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Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) Clinical Registry protocol

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ABSTRACT

Introduction Acute respiratory infections (ARI) are the most common cause of paediatric hospitalisation. There is an urgent need to address ongoing critical knowledge gaps in ARI management. The Pragmatic Adaptive Trial for Respiratory Infections in Children (PATRIC) Clinical Registry will evaluate current treatments and outcomes for ARI in a variety of paediatric patient groups. The registry will provide a platform and data to inform a number of PATRIC clinical trials, testing various interventions in ARI treatment and management to optimise paediatric ARI care.

Methods and analysis The PATRIC Clinical Registry is a single-centre, prospective observational registry recruiting from a tertiary paediatric Emergency Department in Western Australia. Through characterising demographic, clinical, treatment and outcome data, the PATRIC Clinical Registry will improve our understanding of antibiotic utilisation and ARI outcomes in children.

Ethics and dissemination The PATRIC Clinical Registry is conducted in accordance with the Declaration of Helsinki, and the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (CPMP/ICH/13595) July 1996. Approval is provided by the Child and Adolescent Health Service Human Research Ethics Committee (HREC). Study results will be communicated by presentation and publication (HREC: RGS0000003078.)

Trial registration number Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12619000903189. UTN: U1111-1231-3365.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This clinical registry provides a mechanism to optimise acute respiratory infection (ARI) care and a platform for future ARI intervention trials.
⇒ Patient-reported outcomes and use of parents' hand-held devices enable a more flexible approach to registry data collection.
⇒ Emergency department recruitment may result in the enrolment of children with more severe ARI.
⇒ Follow-up is dependent on parental recall and timely data entry by parents.
⇒ Current study materials may not be culturally appropriate for all patient groups (ie, Aboriginal and Torres Strait Islander populations, who experience an increased burden of ARI).

INTRODUCTION

Acute respiratory infections (ARI), inclusive of both upper and lower respiratory tract infections (URTI, LRTI), are common in children. While URTI is mostly mild and self-limiting, LRTIs including pneumonia and bronchiolitis are frequent causes of paediatric hospital admissions. Outside the neonatal period, ARI remains the leading cause of childhood mortality[1] with global data (2019) estimating that LRTI resulted in 671 927 deaths, and 59.2 million disability-adjusted life years for children under 5 years.[2] In Australia, ARI-associated mortality is rare, but the morbidity and economic burden of paediatric ARI remains substantial. It is estimated that, on average, Australian children experience 13 ARI episodes in their first 2 years of life.[3] In Western Australia (WA), ARI is the most common reason for childhood presentation to an emergency department (ED) and hospitalisation,[4] with at least 1 in 4 Aboriginal children and 1 in 15 non-Aboriginal children in WA hospitalised for a chest infection before their fifth birthday.[5]

Most ARI episodes are secondary to respiratory viruses.[6 7] A recent case-control study investigating the viral and bacterial burden of pneumonia in WA children found that one or more respiratory virus was identified in 56% of cases versus 29% of controls.[6] The population-attributable fraction for pneumonia by respiratory syncytial virus, human metapneumovirus, influenza and adenovirus was estimated to 20%, 10%, 6% and 4%, respectively. This is compared with the most frequently detected bacterial species, *Mycoplasma pneumoniae* (attributable fraction; 7%). *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Streptococcus pyogenes* are important bacterial causes of ARI.

Many of the current treatment recommendations for paediatric ARI have not been tested through clinical trials. Antibiotics are frequently prescribed for management of childhood pneumonia and many other ARIs.[6 8] However, given the substantial contribution of respiratory viruses to paediatric ARI, antibiotics may have little or no benefit in most ARI cases. Antimicrobial resistance (AMR) has been identified by the WHO as a serious global threat. Injudicious use of antibiotics for ARI care contributes to the global concern of AMR.[9] Well-designed antimicrobial trials for ARI management, conducted in the era of conjugate pneumococcal and HiB vaccination are few in number[10] and supportive care trials have been infrequently performed.[11]

More than a decade ago, the Infectious Disease Society of America recommended robust time-to-event analyses in ARI trial design.[12] However, despite numerous professional societies noting the limited trial data,[10 13] there has been slow progress towards evidence-based antimicrobial use in ARI management. Traditional randomised controlled trials have inherent design limitations, including increased expense, reduced generalisability and delays in research translation. Provided the ongoing uncertainty about optimal ARI management strategies, the increasing threat of AMR and new therapeutic options expected; barriers to conducting clinical trials for ARI in paediatric populations must be overcome.

To drive and inform evidence-based ARI care, we have established a prospective clinical registry recruiting children with ARI presenting for urgent care at the ED. This has been developed to document risk factors, symptoms, severity and duration of illness, microbiology (when obtained), treatment adherence and disease outcomes and to explore factors associated with rapid symptom resolution. The Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) Clinical Registry serves as a research platform, generating critical baseline data for future clinical trials in ARI, focusing on time-to-event endpoints. Commencing in a single centre, the registry has been designed to expand into a multicentre registry and adaptive clinical trial platform.

Primary objective

The PATRIC Clinical Registry aims to: (1) accurately and efficiently characterise demographic, clinical, treatment and outcome data from eligible participants in order to optimise the care of children with ARI, and (2) provide the underlying preliminary evidence and platform for a pragmatic adaptive clinical trial on childhood ARI, a critical step towards evidence-based ARI care.

Secondary objectives

Secondary objectives are to: (1) demonstrate the willingness of parents and/or guardians (hereafter referred to as parents) to enrol their children in an electronic prospective ARI registry; (2) estimate the distribution of treatment response under alternative management options within different ARI patient subgroups; (3) optimise parent-reported outcomes and refine patient-reported outcome measures for ARI treatment and (4) provide surveillance data to characterise seasonal trends in ARI and real-time data for ARI epidemics as they arise.

Methods and analysis

Study design

The PATRIC Clinical Registry is an observational, prospective cohort of children who present to an ED with an ARI. Information including demographic, symptoms, vaccination history, medical history, treatment and follow-up responses are collected.

The PATRIC Clinical Registry provides the foundation for the PATRIC platform, collecting baseline data to inform the design of and providing tools and mechanism to recruit to ARI intervention trials nested within the platform. While this manuscript describes the methodology for the PATRIC Clinical Registry, each individual trial to be conducted within the PATRIC platform will have an independent protocol, with unique objectives and outcomes. Each PATRIC trial will also have individual ethics and regulatory approvals as required. It is proposed that trials may involve antimicrobial, immunomodulatory and supportive care interventions.

Patient and community involvement

The objectives of the PATRIC Clinical Registry have been discussed with, and supported by, the *Wesfarmers Centre of Vaccines and Infectious Diseases (WCVID) Consumer Reference Group* to ensure the study objectives and procedures are relevant and acceptable for the ARI patient community. An information video, participant information sheet, e-consent forms, e-survey and supportive information sheets were codesigned with input from consumers and tested for usability and acceptance with a pilot group of parents of young children.[14] Intervention in the future PATRIC trials will also be guided by discussions and the priorities of the WCVID consumer reference group as well as other consumer groups.

Study setting

Participants are enrolled from children presenting with physician-diagnosed ARI to the ED. At time of writing, recruitment is underway at Perth Children's Hospital (PCH), WA. The PCH is the only tertiary paediatric hospital for the state of WA (population: 2.6 million[15]). It is intended that the PATRIC Clinical Registry will be implemented across multiple sites in Australia, initially focusing on paediatric EDs. Recruitment started in February 2020 and is ongoing. The PATRIC Clinical Registry is designed to prospectively collect data on eligible participants.

Eligibility criteria, sample size and recruitment procedures

Inclusion criteria

Children and adolescents who meet the following criteria are eligible for registry enrolment:

i. aged≥1 months and <18 years AND

ii. symptoms and signs of ARI: a documented fever ≥37.5°C or history of fever in the past 96 hours AND cough, and/or shortness of breath and/or influenza-like symptoms such as sore throat or fatigue AND
iii. total duration of symptoms <21 days at time of enrolment.

Exclusion criteria

A potentially eligible child who meets any of the following criteria will be excluded from participation:

i. children <1 months old or 18 years and older OR
ii. previous participation in PATRIC within the last 3 months OR
iii. parents whose English is insufficient to understand study materials, OR
iv. parents do not complete the baseline survey, OR
v. parents not willing or able to provide consent.

Patient recruitment and consent

The registry does not have a fixed sample size. ED research nurses will identify and approach parents whose children meet the eligibility criteria. Parents are then presented a departmental electronic tablet to view the 3 min participant information video, information form and electronic consent form. They are also able to access these materials on their own hand-held device using a QR code. On completion of the electronic consent, a copy of the participant information sheet, and signed electronic consent is sent to the parents' email address. As shown in figure 1, the day 0 baseline survey is then sent immediately to the parent/carers mobile phone following completion of the e-consent form. The Research Electronic Data Capture

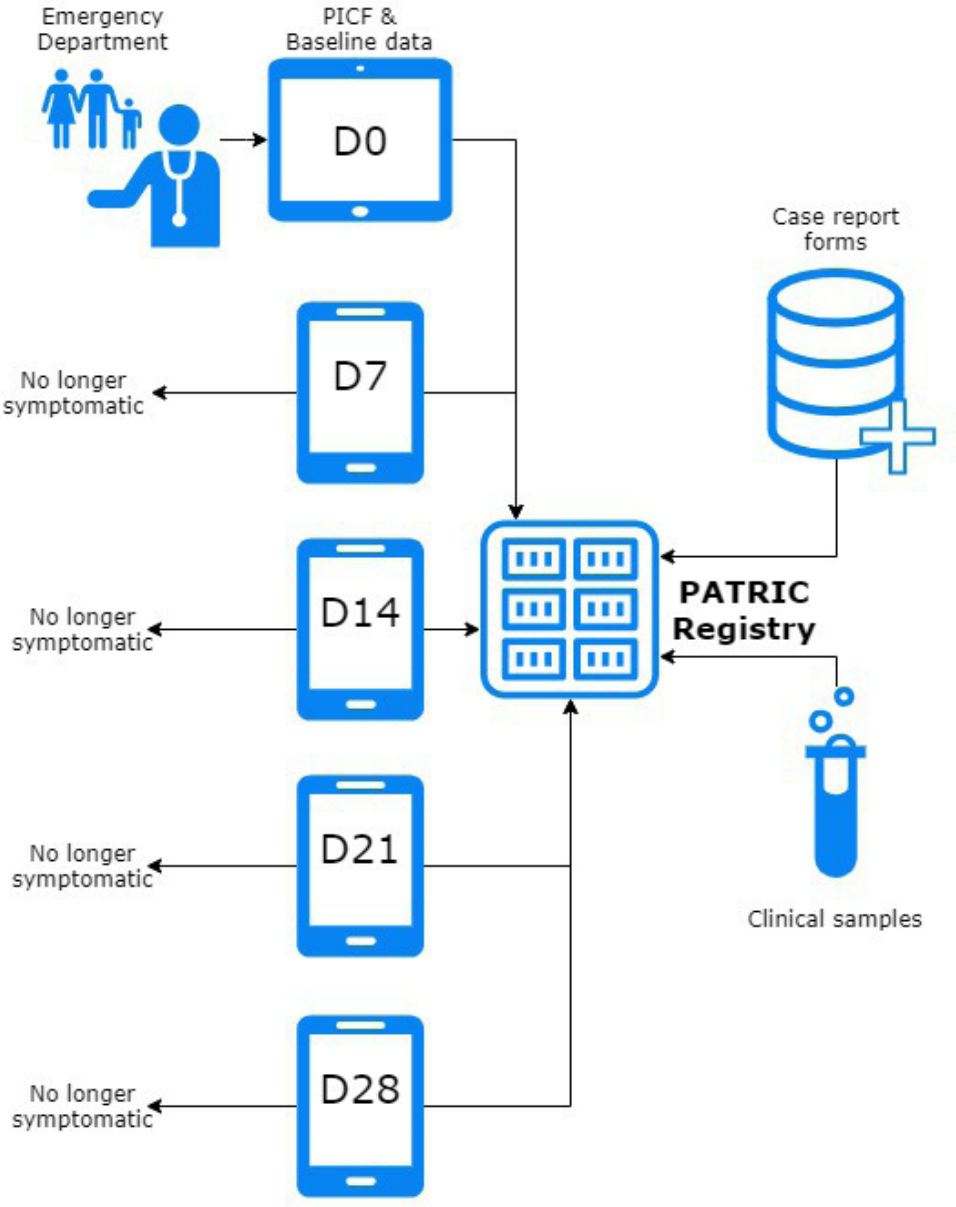

Figure 1 Flow chart of Pragmatic Adaptive Trial for Respiratory Infection in Children (PATRIC) registry design surveys, and the case report form. PICF, participant information and consent form.

application (REDCap; Vanderbilt University, Nashville, Tennessee, USA), application is used for e-consent, follow-up surveys and the case report form (CRF).

Data collection procedures

Day 0 survey

Parent-reported surveys sent on day 0 collect information on demographics, relevant comorbidities (eg, immunodeficiency, chronic heart and lung disease), history of any previous hospitalisation with ARI, household structure (number of children and adults), attendance at out-of-home care/education (playgroup/mothers' group, day-care, kindergarten, preschool or school), symptoms and behaviours observed in the preceding 24 hours (using the Canadian Acute Respiratory Illness and Flu Scale, CARIFS[16]), additional symptoms to better capture lower respiratory involvement (wheezing and difficulty breathing), and antibiotics or antivirals received prior to the ED visit.

CRF, immunisation data and biological samples

In additional to parent-completed day 0 baseline survey, information on a patient electronic CRF is entered by a research nurse, and includes information on demographics (age, sex, postcode and ethnicity), presentation and ED management (health assessments, support required, investigations required and results, discharge diagnosis and medications provided). Immunisations registered with the Australian Immunisation Registry are collected independently and linked to the participant using three identifiers (name, DOB, Medicare number). The e-consent form also provides the option to consent to the salvage of biological specimens collected during routine care for the ARI episode.

Follow-up

Patient-reported outcome and patient-reported outcome measures are recommended as a way of capturing the true impact of disease on children and families over time. Parents receive weekly follow-up surveys every 7 days from day 7 until symptom recovery, or day 28 (whichever occurs earlier), sent to parents' smart phones via automated messaging. The 7-day follow-up was chosen in an attempt to maximise retention, minimise loss to follow-up and ensure the generalisability of results. Parents are also asked to report on the presence and severity of several respiratory, behavioural and activity-based outcomes (using CARIFS) and additional symptoms (wheezing and difficulty breathing) to capture lower respiratory involvement.

Additional outcomes, developed in collaboration with consumers, are also requested at each time point. These include parents answering 'yes' or 'no' to the question: 'Is your child still sick?' In addition, two summary questions are asked: (1) 'Has your child returned to playgroup/mothers' group, day-care, kindergarten, preschool or school in last 7 days?', if yes, 'when'; and (2) 'Is your child as active as usual today?', if yes, 'When did your child return to their usual level of activity?' These questions are used to determine time-dependent outcomes (see secondary outcomes). Parents are also asked if their child has received additional medical care or prescription medication.

If the parent completing a follow-up survey on days 7, 14, 21 or 28 reports that their child is 'still sick', they will be provided with the option to access a link to downloadable supportive information sheet '*Respiratory Tract Infection—General Home Care Advice*'. This resource has been developed in consultation with clinicians and parent groups. The instructions are written at a level of readability appropriate for the general population with accompanying pictograms. Emphasis has also been placed on making the information accessible for all parents including those with low health literacy. The information sheet outlines how to provide supportive care for a child with an ARI, provides links to further resources as well as contact phone numbers for further health advice.

Outcome measures

Primary outcome

The primary endpoint for the registry will be the return to premorbid health state, as assessed by parents, by day 7. This will be determined by the parental survey response on day 7.

Secondary outcomes

The secondary endpoints for the registry are: (1) time to full recovery of ARI symptoms (in days), (2) time to return to normal childhood activities (in days; defined as: sufficient improvement to return to day-care; school; playgroups or other social outings), (3) proportion of children who have returned to their premorbid health state by days 7, 14, 21 and 28, (4) proportion of children who are free from cough by days 7, 14, 21 and 28, (5) proportion of children who are free from fever by days 7, 14, 21 and 28, (6) proportion of children with clinical failure (defined as: repeat emergency presentation or hospitalisation; general practice re-presentation; modification or unplanned prolongation of antibiotic therapy) by days 7, 14, 21, 28, (7) proportion of children intolerant to therapy. These endpoints will be assessed using data from the parental surveys and/or any post enrolment return presentation to the ED.

Data management

Registry data derived from parental surveys (provided at enrolment and at regular intervals thereafter) and CRFs (collected by a research nursing and capturing discharge diagnosis, laboratory, radiology and pharmacy data). All data are directly entered into a web-based database (REDCap). To ensure all data are stored safely in confidential conditions, each participant record will be referred to by a unique study-specific identifier and accessible only by study personnel. Paper materials linking the participant to medical data or any other database material will be maintained on site in a secure location.

Data analysis plan

Proportion reaching the primary outcome and the median time to reach secondary outcomes, as determined by parental surveys, will be assessed in the PATRIC Clinical Registry. Subgroup analysis, by age group, risk factors and treatments prescribed will be performed and compared. Severe outcomes, including hospital representation, will be cross-checked against the medical record. The proportion lost to follow-up prior to return to their premorbid state will also be reported.

Summarised descriptive statistics for individual demographics, risk factors, concurrent medications, allergies, immunisation status, ARI diagnosis and clinical markers of severity (temperature, respiratory rate, oxygen saturations on air) will be reported for all enrolled participants. Subgroup analysis will be stratified by age groups (infants: <12 months; young children: 13–59 months; older children: ≥60 months), antibiotic exposure (before presentation to hospital, prescribed during their hospital stay or by other healthcare provider during follow-up period), laboratory-confirmed viral and bacterial ARI and risk factors (eg, immunocompromising conditions).

Proportions for categorical variables will be summarised as frequency and percent proportion, with 95% CIs. Frequencies below five will be reported as '<5' to ensure confidentiality. Summaries of continuous variables will be reported as mean and SD for symmetric distributions and median and IQR for asymmetric distributions.

Associations between specific covariates of interest and the primary or secondary outcomes will be explored using prediction models. Logistic and cox proportional hazards regression models will be primarily used with random effects models considered if clustering by site is observed post multisite expansion. The adjusted odds of returning to a premorbid health state 7 days after presentation (or hazards if time-dependent secondary outcomes are assessed) can be determined by demographics and risk factors (such as age, ethnicity and previous infection), clinical presentation (such as symptoms, oxygen saturation and respiratory rate), investigations ordered (such as chest X-ray, and nasopharyngeal swabs), and discharge diagnosis.

Use of the platform for nested clinical trials

The PATRIC Clinical Registry provides a framework for intervention studies, randomising participants to specific diagnostic approaches and treatments. PATRIC trials share similar data and use the same clinical outcomes. Data from the registry will continue to inform trial simulations and provided baselines for standard of care.

A pilot clinical trial, assessing the optimal duration of amoxycillin duration in physician-diagnosed community-acquired pneumonia is underway (ACTRN12621000967886). This open-label trial aims to identify a minimum non-inferior dose of antibiotics to the current standard of care, where the interventions include various lengths of amoxycillin therapy and the primary outcome is the proportion returning to a premorbid health state 7 days after presentation. In addition to existing registry surveys, families will receive additional monitoring surveys on days 2, 4 and 10 after presentation to ensure sufficient resolution to compare different durations of therapy. Analysis will be undertaken on an intention-to-treat basis primarily involving estimating dose response. Statistical inference will be computed under a Bayesian framework using Markov chain Monte Carlo methods. Prior distributions for the trial framework will be learnt from accumulated evidence in the registry.

Ethics and dissemination

The PATRIC platform and embedded registry is conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (CPMP/ICH/13595). Platform materials, including protocols and amendments, are submitted to an appropriate human research ethics committee, and host institution for written approval as required. Written consent is obtained from parents during recruitment. PATRIC staff ensure the participants' anonymity is maintained through deidentifying data and using a participant identifier for analysis. All data are collected, stored and removed in compliance with data protection laws. Study results will be communicated by presentation and journal publication.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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