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**Cost-effectiveness analysis of a multi-dimensional intervention to reduce inappropriate antibiotic prescribing for children with upper respiratory tract infections in China**

**Running title: Cost-effectiveness of a trial to reduce APR**

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**What is already known on this subject?**

Overuse of antibiotics in primary care facilities is a major driver to antimicrobial resistance. Multifaceted interventions that targeting both providers and patients/ caregivers are effective in reducing inappropriate antibiotic use; but little is known on its costing implications to implement those interventions.

**What this study adds?**

We conducted cost-effectiveness study of a recent successful trial in rural China using multifaceted interventions to reduce antibiotic use. The study shows that interventions, if embedded into routine clinical practice and management in primary care facilities, costed very little for health providers ($391 per health facility), in achieving reduction of inappropriate antibiotic use. These high cost-effective interventions have strong potential to be adapted in other low and middle-income countries.

**Abstract**

**Background:** We developed a multifaceted intervention to reduce antibiotic prescription rate for children with upper respiratory tract infections (URTIs) among primary care doctors in township hospitals in China. The intervention achieved a 29% (95% CI: 16% to 42%) absolute risk reduction in antibiotic prescribing. This study was to assess the cost-effectiveness of our intervention at reducing antibiotic prescribing in rural primary care facilities as measured by the intervention's effect on the APR for childhood URTIs.

**Methods:** We took a health-care provider perspective, measuring costs of consultation (time cost of doctor), prescription monitoring process and peer-review meetings (time cost of participants) and medication costs. Costs on provider side were collected through a bespoke questionnaire from all 25 township hospitals in December 2016, while medication costs were collected prospectively in the trial. Incremental cost-effectiveness ratios were calculated by dividing the mean difference in cost of the two trial arms by the mean difference in antibiotic prescribing rate.

**Results:** This showed an incremental cost of $0.03 per percentage point reduction in antibiotic prescribing. In addition to this incremental cost, the cost of implementing the intervention, including training and materials delivered by township hospitals was $390.65 (SD $145.68) per healthcare facility.

**Conclusions:** This study shows that a multifaceted intervention programme, when embedded into routine practice, is very cost-effective at reducing antibiotic prescribing in primary care facilities, and has the potential of scale-up in similar resource limited settings.

**Keywords**: cost-effectiveness, resource limited setting, antimicrobial stewardship, antibiotics prescribing, primary care

## Introduction

Antimicrobial resistance is a global health threat which negatively impacts health outcomes and health expenditure [1]. Overuse of antibiotics is an essential factor associated with increased antimicrobial resistance [2, 3]. In 2012, average consumption of antibiotics was 10 times higher in China than in the USA [4]. Consequently, in 2012 the Chinese Ministry of Health launched a national campaign to encourage appropriate use of antibiotics. However, operationalising this policy has proved challenging [5].

Antibiotics are commonly, and incorrectly, prescribed for upper respiratory tract infections (URTIs) [6]. Recent studies showed antibiotics were prescribed for nearly 80% of consultations in China's primary care settings [7, 8]. Interventions are badly needed. Evidence from previous studies, primarily in high income settings, indicate that multifaceted interventions targeting both physicians and patients can effectively reduce inappropriate antibiotics use [9]. However, intervention studies to reduce antibiotic prescribing in primary care are rare in low resource settings [10]. In a natural experimental study, we found that including peer-review within a stewardship programme may reduce antibiotic prescribing [11]. Thus, we developed an intervention package that aimed to reduce prescribing of antibiotics for URTIs in 2-14 year-old outpatients, attending primary care facilities in rural Guangxi, China. We then conducted a cluster randomised controlled trial to test its feasibility and its effectiveness. Full details of the intervention and its development are available in the trial protocol [10]. Briefly, the intervention targeted both the 'provider' (doctors) and 'consumer' (children with URTIs and their caregivers). For healthcare providers within township hospitals the intervention included concise evidence-based clinical guidelines on URTI management, facilitated training on using/applying the guidelines during consultations and monthly peer review meetings assessing providers' antibiotic prescription rates (APR).

Patients and caregivers received information on appropriate antibiotic use, both verbally and via an educational leaflet. Additionally, a video with key messages on appropriate use of antibiotics was played daily in the waiting rooms and public areas of the township hospitals. Township hospitals in the control arm received no intervention components, providers continued prescribing at their own discretion, and patients and caregivers received no educational materials. The main trial results showed that the intervention was highly effective compared to usual care [12]. Consequently, analysis of cost-effectiveness will also be of use to policy makers, both in China to enable scale up, but also in a wider global context [13-15]. This study aims to assess the cost-effectiveness of this intervention and to provide information to policy makers on the costs associated with scale up of interventions of this kind.

**Methods**

Full methods for the trial are available in the trial paper [12]. Briefly, we used a parallel-group, cluster (township hospital) randomized controlled trial design to evaluate the cost-effectiveness of a health behaviour change intervention compared with usual care. We conducted the study in 25 township hospitals, 12 intervention and 13 control, spreading over 2 counties in rural Guangxi southern China. Due to the nature of our intervention (e.g. training and provision of educational leaflets) we could not blind providers or participants to treatment. Randomisation was conducted at the township hospital level and was stratified by county. The primary endpoint was the APR – the proportion of prescriptions containing at least one antibiotic – among prescriptions given to children (aged 2-14 years) for URTIs, and was calculated at the cluster-level from prescriptions collected during the final 3 months of the 6-month intervention period (endline), between 1 July 2015 and 31 March 2016. We then

measured effectiveness as the covariate-adjusted, stratified mean difference in the APR between the intervention and control arms.

The primary endpoint for this study is the cost per percentage point decrease in the APR for childhood URTIs in the intervention arm compared to the control arm. Direct costs and outcomes of patients randomised to the intervention arm of the trial versus usual care were compared over the 6-month time horizon of the trial. As the time horizon of the trial was less than 12 months, no discounting of costs and benefits was required [16]. The perspective adopted for the analysis was that of the healthcare provider.

**Data collection**

We used a bespoke questionnaire to collect data on the resources used to deliver the intervention which was administered to the directors of all 25 township hospitals in December 2016. Respondents reported average salaries, in RMB, for each level of staff in their hospitals and collected information on the duration of consultations by asking three doctors (selected by systematic random sampling using the staff list) how long they spent in one consultation. They also reported the amount of time spent reviewing prescriptions in preparation for peer-review meetings, the frequency and duration of peer-review meetings and the staff involved in each process.

**Estimation of resource use and costs**

Healthcare resource use was recorded as the patient visits to the health facility. We included the cost of consultations, medications and medication reviews. The total per patient cost was calculated as the sum of the three elements.

Consultation: The cost of the consultation was estimated as the average duration of consultations multiplied by the cost of the doctor's time (derived from the salary), plus the cost of information leaflets given to patients/caregivers. If the seniority of the doctor who undertook consultations was unknown, the record of doctors that attended prescription review meetings was used as a panel sample of the doctors at the hospital and the weighted average salary was used.

Medication: Medication costs were obtained from the prescription records that were collected as part of the trial data.

Medication reviews: Costs associated with medication reviews were calculated per patient, from the sum of the cost of staff time: spent on monitoring prescriptions, giving feedback on antibiotic prescribing and attendance at the prescription review meeting.

Total costs to the healthcare provider were calculated for the intention to treat population accounting for clustering and stratification[17]. All costs are presented in US dollars and were calculated using an exchange rate of 1USD=6.9 RMB using 2016 as the price year.

**Estimation of implementation costs**

Implementation costs represent upfront costs and are estimated and reported separately, and not included in the cost-effectiveness analysis. However, policy makers would need to consider these costs when deciding whether to implement the intervention at scale. The implementation costs were calculated for each facility as the sum of: the cost of a trainer to

deliver training on the appropriate use of antibiotics when treating children with URTIs; the cost of staff time to attend training; one handbook per training attendee; desk guides (used as information aids in consultations); educational videos (displayed in waiting areas); and posters (displayed around the hospital). The cost of the trainer, and unit costs for equipment were the same for all facilities due to central organisation. However, total costs varied depending on the salaries of doctors and the number of doctors at the facility. Unit costs used to estimate the average total implementation cost are presented in Table 1. We present the average of all doctors' salaries reported to avoid the ethical problem of reporting identifiable salaries.

**Statistical analysis**

We performed analyses based on cluster-level outcomes to account for between-cluster variation, while also adjusting for stratification and baseline covariates[1][17]. This method is recommended for cRCTs with less than 20 clusters per arm as it results in typically less biased results than the multi-level approach when the number of clusters is small [17]. First, we fitted a logistic regression model to the individual-level data, controlling for the covariates of interest but not the effect of the intervention. We then used the model predicted and observed values to calculate cluster-level difference residuals and estimated the mean covariate-adjusted difference in APR between the intervention and control arms (i.e. the risk difference) based on a weighted average of the cluster-level difference residuals (with weights inversely proportional to the stratum-specific variances), accounting for stratification. We then calculated 95% confidence intervals and a p-value for the effect

[1] Including: stratum (county); cluster-level baseline antibiotics prescription rate (three months prior to the intervention); patients': gender, age and payment type (insured/out-of-pocket); and doctor's: gender, age and qualification level (3 or 5 years)

estimate using a stratified t-test (two-sided)[17]. We analysed the incremental cost in the same way. First applying weights, inversely proportional to the stratum-specific variances, and then conducting a stratified t-test to calculate 95% confidence intervals and test for the significance (at $p < 0.05$) of any difference in costs [18].

**Missing data**

There was no missing outcome data and all facilities provided the additional cost data requested. Where covariate data (used to adjust effect estimates) were missing, these observations were dropped. Salaries of staff that attended medication reviews were used to cost other parts of the intervention, e.g. consultations. If a salary for a specific level of staff was not reported at a facility then the mean salary of staff at that level reported by other facilities was imputed [19].

**Cost-effectiveness analysis**

The primary analysis consisted of a cost-effectiveness analysis over the 6-month trial period. The incremental cost per percentage point reduction in APR was calculated by dividing the mean difference in cost of the two trial arms by the mean difference in APR to produce an incremental cost-effectiveness ratio (ICER) [20], as follows:

$$ICER = (Cost_A - Cost_B)/(APR_A - APR_B)$$

Where $Cost_A$ and $Cost_B$ are the total costs, and $APR_A$ and $APR_B$ are the APRs, associated with the intervention and control arms of the trial, respectively.

As the outcome is measured in natural units there is no pre-defined decision rule for the ICER. However, our analysis may be used to inform a decision maker's value judgement on whether the multi-dimensional intervention to reduce APR is a good use of resources.

All analyses were performed using Stata© Version 14.

**Uncertainty analysis**

The level of sampling uncertainty around the ICER was determined using a non-parametric bootstrap, specifying clusters defined by the township hospital and strata defined by the county in which the hospital was located, to generate 10,000 estimates of incremental cost and benefits which were plotted on the cost-effectiveness plane [18, 21, 22]. For completeness, we also computed the expected value of the incremental costs and percentage point reduction in APR from the bootstrapped estimates, using the same methods as above.

**Sensitivity analysis**

For the primary analysis we used a weighted average of the salaries of the doctors attending the review meeting as the average salary of doctors in a health facility, which was used to calculate the cost of consultations. This assumption was necessary as the seniority of doctors taking consultations was not recorded. We conducted sensitivity analyses to explore scenarios where all consultations were taken by a specific level of staff: junior, middle or senior.

**Results**

Of the 4903 participants whose endline prescriptions were randomly selected to be included in the trial, 4800 with fully complete data (in all covariates of the analysis) were included in

the cost-effectiveness analysis. Outcome and cost data is reported below for this sample population of 2,485 participants from 13 health facilities in the control arm and 2,315 participants from 12 health facilities in the intervention arm.

**Health outcomes**

The proportion of prescriptions in each trial arm which contained at least one antibiotic over the trial are presented in Table 2. We observed a larger, and statistically significant ($p=0.0002$), reduction in APR in the intervention arm than in the usual care arm.

**Resource use and costs**

Mean total healthcare costs are presented in Table 3, broken down by costs associated with the use of healthcare, those associated with the monitoring of prescriptions and those associated with medications. We found no significant difference ($P>0.05$) between the intervention and the control arms in any of the individual cost components or the total costs.

**Implementation costs**

The cost of implementing the intervention was $390.65 (SD 145.68) per facility, including training for doctors and information resources for patients. This represents the upfront cost, per facility, policy makers would need to consider when making decisions about wider implementation of this intervention. This figure is based on an average of 26 (SD 13.98) doctors at facilities in the intervention arm, assuming all doctors are trained, all doctors receive a handbook and that each facility receives 3 posters to put on display.

**Cost-effectiveness results**

The cost-effectiveness results from the primary analysis are shown in Table 4. After accounting for clustering, stratification and a range of covariates, we found the APR in the intervention group reduced by 29.23 percentage points at an additional cost of $1.02 per patient compared to the usual care group, producing an ICER of $0.03 per percentage point reduction in antibiotic prescribing.

**Uncertainty analysis**

The results obtained from the non-parametric bootstrap are also presented in Table 4. The incremental cost and consequently the ICER obtained from the bootstrapped estimates are slightly lower than that obtained from the observed data.

The bootstrapped estimates were plotted on the cost-effectiveness plane shown in Figure 1. This shows a consistent reduction in APR with the intervention. There is uncertainty around the costs as the cloud crosses the x-axis at 0, with 30% of the points indicating a cost saving with the intervention.

**Sensitivity analysis**

We conducted sensitivity analyses exploring scenarios where all consultations were taken by a specific level of doctor: junior, mid-level or senior (Table 5). These results may not accurately present an upper and lower bound to the costs because of the variance in salaries at each level and limited data on salary costs of senior staff (Appendix Table 1). More importantly, the sensitivity analyses show that in each scenario the results change very little. In each case the results of the sensitivity analyses find the conclusions drawn from the primary analysis to be robust.

## Discussion

A 29 percentage point reduction in APR was achieved at an average upfront cost of $390.65 per health facility and an incremental cost of $1.02 per patient in the intervention arm compared with the control arm. This produced an ICER of $0.03 per percentage point reduction in APR, meaning the intervention is close to cost-neutral.

Average total healthcare costs of the two arms were not significantly different ($p>0.05$). Our analysis also indicated that there is uncertainty around whether the intervention will incur additional costs compared with usual care, or whether it would be cost saving. This may be due to similar consultation times (11 (SD 5.3) minutes and 10.5 (SD 5.85) in the control and intervention groups, respectively), and similar consultation costs. Promoting communication behaviours has been shown to reduce parental demand for antibiotics [23]. The development of communication skills was a key component of the training content [10], and we have shown that persuading caregivers not to use antibiotics will not necessarily increase consultation time. Prescription monitoring and review meetings also did not lead to a significant increase in the intervention arm cost compared to the control arm ($p>0.05$). This was aided by the pragmatic design of the trial, which encompassed the strengths of operational research [24], and embedded the intervention within routine practice: it was usual practice to monitor and appraise prescriptions, although without the specific antibiotics component. One hypothesised consequence of reducing antibiotic prescribing was that more expensive treatments and medications would be prescribed instead which could negatively impact patients due to increased out-of-pocket payments (depending on the type and level of health insurance they held) [25]. However, we found no significant difference in medication

costs between the two arms ($p>0.05$), indicating this is unlikely to be an issue. This may be due to the 'zero mark-up' policy implemented since 2009 in China, which limits doctors' incentive to prescribe greater quantities of, or more expensive, medicines [26]. Other low-cost alternatives to antibiotics, such as vitamins, may be considered in other settings because caregivers may demand medicines.

The implementation cost for this intervention ($390.65) is much lower than other multifaceted programmes to reduce antibiotic dispensing in primary care [27]. This may be due to lower costs for trainers' and trainees' time in China. Furthermore, we used face to face training, provided by experts from local county hospitals which improved effectiveness due to their strong connections with doctors in local primary healthcare facilities and reduced costs due to lower fees than provincial or national level experts. Our approach is therefore likely to be appropriate for scale-up in low- and middle-income countries.

Our study fills an urgently-needed gap in the evidence of the cost-effectiveness of multifaceted interventions to improve antibiotic prescribing in contexts of low- and middle-income countries. Few previous intervention programmes to improve antibiotics use reported cost data [27], and no study reported cost-effectiveness analysis [6]. This study is therefore crucial for informing future policy and decisions related to the reduction of antibiotic prescribing to address the global public health issue of antimicrobial resistance. It provides valuable information on effective and cost-effective strategies to reduce antibiotic prescribing as well as evidence on successful ways to achieve engagement with such policies.

This study has several limitations. Firstly, cost data was not collected within the trial and collecting it retrospectively has constrained what was possible within this analysis. For example, it was not possible to collect patient-level data on wider healthcare resource-use or quality of life. However, the information that was collected, along with the expertise of the trial coordinators and cooperation of hospitals and their staff has enabled us to present a rounded, although pragmatic analysis. Secondly, as the implementation costs are derived from the trial data, they could be over-estimated due to additional cost savings through economies of scale if it was implemented nationally. Thirdly, given the limitations in the data available we were unable to include other health service use costs or project future health costs and the effect these may have on individual expenditures. However, we might cautiously expect a reduction in costs in the longer term if the health benefits associated with antimicrobial resistance accrue and are sustained. Fourthly, we did not collect patient return visit or visits to emergency department due to respiratory infections, so we were unable to determine if reducing antibiotics increased bacterial infections. However, patients with bacterial infections were excluded, while most viral URTIs are self-limiting. Similar trials using educational materials reducing antibiotics were unlikely to cause bacterial infections.[28, 29] Finally, the trial was conducted in a relatively short time, which may add uncertainties around the sustainability of effectiveness. Long-term follow-up to monitor the effectiveness of the trial up to 12 months post randomisation is being conducted.

## Conclusion

A multifaceted intervention programme including: operational guidelines on URTI management for healthcare providers; facilitated training on using and applying the guidelines in consultations; monthly antibiotics prescribing peer-review meetings; and additional health education delivered to caregivers (during consultations, via leaflets and a

video), has effectively reduced inappropriate antibiotic prescribing among children with URTIs at a low cost in primary care settings in rural China. This programme has the potential to be scaled up in similar low resource settings.

## Abbreviations

URTIs, upper respiratory tract infections

APR, antibiotic prescription rate

ICER, incremental cost-effectiveness ratio

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**Attached documents**

Table 1: Unit costs - implementation

Table 2: Health outcomes - Antibiotic prescription rate

Table 3: Mean total healthcare costs

Table 4: Cost-effectiveness results

Table 5: Sensitivity analyses

Figure 1: Cost-effectiveness plane

Appendix Table 1: Unit costs