An analysis plan for a pragmatic cluster randomized controlled trial for reducing irrational antibiotic prescribing among children with upper respiratory infections in rural China

Introduction

Irrational use of antibiotics, defined by the World Health Organization as antibiotic prescriptions exceeding 30% of all prescriptions,[1] is a serious issue both within China and internationally. Worldwide, around 50% of medicines are not appropriately prescribed, dispensed or sold.[1] Irrational use of antibiotics not only brings high economic burdens to health systems, but also increases the risk of antibiotic resistance.[1] Acute upper respiratory infections (URIs) are very common among children, but are usually viral and self-limiting, with antibiotic treatment being unnecessary.[2] However, irrational use of antibiotics for URIs in children is very prevalent in primary care settings internationally.[3]

A cross-sectional study in ten provinces in rural Western China showed that antibiotics accounted for over half of all prescriptions, predominantly provided for URIs, and with approximately one quarter of those receiving antibiotics being children under ten years old.[4] Irrational antibiotic use amongst children is known to contribute to higher childhood mortality in countries with inadequate health infrastructure.[5] Several national policies have been issued by the Ministry of Health, including the most recent one limiting antibiotic prescriptions to less than 60% of all prescriptions for inpatients and 20% for outpatients.[6] However, no operational details were provided on how to implement the policy, and no guidelines were provided for the diagnosis and treatment of URIs in children, or related clinician training. Potentially because of this situation, despite attempts at health sector reform there has been no significant improvement in the rational use of antibiotics or cost control in China.[7]

Commonly reported interventions for improving antibiotic use in URI treatment include clinical decision support,[8-11] clinician communication skills training,[12-14] education and feedback,[15] public reporting of antibiotic prescribing rates,[16] discussion and monitoring workshops,[17] governance structure change,[18] and interventions based on behavioural economics and social psychology.[19] However, a Cochrane review demonstrated that while multi-faceted interventions targeting both physicians and patients significantly reduced inappropriate antibiotic use in community settings,[20] single interventions with parents failed to impact on antibiotic prescribing.[21-23]

Therefore, we developed a multidimensional intervention targeting doctors and patient caregivers that aimed to reduce the irrational use of antibiotics for treating URIs in children within China's rural primary care context (specifically within township hospitals). The intervention was developed through exploratory work, and its feasibility, acceptance and the adequate adherence of doctors to the intervention has been confirmed via an internal pilot.

Aims and objectives

This study aims to evaluate the clinical effectiveness of the intervention in realistic primary care settings in rural China, by determining whether the intervention reduces the amount of antibiotics prescribed for URIs in child outpatients within township hospitals, compared to existing prescribing practice.

Study design

The trial has been designed as a pragmatic, parallel-group, cluster randomised, controlled trial. The trial will evaluate the superiority of the intervention within township hospitals, which are therefore the unit of randomization.

Randomization process

In total 25 township hospitals were eligible for the trial, with 14 in Rong County and 11 in Liujiang County. Randomization was stratified by county to avoid imbalances in allocation between counties, because of the potential for important variation in outcomes between the counties. Randomization was further restricted within each county to a subset of all possible allocation ratios. Within Rong County randomization was restricted to only that subset of allocations that resulted in equal numbers of township hospitals in each arm, and in Liujiang County randomization was restricted to only that subset of allocations that resulted in the allocation of township hospitals to the treatment and control arms in a 5:6 allocation ratio. This allocation ratio was chosen to ensure that the allocation ratio was as equal as possible with an odd number of township hospitals, whilst minimizing the logistical costs of the treatment arm by having the additional hospital allocated to the control arm. After all 25 hospitals were randomized, within Rong County 6 hospitals, 3 from each arm, were further randomly selected to become the internal pilot clusters. The remaining 19 township hospitals (8 in Rong County and 11 in Liujiang County) will therefore participate in the main trial, along with the 6 hospitals involved in the internal pilot. Therefore, overall the 25 hospitals were allocated to treatment and control arms in a 12:13 allocation ratio. Randomization was conducted by the study statistician (JPH) using a computer program written in R (version 3.2.0).[24 25]

Outcome data will be collected from at least 5000 prescriptions (approximately 200 per hospital) issued for URIs in outpatients aged between 2 and 14 years old during the three months before the implementation of the intervention to provide baseline data, and during the 4^{th} to the 6^{th} month following randomization of hospitals.

Within intervention hospitals all family doctors will receive training to increase their knowledge on the rational use of antibiotics, and to improve the effectiveness of their communication skills when interacting with caregivers of children with URIs, facilitating the education of caregivers on the rational use of antibiotics. Monthly peer review meetings will also assess doctors' antibiotic prescribing practices, and reinforce desired behaviours. Printed and video-based educational materials will also be provided for caregivers in intervention hospital waiting rooms to improve understanding about the rational use of antibiotics. In control hospitals none of the intervention components will be implemented, and the only apparent impact will be via the collection of prescription data.

Blinding is clearly not possible for doctors or caregivers, but there will be blinded evaluation of all outcomes. A cluster design was chosen due to the difficulty of preventing contamination of both doctors and caregivers, and the need for hospital-wide participation of doctors in the peer review meetings, which are a key component of the intervention.

Sample size

Based on our exploratory study the current APR is approximately 50%, which is therefore assumed for the usual care arm. We expect our intervention to lead to at least a 25% relative reduction in the antibiotic prescription rate within township hospitals, based on a conservative estimate from our systematic review.[26] Consequently, to detect a 25% or greater reduction in the APR (i.e. an absolute reduction to 37.5% APR or less) with 90% power, using two-sided testing at the 5% significant level, assuming a harmonic mean cluster size of 200 and a between cluster coefficient of variation of 0.15 (based on exploratory and pilot work), we estimate that we require 9 township hospitals per arm.[24] Allowing for stratified randomization and a 10% loss of data, due to lost and illegible prescriptions, requires a total of 24 township hospitals. As there are 25 eligible township hospitals within the two counties it was decided to include all 25.

Outcomes and data

All outcome data will be obtained from the prescriptions collected at baseline and during follow-up, either in the form of electronic or photographic records of paper copies of prescriptions. Information collected will include the township hospital, the date of the prescription, the patient's age, symptoms, diagnosis, prescribed medicines, related treatment, related laboratory tests, treatment payment and insurance status.

Primary outcome

The antibiotic prescription rate for childhood URIs. Measured at the township hospital level, and defined as the proportion of prescriptions for URIs among outpatients aged between 2 and 14 years old that include at least one antibiotic. The antibiotic prescription rate is the primary outcome because it should reflect the behaviour change of both doctors and caregivers. Most URIs are caused by viral infection that are self-limiting and do not require antibiotics, and a reduction in this rate will be a clinically beneficial outcome demonstrating increased rational prescribing of antibiotics for childhood URIs. This measurement is also reliable and feasible in the primary care setting because prescriptions are well preserved either electronically or in paper files.

Secondary outcomes

- The childhood URI multiple antibiotic prescription rate: measured at the township hospital level and defined as the proportion of prescriptions for URIs among outpatients aged between 2 and 14 years old that include two or more antibiotics;
- The childhood URI broad-spectrum antibiotic prescription rate: measured at the township hospital level and defined as the proportion of prescriptions for URIs among outpatients aged between 2 and 14 years old that include a broad-spectrum antibiotic;
- The childhood URI quinolones prescription rate: measured at the township hospital level and defined as the proportion of prescriptions for URIs among outpatients aged between 2 and 14 years old that include a quinolone antibiotic;
- Additionally, to understand the medical costs associated with antibiotics prescribing we will measure the mean cost (in Yuan) at the township hospital level of childhood URI prescriptions, based on all prescriptions for URIs among outpatients aged between 2 and 14 years old.

Secondary outcomes were chosen to assess the extent to which the intervention will reduce other commonly observed practices in routine primary care relating to antibiotic prescribing

practices for URIs that are particularly likely to increase drug-resistance, and the intervention's cost effectiveness.

Missing data

An exploration of the patterns of missingness will be conducted, but it is expected that due to the most likely and plausible reasons for missing data (lost paper and electronic prescriptions records, and unreadable paper prescription records), missing data will be missing completely at random. Therefore, only complete case analyses will be conducted unless there is an indication that data may be missing at random, in which appropriate methods to deal with missingness will be employed as sensitivity analyses in addition to the complete case analyses.

Populations

Township hospital eligibility criteria

All township hospitals from the two selected counties in Guangxi who agree to participate in the study will be included. However, we will exclude the two township hospitals located in the two county centres. Compared to all other township hospitals they have much higher staff capacity and equipment levels, and their proximity to the county general hospital is likely to result in patient populations with substantially different characteristics.

Patient prescription eligibility criteria

All outpatient prescriptions for children aged between 2 and 14 years old who are diagnosed with URIs during the study period will be included for analysis. Children under 2 years old will be excluded because they are more vulnerable to secondary bacterial infection, and exploratory work indicated that it was very difficult for doctor's to refuse antibiotics for younger children in China's context. Prescriptions for children diagnosed with pneumonia (where antibiotic prescription is appropriate) or other severe diseases requiring long-term antibiotic treatment (or as prophylaxis) will also be excluded. Prescriptions for inpatients will not be collected.

Populations

The intention-to-treat (ITT) population is defined as all outpatient-prescriptions issued for URIs in children aged 2-14 years old collected from township hospitals, regardless of the compliance of township hospital doctors and/or caregivers to the intervention. All statistical analyses of primary and secondary outcomes will be by ITT.

Data handling

Data monitoring

All personally identifying details will be removed from the study database. Data will be checked weekly for quality and completeness by the study data manager, and any missing data will be followed-up with township hospitals until received (if electronically available), confirmed as set aside for later collection by researchers (if paper-based) or confirmed as not available. Recruitment rates will be monitored on a monthly basis. There is no Data

Monitoring and Ethics Committee or equivalent associated with the study. Data collected from electronic or photographic records of prescriptions will be entered into a password-protected SPSS database (version 20.0, IBM Corp. Armonk, NY.).

Data validation

Prior to analysis the final database will be validated using a STATA program to identify any anomalous, inconsistent and missing data. This program will check/identify:

- Eligibility criteria of prescriptions
- Consistency of prescription issue dates relative to the baseline and outcome data collection periods
- Outlying and anomalous (e.g. incorrect format, impossible value) data
- Missing data

All anomalous, inconsistent or unexpectedly missing data will be checked against original paper or photographic prescription records where feasible. Any anomalous or inconsistent data that can be unambiguously corrected will be, but where any ambiguity cannot be resolved values will be recorded as missing data.

Data analysis

General calculations

Percentage calculations will exclude any missing prescriptions from the denominators. Summary statistics such as percentages and means will be rounded to 1 decimal place, or 1 significant figure for numbers less than 1, but standard deviations will be rounded to 2 decimal places, or 2 significant figures for numbers less than 1. Parameter estimates, including standard errors SEs and 95% confidence intervals (CIs), will be rounded to 2 decimal places, or 2 significant figures for numbers less than 1. All hypothesis testing will be 2-sided and at the 5% significance level. All analyses will be carried out using STATA Version 12.1 (SE) software, but other packages will be employed if necessary. The primary and the secondary outcome analyses will be based on the intention-to-treat (ITT) population. All analyses will be conducted by the study statistician (JPH).

Planned analyses

No interim analyses are planned. Therefore, all outcomes will be analysed after data collection is completed.

Baseline characteristics

The baseline characteristics of the ITT population (including gender, age, insurance type, total prescription fee, total number of medicines prescribed; whether or not they were prescribed an antibiotic, a broad spectrum antibiotic, multiple antibiotics, and which category of antibiotic(s) they were prescribed; whether the antibiotic was delivered via injection or orally; and type of diagnosis) and township hospitals (within township hospitals catchment areas the number of residents, average annual income, number of village clinics and the number of doctors who can prescribe medicines) will be summarised using frequencies (plus sample sizes) and means (plus SDs) as appropriate for each treatment group.

Primary and secondary outcome analyses

The crude and covariate adjusted average effect of the intervention on outcomes will be analysed using methods appropriate for cRCTs with small numbers of clusters per arm.[24] For the primary outcome an estimate of the overall risk ratio between the intervention and control arms will be estimated from the weighted average of the stratum-specific risk ratios, with weights that are inversely proportional to the stratum-specific variances. Stratum-specific risk ratios will be calculated from the unweighted stratum-specific risks (mean township-hospital-level outcomes) in each arm. If the within-arm distribution of risk ratios is found to be strongly skewed for an outcome, a logarithmic transformation will first be applied to the outcome proportions. Formal testing of the null hypothesis that the overall risk ratios are equal to 1 will be conducted using stratified t-tests, and 95% confidence intervals will be adjusted for between-cluster variance and stratification.

Secondary outcomes involving proportions will be analysed using the same methods as the primary outcome, whilst the average cost of childhood URI prescriptions outcome will be analysed using similar methods, but with stratum-specific differences between the mean township-hospital-level outcomes in each arm used in place of stratum-specific risk ratios.

To adjust for potentially important covariates, including baseline values of outcomes, sex, age and additional important individual and township-hospital level factors two-stage adjusted analyses will also be conducted. For the primary outcome a logistic regression model will be fitted to the individual-level data including stratum and the covariates of interest as fixed effects, but without adjusting for the treatment effect. Covariate-adjusted ratio residuals will then be calculated from the ratios of cluster-specific observed and expected values. The covariate-adjusted ratio residuals will then be used in place of cluster-specific proportions to conduct stratified t-tests and calculate 95% confidence intervals using the above methods. To analyse the secondary outcomes involving proportions the same methods will be used as for the primary outcome. To analyse the average cost of childhood URI prescriptions outcome the same two-stage method will be employed, but using a normal regression model instead, and with cluster-specific difference residuals, calculated from the differences between cluster-specific observed and expected values, used in place of stratum-specific differences in means. Following CONSORT guidelines both unadjusted and adjusted results will be presented.

For all outcomes within each treatment arm and strata estimates of the between-cluster coefficient of variation and the intraclass correlation coefficient will also be calculated and made available to facilitate future trial planning and systematic reviews.

Subgroup analyses

Planned sub-group analyses will be conducted on outcomes to determine whether there is any significant heterogeneity (or effect modification) in treatment effects occurring between important groups, such as across patients of different genders and ages, and between hospitals of different sizes. Cluster-level subgroup analyses will be based on cluster-level covariates with two groups only, given the limited number of clusters. The methods for unadjusted cluster-level analyses described above will be used for the cluster-level subgroup analyses, but applied separately to the two groups of clusters, as determined by the relevant cluster-level covariate, to obtain estimates of the treatment effect, its 95% confidence interval and statistical significance within each subgroup. However, if the number of clusters per stratum

are too few for either of the subgroups then a non-stratified version of these methods will be used. To estimate the statistical significance of any differences in treatment effect between subgroups analysis of variance will be used on the cluster-level summary outcome data, with terms for treatment arm, the relevant subgroup and the interaction between them.[24]

Individual-level subgroup analyses will be based on computing the difference in outcome (logged when the outcome effect wanted is a ratio) between subgroups within each cluster, and then comparing the mean difference in the treatment and control arms. To estimate the size (and associated 95% confidence intervals) and significance of any interaction between the treatment effect and subgroups (i.e. effect modification) an unpaired t-test will be conducted on the cluster-level differences between subgroups.[24]

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