General Practitioner Antimicrobial Stewardship Programme Study (GAPS): final summary report

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EXECUTIVE SUMMARY

Background

There is a strong link between antibiotic consumption and the rate of antibiotic resistance. In Australia, the vast majority of antibiotics are prescribed by general practitioners (GPs), and the most common indication is for acute respiratory infections (ARIs).

Our primary objective was to assess the effectiveness of an integrated, multifaceted package of interventions to reduce antibiotic prescribing for suspected ARIs in general practice.

Secondary objectives were:

1. to assess the feasibility and uptake of the integrated package of interventions to reduce antibiotic prescribing for suspected ARIs.
2. to assess and estimate the likely costs and cost-effectiveness of implementing the integrated package of interventions to reduce antibiotic prescribing for suspected ARIs.
3. to estimate the prevalence of bacterial pathogens in the upper respiratory tract (throat and nose) of asymptomatic general practice staff and patients.
4. to assess the feasibility of conducting community antibiotic resistance surveillance by using sentinel GP practices participating in the Australian Sentinel Practice Network (ASPReN).

Study Design

This was a cluster randomised trial comparing two parallel groups of GPs in 27 urban general practices in Queensland, Australia: 13 intervention and 14 control practices. GPs and study participants gave informed consent to participate in the study.

This study evaluated an integrated, multifaceted evidence-based package of interventions implemented over a six month period. The interventions, which have all individually been shown to be effective at reducing antibiotic prescribing were: poster on practice antibiotic prescribing policy; patient information leaflet; online communication training package; delayed antibiotic prescribing; patient decision aids; and near patient testing with C-reactive protein.

The main outcome data were from Australia's national health insurance scheme, Medicare, which were accessed after the completion of the intervention phase. The antibiotic prescriptions of interest were oral antibiotics coded J01 (antibiotics for systemic use) by the Anatomical Therapeutic Chemical (ACT) code. They included the number of antibiotic prescriptions and the number of patient visits per general practitioner for periods before (baseline) and during the intervention. Results compared the change in antibiotic prescription incidence rates in the baseline and intervention phase for both the control versus the intervention practices. The rate of antibiotic prescribing was modelled in two ways - using the numbers of patient visits as the denominator and using the total number of non-repeat prescriptions as the denominator – with intervention versus control group indicators, secular trend and seasonal factors as explanatory variables.

Semi-structured interviews were conducted with the GPs from the intervention practices at the end of the intervention phase to assess the feasibility and uptake of the interventions.

An economic evaluation was conducted to assess and estimate the costs of implementing the package.

In addition, two microbiology sub-studies were nested in the main study to consider whether GP practices were more like the community as opposed to a hospital setting as regards carriage of bacterial pathogens (with implications for Infection Control practice); and to assess the feasibility of conducting community antibiotic resistance using sentinel GP practices in the Australian Sentinel Practice Network (ASPReN).

Findings

A total of thirteen practices were randomised to the intervention arm (56 GPs) and 14 practices were randomised to the control arm (54 GPs). The GP practices randomised to the intervention or control arm in the study were well matched and the characteristics of the GPs in the control and intervention arms were balanced.

Quantitative analysis

Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) data for all 110 participating GPs were obtained three years prior to the intervention – baseline phase (1st June 2012 until 31st August 2015), and 6 months during the intervention phase (1st September 2015 until 29th February 2016). Using the number of patient visits per GP as the denominator, there were measurable declines in antibiotic prescriptions during the intervention phase compared with the baseline phase for both the intervention group rate ratio (RR) =0.90 and control group RR=0.88.

The decrease in antibiotic prescribing continued over the study period. Using the number of patient visits per GP as the denominator (MBS data) for the rates of antibiotic prescribing, there were no differences apparent between the intervention and the control practices. The ratio of change in intervention group to change in control group was RR=1.03 (95% confidence interval 0.98, 1.08), after adjustments for secular and seasonal trends.

However, a number of a number of limitations were identified using the number of patient visits per GP i.e. in the MBS data. Accordingly, a second analysis was undertaken, using all (non-repeat) PBS claims as the denominator. During the intervention phase, this analysis clearly showed a statistically significant reduction in antibiotic prescription rates of 7 % for the intervention group relative to the control group: RR= 0.93 (95% confidence interval 0.89, 0.97), after adjustments for secular and seasonal trends

Based on this analysis, in the intervention group the estimated mean number of antibiotic prescriptions dispensed per GP per month was 55.7 during baseline phase which was reduced to 52.5 antibiotic prescriptions per GP per month during the intervention phase; for the control group the estimated mean number antibiotic prescriptions dispensed per GP per month was 54.8 during baseline phase and increased to 55.5 during the intervention phase. This equates to a nett decrease of almost 4 antibiotic prescriptions per GP per month in the intervention group compared to the control group during the intervention phase.

Qualitative analysis

Semi-structured telephone interviews were conducted with 46 out of 56 (82 %) GPs from the intervention practices to assess the feasibility and uptake of the interventions. Overall the intervention package was well received by the participants. It was considered adaptable to individual practices and provided GPs with the opportunity to reflect on their management of patients with suspected ARIs. The package was practical and complemented the consultation process and GPs welcomed the interventions that help convince, reassure and educate patients about the use of or need for antibiotics. An important advantage of the intervention package was that the ‘one size fits all principle’ was not applied and that the GP was able to choose from a range of interventions depending on his/her consultation preferences and the patient at hand.

Economic analysis

The economic analysis of the GAPS project is based on the study engagement and intervention phases of the program (as opposed to the study set up, monitoring and analysis), excluding all research and evaluation costs, and the value of these resources. The

total value of resources utilised in delivering the GAPS program during this time period was just over $200,000. Cash expenditure accounted for $186,593 (91% of total costs). This was split between staffing (73%) and consumable items (18%). The economic value placed on practice staff time diverted to the intervention accounts for the remaining $18,889 (9% of total costs). The bulk of costs were incurred during the first two months of the program, as one-off start-up costs, whilst ongoing monthly expenditure accounted for only 6% of the total cost.

The economic analysis of the GAPS project uses the perspective of the health system. The opportunity cost of practice staff time devoted to the program accounts for 10% of these costs, with the remainder representing financial expenditure as a mix of program staffing and consumables. One-off start-up costs for the overall program and engagement with the practices account for 40% of costs, whilst ongoing monthly expenditure accounts for 60% of the total cost. The major expense is the program manager (nearly 40% of program costs).

The 7% reduction in antibiotic prescribing achieved by GAPS delivers cost savings from avoided prescriptions of just under $21,000 (including repeat prescriptions avoided), bringing the net cost of GAPS to just under $186,000. This equates to a cost of $121 per prescription avoided. Including the economic benefit of avoided adverse incidents (diarrhea and rashes) and cases of *Clostridium difficile* associated with antibiotics would deliver further cost savings from the reduced prescribing of just over $57,000. This reduces the net monetary cost of GAPS to just under $116,000, or $73 per prescription avoided.

It is likely that economies of scale would be achieved under a large scale roll out, as the cost of the program manager would be shared over a greater number of practices. Using conservative assumptions, a roll out to 250 practices over 3 years has the potential to be cost-saving, with investment in GAPS offset by over $200,000 of cost savings resulting from fewer prescriptions and fewer antibiotic associated adverse incidents and cases of *C. difficile* that would require GP or hospital care.

Microbiological sub-studies

Both microbiology sub-studies collected swab specimens from the upper respiratory tract (throat and anterior nares) of asymptomatic GP practice staff and patients attending the practice without signs and symptoms of an acute infection. Swabs were immediately placed in transport medium and either despatched to the microbiology laboratory using the priority postal service or a courier service. Antibiotic resistance was determined on pathogens isolates both phenotypically and genotypically.

(1) Point prevalence estimates of asymptomatic carriage of bacterial pathogens in GP practice staff and patients

In 138 practice staff, the carriage rate of *Staphylococcus* species in the nose and/or throat was 26.8% and was 31.5% in 124 asymptomatic patients attending a GAPS practice. Gram-negative bacteria were relatively less commonly cultured from the upper respiratory tract than *Staphylococcus* spp.. Significant bacteria cultured included *Klebsiella* spp., *Escherichia coli*, *Enterobacter* spp and *Pseudomonas aeruginosa.* These were isolated in 9.4% of asymptomatic practice staff and in 7.3 % of asymptomatic patients. Overall, there was no difference in the carriage rate of bacterial pathogens in the upper respiratory tract among practice staff and asymptomatic patients, 32.6% and 33.1%, respectively. This suggests that general practice settings are more like the community than a hospital environment, where health care workers have a higher risk of carriage of antibiotic-resistant pathogens.

(2) Rolling out community antibiotic resistance surveillance using sentinel GP practices in the ASPReN network

It is common practice for antibiotic resistance surveillance programs to use microbiological specimens submitted for diagnostic purposes which may not accurately measure true community rates of resistance. This study assessed the feasibility of national surveillance of antibiotic resistance in the community using sentinel GP practices. ASPReN was asked to identify ten GPs from ten different practices across Australia. Each GP obtained a throat and nose swab from five different asymptomatic health care workers or patients who presented with a non-infectious illness. A total of eight GPs from different practices throughout Australia agreed to participate in the study and 39 adults were recruited. Swabs were received in the microbiology laboratory within two days of specimen collection and processed immediately upon arrival: 41% grew *Staphylococcus* spp. and 34% grew Gram-negative bacteria. This shows the feasibility of using sentinel GP practices to collect swabs (in this case from the upper respiratory tract) for isolating bacteria for antimicrobial resistance surveillance.

Antibiotic resistance

Across the two sub-studies, three methicillin-resistant *Staphylococcus aureus* (MRSA) were identified, one from a GP practice staff member.

Conclusion

A multifaceted package containing different interventions to enhance rational prescribing of antibiotics in Australian general practices was successfully introduced and well received by the GPs. It was considered adaptable to individual practices and provided GPs with the

opportunity to reflect on their management of patients with ARIs. The package was practical and complemented the consultation process. An important advantage of the intervention package was that the "one size fits all" principle was not applied and that the GP was able to choose from a range of interventions depending on his/her consultation preferences and the patient at hand.

Interestingly, rates of antibiotic prescriptions were declining in both the intervention and control groups even before this study began, and the decrease continued over the study period. By one measure of the outcome (MBS data as the denominator) there was no statistically significant difference between the intervention and control groups. However , using a better measure (PBS data as the denominator), we found a 7% decrease in the intervention group compared to the control group, corresponding to a nett difference of almost 4 fewer antibiotic prescriptions per GP per month.

This equated to a cost of $121 per prescription avoided. Including the economic benefit of avoiding adverse reactions (diarrhoea and skin rashes) and cases of *Clostridium difficile* infection associated with antibiotic use would deliver further benefits and reduce the cost of avoiding an unnecessary antibiotic prescription to $73. GAPS was only implemented for six months in a relatively small number of GP practices; and the majority of costs were incurred in setting up the intervention package. It is likely that economies of scale would be achieved with a wider and longer roll out. Using conservative assumptions, implementing the package to 250 practices over three years has the potential to be cost-saving, with implementation costs offset by over $200,000 of cost savings with fewer prescriptions and adverse events associated with unnecessary antibiotic prescriptions.

The microbiology sub-studies suggest that GP practices are comparable to the community rather than a hospital environment as regards to carriage of antibiotic resistant pathogens, with implications for infection control practice. Surveillance of antibiotic resistance in the general population is feasible using GP sentinel sites.

In conclusion, a multifaceted package containing different interventions to enhance rational prescribing of antibiotics is effective, acceptable and feasible in general practice. Providing GPs with a choice might enhance uptake and improve appropriateness of prescribing antibiotics in the community (particularly for upper respiratory tract infections). Taken to scale, the interventions have the potential to be cost saving for the health system over just three years. The results of study will help inform policy for future national implementation.

BACKGROUND

Australia is one of the highest consumers of antibiotics in the developed world with 45% of the Australian population being supplied at least one antibiotic per year.[1] The defined daily dose (DDD) in Australia is nearly 23/1000 population/day[1] compared with about 18 DDD/1000 population /day in Denmark and less than 11 DDD/1000 population /day in general practice in the Netherlands.[2-4]

There is a strong link between antibiotic consumption and the rate of antibiotic resistance.[5] Acute respiratory tract infections (ARIs) are the most common reason for prescribing an antibiotic in primary care.[6] In Australia antibiotic resistance in common pathogens causing ARIs has increased over the past 20 years.[7] For example, resistance of *Streptococcus pneumoniae* to macrolide antibiotics has increased from 8.7% in 1994 to 20.4% in 2007, and this trend is continuing.[8] Patients with infections caused by antibiotic-resistant organisms have an increased mortality compared with those infected with antibiotic-susceptible organisms.[9, 10] Reduced antibiotic prescribing has been shown to be associated with reduced levels of resistance.[11] [12]

General Practitioners (GPs) have the potential to be the most influential health care professionals to address the problem of antibiotic resistance as the majority of antibiotics are prescribed in the general practice setting and antibiotics remain the most common class of medicine prescribed.[13] Continued improvements in prescribing practice and a positive influence on individual and community beliefs about antibiotic consumption are essential to limit the spread of antibiotic resistance.[14] Antibiotics are often inappropriately prescribed for patients with ARIs.[6] U.S.A. ambulatory care patients with a diagnosis of acute respiratory conditions accounted for 221 antibiotic prescriptions (per 1000 population) annually, but only half of these prescriptions were concordant with guidelines and therefore considered appropriate. [15] These findings have been confirmed in Australia where more than 50% of people with colds and other upper respiratory tract infections were prescribed an antimicrobial when it was not recommended by guidelines.[16] This suggests that considerable further gains could safely be made in reducing inappropriate antibiotic prescribing.

It is estimated that by 2050, deaths attributable to Antimicrobial Resistance will be greater than cancer. Antibiotics underpin modern medicine as we know it: if they lose their effectiveness, key medical procedures (such as gut surgery, caesarean sections, joint

replacements), and treatments that depress the immune system (such as chemotherapy for cancer) could become too dangerous to perform.[17]

Unfortunately, new antimicrobials are not being developed at a pace that comes anywhere close to meeting the urgent need; therefore, the healthcare system needs to undertake efforts that save one of medicine's most precious and long-standing resources.[18] This was summarised by the World Health Day 2011 slogan 'Combat antibiotic resistance: no action today, no cure tomorrow'. Reducing the inappropriate use of antimicrobials has been shown to improve patient outcomes and reduce adverse consequences of antibiotic use (including antibiotic resistance, toxicity and unnecessary costs).[19]

Antimicrobial stewardship (AMS) is the coordinated set of actions designed to promote and increase the appropriate use of antimicrobials and is a key strategy to conserve the effectiveness of antibiotics. Australia's first National Antimicrobial Resistance strategy for 2015 – 2019 states that there is a need for resources to support the implementation of AMS for all settings including primary health care.[20]

There are a number of interventions that have shown promise at decreasing antibiotic prescribing for ARIs in primary care: delayed prescribing; patient decision aids; communication training; near patient testing with C-reactive protein; and commitment to a practice prescribing policy for antibiotics.[21-23] Prescribers are well placed to convey the importance of informing patients that they are twice as likely to carry resistant bacteria after a course of antibiotics as someone who has not taken them.[24-26] Evidence from general practice demonstrates that patient satisfaction is linked more with good communication than a prescription for an antibiotic.[27, 28] Several studies have demonstrated that GPs trained in communication skills, [29, 30] and specifically in Shared Decision Making [31-33], prescribed antibiotics significantly less than GPs without training. The benefits of patients managed by a GP trained in enhanced communication skills can persist for at least 3 years, and do not appear to compromise repeat consultation rate, patient recovery or patient satisfaction. [29, 30, 34, 35]

Few of these strategies have been adopted in Australia so there is no evidence about their effectiveness in this context, and all have been evaluated in isolation. Evidence from other areas of healthcare suggests that using multiple strategies or interventions in concert could have an even greater impact on prescribing behaviour and induce longer term behaviour

change. This could enable clinicians and health care systems to reduce antimicrobial resistance in the future. [36]

Aim

The aim of our study was to assess the effectiveness of an integrated, multifaceted package of interventions to reduce antibiotic prescribing for suspected ARIs in general practice.

Primary Objective

Our primary objective was to assess the effectiveness of an integrated, multifaceted package of interventions to reduce antibiotic prescribing for suspected ARIs in general practice.

Secondary objectives were:

1. to assess the feasibility and uptake of the integrated package of interventions to reduce antibiotic prescribing for suspected ARIs.
2. to assess and estimate the likely costs and cost-effectiveness of implementing the integrated package of interventions to reduce antibiotic prescribing for suspected ARIs.
3. to estimate the prevalence of bacterial pathogens in the upper respiratory tract (throat and nose) of asymptomatic general practice staff and patients.
4. to assess the feasibility of conducting community antibiotic resistance surveillance by using sentinel GP practices participating in the Australian Sentinel Practice Network (ASPReN).

STUDY DESIGN

The trial protocol was developed by researchers at the University of Queensland, Bond University and Queensland University of Technology in Australia in accordance with the CONSORT statement extension to cluster randomised trials.[37]

Study design

This was a clustered randomised parallel group controlled trial.

Study setting

This study was conducted in South East Queensland, Australia. Twenty-seven urban general practices were purposely recruited and randomised to either the control or intervention group.

Eligibility criteria

All GPs from the recruited general practices were eligible to participate in the study provided they gave consent for the research team to obtain their data on antibiotic prescribing and patient visits from Medicare. General practice staff and patients attending the GP practice for consultation with non-infectious complaints were eligible for the point prevalence nose and throat swab study: asymptomatic carriage of bacterial upper respiratory pathogens.

Implementation of Interventions

An integrated, multifaceted package of interventions was implemented in the intervention practices by research coordinators who were trained in the use of the interventions. The GPs in the control practices continued normal clinical practice while the GPs in the intervention practices were trained in the interventions as described below. In the six month study period, the research coordinators regularly visited the intervention practices to support uptake of the interventions and provide any necessary supplementary training.

Interventions

Evidence based interventions already demonstrated to be effective at reducing antibiotic prescribing for ARIs elsewhere in the world were selected.[36] They were combined into an integrated, multifaceted package with the following components:

1. *Poster on Practice Antibiotic Prescribing Policy*

   This intervention consisted of displaying a poster-sized prescribing policy in the GPs waiting room and/or examination room. GPs are encouraged to insert their photograph as endorsement on the poster. The poster, written at the eighth grade reading level in English emphasises the GPs' commitment to guidelines, i.e. *Therapeutic Guidelines: Antibiotic*,[38] for appropriate antibiotic prescribing and explains why antibiotics are not appropriate in many cases.[21]

2. *Patient information leaflet*

   The leaflet provided information to the patient about inappropriate use of antibiotics for ARIs and the potential harmful effects of antibiotics. It complemented the poster in the GPs' waiting room and/or examination room.

3. *Online communication training package*

   An online communication module was offered in combination with background information on the problem of antimicrobial resistance in primary care and the

effectiveness of antibiotics for most commonly presenting ARIs. The module was based on the GRACE INTRO study [22] and has been adapted carefully for the Australian context as part of the Changing the Antibiotic Prescribing of General Practice (ChAP study)[39], a controlled trial funded by the Royal Australian College of General Practitioners and Therapeutic Guidelines Ltd.[40, 41]

The online communication training was targeted at GPs rather than patients. The training in enhanced communication skills focuses on exploring patients' concerns and expectations, providing information on symptoms, natural course of the disease, treatments, agreement of a management plan, summing up, and providing guidance about when to re-consult. GPs were also provided with a booklet [42] and/or the NPS MedicineWise management plan for the management of respiratory tract infections during consultations which includes information on symptoms, use of antibiotics that are concordant with *Therapeutic Guidelines: Antibiotic[38]* and antibiotic resistance, self-help measures, and when to re-consult. The training was supported by video demonstrations of consultation techniques and was offered as a Continuing Professional Development activity to GPs.

4. *Delayed antibiotic prescribing*

   The GP had the option to offer the patient a delayed antibiotic prescription. This consisted of advice to the patient to only fill the prescription at a pharmacy after a few days if symptoms were not starting to settle or become more severe.[43] A sticker was made available to GPs to apply to the prescription, labelling it as a delayed prescription.

5. *Patient Decision Aids*

   A brief graphical laminated summary of evidence for the management of a number of ARI conditions was provided as a decision aid for use during the consultation. These decision aids that have been developed for the ChAP study[41] were adapted for the GAPS study to assist GP and patient to make an appropriate decision about the management of the condition. The Patient Decision Aids supported the following conditions:

   - acute sore throat;
   - acute rhinosinusitis
   - acute otitis media; and
   - acute bronchitis

6. Near patient testing: CRP study

The CRP test is widely used in some European primary care settings [44] and has been shown to significantly reduce antibiotic prescribing for patients with ARIs.[45]

The intervention practices each had access to a CRP testing machine for three months (with 50 CRP tests per practice provided free of charge) to determine the feasibility and uptake of this type of near patient testing.

Tests were performed using the QuikRead CRP kits (Orion Diagnostica). The research co-ordinator, in conjunction with the distribution company (ABACUS ALS), trained the GPs and practice staff in the use and interpretation of the tests. In addition GPs also had access to an online training module on CRP testing (http://gaps.uq.edu.au).

The following instructions were provided regarding CRP testing:

• CRP testing should only be used within ARI consultations for lower respiratory tract infections and acute rhinosinusitis.

• the GP can decide to perform a CRP test as a complement to the routine consultation (including history and physical examination).

• the CRP test is performed on a finger prick blood sample and the result will be available within a few minutes.

• the CRP test result can be used in addition to the clinical assessment to decide whether to prescribe an antibiotic.

Sample size

The sample size calculation for this study was based on the average change in antibiotic prescription rates in practices in the intervention group (before – after the intervention) compared to the average change in practices in the control group over the same period. For example, an average change in antibiotic prescription rate from 40% to 20% in the intervention practices and no change in the control practices would result in a difference of 0.2 between the two groups. A difference in average change in rates in the range 0.20-0.25, if the standard deviation in rates was about 0.2, was considered clinically significant and plausible. With equal numbers of practices in the two groups, power of 80%, significance level of 5% for a two tailed test, for a difference of 0.24, 12 practices per group would be needed.

Recruitment

GPs were recruited from practices in the Brisbane area and at the Gold Coast. Purposeful sampling as well as practices involved in other research projects or medical student placements were used for recruitment. All GPs within each practice were invited to participate.

The following recruitment approach was used:

- an initial e-mail was sent out to GP practices in the Brisbane area and the Gold Coast;
- a follow up phone call by the research coordinators to the practice manager providing additional information about the project and requesting a lunchtime meeting with the GPs and practice staff;
- the chief investigators and/or research coordinators met with the GPs and practice staff at a lunchtime meeting to provide the GPs with information about the intervention package and project.

The following incentives were also provided to the GPs and practices:

1. Royal Australian College of General Practitioners (RACGP) Continuing Professional Development (category 1 and 2 points) for completing the education activities associated with the study
2. a $1000 payment for each practice to help cover the costs associated with being involved in the study

GPs who had consented to participate in the study were recruited from the selected general practices. General practice staff and patients attending the recruited GP practices for consultation with non-infectious complaints and who had consented to the point prevalence study of asymptomatic carriage of bacterial upper respiratory pathogens have also been recruited.

Randomisation

Practices were randomly assigned to either the intervention or control arm in a 1:1 ratio. A blocked randomisation list with 8 practices per block was generated using the online software package Sealed Envelope Ltd. 2015 available from: https://www.sealedenvelope.com/simple-randomiser/v1.

Microbiology Sub-studies

Two specific microbiology pilot sub-studies were nested in the main study. Both collected swab specimens from the upper respiratory tract (throat and anterior nares) of asymptomatic GP practice staff and patients attending the practice without signs and symptoms of an acute infection. Swabs were immediately placed in transport medium and despatched to the microbiology laboratory using the priority postal service or a courier service.

1 Point prevalence estimates of asymptomatic carriage of bacterial pathogens in GP practice staff and patients

This pilot study assessed the prevalence of common bacterial upper respiratory tract commensals and pathogens in the nose and throat swabs of general practice staff and patients attending the GP practice for consultation with non-infectious conditions; and the rate of antimicrobial resistance in organisms isolated. It was not clear whether general practice settings are more like hospital settings, where staff can have a higher risk of carriage of resistant organisms; or more like the community, with staff having similar carriage and resistance patterns to asymptomatic adults. Properly addressing this question will have implications for the sort of infection control practices necessary in General Practice settings.

Anterior nasal and throat swabs were taken from selectively recruited general practice staff and patients who have consented to be part of the sub-study. A total of 125 general practice staff and 125 patients across the practice sites were included.

Various appropriate bacterial media were used to capture both potential pathogens and normal flora. The swabs were cultured on selective media, such as mannitol salt agar and MacConkey agar to screen for *Staphylococcus aureus* and Gram-negative bacteria such as *Klebsiella pneumoniae*, *Escherichia coli, Enterobacter* speciesand *Pseudomonas aeruginosa*.[46] Organisms isolated were further evaluated for resistance to commonly used antibiotics with standard susceptibility testing.[47] Antibiotic resistant organisms also underwent molecular characterisation to look for potential clonality and spread in the community.[48]

2 Rolling out community antibiotic resistance surveillance using sentinel GP practices from the ASPRen network:

The study assessed the feasibility of surveillance of antibiotic resistance in primary care on a national basis utilising the Australian Sentinel Practice Network (ASPReN). ASPReN is a

national network of GPs involved in surveillance activities including influenza. ASPReN identified general practices in their network. Instructions were provided for taking and transporting throat and nasal swabs. Feedback about the feasibility of this surveillance activity was also provided.

The ASPReN network selected 10 GPs from different practice locations across Australia. Each GP identified five different patients and/or health care workers who presented with a non-infectious illness. The GPs obtained consent and collected a throat and nose swab from each patient and/or health care worker. The swabs were processed as described above.

Ethics

Ethical approval was obtained for the study from the University of Queensland (ref: 2015000988). In addition, administrative review was obtained from Bond University and Queensland University of Technology ethics committees. The Department of Human Services has granted approval for consent to be obtained from the GPs to access their Medicare data (ref: MI4140).

The study protocol has been written up and published (appendix 1)

Details of the interventions that were included in the integrated multifaceted package of interventions under evaluation are included in appendix 2.

FINDINGS

Although 28 practices agreed to participate in the study and were randomised to the intervention arm (n = 14) and control arm (n = 14), after randomisation it was discovered that two of the intervention practices were run by the same organisation and that the GPs worked in both practices. For this reason these two practices were treated as a single unit for analysis. Thus there were 13 practices randomised to the intervention arm with 56 GPs consented to participate in the study. In the control arm there were 14 practices with 54 GPs.

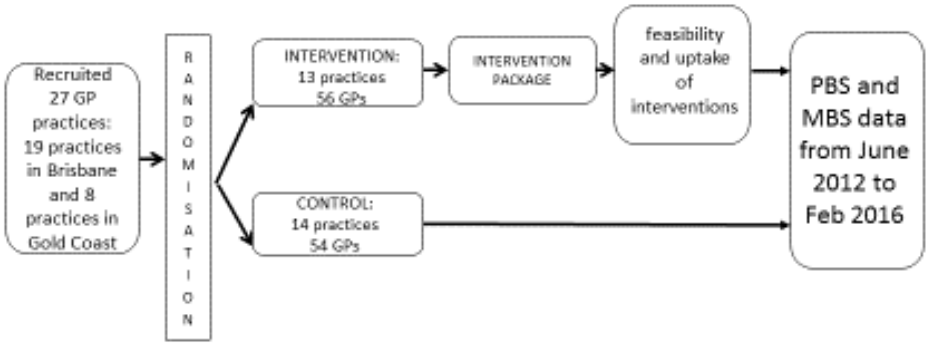

Figure1. Randomisation of GP practices

Characteristics of General Practices and GPs

The GP practices randomised to the intervention or control arm in the study were well matched and the characteristics of the GPs in the control and intervention arms were balanced. (table 1 and 2)

Worksheets were completed by the project staff who interviewed the practice staff to obtain the following demographic characteristics of the GP practices and GPs who participated in the study.

Table 1: General Practice Characteristics

	Intervention n = 13	**Control n = 14**
Practice Structure	**(%)**	**(%)**
Sole Owner	2 (15)	8 (57)
Associateship	2 (15)	0 (0)
Partnership	4 (31)	5 (36)
Corporate Owned	5 (38)	0 (0)
Other	0 (0)	1 (7)
Percentage bulk billing: median (min, max)	70 (30, 100)	78 (26, 100)
Description median (min, max)	**(FTE)***	**(FTE)***
Admin/reception staff	4.5(1,8)	3 (0,8)
Practice manager	1(0,2)	1(0,1)
Nursing	1.7 (0, 4)	1.6 (0, 4.5)
Allied Health	0.65 (0, 8)	1.25 (0.3,7)
Medical GPs	5 (2, 10)	5 (2.5, 9.5)
Patient Appointments		
10 minute standard appointment	6 (46)	4 (31)
15 minute standard appointment	7 (54)	9 (69)
Private patient fee for a standard appointment ($)	70 (62, 75)	68 (25, 85)

*FTE (Full Time Equivalent) = 38 hours per week

Table 2: Characteristics of GPs enrolled in the study

	Intervention	**Control**
GPs in study (n)	**56**	**54**
Female n (%)	26 (46)	24 (44)
Sessions [morning or afternoon] per week; median (min, max)	8 (2, 12)	8 (1, 10.5)

Quantitative Analysis

In Australia the universal health insurance scheme, Medicare, provides access to medical and hospital services for all Australian residents and some visitors. It includes the Medicare Benefits Schedule (MBS) which subsidises the costs of all visits to GPs and medical specialists in non-hospital settings, and the Pharmaceutical Benefits Scheme (PBS) which covers almost all medicines. MBS data include individual records for every government subsidised patient encounter with a GP; GPs were identified by individual provider codes. PBS data include individual records of every prescription dispensed - from July 2012 this covers all prescriptions, regardless of government subsidies. The prescribing GP was identified by an individual prescriber number. There are legislative constraints on linking MBS and PBS records, but de-identified records can be obtained from the Department of Human Services.

For all consenting GPs (in the intervention and control practices) provider records were obtained for each patient encounter billed to the MBS and prescriber records for each prescription reported to the PBS. Each prescription was coded using the Anatomical Therapeutic Chemical (ATC) and those coded J01 (antibacterial for systemic use) are were the outcomes of primary interest. PBS and MBS data from July 2012 were extracted by the Australian Department of Human Services from the Medicare Australia databases on 4th April 2016 capturing all available data at that time (35 days after the end of the intervention period in order to insure that almost all claims had been processed by Medicare). The data include services and medications that qualify for Medicare Benefits Schedule and for which claims have been processed. They do not include services or medications supplied privately or under the Department of Veterans' Affairs National Treatment Account.

MBS and PBS data for all 110 participating GPs were analysed for 39 months prior to the intervention – called the “baseline phase” (1st June 2012 until 31st August 2015), and 6 month during the intervention – called the “intervention phase” (1st September 2015 until 29th February 2016).

MBS data contained 1,483,008 claims for 370 different types of medical benefits. 61 medical benefits which represent all types of consultations that can result in GPs issuing prescriptions for the patient were selected. Other claims for medical benefits such as mental health consultations, maternity care, after surgery consultations, eye/ear/blood tests etc., were removed.

A total of 2,948,619 medications were dispensed during the study period. Each prescription included the Anatomical Therapeutic Chemical (ATC) code.

Details of the inclusion and exclusion criteria that were applied to these records and the data limitations are given in Appendix 3.

The primary outcome of interest was calculated by counting all oral antibiotic coded J01 (antibacterial for systemic use) supplied to patients from original prescription forms prescribed by each GP per month. A report of the types, percentages and delays of dispensing oral antibiotics is in Appendix 4.

The cost of each supplied antibiotic was calculated utilizing Dispensed Price for Maximum Quantity (DPMQ) as extracted from PBS website after the latest price disclosure on 1st April 2016. It was not possible to split the cost into government and patient contributions because these separate components were not included in the extracted data. The mean aggregate cost of all supplied antibiotics was $13.55 (S.D. = $2.61)

The following steps were taken to merge the PBS and MBS datasets:

1- All PBS items supplied to patients using original prescription forms were identified by provider ID and date of prescribing. Other benefits supplied using repeat prescription forms or for doctor's bag items were excluded. Each day's record for each provider included the date, count of number of antibiotic prescriptions (the main outcome) and total number of all medications prescribed (a measure of provider's daily activity).
2- All MBS items supplied to patients were identified by provider ID and date of service. Thus the record for each day for each provider included the date and count of medical benefits supplied (another measure of the provider's daily activity).
3- Data were merged line to line by utilising provider ID and date of service as key matching variables.
4- Daily counts were aggregated to monthly counts for each provider.

Matching the MBS and PBS data for the same GPs either by the day the prescription was written, or for longer periods, identified prescriptions written on days with few or no MBS claims and other implausible results. Likely reasons include mismatch of provider and prescribers numbers because GPs did not provide all their provider numbers on their onsent forms, prescriptions requested by phone without a GP visit, and GP visits that were not bulk-billed and for which there was no claim for reimbursement. To reduce the effect of the anomalies on the robustness of the results several additional exclusion criteria were also used (see Appendix 5). Additionally analyses were repeated with and without using various

exclusion criteria and using different study periods to check the effects on the results; these are all presented in Appendix 5.

As another approach to overcoming the problems apparent from using the MBS data we also analysed the numbers of PBS prescriptions for antibiotics as a proportion of all (non-repeat) prescriptions written by the same GP during the same period (e.g. day or month). The advantage of this approach was that all the data were from the same source, PBS, and few anomalies were apparent. All results are presented in two ways:

- Antibiotic prescriptions per 100 MBS claims.
- Antibiotic prescriptions as a percentage of all non-repeat prescriptions.

Crude prescription rates were compared between the baseline and intervention phases and between the intervention and control groups. Adjusted prescription rates were estimated using generalised linear models with a negative binomial link for the number of antibiotic prescriptions per GP in a specific period (e.g., day or week) with the number of MBS claims (or total number of non-repeat prescriptions) for that period and GP as the off-set (i.e., measures of activity or 'exposure'). The explanatory variables were included in the model to account for: intervention vs control practices; baseline and intervention periods; and temporal variables to account for secular trends and seasonal effects. The models are multi-level to account for nesting of patients within GPs and GPs within practices. Table 3 shows that the numbers of antibiotic prescriptions per 100 MBS claims. For both time periods the crude prescription rates were slightly lower in the intervention group than in the control group. The crude rates declined in both groups during the 6-month period of the study compared to the previous 39 months. However this could be affected by seasonal factors as the trial was conducted in September-February, a low ARI period.

Table 3. Comparison of numbers of antibiotic (AB) prescriptions, MBS claims and AB prescriptions per 100 MBS claims in the intervention and control groups based on data matched by month.

	Baseline phase (June 2012 - Aug 2015)				**Intervention phase (Sept 2015 - Feb 2016)**			
	GP-month	AB	MBS	AB/MBS x 100	GP-month	AB	MBS	AB/MBS x 100
Control	1,440	80,111	536,759	14.92	254	11,378	90,565	12.56
Interventions	1,309	68,654	495,433	13.86	252	11,643	96,107	12.11

The crude and adjusted rates (taking account of seasonal effects and the grouping of GPs within practices and patients within GPs) are shown in Table 4 below. The change was very similar in both groups. The ratio of change in the intervention group to the change in control group was RR=1.03 (95% confidence interval 0.98, 1.08).

Table 4. Crude and adjusted rates and rate ratios for antibiotic prescriptions divided by MBS claims; crude rates based on the data in Table 4.

	Intervention	Control	Intervention/Control (Rate Ratio RR and 95% confidence interval)
Baseline phase (crude rate)	0.1386	0.1492	
Intervention phase (crude rate)	0.1211	0.1256	
Intervention/Baseline phase (crude RR)	0.874	0.842	**1.04 (1.01, 1.07)**
Intervention/Baseline (adjusted RR)	0.900	0.877	**1.03 (0.98, 1.08)**

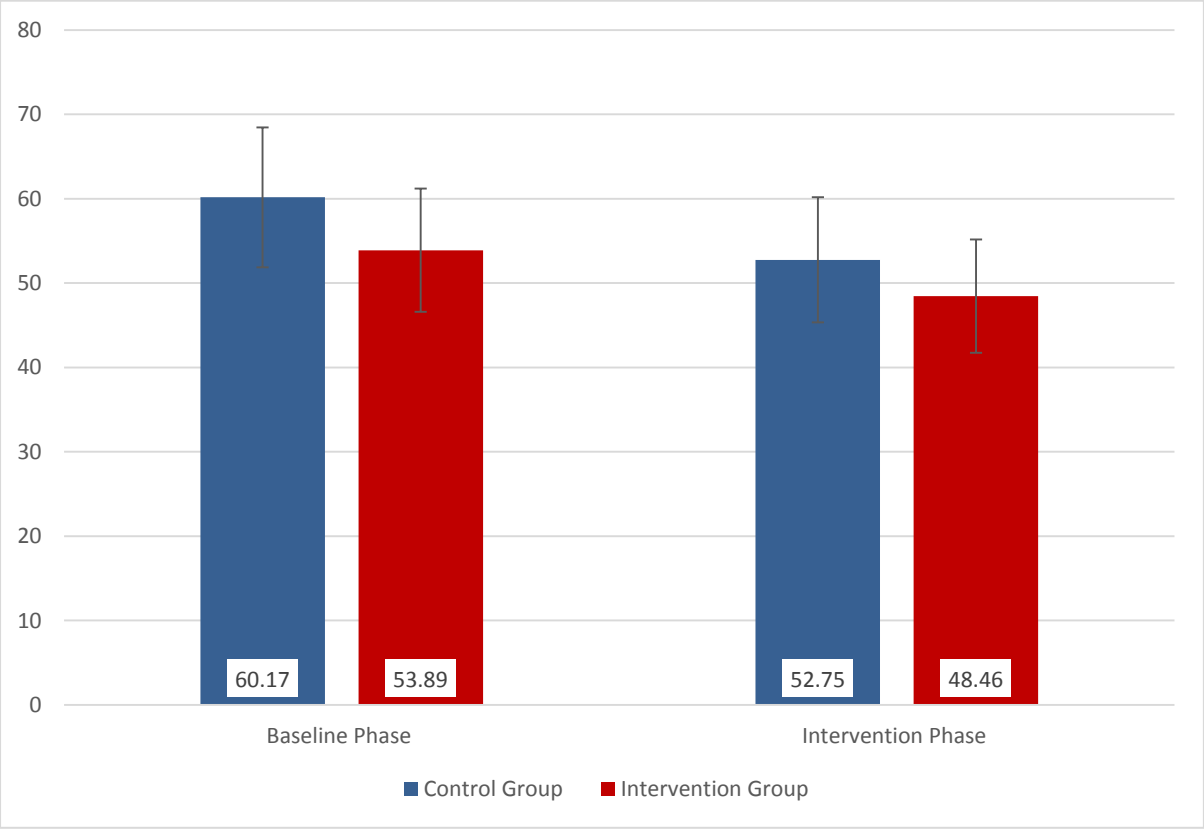

Figure 2. Estimated mean number of monthly antibiotic prescriptions per GP for each group in the baseline and intervention phases

The estimated mean count of monthly antibiotic prescriptions per GP for each group in the baseline and intervention phases is shown above in Figure 2. This graph is based on the model adjusted for seasonal and other effects. Small declines in antibiotic prescriptions are apparent over time but they are very similar in both groups.

Table 5 below shows that the (non-repeat) antibiotic prescriptions as a percentage of all (non-repeat) prescriptions also declined in both groups during the 6-month period of the study (intervention phase) compared to the previous 39 months (baseline phase). But the change was slightly larger in the intervention group.

Table 5. Comparison of numbers of antibiotic (AB) prescriptions, total prescriptions (PBS) and AB prescriptions as a percentage of total prescriptions in the intervention and control groups based on data matched by month

	Baseline phase (July 2012-Aug 2015)				**Intervention phase (Sept 2015-Feb 2016)**			
	GP-month	AB	PBS	AB/PBS×100	GP-month	AB	MBS	AB/PBS×100
Control	2,067	110,425	553,748	19.94	324	14,470	75,038	19.28
Intervention	2,042	106,443	548,661	19.40	331	14,435	81,377	17.74

The extent of the difference is shown in Table 6 with estimates using the crude rates and adjusted rates obtained from the model which included seasonal and other effects. These results confirm a clear and statistically significant effect: RR= 0.93 (0.89, 0.97). This equates to a 7% lower prescribing rate in the intervention compared to the control practices.

Table 6. Crude and adjusted rates and rate ratios for antibiotic prescriptions divided by all (non-repeat) prescriptions; crude rates based on the data in Table 6

	Intervention	**Control**	**Intervention/Control (Rate Ratio and 95% confidence interval)**
Baseline phase (crude rate)	0.194	0.199	
Intervention phase (crude rate)	0.177	0.193	
Intervention/Baseline (crude rate ratio)	0.914	0.967	**0.95 (0.92, 0.97)**
Intervention/Baseline (adjusted rate ratio)	0.943	1.012	**0.93 (0.89, 0.97)**

This effect is illustrated in Figure 3 (below) which shows the estimated mean number of antibiotic prescriptions per GP per month for each group in the baseline and intervention

phases calculated from the model adjusted for seasonal and other effects. In the intervention group the antibiotic prescriptions rate decreased from 55.66 per GP per month during baseline phase to 52.53 antibiotic prescriptions per GP per month during the intervention phase. For the control group the mean number of antibiotic prescriptions per GP dispensed per month was 54.82 during baseline phase which increased to 55.50 during the intervention phase. The nett difference in number of prescriptions per month per GP for the intervention group compared to the control group was 3.8.

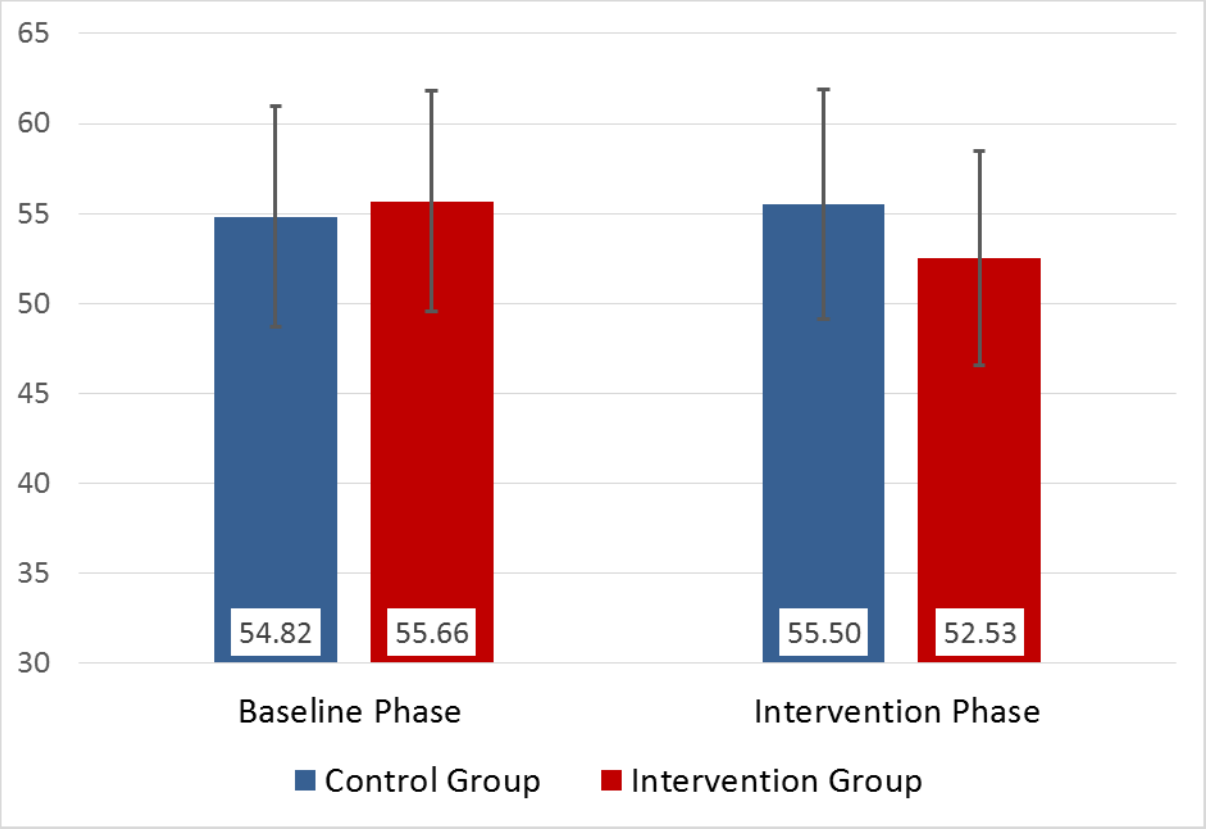

Figure 3. Estimated mean number of monthly antibiotic prescriptions per GP for each group for the baseline and intervention phases estimated from the model adjusted for seasonal and other effects.

Interpretation

The short GAPS intervention period, over summer when ARIs are less common, meant that it was especially important to take seasonal effects into account. These were estimated from data obtained for the period of more than 3 years before the study began. Similarly it was possible to estimate the background trend of declining rates of antibiotic prescriptions.

The results show that rates of antibiotic prescriptions were declining in both the intervention and control groups from a period before the study began. The decrease continued over the study period.

By one measure of the outcome, which attempted to link MBS with PBS data, there was no statistically significant difference between the intervention and control groups during the intervention period. However there were unexpected limitations in using the MBS data. There was evidence of mismatches between the provider numbers used to extract the MBS data and the prescribers numbers used to extract the PBS data. For example, some GPs had periods with no MBS claims for reimbursement for GP visits but many PBS records of prescriptions written during these periods. Similarly there were periods with unusually high or unusually low prescription rates.

There are several possible reasons for these discrepancies

- GPs provided correct prescriber numbers (which are unique to each doctor and consistent over time) but did not necessarily provide all their relevant provider numbers (which relate to the practice where they are working).
- Some prescriptions may have been provided following phone calls rather than patient visits
- Some GP visits were not bulk-billed and the patient had to contact Medicare for reimbursement. However the request for reimbursement may not have occurred or had been delayed, resulting in no MBS record.

As a consequence of these limitations in the MBS data an alternative analysis was undertaken. This used data from just from one source, PBS, with the total number of (non-repeat) PBS prescriptions as the measure of GP activity. With this more robust approach, there was a clear and significant 7% reduction in the rate of antibiotic prescribing between the intervention and control practices, which equated to a nett difference of almost 4 fewer antibiotic prescriptions per GP per month.

This finding was robust in numerous sensitivity analyses (see Appendix 5).

Qualitative Analysis

Semi-structured telephone interviews were conducted with the GPs from the intervention practices after the intervention phase of the study. Questions focused on the acceptability and feasibility of the interventions, including the near patient testing (CRP study) in the practice and perceived impact on the management of ARIs. All participating GPs, who were allocated to the intervention arm of the study, were invited to participate in an interview to share their perception and experience in using the intervention tools. The interviews focused on the acceptability and feasibility of the interventions, perceived impact on the management of acute respiratory tract infections, and the management of the program.

GPs were interviewed in two phases. Phase One (November – December 2015): interviews of GPs who tested the CRP machine from September to November 2015; Phase Two (March 2016): interviews of GPs who tested the CRP from December 2015 to February 2016.

All participants were interviewed by telephone and followed an interview guide, which was informed by a similar study.[49] The method of a semi-structured interview was used in this study to ensure important dimensions of the interventions were covered. Participants also had the opportunity to discuss and raise further issues or concerns.[50] In general, interview questions explored which elements of the intervention were found useful and why, which elements GPs thought to have changed practice, and which parts of the intervention could be improved.

All Phase One interviews were digitally recorded and transcribed verbatim by the interviewer. The transcripts were then analyzed using the method of inductive thematic analysis.[51] Two researchers (LD and CWL) independently coded the interviews. The themes identified were then compared with differences considered and resolved through discussion between the two researchers.

Preliminary findings of Phase One were used to refine the interview schedule in Phase Two. A single researcher (LD) then conducted the Phase Two interviews and used the resulting thematic framework from Phase One to code the new data.

Findings

In total 46 GPs were interviewed. Nineteen of them were interviewed in Phase One (November - December 2015) and 27 GPs were interviewed in Phase Two (March 2016). The mean duration of the interview was 11 minutes (SD = 3.32).

Major findings from the interview are summarised and discussed in the following four themes:

1. perception of over-prescribing
2. reception of the interventions
3. impact on practice
4. feedback on specific tools

These themes are discussed in more detail below.

1. Perceptions of over-prescribing

GPs agreed that too many antibiotics are prescribed. Although the interview focused on the feasibility and acceptability of the intervention, some GPs commented on possible causes of over-prescribing antibiotics. Reasons for over-prescribing were patients' misconceptions and pressure, and the fee-for-services system in contrast to a bundled or capitation payment system.

> GP4, female, 22 years of experience: *"the reason GPs prescribe antibiotics more often than they probably should is because of patient pressure, you know it's actually the patient's expectation and then the GP ends up succumbing to that."*

> GP16, male, 20 years of experience: *"it's a sort of balance between what the patient is expecting and demanding versus what we think they need, plus we have the issue of running as a business, if the patients are dissatisfied with what they get at the end of a consultation, they are likely to just go to another practice and try again until they get what they want"*

Other reasons for over-prescribing were prescribing by other doctors or out-of-hours services, and fear of litigation.

Participants mentioned that education of patients is important, and that we should target certain populations specifically, such as older people, who may have been prescribed antibiotics for the same symptoms. Also parents of young children often demand antibiotics as a result of the child-care centre regulations.

> GP2, male, 8 years of experience: *"it's about changing general perceptions and then the rest becomes easier later on."*

GP36, male 32 years of experience: *"certainly amongst the younger population they are more educated about antibiotic usage, whereas the older population they just have expected that over the years if they don't get one they think there is something wrong, so you know it's the patient group."*

GP23, female, 8 years of experience: *"parents will bring this you know green snotty nose, you know germ-factory in and they'll say "day-care say is they can go back in if they are on antibiotics" and you look at them and you know it's clearly like a rhinovirus, it doesn't need antibiotics it needs to be kept away from the other children."*

Some GPs also mentioned that there are several barriers to patient-education (e.g. short consultation time or busy practice).

GP4, female, 22 years of experience: *"so for the future, we can try and re-educate and re-train the patient's way of thinking. It takes a long time, it takes more than standard consultation, longer than a standard consultation to educate a patient and try to convince them away from the inappropriate use of antibiotics."*

2. <u>Reception of the interventions</u>

Overall the interventions were well received and GPs welcomed the tools that they thought help convince, reassure and educate the patients about the use of/need for antibiotics. Also the patient's reaction to the interventions was perceived to be positive. In this respect GPs mentioned that patients really appreciated the extra explanation and the fact that inappropriate prescribing may affect them personally, rather than it being 'just' a global problem.

GP13, female, 14 years of experience*: "I've actually really enjoyed it* [being part of the study]. *Like I'm so big on the appropriate antibiotic prescribing and it really annoys me how many antibiotics are given out inappropriately."*

GP10, female, 7 years of experience: *"I think most patients were pretty positive about it* [i.e., the use of the tools] *and they found some of the statistics about the number needed to treat and the number needed to harm very helpful, I think it helped them to know that you are not just avoiding antibiotics for you know some global process, but that it actually you know – overall was better for them."*

Some GPs mentioned that the interventions were probably better suited for younger doctors and in this respect many doctors also stated that reducing the prescribing of antibiotics was already high on their agenda – *"you're preaching to the converted"* (GP016, male, 20 years

of experience) – and thus the interventions may not have had an effect on their prescribing behaviour. Nevertheless, the GPs often mentioned that the interventions were reinforcing and that it was nice to have several tools to choose from to help convince the patient.

> GP9, male, 19 years of experience: *"yeah it's reinforcing but it hasn't really changed what I do because it is something we are already doing."*

> GP13, female, 14 years of experience: *"I didn't find a big difference between what I am trying to do every day and being part of the study, it was just that I had these little aids to use, which I found useful."*

As barriers to the use of the resources, GPs mentioned that they were not used to the interventions and that it takes time to change their habits and to integrate these tools in their practice. Furthermore, GPs often felt that this study, but also other campaigns in general, focus too much on not prescribing antibiotics rather than appropriate indications for prescribing.

> GP25, male, 2 years of experience: *"it seemed that a lot of the focus of the study was on how to not give antibiotics and it seems like not giving antibiotics is like a win but I guess that's not always the case. The thing I would have appreciated is some discussion about appropriate settings to give antibiotics."*

3. Impact on practice

Overall, the availability of several interventions to choose from was perceived as a positive aspect of the study:

> GP2, male, 8 years of experience: *"it's a nice thing to have in the armoury."*

> GP30, female, 13 years of experience: *"because I had all this material at my fingers I could persuade them that they didn't need it [antibiotics]."*

Some GPs mentioned that the interventions did influence their behaviour to a certain extent. For example, the interventions made them think twice about prescribing, and tools like Patient Decision Aids and patient information leaflets were deemed helpful in communicating with patients. The interventions helped in convincing, reassuring and educating patients about the use of/need for antibiotics.

> GP12, female, 14 years of experience: *"I would think more before giving the patient antibiotics, that's the main thing."*

GP10, female, 7 years of experience: *"I thought that it was helpful in terms of having a few extra tools to help remind […] that they don't always help, that they can do more harm than good, and also just having some of the prompts to help sort of drive the point home was quite helpful."*

GP13, female, 14 years of experience: *"I think that patients appreciate the explanation, so I think if you can give them the information and especially if you can show them something visually like the smiley faces and things like that I think it actually does get through, I think they actually appreciate the explanation...."*

However, there was no clear preference for a specific tool in the intervention package among participants. GPs rarely used all the tools provided to them. Instead, they selectively used interventions that fitted their own communication style or the needs of the patient (e.g. CRP test and Patient Decision Aids were often used for difficult patients only as a tool for convincing them). The "one size fits all" does not seem applicable in this context and the diversity of tools in the intervention package was seen as an important strength of the study:

GP1, female, 8 years of experience: *"I think the strength of the project is that they gave us a sweep of tools and you can pick and choose which you liked, so it is not one size fits all … whereas if it would only have been the decision tool then I would have probably zoned out fairly quickly."*

The majority of GPs said that their consultation time remained the same with the use of the interventions, but some GPs admitted that they would not allow their consultation time to be affected. Two GPs even thought the material helped to speed up the consultation.

GP20, female, 2 years of experience: *"I think it was the same or less. I got to the point more quickly than previously."*

4. Feedback on specific interventions

As GPs used the interventions that suited their own preferences, their opinions on the specific interventions were quite diverse, with each intervention eliciting both positive and negative reactions.

4.1 Poster on Practice Antibiotic Prescribing Policy and Patient Information Leaflet

The poster and Patient Information Leaflet targeted the patient's perception on antibiotics rather than the prescribing behaviour of the GPs. Therefore GPs were not in the position to judge the impact of the posters and Patient Information Leaflet. Nevertheless the majority of GPs were happy to have the extra material in the waiting rooms.

Only a handful of GPs received feedback from the patients and mentioned that the patient's reaction to the poster or Patient Information Leaflet was positive. One GP mentioned that it impacted on his consultation because the patient was already informed about antibiotic prescribing, which made it easier for him to get the point across:

> GP14, male, 18 years of experience: *"The good thing about it is that I could talk to patients because they had already seen the poster so when educated they accepted more than if they are not educated at all."*

4.2 Online communication training

Twenty-one out of 46 GPs completed the online communication training. Their feedback was generally positive. They mentioned that the module was reinforcing but maybe more suitable for GP registrars as it was demonstrating what the GP already knew. However, one GP found that the online training increased her confidence not to prescribe:

> GP20, female, 2 years of experience: *"I think that that's where I've got the confidence […] it just somehow made it seem like "right we're serious about it we are doing it" that was just permission to go ahead."*

One GP found the communication examples too patronizing:

> GP23, female, 8 years of experience: *"I didn't like it. I found it was sort of encouraging you to talk to the patient like they were an idiot and you know using lots of small words and lots of feeling words like "I understand that you have a cough is that something that you are concerned about" off course they are concerned about it, that's why they came to see you. So yeah it was a bit patronizing."*

4.3 Delayed prescribing

The majority of GPs found the delayed prescribing stickers useful. Some were already using the principle of delayed prescribing before the study, but they agreed that the sticker was a good eye-catcher and probably more effective than a hand-written note on the script.

> GP31, male 8 years of experience: *"I was using the principle already, but I think actually having the formal stickers to put on the script – I think that helped reinforce to the patient. It made it look formal so it made it look like it was a standardized sort of procedure, so I think a lot of the patients were a lot happier with it."*

One GP also mentioned that patients appreciated the delayed prescribing because it provides them with a safety-net.

> GP25, male, 2 years of experience: *"I think patients appreciate the delayed prescription, knowing that there is an option there like there is a bit of safety net but at the same time that we do not want to overdo things, I think they like that."*

The only concerns some GPs expressed was that they were not able to judge the actual effect of using the delayed prescribing strategy or whether the patient is able to judge when it is necessary to start the antibiotic.

> GP16, male, 20 years of experience: *"I don't know how many of those patients don't immediately go out and get the antibiotic anyway."*

> GP42, female, 32 years of experience: *"I still have concerns about it, I am not really sure how the patient has the insight to recognise when it is time to start the antibiotics. The concept of giving the patient a prescription and saying "if you are not better in three days then start taking the antibiotic", is not necessarily to me a good way of practising, I would prefer to review the patient to decide if they need antibiotics."*

4.4 Patient Decision Aids

The Patient Decision Aids were not often used in practice, some GPs found them too childish (charts displayed smiley faces) and only used them for specific patients. Nevertheless, the evidence supporting the Patient Decision Aids was deemed useful and used in their communication with patients.

> GP10, female, 7 years of experience: *"I haven't used them heaps and heaps, but I found just going through it and just getting sort of the general idea myself and just kind of verbally telling them how many people wouldn't be harmed and how many would be helped was helpful. I have pulled it out for some patients where I felt it would be useful for them to actually physically see that."*

One GP mentioned that it increased her confidence, because she had the Patient Decision Aids as her backing:

> GP20, female, 2 years of experience: *"the fact that I knew it was there, you know I knew I had this backing, I had something tangible backing what I was saying, but then once I started perhaps saying it more confidently"*

In contrast, one GP was worried that the Patient Decision Aids actually highlighted the fact that there was a difference.

> GP1, female, 8 years of experience: *"if that's a half day earlier at work and half a day not missing out on pay – then the choice of having antibiotics would often tend to having antibiotics for the patients."*

4.5 CRP point of care testing

Especially for the CRP test there appeared to be groups of believers and non-believers. About half of the GPs found the CRP-test useful whereas the other half were not convinced of its added value. This seemed mostly determined by the GPs' pre-existing beliefs about the value of the CRP test. Other reasons for not using the CRP test were that it increased consultation time, the impression that doctors are already using too many tests, and that they should rely on their clinical judgment rather than a machine.

The majority of GPs who were not convinced of the potential value of the CRP test never used it and did not go through the extra educational material. For example, the following GP did not use the CRP-test because she thought it would have no impact on her clinical decision-making and she found that it would be time-consuming:

> GP19, female, 2 years of experience: *"I mean it is largely a clinical sort of decision, rather than based on a number, you know someone that's unwell the CRP is probably gonna be high anyway. It is time as well definitely, but it is not really gonna change what I do necessarily."*

A minority of GPs didn't use the CRP test because they work part-time and missed the educational session. Also, they did not think about using the CRP test, as they rarely saw patients with acute respiratory tract infections.

> GP42, female, 32 years of experience: *"because I have been in practice for a long time, I don't get to see a lot of the acute respiratory infections, it's mainly the younger doctors who aren't booked up ahead who get to see the acute respiratory infections."*

However, about five GPs did go through the educational material, but were not convinced of its value because the CRP readings did not always correspond to the clinical picture. In this respect, one GP found that the cut-off scores for the CRP results were inappropriate.

> GP29, male, 17 years of experience: *"if the reading was high but they did not look that unwell, I still wasn't convinced they needed to use antibiotics or if it was vice*

versa sometimes if they were clinically quite unwell, but the readings didn't correspond to that so."

GP35, male, 37 years of experience: *"I just felt that the criteria for using the information that came from testing the CRPs, I thought it was quite inappropriate. In my experience a CRP over 50 would indicate a quite serious infection, long past when you would be talking about antibiotics, and they were talking about CRPs of 100, a CRP of 100 normally is a patient who is in hospital so a very serious condition, so I didn't find this appropriate."*

The GPs who found the CRP-test useful generally used it to convince or reassure the patient, whereas only a minority found it helpful in their clinical decision-making.

GP14, male, 18 years of experience: *"The CPR test was reassuring for the patient and when I did the test I convinced a few patients not to have antibiotics."*

Amongst this group, the views on the time needed to conduct a CRP-test were also very diverse: some said it did not affect their consultation time at all, while others said it did.

Furthermore, some GPs mentioned that the CRP-test might be especially useful in more remote settings.

GP33, female, 5 years of experience: *"Yes really useful…. especially here, as we are a bit far from the hospital, that you have sometimes these borderline patients that you are not sure like – hmm is it serious or is it really serious."*

Interpretation

Overall the intervention package was well received by the participants. It was considered adaptable to individual practices and provided GPs with the opportunity to reflect on their management of patients with ARIs. The package was practical and complemented the consultation process and GPs welcomed the interventions, which helped them to convince, reassure and educate the patients about the use of, or need for antibiotics. An important advantage of the intervention package was that the "one size fits all" principle was not applied and that the GP was able to choose from a range of interventions depending on his/her consultation preferences and the patient at hand.

Our findings are in line with the large European study, GRACE INTRO (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe INternet TRaining for antibiOtic use), which used similar tools and also found that these were perceived useful in negotiating with the patient.[49] The GRACE INTRO study however, showed that the

intervention increased GPs knowledge and confidence in diagnosing an infection. In the current study the participants did not express this as clearly. The intervention was mainly found useful to convince and reassure the patients.

This might be explained partly by the different perceptions on the CRP test; it seemed that participants of the current study were more critical about the usefulness of the CRP-test. In line with previous studies, GPs addressed concerns about accuracy, misleading results, and over-reliance on diagnostic tests.[52] [53]Nevertheless, those who did use the CRP test, thought it was useful for the same reasons as reported in the GRACE INTRO study; a tool to decrease diagnostic uncertainty, to support non-prescription decisions, and to reassure patients [49]. Furthermore, it was acknowledged that it takes time to change habits and to integrate these tools into the GPs' practice. In this respect it was shown that also in the UK, clinicians were initially sceptical about the use of point-of-care tests and experienced problems using them in practice, but that these issues diminished with increasing experience in using the tests.[54]

This qualitative study incorporated the views of 46 out of 56 participants of the intervention arm. Nevertheless, this study is not without limitations. For example, the intervention phase of the study was conducted during the summer months from September 2015 to February 2016. As such, GPs did not encounter as many ARIs compared to the winter months – often referred to as "flu-season". This might have hampered the GPs' opportunity to incorporate the tools into practice. For example, the CRP-test was only available for three months and some GPs mentioned that in that period they did not see any patients to use it with. These were mainly older GPs who acknowledged that they were usually fully booked well in advance and therefore rarely saw patients with acute diseases such as ARIs. Nonetheless, the timing of the study might have affected the uptake of the different interventions.

Another limitation of the study is that interviews were conducted via telephone as opposed to face-to-face. This results in the loss of contextual and nonverbal information. Nonetheless, telephone interviews may allow participants to feel relaxed and able to disclose sensitive information, and there is no evidence indicating that they produce lower quality data compared to face-to face interviews.[55]

Economic analysis

We estimated the cost of delivering GAPS from a health system perspective. We used costing worksheets to collect data on the resources directed to the project both at the centralised level and the practice level. Resources were grouped into five categories: centralised project staffing, practice staff time, consumables, communications module training (CMT) and C-Reactive Protein (CRP) machine training and usage.

Centralised resource use data was collected by the Project Manager over the course of the trial on a centralized spreadsheet. Practice staff time and usage of consumables was estimated retrospectively based on interviews with project and practice staff and a review of project management and financial records. 46 GPs were interviewed directly to estimate time allocated to CMT and CRP training, estimates for 2 GPs were provided by the practice manager. For the remaining 8 GPs we estimated their time allocation as the mean of the other GPs.

Centralised staffing costs were valued based on employee salaries including superannuation. Consumable items were valued in 2015 AUD based on expenditure detailed in project accounting records, or (where items had been provided free of charge for research purposes) based on quotes from the relevant industry supplier.

CMT costs were estimated considering the licensing fees for the material and costs of annual updates to the educational material. As there is no fee for licensing if hosting on an existing server, this cost was estimated to be zero. The cost of annual updates to the communications module training materials was estimated to cost $5000/year (communication with Professor Lucy Yardley (April 2016), a key developer of the communications training module).

CRP machine rental costs were based on a quote provided by Abacus ALS in March 2016 for ongoing usage of machines as a government or health service initiative. The quote provided was for a yearly rental agreement without ownership at the end of the rental term and included warranty, training, test kits, control vials (for machine calibration), freight and GST. Practices only had access to the CRP machines for 3 months rather than the full 6, we assumed that usage would remain constant over time, so estimates of usage and staff time for testing were doubled to give a 6 month estimate.

Staff time was valued according to professional salary rates as reported in national surveys.[56, 57] Where necessary figures were adjusted to 2015 prices using the Australian

Bureau of Statistics Consumer Price Index specific to Health.[58] Salary rates used are presented in Table 7 and reflect annual gross salaries (excluding bonuses, allowances and superannuation) as reported by practitioners. To derive hourly rates, the gross salary for each professional group was divided by 52 weeks and then by the reported average number of weekly working hours (full time equivalent), which was 39.4 for GPs, 38.84 for practice managers, and 36.25 for other practice staff.

Table 7. Average annual gross salaries used for valuation of practice staff time

Staff member	Average annual gross salary	Average hourly rate
General practitioner	$247,257	$120.68
Practice manager	$77,500	$38.37
Practice nurse	$67,500	$35.81
Administrative assistant	$47,500	$25.20
Receptionist	$42,500	$22.55

The cost savings from reduced prescribing were estimated at $13.55 per original prescription as per the average prescription cost in our dataset.

We estimated the cost-effectiveness of GAPS from the perspective of the health system. To allow comparison with other prescribing interventions described in the literature we calculated the cost per practice and per GP included in the intervention, as well as the cost per % reduction in prescribing and the cost per prescription avoided. For the latter analyses, we used results from the quantitative analysis based on comparison of antibiotic prescriptions as a percentage of total prescriptions (PBS data as denominator) as these data were believed to be a more valid measure of changes in prescribing patterns.

We built an economic model to estimate the net monetary cost of GAPS. The model was built in Microsoft Excel. All parameter estimates used in the model were assigned appropriate distributions (beta for probabilities, gamma for costs and time allocations, lognormal for relative risks) and probabilistic sensitivity analysis was used to capture uncertainty in the results arising from sampling error in the underlying data. This allows us to present results as an estimate of the net monetary cost of GAPS with 95% confidence intervals.

In our baseline scenario the net monetary cost of the intervention was estimated as the cost of delivering GAPS minus the cost-savings from reduced prescriptions (estimated from the quantitative analysis). A number of scenario analyses were then run to test assumptions

made in the model. First we modelled 2 different scenarios for the valuation given to practice staff time. We included a scenario where a higher valuation was placed on GP time. Instead of basing the valuation on wage rates, we based it on the Medicare Level B consultation rate of $37.05. In our intervention practices, 7 operated 15 minute standard appointments, whilst 6 operated 10 minute standard appointments. To give a maximum estimate for the value of GP time we assumed a 10 minute standard appointment time to give an average hourly rate of $222.30 for GP time. We also included a scenario where no value was placed on practice staff time. This is akin to only considering the financial expenditure on GAPS, so could be thought of as representing the economic perspective of the Department of Health if no incentive payments are provided to practices.

We looked at four other scenarios where we modelled additional cost savings from GAPS beyond the number of original prescriptions avoided. In the first scenario we included the additional cost savings from repeat prescriptions avoided based on observation that 21% of prescriptions in our dataset were repeats. We conservatively assumed that repeat prescriptions were for only a single repeat and valued these repeats at the same cost of original prescriptions ($13.55).

The second scenario included additional cost savings from antibiotic related adverse incidents. Based on the findings of a recent meta-analysis[59] we included three common adverse incidents associated with use of amoxicillin and amoxicillin-clavulanic acid; diarrhoea (19%), candidiasis (4%) and rash (4%). We also included diarrhoea in association with macrolides (14%)[60] and cephalexin (4%).[61] Adverse incidents potentially associated with other antibiotic classes were not considered due to the absence of rigorous data to estimate their occurrence. We applied these adverse incident probabilities to the proportion of prescriptions observed in our dataset for amoxicillin and amoxicillin-clavulanic acid (38%) and macrolides (16%) to estimate the number of adverse incidents avoided due to reduced prescriptions. The value of these adverse incidents was estimated from the perspective of the health system as requiring one additional GP Level B consultation ($37.05). Under the health system perspective used for our analysis we did not include patient out-of-pocket costs, lost productivity or additional morbidity associated with these adverse incidents.

In the third scenario, we included the cost savings from avoided cases of antibiotic associated *Clostridium difficile*, based on data from the international scientific literature. We used data from a recent meta-analysis[62] to estimate the risk of community-associated *C. difficile* associated with exposure to antibiotics in the primary care setting. We valued each case of *C. difficile* based on assumptions made from the epidemiological literature that 60% of cases would be managed in the primary care setting, 40% would require hospitalisation,

and of those hospitalised half would have severe infections.[63] The cost of *C. difficile* infection was based on Australian treatment guidelines and healthcare costs. The cost of diagnosing infection was estimated at $28.65 based on the MBS rebate. Antibiotic treatment costs were sourced from PBS and calculated using regimen guidelines in ASID guidelines for management.[64] We assumed non severe cases managed in the primary care setting were assumed to require an additional GP Level B consultation and receive oral metronidazole at 400mg 3xdaily for 10 days at a cost of $20.38. Non-severe cases managed in hospital were assumed to spend 4 days on a general medical ward at a cost of $800 per day,[65] and receive oral metronidazole. Severe cases were assumed to spend 4 days in ICU at a cost of $3,000 per day,[63] and receive oral vancomycin at 125mg 4xdaily for 10 days at a cost of $462.50.

In the fourth scenario we included the additional cost savings from avoided repeat prescriptions, avoided adverse incidents and avoided cases of *C. difficile* to give an overall estimate of the efficiency of GAPS.

We did not include a scenario where we included the cost of harms such as increased disease severity or duration due to “missed cases” from non-prescribing, as previous studies have found no increase in these events following reductions in prescribing.[5] We also did not include a scenario where we attempted to predict the impact of reduced prescribing on rates of resistant infection as current literature does not allow us to accurately quantify this relationship. This is covered further in the discussion.

Finally we undertook an exploratory analysis, estimating the cost and cost-effectiveness of running GAPS over a three year time frame in the original 13 practices (with 56 GPs), assuming that the ongoing levels of resource usage in months 2-6 of the trial were maintained for the three year period and that the same impact on prescribing was maintained. We also modelled a scenario where GAPS was rolled out on a larger scale to 250 practices (assuming 1075 GPs based on the average number of GPs per practice observed in GAPS). For this scenario we assumed that we achieved the same impact on prescribing, that only 1 project manager was required to run the scaled up model of GAPS, and that resource usage for each practice was equivalent to the average start up and ongoing monthly investment per practice as observed in the GAPS trial.

Table 8. Resources used in the GAPS 1 month engagement and 6 month intervention phase

Cost Group	Staff / consumables	Number of Units	Total Cost	Average cost per practice	Cost Standard deviation
Centralised GAPS Staffing	GAPS project manager	7 months	$81,031.6	$6,233.2	-
	GAPS project coordinators - implementation phase (Aug-Sept)	492.2 hours	$29,635.3	$2,279.6	-
	GAPS project coordinators - maintenance phase (Oct-Feb)	657.9 hours	$39,612.1	$3,047.1	-
	SUB-TOTAL		**$150,279**	**$11,560**	
Consumables	GAPS staff travel	-	$3,646.3	$280.5	-
	Laptops	5	$7,500	$576.9	-
	Project website (inc. maintenance and hosting)	1	$2,000	$153.9	-
	Mobile phone expenditure	5x7 months	$350	$26.9	-
	Consumables (Initial engagement lunch, leaflets, stickers, patient decision aids, posters)	-	$1,558.6	$119.9	43.6
	SUB-TOTAL		**$15,055**	**$1,158**	**-**
Communication training	GP time - training	1076 mins	$2,163.6	$166.4	141.7
	Software licensing & annual update fee	1	$5,000	$384.6	-
	SUB-TOTAL		**$7164**	**$551**	**-**
CRP machine	6mth machine rental (inc. training, warranty, test & control kits)	13	$16,259.1	$1,250.7	-
	GP time - background training	369 mins	$742.2	$57.1	41.7
	Staff time* - machine operation training	1610 mins	$2,061.4	$158.6	130.5
	Staff time* - machine operation^	3702 mins	$2,159.4	$166.1	75.7
	SUB-TOTAL		**$21,222**	**$1,633**	**-**
Practice Staffing	Staff time* - initial lunch	3880 mins	$6,493.9	$499.5	335.4
	Staff time* - implementation meeting	425 mins	$283.8	$21.8	9.9
	GP time - individual setup	1700 mins	$3,417.0	$262.8	354.7
	Staff time* - ongoing project activities	4110 mins	$2,590.8	$199.3	147.3
	SUB-TOTAL		**$12,786**	**$983**	**-**
TOTAL COST			**$206,508**	**$15,885**	

*Staff time indicates that a mix of practice staff were involved, including practice managers, nurses, administrative staff and GPs. ^ Practices only had access to the CRP machines for half the intervention period so usage was doubled for cost estimates

Table 9. Recurrent cost items in the GAPS 6 month intervention period

Cost items	Monthly cost	Monthly cost per practice
GAPS project manager – maintenance phase	$11,576	$890
GAPS project coordinators - maintenance phase	$7,922	$609
GAPS staff travel	$521	$40
GAPS staff mobile phone expenditure	$50	$4
Consumables (stickers, pt decision aids)	$91	$7
Monthly CRP machine rental (inc. training, warranty, test & control kits)	$2,710	$209
Practice staff time - CRP machine operation	$827	$64
Practice staff time - ongoing project activities	$518	$40
TOTAL COST	**$24,215**	**$1,863**

Table 10. Practice staff time involvement for the GAPS 6 month intervention phase

Staff	Activity	Total time (mins)	Average per practice
GPs	Initial lunch	2,945	
	Implementation meeting	15	
	Individual setup	1,700	
	Communications training	1,076	
	CRP background training	369	
	CRP machine operation training	775	
	CRP operation*	20	
	TOTAL	**6902**	**531**
Practice manager	Initial lunch	445	
	Implementation meeting	370	
	Ongoing project activities	3,930	
	CRP machine operation training	65	
	TOTAL	**4,810**	**370**
Nurse & admin staff	Initial lunch	490	
	Implementation meeting	40	
	Ongoing project activities	180	
	CRP machine operation training	770	
	CRP operation*	3,682	
	TOTAL	**5,162**	**397**
TOTAL TIME		**16,874**	**1,298**

* 3 month usage was doubled to provide a 6 month estimate of staff time involvement

Table 11. GP participation in GAPS intervention activities

	Number of GPs in attendance	Percentage
Initial lunch	53 / 56	95%
Individual GP setup meeting	46 / 56	82%
Communications training	23 / 48*	48%
CRP background training	22 / 48*	46%
CRP machine operation training	25 / 56	45%

*only 48 GPs interviewed

The GAPS program was rolled out to 56 GPs in 13 practices. It was able to reduce prescribing amongst intervention GPs by 7%, which represents an absolute reduction in prescriptions of 3.8 per GP per month (or 1270 in total in the 6 months of the intervention). The cost-effectiveness of the intervention expressed as a range of outcomes is presented in Table 12 to enable comparison with other prescribing interventions that have been evaluated in the literature.

Table 12. Cost-effectiveness

Metric	No.	Cost-effectiveness ratio
Cost per GP	56	$3,380 per GP
Cost per practice	13	$14,561 per practice
Cost per % reduction in prescribing	7%	$27,042 per % reduction in prescribing
Cost per prescription avoided	1270	$149 per prescription avoided

The total monetary net cost of GAPS given the uncertainty in the underlying data is presented in Table 13. Under the baseline assumptions made in the economic model the net monetary cost of GAPS is just under $190,000. This represents a cost of $149 per original prescription avoided. Table 13 also presents the results of our scenario analyses. If no value is placed on practice staff time (i.e. only the financial expenditure on GAPS is considered) then the net cost drops to just under $170,000, conversely if a higher value is placed on GP time, then the net cost rises to just over $200,000.

Our scenario analyses including adverse events associated with antibiotics estimated that an additional 267 courses of antibiotics would be avoided based on the proportion of repeat prescriptions issued by our GP cohort. In addition, we estimated that 127 cases of diarrhoea, 21 cases of candidiasis, 17 rashes, and 16 cases of *C. difficile* would be avoided due to the reduction in antibiotic prescriptions. Including the cost savings from all these avoided events reduces the net cost of GAPS to around $117,000. This would represent a cost of $76 per prescription avoided (including repeats).

Table 13. Total monetary net cost of GAPS under different scenarios

Orange shading shows costs incurred, Green shading shows cost savings

Scenario	Cost of GAPS	Rx cost savings	Additional cost savings	Total net cost
Baseline	206,508 (206,350 - 208,297)	17,215 (17,110 – 17,221)	none	189,293 (189,183 – 191,134)
No value on practice staff time (financial expenditure only)	186,594 (186,510 - 188,434) *decrease*	17,215 (17,110 – 17,221)	none	169,379 (169,343 - 171,271)
High valuation GP time	218,240 (218,135 - 220,138) (217,669 - 219,648) *increase*	17,215 (17,110 – 17,221)	none	201,026 (200,968 - 202,974)
Including avoided repeat prescriptions	206,508 (206,350 - 208,297)	20,830 (20,703 - 20838) *increase*	none	185,678 (185,577 - 187,529)
Including avoided adverse incidents	206,508 (206,350 - 208,297)	17,215 (17,110 - 17,221)	6,155 (6,123 - 6,157) *increase*	183,138 (183,041 - 184,994)
Including avoided cases of *C. difficile*	206,508 (206,350 - 208,297)	17,215 (17,110 - 17,221)	50,407 (50,201 - 50,499) *increase*	138,886 (138,814 - 140,802)
Including avoided repeats & adverse incidents	206,508 (206,350 - 208,297)	20,830 (20,703 - 20838) *increase*	68,440 (68,151 - 68,553) *increase*	117,238 (117,191 - 119,207)

Finally Table 14 below shows the results of our modelling for roll out scenarios for GAPS. If the intervention is continued in the 13 original practices for a 3 year program, then the cost per original prescription avoided in our baseline scenario is $110. This falls to $44 per prescription avoided if repeat prescriptions and all adverse events as described above are considered. If the program is rolled out to 250 practices as a 3 year program, there are large gains in efficiency. The cost per prescription avoided drops to $55 when only the cost savings from avoided original prescriptions are considered. If the additional cost savings from avoided repeat prescriptions, adverse incidents and cases of *C. difficile* are included the intervention becomes cost saving.

Table 14. Results of GAPS scale up scenario analyses

Orange shading shows costs incurred, Green shading shows cost savings

Scenario	Total cost of GAPS	Total cost savings	Total net monetary cost (NMC)	Annual NMC	Annual NMC per practice	Cost per Rx avoided
6 month program: Baseline scenario	$206,508	$17,215	$189,293	$189,293 part year	$14,561 part year	$149
6 month program: All avoided events	$206,508	$89,270	$117,238	$117,238 part year	$9,018 part year	$76
3 year program: Baseline scenario	$943,258	$103,288	$839,970	$279,990	$21,537	$110
3 year program: All avoided events	$943,258	$535,618	$407,640	$135,880	$10,452	$44
3 year program, 250 practices: Baseline scenario	$10,057,649	$1,982,756	$8,074,893	$2,691,631	$10,767	$55
3 year program, 250 practices: All avoided events	$10,057,649	$10,281,946	-$224,296	-74,765	-$299	cost-saving

The cost of delivering GAPS to 13 practices over 6 months was just over $200,000. Ten percent of this total is the opportunity cost of practice staff time devoted to the program, with the remainder representing financial expenditure as a mix of staffing and consumables. The reductions in antibiotic prescribing achieved by GAPS resulted in cost savings from reduced prescribing of just under $21,000 (including repeat prescriptions avoided) and cost savings from avoided adverse incidents and cases of *Clostridium difficile* associated with antibiotics of just over $68,000. As such we estimated that the net monetary cost of GAPS over the 6 months was around $117,000. This equates to a cost of $76 per prescription avoided.

The intervention run at a small scale does not become more efficient over longer time frames if, as assumed in our analyses, practices require the same level of centralised support on an ongoing basis. It would be worth investigating the impact of reducing centralised support to practices after the initial 6 month phase trialled in this study, as a way to improving the efficiency of the intervention over the longer term. If practitioners maintain lower levels of prescribing even after the support of GAPS staff is removed, then the intervention is likely to be more efficient than estimated here due to the future cost savings that will accrue from reduced prescriptions and adverse events in future time periods. Further research would be needed to look at the impact on sustainability and efficiency of the intervention with different levels of ongoing centralised support as if the impact on prescribing behaviour change was compromised this would soon offset any cost savings from reduced staffing costs.

It is likely that economies of scale would be achieved under a large scale roll out. Many cost categories, including consumables, CRP usage, practice staff time and the number of project coordinators required would increase in proportion to the number of practices involved in the project. However, the cost of the program manager (which represents nearly 40% of program costs) would be shared over a greater number of practices. Our initial modelling shows that a roll out to 250 practices has the potential to be cost-saving, with the investment in GAPS offset by cost savings from fewer prescriptions and fewer adverse incidents and cases of *C. difficile*.

This finding is driven by the estimated cost savings from avoided cases of *C. difficile*, a condition which is on the increase in Australia. Our estimate of the cost of *C. difficile* infection was based on the best available scientific evidence, however, as much of the literature around the economic burden has focused on hospital onset or hospital acquired *C. difficile* (which has been shown to be associated with higher morbidity than community-

associated *C. difficile*) we had to augment this evidence with a number of assumptions based on expert clinical opinion. We believe that our assumptions about the incidence of *C. difficile* following antibiotic exposure and the costs of treating and managing these infections were conservative. We did not factor in recurrence of infection and the need for readmission or repeat primary care visits, nor did we place an economic value on the patient morbidity and mortality associated with the infection. Therefore if anything we would expect to see greater cost savings than those estimated here. However, given the extent to which the cost assigned to community-associated *C. difficile* influences the overall estimate of the efficiency of GAPS (and the evaluation of any programs directed at optimising use of antibiotics) future work may want to focus on better understanding the cost of managing these infections.

Comparison to earlier studies

A recent study from the UK evaluated a large scale feedback intervention where high prescribing practices received a personalised letter from England's Chief Medical Officer.[66] They estimated that their intervention cost 0.06 pounds per prescription avoided. However, they did not include staff time costs of the intervention in their analysis. Time costs included in our study are those of the practice staff and the centralised GAPS staff, which together account for 79% of the cost of GAPS. Removing these costs from the GAPS analysis would give a cost of $ 15 per prescription prevented, which is still substantially higher than the UK study and reflects the more extensive range of interventions included in the GAPS package. However, GAPS did achieve a greater reduction in prescribing rates than observed in the UK study, therefore, further research would be needed to understand whether economies of scale could be achieved in a large scale or longer term roll out of GAPS to the extent that the efficiency of the two interventions were comparable.

It is also worth noting that GAPS was conducted in a general GP practice population (rather than focusing on high prescribers). It may be that we need to be prepared to invest more in changing prescribing behaviour in moderate as compared to high prescribers. In addition, further research would be required to understand if the intensity of the GAPS intervention held other advantages over the UK intervention such as greater sustainability of behaviour change which may justify the higher level of investment required for GAPS. Finally, it is worth noting that an earlier study in Australia using a similar intervention to the UK one did not observe a reduction in prescribing, but rather a shift away from commonly prescribed antibiotics to more expensive second line treatments with an associated increase in healthcare expenditure and poorer patient outcomes.[67]

Caveats to costing methods

Several items used in the GAPS intervention were provided free for the purposes of the trial meaning that we could not use price as a proxy for the opportunity cost of these resources. As such values for a number of items are based on quotes rather than actual expenditure and may alter under a potential roll out of the intervention. For example, the price per month for CRP machines may increase or decrease depending on price negotiation, the rental period and whether selecting a rent-to-own contract.

The value placed on practice staff time (particularly GPs) is controversial as base salary rates may not adequately reflect opportunity cost. If time was valued according to the MBS reimbursement for standard consultations then the value placed on GP time would increase by over 50% to 3.71 per minute. As most practices have a consultation charge in excess of the bulk billing rate, their valuation of GP time may be even higher. This has implications for our cost-effectiveness analysis as it would underestimate the cost of the intervention making it appear more efficient. It also has implications for the acceptability of the intervention; if practices perceive that the value of GP time involvement is too high they may be reluctant to engage with the intervention, especially if there are no financial incentives for them to do so.

GP engagement with activities

While the majority of GPs attended the initial recruitment and project setup meetings, less than half completed the communications module training, the CRP machine background training and the CRP machine operation training. This could reflect differences in the delivery of program activities and materials, or the expectations that GPs would complete CMT and CRP background training in their own time. Further, if the expectation was that nurses would operate the CRP machine, this may have reduced GP participation in the CRP training. The discrepancy between the amount of time spent on CRP background training and compared to the practical CRP machine operation training may support this view. Increasing engagement of GPs with the CMT and background training would increase practice staff time costs.

CRP usage

Usage of the CRP machines was variable between practices and was generally quite low. Because the interventions included in GAPS were offered as a package, it is not possible to understand the contribution of individual elements to the observed reduction in prescribing. However, given that the cost of providing the CRP machines represents 10% of the total cost

of GAPS, further research would be warranted to understand whether this component of the intervention represents an efficient addition to the package.

Non-inclusion of resistant organisms scenario

We did not include a scenario where we attempted to model the impact on rates of infection with resistant organisms. Surveillance data from the US and several European countries from the early 2000's showed stabilisation and then declines in the rates of macrolide and penicillin resistant pneumococci following large scale reductions in antibiotic prescribing,[68-70] but suggest this may have come at the expense of resistance to other antimicrobial classes as fluoroquinolone resistance rates did not level off.[71] In addition the widespread use of pneumococcal conjugate vaccine is thought to have greatly reduced the prevalence of resistant strains in the population.[72] An early study from Finland showed reductions in rates of erythromycin resistance in streptococci following large scale reductions in prescribing, however, this study have not been updated in the last two decades.[73] A more recent study from Sweden looking at penicillin resistant streptococci demonstrated a 13% reduction in prescribing, and curbing of a regional epidemic, but still observed an overall increase in resistance rates nationally from 4% to 6% during the 10 year time period of the study.[74] This is not to say that we believe there is no impact of prescribing in primary care on resistance rates, but rather that the relationship is complex. Mathematical modelling studies predict that rates of resistance decay more slowly than they emerge and there is interaction between classes of antibiotics.[75] As such there is not sufficient quantitative data to adequately capture this important benefit of reduced prescribing within our economic model, but this benefit should be considered alongside the quantitative economic evidence when considering the value of investing in GAPS.

Use of a healthcare system perspective

We evaluated the efficiency of GAPS from the perspective of the healthcare system. This perspective captures all of the economic costs involved in delivering GAPS, but excludes many economic consequences resulting from the intervention that would be captured under a broader perspective. These include the cost savings from avoided patient out of pocket costs for items like probiotics which are commonly purchased by Australian patients taking antibiotics, and avoided out of pocket costs related to managing adverse reactions to antibiotics, for example anti-fungal treatment for candidiasis. In addition, the analysis does not capture changes in patient morbidity from avoided adverse incidents or changes in resistance patterns amongst infections. Including these additional benefits would make GAPS appear more efficient.

Microbiological sub-studies

Both microbiology sub-studies collected swab specimens from the upper respiratory tract (throat and anterior nares) of asymptomatic GP practice staff and patients attending the practice without signs and symptoms of an acute infection. Swabs were immediately placed in transport medium and either despatched to the microbiology laboratory using the priority postal service or a courier service. Antibiotic resistance was determined on pathogens isolates both phenotypically and genotypically.

(1) Point prevalence estimates of asymptomatic carriage of bacterial pathogens in GP practice staff and patients

A total of 262 participants from the GAPS GP practices consented to participate in the study. These comprised 138 general practice staff (health care workers – HCW) and 124 patients (non- health care workers – non-HCW) who presented with non-infectious conditions (table 15). The occupations of the HCWs included doctors, nurses, receptionists, pharmacists including pharmacy assistants, phlebotomist, theatre operator, pathology couriers and practice managers. Of note, retired HCW were classified as non-HCW.

Colonisation in the nose and/or throat by *Staphylococcus* species (spp) among HCW and non-HCW was 26.8% and 31.5%, respectively. Gram-negative bacteria were relatively less common than *Staphylococcus* spp. with key Gram-negative bacteria which include *Klebsiella* spp., *Escherichia coli*, *Enterobacter* spp. and *Pseudomonas aeruginosa* 9.4% among HCW and 7.3% among non-HCW. Overall, there was no difference of the carriage of *Staphylococcus* spp. and key Gram-negative bacteria in nose and throat among HCW and non-HCW, 32.6% and 33.1%, respectively (table 16).

This suggests that general practice settings are more like the community than a hospital setting, where asymptomatic health care workers have a higher risk of carriage of antibiotic-resistant pathogens. This observation needs to be confirmed and will have important implications for the intensity of infection control practices that are recommended for GP settings which are more based on hospital standards.

(2) Rolling out community antibiotic resistance surveillance using sentinel GP practices from the ASPReN network

It is common practice for antibiotic resistance surveillance programs to use microbiological specimens submitted for diagnostic purposes which may not accurately measure true community rates of resistance. This study assessed the feasibility of national surveillance of antibiotic resistance in the community using sentinel GP practices.

ASPReN was asked to identify ten GPs from ten different practices across Australia. Each GP obtained a throat and nose swab from five different asymptomatic HCWs or patients who presented with a non-infectious illness. The GPs were offered an incentive payment of $ 150 to help cover the costs associated of being involved in the study. The GPs obtained consent and collected a throat and nose swab from each patient and/or HCW.

Eight GPs from different GP practices across Australia agreed to participate and a total of 39 participants comprising of 8 HCW and 31 non-HCW were recruited (table 15). Thirty nine adults were included in the study. Swabs were collected from the nose and throat, placed in transport medium and posted to the laboratory. The swabs were received within two days from the specimen collection and processed immediately upon arrival. All swabs collected through ASPReN showed similar growth of pathogens and commensals as per the specimens collected through GAPS (table 17).

Coordinating the recruitment of GPs was undertaken by the ASPReN network. This was deemed to be both feasible and practical in that 8 out 10 GPs participated in the pilot project. The GPs were required to recruit and obtain the swabs form the participants whereas in the GAPS study the research coordinators performed this activity. Therefore, the recruitment of the participants in the ASPReN pilot was a lot more practical in term of the man power required to consent and undertake the swabbing of the participant. The GPs were able obtain the swabs correctly and return them in good condition with the requested completed paperwork.

Microbiological characterisation of the pathogens isolated

The rate of antimicrobial resistance in the commensals from the GAPS and ASPReN substudies was determined phenotypically using disk susceptibility testing and minimum inhibitory concentration (EUCAST); and genotypically using PCR detection for *mecA* gene on *Staphylococcus aureus.*[76] Three methicillin-resistant *Staphylococcus aureus* (MRSA) were identified, one from HCW.

Of the 69 participants colonised with *S. aureus*, 53 participants were from GAPS (25 HCW and 28 non-HCW) and 16 participants were from ASPReN pilot study (4 HCW and 12 non-HCW) (Table 17). Seventy four *S. aureus* strains were isolated from 53 participants in GAPS. Twenty four *S. aureus* strains were isolated from 16 participants from ASPReN specimen collection. Overall, moderate to heavy colonisation of *S. aureus* were common amongst both HCW and non-HCW (table 17) These *S. aureus* strains were representative strains from each site of specimen per participant who were at least moderately to heavily colonised by *S. aureus*. Of note, the detection limit of these screening was 20 colonies of *S. aureus* per swab. Moderate and heavy colonisation by *S. aureus* was equal to 10^3 and 10^5 colony forming (cfu) unit per swab.

The clonal relationships of isolates of *S. aureus* were characterised by a semi-automated method, repetitive sequence-based PCR (rep-PCR) typing (DiversilabTM, bioMerieux). Here, we found diverse strains of *S. aureus* from GAPS and ASPReN with 15 unique clones. Of these, four major unique clones of *S. aureus* (A, D, E and F) were identified among the 98 S. aureus (table 18). Clones D1 and A1 were the two most dominant clones. No evidence of transmission of *S. aureus* strains were demonstrated between HCW and non-HCW.

Gram-negative bacteria were relatively less common than *Staphylococcus* spp.and generally low to moderately colonised the nose and throat (<10^4) (table 16). Of note, the minimum detection limit of Gram-negative bacteria was also 20 colony forming unit.

Table 15. Participants of nose and throat swabbing from GAPS and ASPReN

	HCW	Non-HCW	Total participants
GAPS	138	124	262
ASPReN	8	31	39
TOTAL (all participants)	**146**	**155**	**301**

Note: HCW = health care workers; non-HCW = non-health care workers.

Table 16. Colonisation by *Staphylococcus* spp. and Gram-negative bacteria from nose and throat swabs.

Site[1]	**GAPS (*n*=262)**		
Species	***Staphylococcus* spp.**	**Key Gram-negative bacteria**[1]	**Carriage rate**
HCW (n = 138)	37 (26.8%)	13 (9.4%)	45 (32.6%)
Non-HCW (n = 124)	39 (31.5%)	9 (7.3%)	41 (33.1%)

[1] Key Gram-negative bacteria comprised of *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Escherichia coli*, *Enterobacter aerogenes*, *Enterobacter cloacae* and *Pseudomonas aeruginosa.*

Table 17. Colonisation by *Staphylococcus* spp. and Gram-negative bacteria from nose and throat swabs.

Site[1]	**GAPS (*n* = 262)**			
Species (%)	***Staphylococcus aureus*[2] (%)**	**Gram-negative bacteria[2] (%)**		
		K. pneumoniae or *K. oxytoca*	*P. aeruginosa*	*E. coli* or *Enterobacter* spp.[3]
HCW (*n* = 138)	25[4](18.1)	7 (5.1)	2 (1.4)	4 (2.9)
Non-HCW (*n* = 124)	28 (22.6)	5 (4.0)	1 (0.8)	3 (2.4)
Total (*n* = 262)	**53 (20.2)**	**12 (4.6)**	**3 (1.1)**	**7 (2.7)**
Site[1]	**ASPReN (*n* = 39)**			
Species (%)	***Staphylococcus aureus*[2] (%)**	**Gram-negative bacteria[2] (%)**		
		K. pneumoniae or *K. oxytoca*	*P. aeruginosa*	*E. coli* or *Enterobacter* spp.[3]
HCW (*n* = 8)	4 (50)	1(12.5)	0	1 (12.5)
Non-HCW (*n* = 31)	12[5] (38.7)	3 (9.7)	2 (6.5)	6 (19.4)
Total (*n* = 39)	16 (41.0)	4 (10.3)	2 (6.5)	7 (17.9)
Total GAPS and ASPReN (*n* = 301)	**69 (22.9)**	**16 (5.3)**	**5 (1.7)**	**14 (4.6)**

[1] Swabs were obtained from either participants recruited through GAPS or ASPReN.
[2] Percentage of participants colonised with the *Staphylococcus* spp. or Gram-negative bacteria which were calculated against the total number of participants recruited from respective recruitment site, i.e. GAPS or ASPReN
[3] *Enterobacter* spp. comprised of *Enterobacter aerogenes* or *Enterobacter cloacae*
[4] One HCW participant was positive with MRSA.
[5] Two non-HCW participants were positive with MRSA

Table 18. Clones of *S. aureus* from GAPS and ASPReN.

Clones	**Total**	**Number of positive participants**			
		GAPS		**ASPReN**	
		HCW	**Non-HCW**	**HCW**	**Non-HCW**
A	11	1	5	1	4[1]
B	2	1	1	0	0
C	3	2	1	0	0
D	18	2	11	1[1]	4
E	11	4	3	2	2
F	16	9	6	0	1
G	4	3[1]	1	0	0
H	3	0	2	1	0
I	5	4	0	0	1
J	4	3	1	0	0
Singleton	5	1	0	0	4
Subtotal	82	30	31	5	16
TOTAL	**82**	**61**		**21**	

Note: [1] = methicillin-resistant *S. aureus* or MRSA, which were confirmed by genotyping of *mecA* with minimum inhibitory concentration of ≥48 µg/mL of cefoxitin or oxacillin.

Interpretation

In the GAPS microbiology sub-study, we found the colonisation in the nose and/or throat by *S. aureus* among HCW and non-HCW were 18.1% and 22.6%, respectively. Interestingly, nose and throat swabbing showed a very similar rate of carriage of *S. aureus* (20.2%) to the nasal carriage of *S. aureus* in a large European study which recruited 28,929 participants (21.06%).[77] It is known that the colonisation by *S. aureus* amongst patients with blood stream infections by *S. aureus* is high, 58%.[78] A relatively high prevalence of nasal carriage of *S. aureus*(36%) has also been found amongst pathology staff members in Australia.[79]

Thus far, there are no Australian data of *K. pneumoniae* and *P. aeruginosa* nasal carriage, the two important Gram-negative pathogens. In our study we found 5.3% nose and/or throat carriage of *Klebsiella* spp., mostly *K. pneumoniae*. The significance of Gram-negative nasal carriage is uncertain. Nasal carriage of *K. pneumoniae* was associated with an outbreak of infections in a German hospital.[80] .

Two major limitations of the GAPS nose and throat swab study were the number of participants and the time constraints to complete the screening and identification of S. aureus, molecular analysis for potential transmission of *S. aureus* between HCW and non-HCW and genotyping confirmation of methicillin-resistant *S. aureus* (MRSA). The number of participants of this point-prevalence GAPS nose and throat sub study was considered small in comparison to an extensive European study which assessed 28,929 nasal swabs from healthy people.[77] The second limitation was the man power required to obtain the recruit and obtain the study participants which was considerable. In this study we utilised our research coordinators who were qualified nurses for the recruitment and collection of the swabs.

Given that these microbiology sub studies were both pilot studies, they will need to be repeated before more definitive conclusions can be drawn. Given the central role of infection control in hospitals, but also the costs and time involved routinely to implement these measures it is important to more definitively characterise how similar or not GP practices are to hospital settings to guide appropriate infection control practice.

Using sentinel GP practices for general population antibiotic resistance surveillance seems to be feasible at least for upper respiratory tract sampling. Collecting other samples can be evaluated (skin, urine, faeces) if there is any interest in general population Antimicrobial Resistance (AMR) surveillance in Australia. Any further work would carefully need to assess the costs of such surveillance.

DISCUSSION

Summary of main findings

The package of interventions was successfully introduced into general practices and was well received by the GPs. It was considered adaptable to individual practices and provided GPs with the opportunity to reflect on their management of patients with ARIs. The package was practical and complemented the consultation process. An important advantage of the intervention package was that the "one size fits all" principle was not applied and that the GP was able to choose from a range of interventions depending on his/her consultation preferences and the patient at hand.

Rates of antibiotic prescriptions were declining in both the intervention and control groups when the baseline phase (three years before the intervention) was compared to the intervention phase. This suggests there was already some action being taken by GP practices to reduce unnecessary antibiotic prescribing. On top of this secular trend, there was a 7% decrease in antibiotic prescribing in intervention compared to control practices in the intervention phase of the trial. This corresponds to a nett difference of 3.8 fewer antibiotic prescriptions per GP per month in practices using the GAPS package.

Strengths and Limitations of study

Our recruitment strategy was by GP practice and GPs then consented to participate in the study. Despite this the GPs in the control and intervention group were comparable in terms of characteristics of GP practices and GPs. We have included a wide range of GPs from a number of practice settings with differing interests in AMS, and believe that the findings of the study are of importance and relevance within the Australia as a whole.

The study was conducted during the summer months for a six month period. Traditionally there is are lower rates of ARIs in the summer which might have limited the uptake and the impact of some of the interventions such as the CRP into practice. The timing of the study might have affected the implementation of the different interventions by the GPs. In addition, due to the short time period of the intervention phase there may have been insufficient time for the uptake and full implementation of the interventions. GPs are conservative adaptors and it takes time for them adopt and implement new strategies.[52]

Although this study was conducted in urban areas, the interventions are relatively simple and easy to use therefore the package should be fairly adaptable to be implemented on a larger scale in a variety of geographical settings. In addition, the data were sourced from the Australian Government Department of Human Services PBS and MBS claim data base and

for the purpose of this study the GP practice was not required to contribute the data collection process. This facilitated the recruitment process of the GP practices as the study was perceived as having minimal impact on the GP practice work flow. Although we were not able to obtain individual prescribing data for the patients and determine appropriateness of antibiotic therapy we were able to determine rates of antibiotic prescriptions for the GPs. The package of interventions were well received and showed a decrease in antibiotic prescribing rates. However, the study was not powered to evaluate the effect of each of the components in this multifaceted package of interventions but instead evaluated the feasibility and effectiveness of providing the intervention as a bundle.

Each GP will be provided feedback about their individual antibiotic prescribe rates in comparison to his/her peers for the baseline and intervention phase at the end of the study. Unfortunately due to the short duration of the study there is insufficient time to evaluate the outcome of this intervention. Social norm feedback has shown to substantially reduce antibiotic prescribing at low cost and at national scale; which makes it a worthwhile addition to antimicrobial stewardship programmes.[66]

The health economics studies identified the costs of reducing unnecessary antibiotic prescribing by GPs using the intervention package. Without any other benefits considered, it equates to a cost of $121 per prescription avoided. Including the economic benefits of adverse events avoided reduces the cost per prescription avoided to $73. The study was conducted over a short 6-month period and during the summer when ARIs are less common. Much of the cost of the intervention was in the start-up phase. Taking the intervention to scale, covering 250 GP practices for 3 years, is cost-saving for the health system: using the same effect size, and conservative assumptions, suggest cost savings of $200,000.

Comparison with existing literature

Attempts to improve outpatient antibiotic prescribing likely require two complementary strategies: (1) changing clinician behaviour to alleviate concerns related to diagnostic uncertainty, alienating patients, and not conforming to peer practices and (2) educating patients and families about the role of antibiotics in medical care.[81] Our study has been able to demonstrate that a package of interventions that are relatively simple and easy to use were able to improve antibiotic prescribing in primary care. Previous work has shown that even though improving antibiotic use in the outpatient setting seems like a daunting task, significant progress can be made with relatively minor interventions. For example, Meeker et al demonstrated that displaying a poster in patient waiting rooms indicating a

commitment to avoiding inappropriate antibiotic prescriptions for acute respiratory tract infections was associated with a 20% decrease in antibiotic prescribing. [21]

Overall practitioner attitudes towards the adoption of the package of interventions in our study were encouraging. Interventions are more likely to be adopted and implemented if they are time efficient and acceptable to both clinicians and patients.[82] Clinicians have confirmed that they need feasible and more effective communication strategies to successfully change their prescribing.[83] Patients with common infections consult with a variety of expectations and may go away with these unfulfilled.[84] and with unexpected, unnecessary antibiotics.[85] Patients' lack of participation in consultations and 'unvoiced agendas' were associated with misunderstandings, unnecessary and unwanted prescriptions and poor adherence.[86] Although the main focus of this study was decreasing antibiotic prescribing by the GP, the consumer plays an important role and successful AMS programs need to include the consumer. The poster and patient information leaflets contributed towards the education of the patient and the GPs in our study mentioned that patients were easier to counsel if they were already informed about appropriate antibiotic prescribing.

Our findings are similar to a recent study by Fredericks et al where nearly one in ten antibiotics (9.0%) was dispensed from all antibiotic prescriptions (i.e. original and repeats) prescriptions that were more than a month old. However, if you exclude repeats (i.e. original antibiotic prescriptions only), then 90% were dispensed on the day of prescribing. In addition, we also reported that over one in five (22.1%) were dispensed from a repeat prescription which is similar to Fredericks et al.[87] In our study the delayed antibiotic prescribing stickers was found to be useful by the GP. In addition, the GPs in our study felt that the patients also appreciated this intervention. Our study was not designed to evaluate the effect of this intervention on its own; however other studies have shown delayed antibiotics resulted in a significant reduction in antibiotic use compared to immediate antibiotics.[23] Health system factors may contribute to inappropriate antibiotic use in Australia, including availability and validity of repeat antibiotic prescriptions. Government health departments, prescribers, pharmacists, other health professionals and consumers have to share the responsibility of ensuring that antibiotics are used appropriately.[87]

Some of the barriers identified with implementing AMS strategies in primary care will require an appropriate funding model and reimbursement strategy which will require policy change if widespread adoption is to be achieved.[52] In addition, it is essential that clear guidelines exist to govern how and when Point of Care CRP testing should be used, and establishing antimicrobial stewardship into quality improvement frameworks may achieve this.[52] Rapid

diagnostics could transform the way we use antimicrobials in humans and animals: reducing unnecessary use, slowing AMR and so making existing drugs last longer.[17]

Successful adoption models in the European countries showed a distinct pattern: a slow and long early adoption phase followed by policy changes that then trigger large-scale adoption. In addition, a few opinion leaders became early adopters, recognising the importance of using AMS strategies to support their decision-making in antibiotics prescriptions. It also requires national professional bodies to become advocates of these AMS strategies.[52]

One reason why we were able to demonstrate effective uptake of the intervention package and a decrease in antibiotic prescribing in a short time period was the support provided by the research coordinators to GPs and practice staff through their regular site visits. Uptake of an intervention does not happen spontaneously, rather an active implementation approach is required. [88] Gerber et al was able to show that a combination of clinician-specific education and audit and feedback significantly reduced prescribing of antibiotics in primary care.[89] Following the removal of audit and feedback, however, the initial benefits of this outpatient antimicrobial stewardship intervention were lost.[90] Ideally, an Antimicrobial Stewardship program should be a combination of education, guidance, and interventions.

Interestingly, rates of antibiotic prescriptions were declining in both the intervention and control groups even before this study began, and the decrease continued over the study period. Antibiotic rates have decreased from the peak in in 2008 when evaluated by both number of prescriptions and DDD/1000 population/day.[1] In addition, the trend for inappropriate prescribing for upper respiratory tract infections is decreasing.[16] This may be reflective of the ongoing campaigns promoting the appropriate use of antibiotics. However, Australia is still one of the highest consumers of antibiotics in the developed world [1] with high volumes of antimicrobials being prescribed unnecessarily for upper respiratory tract infections. Inappropriate use of antibiotics needs to be minimised to prevent and contain Antimicrobial Resistance.[16] Our study was able to show a significant reduction in antibiotic prescription rates for the intervention group compared to the control group by utilising a package of interventions that were relatively simple and easy to use to improve antibiotic prescribing in primary care.

Surveillance is one of the cornerstones of infectious disease management, yet has often been ignored and remains under-resourced. With oversight from the WHO, governments must build on these efforts. [17] Using sentinel GP practices for AMR surveillance in the general population, as opposed to diagnostic specimens, appears feasible to track the longer term impacts of AMS in general practice; but needs further evaluation.

Implications for practice

The bundle of interventions offered can successfully reduce antibiotic prescribing for ARI symptoms in the short term and in the summer (non-ARI) season. This impact is on top of the secular trend, a small decline in antibiotic prescribing we identified over time in the three years preceding implementation. It is predicted to be cost-saving for the Health Sector if it is taken to scale and the benefit is sustained.

The qualitative and economics studies, complimented by the rich experience of the implementation team, have given us some insight into what will be required to sustain the impact of the GAPS intervention with wider roll-out. It should be noted that the study was not designed or powered to evaluate the individual interventions, but instead looked at the feasibility and effectiveness of providing the intervention as a bundle.

The study team was able to roll out the intervention effectively to GPs to have an impact on antibiotic prescribing in a very short time period. The study manager and four research coordinators played a crucial role in providing support to GPs and practice staff through their regular site visits to the practices. Over 70% of the resources to implement GAPS were project staff costs. However, it is not clear whether the same intensity of visits and practice support will be necessary to sustain the impact or whether less intensive schedules of visits will be as effective. But some level of ongoing practice support will be needed.

The intervention package was well received by GPs who appreciated its adaptability to a range of contexts. It provided GPs with the opportunity to reflect on their management of patients with ARIs. GPs were able to choose: a one-size does not fit all. It was flexible to allow for GPs with different levels of experience, different consultation styles and different patient mixes to pick and mix. New or redesigned tools can be added as and when they become available. Continuing to provide choice is feasible and acceptable, and will be a key element to sustain the impact on prescribing over time.

The study team sought buy-in from a wide range of professional groups when implementing the bundle. With broader roll-out, national and regional stakeholder meetings may be needed to more systematically support delivery and sustain impact. Key opinion leaders should also be mobilised to support AMS.

Implementing the bundle relied on two incentives: a small cash payment to each practice to compensate the practice for the time investment needed to engage with the research; and

RACGP continuing professional development CPD category 1 and 2 points for completing the education activities associated with the study. The cash payment may not be necessary in a wider roll-out and should probably not be used if AMS becomes standard national practice. More could undoubtedly be done to incentivise GPs with more structured CPD points over a longer roll-out period. Policy options include the potential for ISO certification and quality accreditation for the practices themselves. Reimbursement for point of care CRP test machines and consumables will also need to be considered if they remain part of the scaled up implementation package.

Any attempt to take the GAPS package to scale should adopt a systems approach to promote the implementation and uptake of the package. It is important carefully to consider integration with other schemes to avoid over burdening GPs and GP practices who remain involved in several interventions and standard setting activities. With GP surgeries being more like the community than a hospital environment, there seems little need to follow strict and more costly Infection Control Practices based on hospital practice.

Ultimately AMS in primary care aims to drive down antibiotic resistance in the general population through more effective antibiotic prescribing. National antimicrobial resistance surveillance is feasible through sentinel GP sites such as the ASPReN network. We found that this was a very efficient way of collecting swabs from the community and it is worthwhile exploring the possibilities of extending this feasibility study.

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LIST OF ABBREVIATIONS

Acute Respiratory Infections (ARI)

Antimicrobial Stewardship (AMS)

Anatomical Therapeutic Chemical code (ATC)

Australian Sentinel Practice Network (ASPReN)

Antimicrobial Stewardship (AMS)

Antimicrobial Resistance (AMR)

Antimicrobial Use and Resistance in Australia (AURA)

Changing the Antibiotic Prescribing of General Practice (ChAP study)

C-reactive protein (CRP)

General Practitioner Antimicrobial Stewardship Programme Study (GAPS)

General Practitioners (GPs)

Health care workers (HCW)

Non-health care workers (non-HCW).

Medicare Benefits Schedule (MBS)

Pharmaceutical Benefits Scheme (PBS)

COMPETING INTERESTS

The authors declare that they have no competing interests except Chris Del Mar.

Consultancy, fees/honoraria:

- National Prescribing Services (NPS) consultations
- RACGP's 'Red Book' preventive guidelines committee
- Therapeutic Guidelines (eTG), guidelines development
- Remote Primary Health Care Manuals Editorial Committee
- Royalties for 3 books (Wileys and BMJ Books) on EBM, and clinical thinking
- Editorial work (MJA Deputy Editor; ACP Journal Club; BMJ)
- Consultation work for BUPA (UK) on shared decision making
- Australian Medicine Handbook, guidelines development

Grants:

- NHMRC (Australia)
- NIHR and HTA (UK)
- from a private donor (for the Cochrane Collaboration ARI Group)
- Australian Commission on Safety and Quality in Health Care (for the provision of decision aids x 3; an education module on risk communication)

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APPENDICES

1. Protocol

AventGAPSprotocolB
MCfamilypractice201(

2. Interventions

The interventions included:

- A web-based module on communication training


GAPS Communication Trai

- Point of care test C-reactive protein (CRP)


C-Reactive Protein_information.p

Point of care test C-reactive protein (CRP) is performed on a finger prick blood sample and the result is available during patient consultation and can, therefore, guide antibiotic use. For more information about how to use CRP testing in general practice within consultations for acute respiratory tract infections please see embedded pdf training module.

By reviewing the material the GPs will be eligible to claim 2 (Category 2) points in QI&CPD Program for the 2014–16 triennium.

- Patient Decision Aids

Patient Decision Aids are brief summaries of evidence for the management of a number of ARI conditions. The decision aids have been developed to assist the patient to make an appropriate decision about their condition in conjunction with the GP.


Patient Decision Aids.pdf


Antibiotics for Acute Bronchitis.pdf


Antibiotics for Acute Otitis Media - pain.pd


Antibiotics for Acute Rhinosinusitis.pdf


Antibiotics for Sore Throat.pdf

- poster on practice prescribing policy for antibiotics.

This intervention consists of displaying a poster-sized commitment letter in the practice waiting room and/or examination room

Final Poster no photos.pdf

- Patient Information leaflet

This intervention consists of an information leaflet which provides more information to the patient about the poster-sized commitment letter in the GPs waiting room and/or examination room. The patient information leaflets are on display in the GP practice waiting area.

Pamphlet Final Small.pdf

- Delayed Antibiotic Prescribing

The GP can choose to provide the patient with a delayed antibiotic prescription with advice to the patient to only have the prescription filled at a pharmacy after a few days if symptoms are not starting to settle or become more severe. A sticker (see below) can be applied to the prescription labelling it as a delayed prescription.

3. Report of PBS and MBS data

PBS data

Exclusion Criteria:

- Medications supplied as a doctor's bag item.
- Medications supplied as a repeat prescription.

Amounts of data

PBS claims obtained by date of prescribing for 54 GPs in the control arm during the baseline period covered 2067 person-months (for n=39 person-months, 2%, there were no PBS claims data), and in the during/after intervention period covered 324 person-months (all with PBS claims). In the intervention arm PBS claims for 56 GPs during the baseline period covered 2184 person-months (but for n=142 person-months, 7%, there were no data), and in the during/after intervention period covered 331 (n= 5 person-months, 1% had no data). Periods with PBS data for a GP may be because the GP was on holidays or not practising.

Table 1. PBS data.

	Baseline Phase		**Intervention Phase**	
	Total Period (Person-month)	No data (%)	Total Period (Person-month)	No data (%)
Control n=54	2106	39 (2%)	324	0 (0%)
Intervention n=56	2184	142 (7%)	336	5 (1%)

MBS data

Exclusion Criteria:

- Claims recorded with negative schedule fees, which represent adjustments for incorrect claims. These records were less than 0.01% of the total records.
- Claims for skin neoplasm removals or skin grafting.
- Claims for mental health consultations.
- Claims for before or after surgery consultations.
- Claims for maternity follow up or pregnancy tests.
- Claims for blood tests, eye tests or audiograms.

- Claims for fracture or wound treatment.

Amounts of data:

MBS claims obtained for 54 GPs in the control arm during the baseline period covered 1440 person-months (n=666 person-months, 32%, had no MBS claims data), and for the intervention period covered 254 person-months (n=70 person-month, 22%, with no MBS data). In the intervention arm MBS claims for 56 GPs during the baseline period covered 1309 person-months (n=875 person-months, 40%, with no MBS data), and for the intervention period covered 252 (n= 84 person-months, 25% with no MBS data). Absence of MBS data may be because the GPs were on holiday, were not practising, or were practising in non-participating practices for some months during the study period; also patients may not have submitted claims to MBS for visits that were not bulk-billed.

Table 2. MBS missing data.

	Baseline Phase		**Intervention Phase**	
	Total Period (Person-month)	No data (%)	Total Period (Person-month)	No data (%)
Control n=54	2106	666 (32%)	324	70 (22%)
Intervention n=56	2184	875 (40%)	336	84 (25%)

It is obvious that GP-periods with no MBS data were considerably more common than GP-periods with no PBS data. This difference could be because MBS data were extracted using each GP's provider numbers included in the consent forms. The provider number is site specific and each GP could have multiple numbers if they worked in multiple practices. In the other hand PBS data were extracted using the GP's prescriber number which was included in the consent forms. The prescriber number is a fixed number for each GP and does not change even if the GP practises in multiple locations.

This inconsistency between MBS and PBS caused a substantial loss of data after merging both data sets. Additional problems with the MBS data are outlined in Appendix 5.

4. Report of oral antibiotic prescriptions

Table 1. All supplied medications and oral antibiotics by original and repeat prescription forms, with column and row percentages.

	All Supplied Medications (Column %)	All supplied oral Antibiotics (Column %)	Row %
Original Prescription	1,258,824 (43%)	245,773 (79%)	20%
Repeat prescription	1,684,841 (57%)	65,727 (21%)	4%
Other**	4,954		
Total	2,948,619	311500	11%

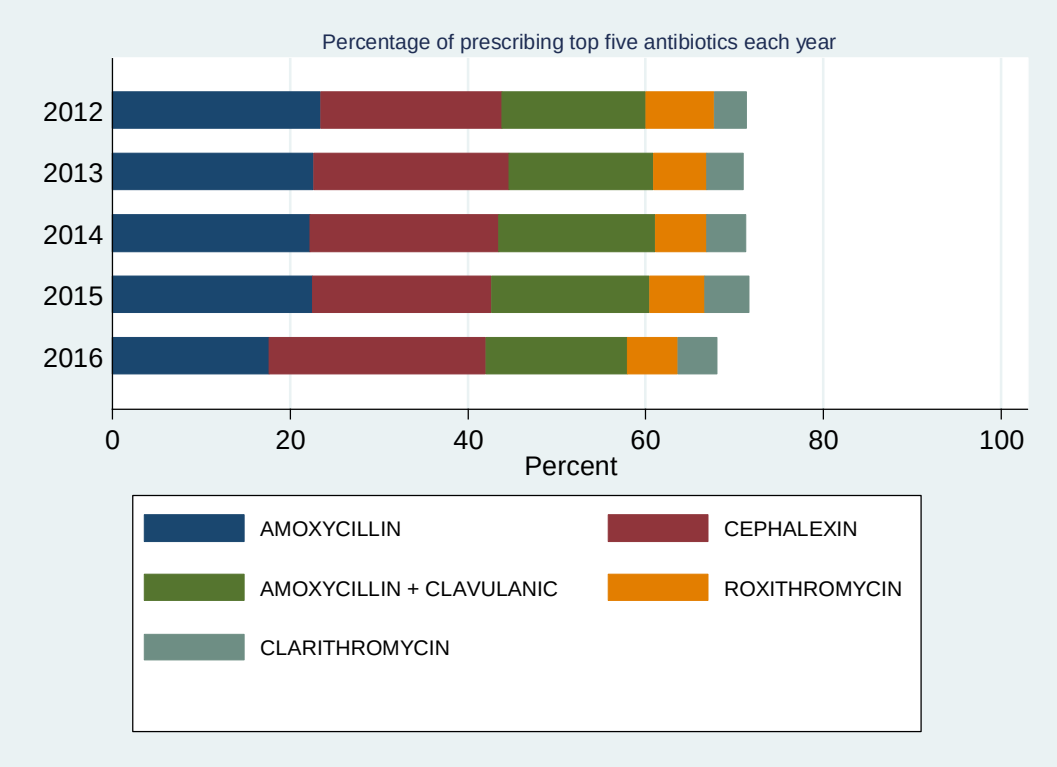
** Items supplied as doctor's bag

20% of original prescriptions, and 11% of all supplied medications were oral antibiotics.

Table 2. Top ten most prescribed oral antibiotic showing percentage of prescriptions supplied on day of prescribing and less than 4 days of prescribing.

	ATC	NAME	Original Script No. (%)	% original supplied on day of prescribing	% Original supplied < 4 days after prescribing
1	J01CA04	AMOXYCILLIN	54,207 (22%)	86%	94%
2	J01DB01	CEPHALEXIN	50,855 (21%)	84%	94%
3	J01CR02	AMOXYCILLIN + CLAVULANIC	41,178 (17%)	85%	93%
4	J01FA06	ROXITHROMYCIN	15,039 (6%)	85%	94%
5	J01FA09	CLARITHROMYCIN	11,921 (5%)	87%	94%
6	J01AA02	DOXYCYCLINE	10,663 (4%)	75%	86%
7	J01EA01	TRIMETHOPRIM	9,785 (4%)	83%	93%
8	J01FA01	ERYTHROMYCIN	9,511 (4%)	88%	95%
9	J01XD01	METRONIDAZOLE	5,978 (2%)	80%	91%
10	J01CE02	PHENOXYMETHYLPENICILLIN	5,589 (2%)	92%	97%

Graph 1. Percentage of the most common 5 antibiotics prescribed each year during the study period.



5. Report of additional quantitative analyses

After exhaustive investigations of time series graphs of the MBS, PBS and antibiotic claims, the following inconsistencies were found:

1- For many GPs there were some periods with very low or no MBS claims, whereas their total PBS prescriptions claims were either high or within their normal pattern. This anomalous pattern was more common at the early stages of the baseline period however it continued until last month of the intervention period.
2- For a few GPs, the number of MBS claims was very high compared to their prescribing rate or to average monthly claims of other GPs.

In order to reduce noise in the data due to these extreme patterns, the analyses were repeated multiple times after implementing different exclusion criteria as listed below

1. Merge data either: day by day, week by week or month by month, then excluding any observation with no MBS claims.
2. Reduce baseline phase to 12 months instead of 39 months.
3. Generate the distribution of the MBS claims for all GPs and exclude any day, week or month (depending on the merging strategy), with MBS claims more than one or two standard deviations away from the mean.
4. Repeat step 3. but by generating the distribution for each GP separately, then excluding any observation with MBS claims more than one or two standard deviations away from that GP's own mean.

Results of the repeated analyses (not shown here) were almost identical, showing that the numbers of antibiotic prescriptions per 100 MBS claims declined in both groups during the 6-month period of the study compared to the previous 39 months. The change was quite similar in both groups. The results shown in this report were based on keeping all baseline phase (39 months) data, and merging utilising a month by month strategy, then excluding observations with MBS claims more than 2 standard deviations away from mean of the distribution of all GPs.

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