
% Medical card patients	68.1	62.1	55.3

Table 2: Unit Cost Estimates

Resource item	Activity	Unit Cost 2013 €	Source
Intervention Resources			
Intervention Set-Up	Per practice	€661.86	Study Accounts
Audit and Feedback Report: Arm A	Per practice	€886.35	Study Accounts
Audit and Feedback Report: Arm B	Per practice	€811.64	Study Accounts
Other Resources			
GP initial consultation	Per consultation	€50	The Competition Authority Dublin
GP re-consultation	Per consultation	€25	The Competition Authority Dublin
GP time	Per hour	€124.50	The Competition Authority / Irish Health Service Pay Scales *
Practice manager time	Per hour	€53.02	Irish Health Service Pay Scales 2013*
Dipstick test	Per consultation	€0.16	Med Guard (www.medguard.ie)
Urine sample container#	Per urine sample	€0.36	Med Guard (www.medguard.ie)
Laboratory costs culture	Per urinanalysis	€15	Galway University Hospital
Laboratory costs (if susceptible)	Per urinanalysis	€40	Galway University Hospital
Antimicrobial costs	Per prescription	n/a	National Pharmacy Data *

***Source*:** Health Service Executive Payscales; Health Service Executive Primary Care Reimbursement Scheme; ** HIPE data

Table 3: Antimicrobial Prescriptions & General Practitioner (GP) Consultation Resource Usage

Variable/Analysis	**Intervention Arm A**	**Intervention Arm B**	**Control**
Number of Consultations	743	738	783
	%	**%**	**%**
Antimicrobial Prescriptions	78.6	75.8	66.5
Type of Antimicrobial Prescription	**%**	**%**	**%**
Nitrofurantoin	64.3	63.8	35.9
Trimethoprim	3.9	2.7	8.2
Quinolones	2.6	2.2	6.6
Co-amoxyclav	5.0	3.3	10.3
	Mean (SD)	***Mean (SD)***	***Mean (SD)***
GP Consultations per patient	1.3 (0.2)	1.3 (0.2)	1.2 (0.3)

Table 4: Incremental Cost Effectiveness Analysis

Variable/Analysis	**Intervention Arm A**	**Intervention Arm B**	**Control**
Number of Consultations	743	738	783
Cost (€) per Consultation	***Mean (SD)***	***Mean (SD)***	***Mean (SD)***
Intervention Set Up	8.44 (0)	8.44 (0)	0 (n/a)
Audit and Feedback	7.82 (0)	7.92 (0.33)	0 (n/a)
GP Care & Laboratory Analysis	63.87 (22.73)	67.28 (23.56)	62.27 (24.10)
Antimicrobial Prescriptions	5.05 (3.40)	5.19 (3.45)	5.27 (4.01)
Total Cost	84.20 (24.56)	88.72 (24.29)	67.00 (26.07)
Health Outcome per Consultation	***%***	***%***	***%***
% First Line Antimicrobial Prescriptions	68.2	66.5	44.1
Incremental Analysis		**Intervention Arm A versus Control**	**Intervention Arm B versus Control**
Difference in Mean Total Cost (€) (95% CI's)		14.70 (5.14, 24.25)	17.29 (7.73, 26.86)
Difference in % First Line Prescribing for UTI (95% CI's)		22.9 (14.1, 31.7)	16.4 (7.2, 25.7)
ICER (€) per % increase in First Line Prescribing for UTI (95% CI's)		64.19 (22.03, 121.76)	105.43 (46.55, 241.69)
Probability that Intervention is Cost Effective at Threshold Value (λ) per % increase in First Line Prescribing for UTI		**Intervention Arm A versus Control**	**Intervention Arm B versus Control**
λ = €0		0.000	0.000
λ = €50		0.280	0.121
λ = €100		0.897	0.590
λ = €150		0.995	0.863
λ = €200		0.999	0.961
λ = €250		1.000	0.985

Figure 1 – Cost Effectiveness Acceptability Curves