A multifaceted intervention to reduce antibiotic prescribing among CHIldren with acute COugh and respiratory tract infection: the CHICO cluster RCT

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Scientific summary

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Scientific summary

Background

Respiratory tract infections (RTIs) in children are common and present major resource implications for primary care. Unnecessary use of antibiotics is associated with the development of antimicrobial resistance. Qualitative work from our National Institute for Health and Care Research (NIHR) TARGET Programme for Applied Research in 2016 identified clinician uncertainty regarding children's prognosis as a major driver of antibiotic prescribing and that improved identification of children at very low risk of future hospitalisation could increase confidence to withhold antibiotics. We developed an intervention that included: (1) eliciting carer concerns during consultation; (2) a clinician-focused algorithm to predict future hospitalisation for children with cough and RTI and (3) a carer-focused personalised printout recording decisions made at the consultation and safety-netting information. The intervention was not intended to replace but rather supplement clinical judgement.

In the feasibility trial, we found a recruitment differential at baseline in that intervention children were significantly more unwell than those recruited to the control group. We also found that recruitment procedures and using a stand-alone tool increased consultation times by 5 minutes. Learning from this, we proposed a more 'efficient' study design. We recruited practices rather than individual patients via Clinical Commission Groups (CCGs) and the national NIHR Clinical Research Network (CRN) and rather than trawl through the practice notes to collect primary outcome data, we utilised routinely collected data by the National Health Service (NHS) and CCGs. We also took a 'lighter touch' to data collection using short baseline and follow-up questionnaires filled in by designated practice champion [general practitioner (GP), nurse, practice manager or pharmacist] and embedded the intervention within the practice system rather than as a stand-alone tool. We hoped that this would not only mitigate recruitment differential but would also be resource efficient.

Objectives

Our aim was to assess whether embedding a multifaceted intervention into general practice for children (aged 0–9 years) presenting with acute cough and RTI would reduce antibiotic dispensing (superiority comparison) without impacting (non-inferiority comparison) on hospital attendance for RTI. We included a qualitative study to explore the use of the intervention, how it was embedded into practice and whether it was used appropriately and an economic evaluation of a between-arm comparison of secondary and primary care costs from an NHS perspective. We also report on the barriers and facilitators of using an efficient design.

Methods

The CHIldren with Cough (CHICO) randomised controlled trial (RCT) was an efficient, pragmatic, open-label, two-arm (intervention vs. control) trial of children in England aged 0–9 years presenting with an acute cough and RTI. The study received ethical approval (ref: 18/LO/0345) on 14 November 2018. Recruitment of practices was via CCGs and CRNs, between October 2018 and October 2020. Inclusion criteria were GP practices using the Egton Medical Information Systems (EMIS®) patient record system (used in 56% of English practices) where the local CCG had agreed to provide primary outcome data and the practice consented to take part. Practices were excluded if they were participating in any antimicrobial stewardship activities during the study period (12 months) involving potentially confounding concurrent intervention studies or were merging or planning to merge with another practice. Randomisation of

practices on a 1 : 1 basis was stratified by CCG and minimised for list size and previous dispensing rate in the 12 months before data collection was conducted by the independent Bristol Randomised Trials Collaboration (BRTC) unit.

A practice champion was appointed at each intervention practice to distribute training materials within the practice, co-ordinate training of prescribing staff, encourage all clinicians to use the intervention appropriately and report from the EMIS® system how many times the intervention was used. Intervention practices were sent instructions including screenshots on how to install the intervention on the EMIS® system. E-mail support was offered to the practice champion to help implement this and encourage appropriate use of the tool.

When a child was in the age range, the healthcare professional received a 'soft' (i.e. a reminder) pop-up on their screen asking if the child was presenting with RTI. The pop-up gave the option of opening the CHICO Intervention. The Intervention screen would also open if the healthcare professional input a RTI-specific EMIS® code during the consultation. The algorithm included seven predictors two of which (age of patient and history of asthma) were already available for automatic entry, the other five predictors (short illness duration, temperature, intercostal or subcostal recession on examination, wheeze and moderate or severe vomiting) were entered during consultation. The algorithm reported whether the child was at elevated, average or very low risk of hospitalisation in the following 30 days along with antibiotic prescribing guidance. The health professional also had the option to print a short personalised letter with safety-netting guidance for the carer. The intervention was used in practices over a 1-month period.

The clinicians in practices randomised to the comparator arm were asked to treat children presenting with acute cough and RTI as they would normally.

The co-primary outcomes for children aged 0–9 years over a 12-month period were the rate of dispensed amoxicillin and macrolide items prescribed, for all indications (superiority comparison) collected routinely by NHS Business Services Authority (NHSBSA) ePACT2 and the rate of hospital admission for RTI (non-inferiority comparison) routinely collected by CCGs. The denominator was those 0–9-year-olds registered at each practice. Baseline data surrounding the characteristics of the practice and follow-up data after 12 months were collected. A secondary outcome looking at the rate of accident and emergency (A&E) attendances for RTI was collected in a similar way to hospitalisations.

A roll-out to three CCGs was performed initially to address any teething issues with the intervention, the internal pilot phase lasted 3 months and included a further four CCGs to help establish best practice for recruiting and communicating with practices before widening to the remaining CCGs.

Both sample size calculations assumed 90% power and a conservative two-sided alpha of 0.025 to take account of the two co-primary outcomes, an intracluster correlation coefficient of 0.03 and an estimated coefficient of variation of 0.65 along with an assumption of 750 children aged 0–9 years registered per practice. A 10% difference in dispensing data and no more than a 1% difference in hospital admission yielded 155 practices per arm. All primary and secondary analyses were conducted on an intention-to-treat (ITT) basis. A full CHICO statistical analysis plan was developed and agreed by the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC). Mixed models were used to account for the within- and between-CCG level variation, incorporating the latter as a random effect. A random-effects Poisson regression model was used to analyse both co-primaries by arm, including list size as the exposure and baseline rate as a covariate. All analyses were carried out in Stata 17.0 and the results were described in terms of 'strength of evidence' rather than significance.

For the qualitative analysis, anonymised transcripts from interviews with clinicians (GPs and practice nurses) were checked for accuracy and then imported into NVivo Pro (version 10/11) using thematic analysis and the four normalisation process theory (NPT) constructs to develop themes across the data

sets. For the economic evaluation, the comparison of between-arm costs used a two-way mixed-effect linear regression that accounted for the nesting of practices in CCG clusters. The primary economic analysis regressed total costs on arm and covariates for list size and dispensing rate, both of which were used for minimisation at randomisation.

Results

In 2018, there were around 200 CCGs in England, 110 were assessed as eligible (≥ 15 EMIS® practices), 52 consented to take part and 47 provided at least one practice. We also used all 15 CRNs in England to help with recruitment. Recruitment took 24 rather than 12 months continuing to October 2020 (due to slow response of some CCGs and impact of the COVID-19 pandemic). Of the 310 practices required, 294 (95%) were recruited (144 intervention and 150 controls) representing 336,496 registered 0–9-year-olds (5% of all 0–9-year-old children in England). Included practices were slightly larger and had slightly lower baseline dispensing rates, compared with practices not included from their CCG. They were also located more commonly in deprived areas reflecting the geographical distribution of practice postcodes nationally. Of the 294 practices, 12 (4%) subsequently withdrew (6 related to the pandemic).

The two arms were well balanced with respect to baseline characteristics. There were four serious adverse events (three intervention, one control) reported, none related to the intervention. Across the 121 (84%) intervention practices that provided at least 1 month of intervention usage data, a total of 11,944 intervention uses were recorded {median 70 [interquartile range (IQR) 9–142])}. Twenty practices (17%) recorded zero usage over the 12-month period. The median number of users per practice was nine (IQR 3–16). Of these, 74% were GPs, 14% were nurses, 6% were office staff, 3% were other clinicians, 3% were locum GPs and 1% were pharmacists. The baseline and follow-up data collection periods spanned October 2017–October 2021 thus included the COVID-19 pandemic which began in the spring of 2020. Both the use of the intervention and antibiotic dispensing data followed the expected seasonal winter peak until the pandemic during which the intervention usage dramatically fell and seasonal pattern disappeared with a notable decrease in antibiotic dispensing during pandemic lockdowns.

The main ITT analysis showed no evidence that the antibiotic dispensing rate in the intervention practices {0.155 [95% confidence interval (CI) 0.135 to 0.179])} differed from the controls [0.154 (95% CI 0.130 to 0.182)] with a relative risk (RR) of 1.011 (95% CI 0.992 to 1.029); $p = 0.253$. On average, this translates into 15 amoxicillin/macrolide items dispensed a year, per 100 registered patients aged 0–9 years. The pre-planned per-protocol analysis produced strong evidence of increased dispensing in the intervention arm [0.166 vs. 0.154, RR = 1.052 (95% CI 1.029 to 1.076), $p < 0.001$], although many non-compliant practices joined in the latter half of the study, when COVID-19 had lowered all dispensing rates leading to a surplus of 'low dispensing' practices in the control arm. There was weak evidence that the intervention decreased dispensing in the older children [RR = 0.965 (95% CI 0.935 to 0.997), $p = 0.030$] but increased dispensing in the younger children [RR = 1.037 (95% CI 1.014 to 1.060), $p = 0.001$]. Accounting for COVID-19 by including an indicator variable did not alter the primary finding. A post hoc analysis, removing all follow-up data after March 2020, led to reduced dispensing in the intervention arm [0.192 vs. 0.204, RR = 0.967 (95% CI 0.946 to 0.989), $p = 0.003$]; this equates to a 5.9% reduction but this observation is both post hoc and underpowered. Sensitivity analyses surrounding patient age, exclusion of pilot practices, a focus on amoxicillin only, delayed implementation and replacing the CCG random effects with Primary Care Network (PCN) random effects did not materially change dispensing rates. Some pre-defined subgroup analyses did interact with the treatment effect, with evidence of increased dispensing rates in the intervention arm among practices located in areas with a higher level of deprivation ($p = 0.004$), practices with more than one site ($p < 0.001$) and practices with a higher proportion of prescribing nursing staff ($p < 0.001$).

We found no difference in the rate of hospitalisations at 0.019 (95% CI 0.014 to 0.026) and 0.021 (95% CI 0.014 to 0.029) for the intervention and control arms, respectively [incidence rate ratio (IRR) was 0.952 (95% CI 0.905 to 1.003)]. As 1.003 lies below the 1.01 non-inferiority margin we set, the intervention was considered non-inferior to the controls. Pre-specified sensitivity analyses did not change these results. The usual winter peak of hospital admissions was absent during the pandemic. The secondary outcome of A&E attendance rates were 0.049 (95% CI 0.037 to 0.066) and 0.045 (95% CI 0.032 to 0.063) for the intervention and control arms, respectively. The IRR was 1.013 (95% CI 0.980 to 1.047); $p = 0.437$.

Twenty-six clinicians (20 GPs and 6 practice nurses) were interviewed via telephone from 24 practices and 13 CCGs. The qualitative findings confirmed that intervention clinicians started using the tool and then stopped over time. The clinicians liked the intervention and used it as a supportive aid during consultations rather than a tool to change behaviour. They really liked the safety-netting advice leaflet, and this was seen to be the most useful intervention component, especially for facilitating discussions with parents about treatment decisions. The intervention was believed to be more useful in patients who were seen as 'borderline'. Clinicians initially welcomed CHICO in theory but for some it proved difficult to align the intervention flow with that of the consultation, especially if the data entry of the patient's record was normally made after the consultation. In the follow-up questionnaire, when asked if they would use the intervention again, 73% of the practitioners said that they would.

For the economic evaluation, NHS costs were calculated from the costs of the intervention itself, prescriptions of amoxicillin and macrolides per the co-primary outcome, A&E attendances and hospital admissions. Data were complete. There was no evidence of a difference in mean NHS costs in those practice randomised to use the intervention compared to those that did not. This conclusion held under various sensitivity analyses, including a per-protocol analysis.

The 'efficient design' was viable and relatively easy to implement. Recruited practices included 5% of all 0–9-year-old children in England with wide geographical cover. Engagement with CRNs and installation of the intervention was straightforward although the impact of updates to practice IT systems and lack of practice IT skills required extended support in some practices. Engagement with CCGs and their understanding of their role in research was variable. Data on the co-primary outcomes using routine dispensing information from the NHSBSA ePACT system and routine hospital attendance from CCGs were almost 100%.

Conclusions

This study did not produce evidence that embedding a multifaceted intervention into general practice for children presenting with acute cough and RTI could reduce antibiotic dispensing or impact on hospital attendance for RTI. Inference of the findings was made difficult as the pandemic affected intervention usage, dispensing levels and hospital attendance. The clinicians liked the intervention and used it as a supportive aid during consultations rather than a tool to change behaviour. The use of an efficient design was successful in this trial suggesting using routinely collected data for primary outcomes at the practice level is viable in England and should be promoted for primary care research where appropriate. Although the intervention does not appear to change prescribing behaviour, elements of the approach may be used in the design of future interventions.

Trial registration

This trial is registered as ISRCTN11405239 (date assigned 20 April 2018) at www.controlled-trials.com (accessed 5 September 2022). Version 4.0 of the protocol is available at: https://www.journalslibrary.nihr.ac.uk/ (accessed 5 September 2022).

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This report

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