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TITLE:
Effectiveness of a cough management algorithm at the transitional phase from acute to chronic cough in Australian children aged <15 years: protocol for a randomised controlled trial

ABSTRACT:
INTRODUCTION: Acute respiratory infections (ARIs) are leading causes of hospitalisation in Australian children and, if recurrent, are associated with increased risk of chronic pulmonary disorders later in life. Chronic (>4 weeks) cough in children following ARI is associated with decreased quality-of-life scores and increased health and societal economic costs. We will determine whether a validated evidence-based cough algorithm, initiated when chronic cough is first diagnosed after presentation with ARI, improves clinical outcomes in children compared with usual care. METHODS AND ANALYSIS: A multicentre, parallel group, open-label, randomised controlled trial, nested within a prospective cohort study in Southeast Queensland, Australia, is underway. 750 children aged <15 years will be enrolled and followed weekly for 8 weeks after presenting with an ARI with cough. 214 children from this cohort with persistent cough at day 28 will be randomised to either early initiation of a cough management algorithm or usual care (107 per group). Randomisation is stratified by reason for presentation, site and total cough duration at day 28 (<6 and ≥6 weeks). Demographic details, risk factors, clinical histories, examination findings, cost-of-illness data, an anterior nasal swab and parent and child exhaled carbon monoxide levels (when age appropriate) are collected at enrolment. Weekly contacts will collect cough status and cost-of-illness data. Additional nasal swabs are collected at days 28 and 56. The primary outcome is time-to-cough resolution. Secondary outcomes include direct and indirect costs of illness and the predictors of chronic cough postpresentation. ETHICS AND DISSEMINATION: The Children's Health Queensland (HREC/15/QRCH/15) and the Queensland University of Technology University (1500000132) Research Ethics Committees have approved the study. The study will inform best-practice management of cough in children. TRIAL REGISTRATION NUMBER: ACTRN12615000132549.

Study objectives ::: Introduction:
Our primary objective is to determine if children aged <15 years with chronic (>4 weeks) cough post-ARI and managed according to an evidence-based cough algorithm have better clinical outcomes (faster cough resolution) than those receiving standard care.
Our secondary objectives are to:
Determine the cost-effectiveness of early intervention in chronic cough following an ARI compared to standard care.Identify the microbiological predictors of chronic cough following an ARI.Characterise the epidemiological, clinical, socioeconomic and cultural predictors of chronic cough following an ARI.Establish the epidemiological, clinical, socioeconomic and cultural predictors of success or failure of an early intervention in chronic cough following an ARI.
Our study tests the primary hypothesis that among children aged <15 years with chronic (>4 weeks) cough post-ARI, initiation of a cough management algorithm at the transition from acute to chronic cough will reduce cough duration.

Study design ::: Methods and analysis:
A nested, open-label RCT (with concealed allocation) within a prospective cohort study of children aged <15 years presenting to three primary healthcare services with an ARI that includes cough as a symptom, and who are followed for 56 days (figure 1).

Eligibility ::: Methods and analysis:
Inclusion criteria are:
Aged <15 years,At the time of attending the clinic, the child is identified as having a possible respiratory illness (including those reported to have fever or viral/bacterial illness) that has parent-reported cough as a symptom,Provision of written informed consent from the parent/guardian and assent from children aged 12—<15 years,Siblings are permitted if each meets the above criteria.
The exclusion criteria are: known diagnosis of an underlying medical condition, including chronic pulmonary disorders (excluding asthma); immunosuppressive illness, such as primary immunodeficiency, HIV infection or receiving immunomodulating drugs (except short-course (<2 weeks) oral and ongoing maintenance inhaled corticosteroids) in the 30 days prior to presentation; current or planned participation in another intervention study during the 8 weeks of follow-up;

severe ARI requiring hospitalisation, and/or insufficient English inhibiting provision of written informed consent or completion of participant interviews.

Recruitment ::: Methods and analysis:
Eligible children are identified when presenting to one of three primary healthcare centres in subtropical, Southeast Queensland, Australia, involving metropolitan Brisbane (population 2.2 million), the regional city of Toowoomba (110 000) and the rural town of Warwick (14 000). Parents and their child(ren) will be approached by clinic personnel and informed consent/assent obtained using written and/or pictorial plain language statements.

Data collection, follow-up and intervention ::: Methods and analysis:
Children enrolled in each of the three primary healthcare centre cohorts undergo baseline clinical assessments that include demographic details, medical history, risk factors for ARI and cough, presenting features, vital signs, investigations, treatment and cost-of-illness data (figure 1). Weekly telephone and/or email and/or face-to-face contacts collect cough status, type (ie wet, dry variable) and cough score,33 medication (including over-the-counter remedies) and health service provider use for the cough and cost-of-illness data. Wet and dry cough are classified as per parent/carer reports, which were found previously to be accurate (compared with respiratory physician and bronchoscopy) in a study of children with chronic cough.34 The cost-of-illness data are collected at each parent/carer contact, specialist review and from examining medical records. A minimum of three contact attempts are made at each weekly time-point. We did not employ daily diary cards as planned originally, since although their use in chronic cough studies was reliable, we found that in children with acute cough diary completion and return rates were low during preliminary work undertaken for this study. We also could not use smartphone apps as the ownership of smart phones in the target communities is low. Thus, instead we relied on weekly parent recall of acute child illness, which has been shown to introduce minimal bias (<10%) in prevalence studies.35
At day 28, any child with persistent cough (ie, ≤3 day break in cough in the preceding 28 days) is randomised (1:1 allocation) to clinical review and initiation of the cough management algorithm or to continue weekly follow-up. All study participants continue weekly follow-up until day 56 and any child still coughing at that time point undergoes clinical review until a definitive diagnosis is established or the child exits the protocol. The decision to follow children until day 56 was based on data from our ED cough study, suggesting 42% of children with persistent cough at day 28 will be diagnosed with PBB (manuscript in preparation) that resolves with a 14-day course of amoxycillin–clavulanic acid. Children requiring ongoing care beyond two study physician reviews are referred to a tertiary paediatric respiratory medicine service.
The study intervention involves study physician clinical review within 2 weeks of day 28 where the cough management algorithm (figures 2 and 3) is implemented depending on whether the child has a specific or non-specific cough. Children in whom the cough has resolved spontaneously between randomisation and physician review, and at that point are deemed by the study physician to require no further management, will not contribute to the primary analysis.
Children in the control group follow a standard care pathway. This reflects what occurs normally in the community for children with cough where the general waiting period for review by a paediatric respiratory physician is on average 6 weeks following referral from a family physician. The parents/guardians of children randomised to the control group are advised to continue follow-up with instructions that they will be reviewed by a study doctor following day 56 if they are still coughing. They are also counselled to seek advice from their family physician or other healthcare provider if their child becomes unwell or they are worried, otherwise to continue to self-manage their child's cough as they see fit.

Randomisation, allocation and blinding ::: Methods and analysis:
An independent biostatistician prepared the randomisation code using a permuted blocking design (block size of 4) to maintain group balance. Randomisation was stratified by reason for presentation (ARI with cough or another reason with an ARI noted incidentally), site and cough duration at day 28 (<6 or ≥6 weeks). Group allocation is concealed in opaque, consecutively numbered envelopes kept in a locked cabinet at the Centre for Children's Health Research, South Brisbane. At randomisation, the child's cough history over the past 28 days and study-specific strata are confirmed by the Central Coordinating Site. The Study Coordinator selects the next consecutively numbered, opaque, sealed envelope from the relevant strata pack, opens the envelope and extracts the randomisation code. Two people check the allocation and the code is

assigned to the participant. The Study Coordinator then arranges for the study physician to review within 2 weeks of randomisation those children allocated to the intervention arm. If siblings are also enrolled and each child is still coughing at day 28, randomisation occurs for the first child enrolled (ie, earliest study number) and all siblings are allocated subsequently to the same arm. Differences in strata (eg presentation type and cough duration) will be accounted for in the analysis.
Blinding is not undertaken in this study; however, parents are not informed at enrolment that their child will be randomised at day 28 to a specific intervention if the child has a persistent cough. Instead, they are informed that children who develop persistent cough will be reviewed by a paediatrician during the study with some children being seen earlier and some later in the 8-week follow-up period. Limited disclosure is permitted under the Australian ethical standards for human research36 if it is scientifically justifiable and does not present an increased risk of harm to the participant.

Definitions ::: Methods and analysis:
Definitions used for the clinical management pathway23
27 are as follows:
Asthma: recurrent (>2) episodes of wheeze and/or dyspnoea that responds (within minutes) to inhaled β2 agonist or demonstrates bronchodilator responsiveness documented on spirometry (≥12% change in the percentage predicted forced expiratory volume in 1 s after 400 µg of salbutamol).Cough resolution: improvement ≥75% or total resolution according to cough diary data for ≥3 consecutive days.37
38 When cough diary data are unavailable, resolution is defined as total cessation of cough according to parent/guardian verbal report.Chest radiograph abnormality: any abnormality (other than peribronchial thickening) identified by a paediatric respiratory physician or radiologist.Spirometry abnormality: as determined by the American Thoracic Society and European Respiratory Society criteria with Australian predicted values used.39Primary diagnosis of cough aetiology: diagnosis confirmed by subsequent specific treatment that resulted in cough resolution within 3 weeks.26
37 The diagnostic criteria are defined a priori following published guidelines:6
PBB: presence of an isolated chronic wet or productive cough, without signs of another cause and which responds to at least a 2 weeks course of an appropriate antibiotic, such as amoxicillin-clavulanate.Recurrent PBB: ≥3 episodes over a 12-month period.Reversible airway obstruction: in accordance with American Thoracic Society and European Respiratory Society criteria and adopting Australian predicted values.39Secondary diagnosis: diagnosis found on objective tests, but where: (1) specific treatment did not lead to resolution or improvement in the cough; or (2) no treatment for this diagnosis was trialled and the cough either resolved spontaneously or with other therapies.6Specific cough pointers: presence of any of the following: auscultatory abnormality (wheezes, crackles or differential breath sounds), classical cough characteristics, cardiac abnormalities, chest pain, chest wall deformity, daily moist or productive cough for >3 months, digital clubbing, dyspnoea (exertional or at rest), failure to thrive, feeding difficulties (including choking/vomiting), haemoptysis, immune deficiency, neuro-developmental abnormality, recurrent pneumonia and wheeze. These pointers are explained in the Thoracic Society of Australia and New Zealand position statement.37Tertiary hospital management: that usually requires investigations to be conducted at a paediatric tertiary centre (eg, flexible bronchoscopy with bronchoalveolar lavage, chest high-resolution CT scan, fluoroscopic swallow screening, etc).

Specimen collection ::: Methods and analysis:
At recruitment, exhaled carbon monoxide (eCO) measures from the child (if aged ≥ 3 years and can provide an adequate sample) and parent/guardian are collected to provide an objective, non-invasive assessment of cigarette smoking status and exposure40 using a portable eCO monitor (Smokerlyzer, Bedfont Scientific, England).
All children have bilateral anterior nasal swabs collected at enrolment and at days 28 and 56. Anterior nasal swabs rather than nasopharyngeal swabs are being used as: (1) they are more acceptable to children; (2) in our experience have comparable sensitivity to nasopharyngeal specimens41 and, besides, any loss in sensitivity is considered acceptable when the purpose of the specimen is epidemiological rather than for a clinical diagnosis42 and (3) they permit more extensive swabbing of the nares. Nasal swabs are collected using Virocult plain cotton tip swabs with viral transport medium (Virocult, MW951, Medical Wire and Equipment, England) inserted 1 cm into the nostril and rotated four times on the right side and then on the left side. Swabs are

stored locally in −20°C freezers before being transported to the research laboratory where they are stored at −80°C until processing occurs.

Laboratory methods ::: Methods and analysis:
Swabs are batch-tested for respiratory viruses and bacteria using validated real-time PCR assays described previously.42
43 Virus testing includes rhinoviruses, adenovirus, respiratory syncytial virus, influenza virus types A and B, parainfluenza virus types 1–3, human metapneumovirus, human coronaviruses (OC43, 229E, NL63, HKU1), human bocavirus and human polyomaviruses KI and WU. Bacterial testing includes Bordetella pertussis, Mycoplasma pneumoniae, Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae (including differentiating between encapsulated and non-encapsulated strains and Haemophilus haemolyticus) and Moraxella catarrhalis.

End points ::: Methods and analysis:
Participation is completed 56 days (+3 days) following enrolment or, for children in the RCT, when a final diagnosis is determined by the study physician. Other exit points are serious protocol violations and worsening of the child's condition that requires hospitalisation or other active intervention elsewhere. Children meeting the exit criteria will continue to be followed until the end of the study period.

Outcome measures ::: Methods and analysis:
Primary clinical outcome: Time-to-cough resolution in days.
Secondary cost-effectiveness outcomes: Total direct and indirect costs of illness calculated according to the criteria outlined in table 1.
Secondary microbiological outcomes: Anterior nasal detection by PCR of respiratory viruses and bacteria at days 28 and 56.

Sample size ::: Methods and analysis:
Sample sizes for each of the primary healthcare cohorts comprising this study are based on the expected number of eligible children with ARI presenting to each of these services over the study's timeframe and derived from our current studies of chronic cough post-ARI in children.22 52 Between July 2015 and June 2017, we anticipate 750 eligible children will present to the primary healthcare services participating in this study.
Our preliminary data from a cohort study of Indigenous children aged <5 years22 suggest 20% of Indigenous children with an ARI will have chronic cough at day 28. Based on data from the first study of the algorithm28 for the primary end point of cough resolution at day 56, we anticipate a 54% reduction in the proportion of children (54.3% in the early arm compared with 29.5% in the delayed arm) with persistent cough at day 56. Hence, 89 children per group with complete evaluable data at day 56 will provide 90% power (α=0.05), to detect this 54% reduction for our primary aim. Assuming a 20% loss to follow-up and spontaneous resolution of cough of between randomisation and physician review of 5%, we will therefore randomise a minimum of 112 children per group at day 28 across all 3 sites.
Given that the entire cohort study will have a 2-year recruitment period, and the natural history and predictors of chronic cough and cost-effectiveness of the intervention are important secondary outcomes, we will not limit recruitment to the RCT arm once 224 children have been randomised. Ongoing enrolment will hence increase study power to address the primary and secondary objectives. This approach has approval from the all relevant human research ethics committees (HREC).

Data management ::: Methods and analysis:
Data will be entered into a password-protected, custom-built, Filemaker Pro Advanced V.14 (Filemaker, Santa Clara, USA) database. The database has been designed to incorporate automatic data checking including logic and inaccurate ranges and maintains a log of any changes to the data. Data fields cannot be left blank and missing data must be coded as such in the database. A specific data management protocol compliant with the Queensland University of Technology's data management policies and principles is in place.

Primary objective ::: Statistical methods ::: Methods and analysis:
Intention-to-treat analyses will be employed. Time-to-cough resolution will be compared between groups using the Cox proportional hazard methods, adjusting for independent explanatory

variables, subject to modelling assumptions being met, particularly proportionality of hazards. All analyses will be performed on the whole cohort and then additional analyses will be performed using frailty models54 that account for the clustering effects of siblings and site of recruitment.

Economic objectives ::: Statistical methods ::: Methods and analysis:
Costing of the intervention will be performed according to established methods,55
56 including detailed subanalyses of data that account for epidemiological, social, cultural, risk factor and microbiological variables. Cost-effectiveness analysis (CEA) will be modelled using the health sector perspective. Broader societal issues using data from the trial as described above and augmented by the evidence from the literature, especially systematic reviews, will also be taken into consideration. The CEA approach will involve: identification of resources using the intervention pathway (activities, probabilities and unit costs); measurement of resource use/ outcomes; and valuation of costs using unit costs published in the literature and from the trial itself. The time horizon will be specified and current practice (standard care) will be the comparator; and future costs and benefits will be discounted at 3% to present values. Central to this analysis will be the modelling of uncertainty surrounding data quality and gaps using sensitivity analyses, and extension of time horizon, using Treeage software (Treeage Software, Williamstown, Massachusetts, USA). The key outcomes will be incremental cost-effectiveness, and cost-savings to the health system due to the interventions.

Other objectives ::: Statistical methods ::: Methods and analysis:
Multivariable modelling will be employed to: (1) evaluate the microbiological predictors of chronic cough following an ARI as determined at days 28, 42 and 56 postenrolment; (2) evaluate the epidemiological, clinical, socioeconomic and cultural predictors of chronic cough at day 28 post-ARI; (3) evaluate the epidemiological, clinical, socioeconomic and cultural predictors of success or failure of the intervention at day 56 and (4) to compare these predictors between the three study populations. Crude and adjusted relative risks and the respective 95% CIs will be presented, with differences considered statistically significant at $p<0.05$.
Subgroup analyses will be performed for all primary and secondary objectives to examine potential differences by study-specific strata. Univariate and multivariate analyses will be performed to evaluate variables independently associated with study end points and to assess potential confounding factors in the association between vaccination and disease. Multiple imputation models will be used to evaluate the effect of missing data. Additional analyses will be undertaken to assess the effect of multiplicity in the assessment of microbial associations with cough outcomes.

Participant safety ::: Statistical methods ::: Methods and analysis:
Parents/guardians of all participants will be informed of any new information that arises during the study that may indicate potential harm to the child if he/she were to continue in the study. Any trial-related adverse events will be documented and reported to the relevant HREC. Serious adverse events will be reported to the HREC within 24 hours of notification and will be followed until resolution. A decision to withdraw the child following a serious adverse event will be made in consultation with the HREC, investigating team and the child's primary physician. If an adverse event is deemed related to study procedures, the child and his/her family will be eligible for compensation under the Clinical Trial Insurance policies in place for the duration of the study. All participant data will be kept confidential and stored securely in accordance with Australian Privacy Laws. Identifying data will not be provided to any persons outside of the study team unless required by Australian law (eg, in the event of the diagnosis of a notifiable disease). Published data will be deidentified and presented in aggregate form.

Independent monitoring and quality control ::: Statistical methods ::: Methods and analysis:
Independent study monitors have been engaged to undertake regular data quality audits, assess compliance with Good Clinical Practice guidelines and ensure that the study is being conducted according to the study protocol and ethical approvals. Inbuilt data quality monitoring and generation of data queries are established within the trial database, with data queries sent to study sites weekly for resolution.

Protocol amendments ::: Statistical methods ::: Methods and analysis:

All protocol amendments will be submitted to the study's HREC (see below) for approval prior to implementation. If any amendments have the potential to affect a family's willingness to continue in the study, all participants will be reconsented to the amended protocol.

Study status ::: Statistical methods ::: Methods and analysis:
Recruitment began in July 2015.

Dissemination:
Participants will be provided with regular study progress reports and a written letter outlining the results of the study. The trial results, including any negative findings, will be published in open-access peer-reviewed journals and presented at scientific conferences, paediatric society and general practitioner meetings and other fora. The primary author of the main paper will be the principal investigator (KFO). The trial findings are likely to be incorporated into clinical management guidelines. Study data will be held in metadata repositories until the youngest child turns 25 years of age at the Queensland University of Technology. Deidentified study data will be made available to external parties on request and, if relevant, with the appropriate HREC approvals.

Discussion:
Chronic cough in children is a defining symptom of several chronic pulmonary disorders worldwide. Preventing persistent cough in children may lead to important short and long-term health benefits. Our proposed intervention22
26 is similar to the existing Australian guidelines,57 but also has some differences that were developed following the incorporation of new data unavailable at the time the guidelines were published. The use of guidelines by clinicians depends on several factors, which include level of evidence, feasibility, degree of implementation and inherent clinician factors.58 Using an algorithm facilitates clinical guideline implementation by clearly describing pathways of care based on whether the child presents with a specific or non-specific cough. While this study uses specific study physicians, the overall goal is widespread adoption of the guidelines and management algorithm in the primary healthcare setting. Our extensive data collection, including direct and indirect costs of illness and healthcare provision, are important in achieving this goal. The study will also provide an avenue for assessing the extent to which these guidelines are being used currently in different clinical settings given. We will collect data on any intervention a child may receive external to our study.
Study site selection was based on several factors, including existing relationships, feasibility and how they incorporated geographically and demographically different Indigenous communities. Studies evaluating ARI and chronic cough have had differing study designs, objectives and end points between populations. Australian data suggest cough burden is independent of age and aetiology, but dependent on clinical setting.29 In Australia, there are clear risk and burden distinctions between children from urban and remote areas and between Indigenous and non-Indigenous children.59 Indigenous children in urban areas have received much less attention than those in remote centres. Failure to account for these differences may lead to inappropriate interventions or implementation of management guidelines that may not be applicable across all settings.
The economic data and analyses in this study will be the first to describe the cost of ARI and its outcomes in Indigenous children in Australia, and one of the few worldwide. Further, the CEA of the intervention will provide data critical to clinical and public policy decisions with respect to incorporation of the intervention into routine care at the primary and tertiary healthcare levels. Such decisions will be enhanced by our incorporation of direct and indirect costs to the family, the community and the healthcare sector,60 particularly given the focus on resource allocation in Indigenous health in Australia,61 and the different mechanisms for delivery of primary healthcare services compared with mainstream Australia.62
We have incorporated microbiological components into the RCT as the role of infectious agents in the transition from ARI to chronic wet cough remains largely unknown. Whether persistent shedding, new acquisition and/or virus–bacteria interactions are associated with the development of chronic cough post-ARI is a clinical and research gap needing to be addressed. A study of 170 children aged 5–16 years presenting to their family physician with a cough lasting >14 days detected M. pneumoniae and B. pertussis in 12.9% and 36.6%, respectively.63 Cough duration was shorter in M. pneumoniae than B. pertussis cases and codetection with respiratory viruses was not associated with cough duration.63 An important limitation of this study63 was that data

were not collected from the time of ARI onset. Other studies64 have also tested for bacteria and viruses in nasopharyngeal specimens, but to date none have followed children from ARI onset and examined the association with developing chronic cough. In the analyses of microbiological data collected in our study of children attending an ED with cough, M. cattarhalis detected by PCR in anterior nasal swabs collected at time presentation was the only organism independently associated with persistent cough at 4 weeks after controlling for age, gender and the presence of any viruses.5 Our Brisbane-based lower airway studies of children with chronic cough from PBB found intense neutrophilic airway inflammation and evidence of innate immune activation, suggesting that PBB may follow a single ARI episode with impaired pathogen clearance from the airways, either permanently or temporarily leading to a cycle of chronic inflammation.65 Small case series from the late 1990s have reported chronic pulmonary sequelae following influenza infection in young children66 and a relationship between adenovirus infection and bronchiectasis.67

The major threats to the validity of our proposal are loss to follow-up and potential for contamination of the control group based on the type of standard care they may receive. In our current ARI study in urban Indigenous children, loss to follow-up at the 4-week time point post-ARI is 23%. Procedures to minimise this loss include: home visiting by Indigenous research personnel, regular text and email messaging, and personal letters to families. Analysis plans will include measures to account for missing data and sensitivity analyses to assess the extent of bias.

Although contamination of the control group is possible, based on a multicentre RCT conducted in five major Australian cities,29 it is unlikely that a child in standard care will receive treatment similar to the intervention arm. In another of our studies,52 just 27% of children sought further medical advice for cough in the 4 weeks following presentation to an ED for an illness with cough as a symptom (unpublished data). Furthermore, of the 9.7% receiving antibiotics during this 4-week period,5 most were prescribed antibiotics at the time of the original ED presentation. Hence, it is unlikely this will influence the validity of our RCT for several reasons: (1) We can assess any intervention either group receives outside of the RCT since our weekly follow-up data collection captures these events. (2) In the possible, but unlikely event of a change in treatment in the control group, the effect size of the intervention will be smaller requiring a larger sample size. The a priori sample size is conservative with 90% power and a smaller effect size will still be detectable within the available study population (eg, a 35% difference with power of 80% requires 114 per group). (3) To ensure robustness, an independent person will recalculate the sample size when 50% of children have completed the RCT component.

In summary, our RCT will be the first to examine the impact of a cough management algorithm implemented at the transitional stage from acute to chronic cough in Indigenous children. Clinical effectiveness will be evaluated concurrently with detailed epidemiological, clinical, microbiological and economic determinants of ARI and cough persistence in this population. If successful, the study may provide the data necessary to facilitate the uptake and implementation of cough management guidelines in the primary healthcare setting, potentially reducing the long-term burden of disease on the child, family, community and healthcare sector.