

BMJ Open Randomised controlled trial of paracetamol or ibuprofen, as required for fever and pain in the first year of life, for prevention of asthma at age 6 years: paracetamol or ibuprofen in the primary prevention of asthma in Tamariki (PIPPA Tamariki) protocol

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ABSTRACT

Introduction Asthma is one of the most common diseases in the world and is a global public health burden. There is an urgent need for research that leads to evidenced-based primary prevention strategies to reduce the prevalence of asthma. One novel risk factor that might have a role in the pathogenesis of asthma is the use of paracetamol in early life. This trial aims to determine if paracetamol, compared with ibuprofen use, as required for fever and pain in the first year of life, increases the risk of asthma at age 6 years.

Methods and analysis The Paracetamol and Ibuprofen in Primary Prevention of Asthma in Tamariki trial is a multicentre, open-label, two-arm parallel randomised controlled trial. 3922 infants born at ≥32 weeks' gestation will be randomly allocated to receive only paracetamol or only ibuprofen for treatment of fever and pain, if required in the first year of life. The primary outcome is asthma at 6 years of age, defined as the presence of wheeze in the preceding 12 months. Secondary outcomes include hospital admissions for bronchiolitis, wheeze or asthma in the first year of life, and within the first 6 years of life; wheeze at 3 years of age; eczema within the first year and at 3 and 6 years of age; atopy at 3 and 6 years of age.

Ethics and dissemination The trial has been approved by the Northern A Health and Disability Ethics Committee of New Zealand (17/NTA/233). Dissemination plans include publication in international peer-reviewed journals, and presentation at national and international scientific meetings, assimilation into national and international guidelines, and presentation of findings to lay audiences through established media links.

Trial registration number ACTRN12618000303246; Pre-results.

Strengths and limitations of this study

- The Paracetamol and Ibuprofen in Primary Prevention of Asthma in Tamariki trial addresses the worldwide asthma burden by investigating a novel primary prevention strategy.
- This trial will be the first to determine if paracetamol use in infancy causes asthma in mid-childhood.
- New Zealand's universal public health system is uniquely placed to enable long-term follow-up of participants with linkage to pharmaceutical dispensing and hospital admission data.
- A placebo arm would be unacceptable for ethical reasons; thus, our pragmatic trial will be unable to exclude the possibility that the comparator, ibuprofen, may also be associated with increased risk of childhood asthma, although such an association is not supported by the current epidemiological evidence.
- The success of the trial depends on exclusive use of a single analgesic/antipyretic in the first year of life and multiple strategies are in place to prevent medicine use crossover.

INTRODUCTION

Asthma is one of the most common diseases worldwide and represents a substantial public health burden.¹ In recent decades, research efforts and public health measures have yielded significant advances in the assessment and management of asthma. However, progress in reducing the population burden of mortality and morbidity has stalled in the last 10 years, despite increasing

investment in treatment.^{2,3} There is an urgent need for research that leads to evidenced-based primary prevention strategies to reduce the prevalence of asthma in children.⁴ Unfortunately, none of the primary prevention strategies that have undergone scrutiny in randomised controlled trials have provided sufficient evidence to lead to widespread public health implementation.⁴ Recent attention has turned to investigation of novel risk factors in the pathogenesis of asthma.

One novel risk factor that might contribute to the development and severity of asthma is early life exposure to paracetamol.⁵ Paracetamol is the most commonly prescribed medicine in children,⁶ and there is a temporal association between the increased use of paracetamol over the past 50 years and the rise in asthma prevalence worldwide.⁷ The International Study of Asthma and Allergies in Childhood (ISAAC), in 72 sites in 31 countries, found that administration of paracetamol to infants was associated with an increased probability of wheeze at age 6–7 years: OR 1.46 (95% CI 1.36 to 1.56). An association was also identified with eczema and rhinoconjunctivitis.⁸ Subsequent systematic reviews and further epidemiological studies also report an association between paracetamol use in infancy and asthma with a pooled OR for association of approximately 1.5.^{9,10}

Biological evidence suggests this association is causal. Paracetamol reduces the concentration of the antioxidant glutathione in the lung, leading to oxidant-induced airway inflammation.¹¹ Lower levels of glutathione may also produce a shift away from type 1 towards type 2 T helper cytokine production, which increases the phenotypic expression of atopic diseases including asthma.¹² Fever reduction associated with paracetamol may also reduce the cytokine production that is part of the febrile response, reducing interferon gamma and interleukin-2, which are key agents that usually induce type 1 T helper cell profiles.¹³

However, association and a plausible biological mechanism does not mean that paracetamol exposure in infancy causes later asthma and related allergic disorders. In particular there could be confounding of this association because this agent is used for respiratory tract infections, which themselves may be causal. Attempts to adjust for this confounding in epidemiological studies have not definitively answered whether paracetamol exposure in infancy results in an increased risk of childhood asthma and related allergic disorders.^{14,15} Clinical trials comparing the long-term risk of asthma in children who are naïve to paracetamol, or use paracetamol, in early infancy are needed.

The Paracetamol and Ibuprofen in Primary Prevention of Asthma in Tamariki (PIPPA Tamariki; 'Tamariki' is Te Reo Māori (the indigenous language) for children) trial will determine if use of paracetamol, compared with ibuprofen, for fever and pain in the first year of life, increases the risk of asthma and atopic disease in childhood

METHODS

Trial objectives

The primary objective of the PIPPA Tamariki trial is to determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of asthma at age 6 years. Asthma will be defined using the ISAAC phase III core question 'Has your child had wheezing or whistling in the chest in the past 12 months?'.¹⁶

The secondary objectives are to determine if paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of:

1. Hospital admissions with bronchiolitis, viral-induced wheeze or asthma in the first year of life.
2. Eczema in the first year of life.
3. Wheeze at 3 years of age.
4. Eczema at 3 years of age.
5. Atopy at 3 years of age.
6. Hospital admissions with bronchiolitis, wheeze or asthma in the first 6 years of life.
7. Eczema at 6 years of age.
8. Atopy at 6 years of age.

Trial design

PIPPA Tamariki is a multicentre, open-label, two-arm parallel randomised controlled trial with 1:1 allocation comparing paracetamol treatment versus ibuprofen treatment, as required for fever or pain in the first year of life.

Trial setting

The trial is being conducted in two New Zealand regions: Auckland and Wellington. These regions collectively include 43% of the national birth cohort.

Eligibility criteria

Infants who are born ≥ 32 weeks' gestation within Auckland and Wellington regions, and who are < 8 weeks of age are eligible for this trial. Infants are excluded if they are:

1. Unlikely to remain in New Zealand for the first 6 years of life.
2. Have a chronic disease associated with limited life expectancy (ie, less than 6 years).
3. Have been exposed to paracetamol or ibuprofen since birth.

Interventions

Parents/caregivers are asked to give their infant(s) only the allocated trial medication in the first 12 months of life, if required for fever or pain. Dosing is based on the New Zealand Formulary for Children¹⁷ as follows:

Paracetamol group

For < 1 month of age: 15 mg/kg every 6 hours as required, to a maximum daily dose of 60 mg/kg. At this age paracetamol is only to be given under the advice of a health professional.

From 1 month of age: 15 mg/kg every 4 hours as required, to a maximum daily dose of 60 mg/kg.

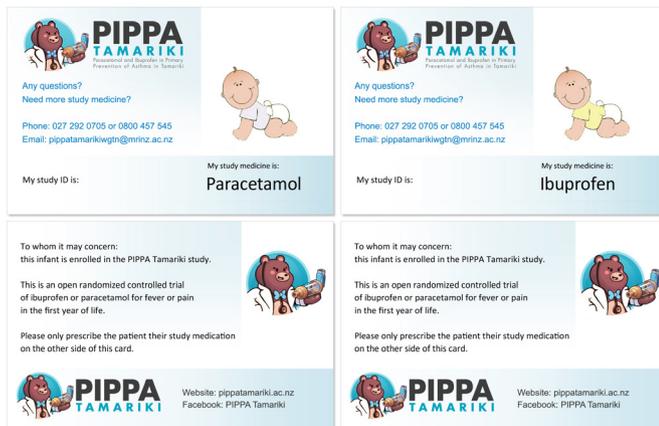


Figure 1 Wallet-sized trial reminder cards. PIPPA Tamariki, Paracetamol and Ibuprofen in Primary Prevention of Asthma in Tamariki.

Ibuprofen group

For <1 month of age: 5 mg/kg every 6 hours as required, to a maximum daily dose of 20 mg/kg. At this age ibuprofen is only to be given under the advice of a health professional.

From 1 to 3 months of age: 5 mg/kg every 6 hours as required, to a maximum daily dose of 20 mg/kg.

From 3 months of age: 10 mg/kg every 6 hours as required, to a maximum daily dose of 30 mg/kg.

To maximise adherence to the allocated intervention, participants are supplied with trial medication via post at approximately 2 weeks of age (or a few days after enrolment if older than 10 days at enrolment). A toll-free telephone line, email address, web portal, website and Facebook private message system are available for parents/caregivers to request additional trial medication at any time. Families may choose to receive additional trial medication by one of three routes: (1) mailing a prescription for parents/caregivers to fill; (2) faxing a prescription to the local pharmacy of the parents/caregivers' choosing; or (3) delivery of the trial medication if access to a pharmacy is limited. New Zealand's universal public healthcare system provides free prescriptions for all children ≤ 13 years of age.

If families wish to be supplied trial medication prescriptions after 12 months, this will be allowed in order to facilitate trial retention to 6 years. No trial medication prescriptions will be supplied after completion of the 6-year follow-up.

Parents/caregivers are provided with wallet-sized trial reminder cards (figure 1), as well as paper-based and electronic trial diaries (via the PIPPA Tamariki web portal) to record the number of doses of the trial medication given to each participant. During follow-up at 1, 3, 6 and 9 months of age, parents/caregivers are further reminded of the trial requirements.

The participants' general practitioners are advised of their participation in the trial and their assigned intervention group. Electronic alerts are placed in local hospital records stating that the participant is in the trial

with details of the intervention group to which they have been assigned. Wall charts (figure 2) have been placed in emergency departments and paediatric wards to remind clinical staff to prescribe only the allocated trial medication, should participants need antipyretic treatment or analgesia. Posters have also been placed in these areas to remind parents/caregivers to inform staff if their infant is a PIPPA Tamariki trial participant.

To assist parents/caregivers with participant adherence to the allocated intervention, trial medication is also offered to other household members under 10 years of age, in accordance with the New Zealand Formulary for Children.¹⁷ Respective general practitioners are advised that these children are being prescribed the trial medication for the period that the index infant is receiving trial medication.

Criteria for discontinuation of allocated intervention include ineligibility (either arising during the trial, or retrospectively), significant protocol deviation, an adverse event which requires discontinuation of the trial medication and withdrawal of consent.

Outcomes

The primary outcome is asthma at 6 years of age (mid-childhood). This will be defined using the ISAAC phase III core question 'Has your child had wheezing or whistling



Figure 2 Wall charts for emergency departments and paediatric wards.

in the chest in the past 12 months;¹⁶ and denominated as: wheeze in the last 12 months. The primary outcome is assessed at 6 years of age because of clinical uncertainty in the diagnosis of asthma before the age of 5 years,¹⁸ and because the majority of children who wheeze during early childhood do not develop asthma.^{19 20} Secondary outcomes are shown in [table 1](#). These will be measured at the prespecified time points of infancy (1 year of age), early childhood (3 years of age) and mid-childhood (6 years of age). Additional secondary outcomes include hospitalisation for adverse reactions and serious adverse events of special interest (SAESI) up to 1 month post the intervention year.

Participant timeline and assessments

We will enrol 3922 infants who will be followed up until 6 years of age according to the schedule in [table 2](#).

The following data are collected at enrolment: maternal demographics, maternal atopic history, pregnancy history, paternal demographics, paternal atopic history, birth history, infant demographics, and sibling/household members <10 years of age (for each: date of birth; relationship to index infant; National Health Index number; current or last known weight; history of asthma, eczema and hay fever; history of allergy to assigned medication or other medications; history of liver failure, kidney failure or bleeding disorders; general practitioner details).

Parents/caregivers will be asked to complete follow-up questionnaires (either by telephone or electronic based on parent/caregiver choice) at 1, 3, 6, 9 months, and 1, 3 and 6 years. All parents/caregivers will be given a telephone call at 1 month, 1 and 6 years, reminding them of participation in the trial and completing any outstanding follow-up questions from the follow-up questionnaires. At 1, 3, 6 and 9 months parents/caregivers are asked about their infant's use of medications, history of wheezy or respiratory illnesses, hospital admissions and adverse reactions. Supply of the allocated medication is checked, and the correct dose for weight confirmed. At 1 year, in addition to respiratory symptoms and illness, information is collected about pet exposure, sleeping environment, smoke exposure, quality of housing, feeding and diet, history of eczema and food allergy in the preceding 12 months. At 3 and 6 years parent/caregivers are asked about their child's ongoing use of paracetamol or ibuprofen; history of wheezy or respiratory illnesses; history of eczema, rhinitis and food allergy; current medication use; hospital admissions; quality of housing and smoke exposure. The end date of the trial is the completion of the 6-year assessment.

Sample size

The primary outcome is asthma at 6 years of age, defined as wheeze in the last 12 months using the ISAAC phase III study questionnaire.¹⁶ For New Zealand children, the ISAAC phase III study prevalence of wheeze in children aged 6–7 years in the last 12 months was 22.2%. This was very similar to the prevalence estimate from the earlier

ISAAC phase I study of 23.6%.²¹ In the full ISAAC phase III data, based on records from 194555 children aged 6–7 years in 29 countries, use of paracetamol for fever in the first year of life was associated with an increased probability of wheeze in the last 12 months: OR 1.46 (95% CI 1.36 to 1.56).⁸

We plan to recruit 3922 infants allocated in equal proportions to paracetamol or ibuprofen use. This size study has 90% power to detect a reduction in prevalence of asthma at 6 years of age from 22% to 17% (absolute risk reduction 5%, relative risk reduction 23%). The sample size calculation assumes a two-tailed alpha of 0.05, withdrawal/loss to follow-up rate of 10% and an efficacy dilution factor of 10% due to participants being exposed to the alternative intervention within the first year of life.

Recruitment

Infants are being recruited primarily from postnatal wards, as our previous pilot study showed that this was the most successful recruitment domain.²² Women are approached by a research team member and provided with an information sheet, after which they are given time to consider the trial and discuss it with their partner and family. Research personnel are available to discuss the trial with parents and to answer any questions they may have. If parents indicate an interest in enrolling their infant into the trial, research staff will check that parents understand the requirements of the trial before obtaining written informed consent (online supplemental file).

In addition to face-to-face recruitment after birth, we are seeking to identify potential participants during pregnancy through media promotion within the relevant catchment areas via childbirth education classes, antenatal clinics, general practices and lead maternity carers (obstetrician or midwife), and on Facebook. During pregnancy, parents can submit a 'registration of interest' on the trial website after which they will be contacted by a member of the research team. This will allow early opportunity for parents to have any questions answered, and to indicate interest in enrolling their infant into the trial.

A pilot recruitment study by our trial team indicated that 3922 participants will be able to be recruited over a 44-month period at the three proposed trial sites.²² Based on the 16555 annual births at the three proposed sites (2013 data), this represents a conservative recruitment target of 1 in 17 births. Recruitment began in April 2018 and is planned to be completed in 2022.

Assignment of interventions

Sequence generation

The randomisation sequence is computer generated using random permuted blocks, stratified for site, maternal asthma status and multiple birth status.

Allocation concealment and implementation

Participants will be randomised by research staff using the Research Electronic Data Capture (REDCap) system,²³ a secure US Health Insurance Portability and Accountability

Table 1 Secondary outcomes

| Outcome | Definition |
|--|--|
| Outcomes to be measured at infancy (at 1 year of age) | |
| Hospitalisation for bronchiolitis, viral-induced wheeze or asthma in the first year of life | Proportion of participants with at least one hospitalisation for bronchiolitis, viral-induced wheeze or asthma by 1 year of age using ICD-10 codes ³¹ and querying the New Zealand Ministry of Health datasets: 'National Non-Admitted Patient Collection' and 'National Minimum Dataset.' |
| Prescription for asthma medication in the first year of life | Proportion of participants completing at least one prescription for ICS, SABA, LABA or montelukast in the first year of life, by querying the New Zealand Ministry of Health dataset: 'Pharmaceutical Collection.' |
| Eczema in the first year of life | The proportion of participants whose parent/caregiver answers 'yes' to the questions 'In the last year, has your child had an itchy skin condition—by itchy, we mean scratching or rubbing the skin?' and IF YES 'Has this skin condition ever affected the skin creases in the past—by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck or around the eyes?' using the UK Diagnostic Criteria for Eczema Questionnaire. ³² |
| Hospitalisation for eczema in the first year of life | Proportion of participants with at least one hospitalisation for eczema in the first year of life using ICD-10 codes ³¹ and querying the New Zealand Ministry of Health datasets: 'National Non-Admitted Patient Collection' and 'National Minimum Dataset'. |
| Prescription for eczema medication in the first year of life | Proportion of participants completing at least one prescription for topical steroids in the first year of life, by querying the New Zealand Ministry of Health dataset: 'Pharmaceutical Collection'. |
| Outcomes to be measured at early childhood (at 3 years of age) | |
| Wheeze at 3 years of age | The proportion of participants whose parent/caregiver answers 'yes' to the question 'Has your child had wheezing or whistling in the chest in the past 12 months?' using the ISAAC Phase III Core Questionnaire for Asthma for children 6–7 years old. ¹⁶ |
| Hospitalisation for bronchiolitis, viral-induced wheeze or asthma in the first 3 years of life | Proportion of participants with at least one hospitalisation for bronchiolitis, viral-induced wheeze or asthma in the first 3 years of life using ICD-10 codes ³¹ and querying the New Zealand Ministry of Health datasets: 'National Non-Admitted Patient Collection' and 'National Minimum Dataset'. |
| Prescription for asthma medication in the first 3 years of life | Proportion of participants completing at least one prescription for ICS, SABA, LABA, montelukast in the first 3 years of life, by querying the New Zealand Ministry of Health dataset: 'Pharmaceutical Collection'. |
| Eczema at 3 years of age | The proportion of participants whose parent/caregiver answers 'yes' to the questions 'In the last year, has your child had an itchy skin condition—by itchy, we mean scratching or rubbing the skin?' and IF YES 'Has this skin condition ever affected the skin creases in the past—by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck or around the eyes?' using the UK Diagnostic Criteria for Eczema Questionnaire. ³² |
| Hospitalisation for eczema in the first 3 years of life | Proportion of participants with at least one hospitalisation for eczema in the first 3 years of life using ICD-10 codes ³¹ and querying the New Zealand Ministry of Health datasets: 'National Non-Admitted Patient Collection' and 'National Minimum Dataset'. |
| Prescription for eczema medications in the first 3 years of life | Proportion of participants completing at least one prescription for topical steroids in the first 3 years of life by querying the New Zealand Ministry of Health dataset: 'Pharmaceutical Collection'. |
| Atopy at 3 years of age | The proportion of participants whose parent/caregiver answers 'yes' to the question 'Has your child had wheezing or whistling in the chest in the past 12 months?' using the ISAAC Phase III Core Questionnaire for Asthma for children 6–7 years old. ¹⁶ AND/OR 'yes' to the questions 'In the last year, has your child had an itchy skin condition—by itchy, we mean scratching or rubbing the skin?' and IF YES 'Has this skin condition ever affected the skin creases in the past—by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck or around the eyes?' using the UK Diagnostic Criteria for Eczema Questionnaire, ³² AND/OR 'yes' to the questions 'In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the influenza?' and IF YES 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?' using the ISAAC Phase III Core Questionnaire for Rhinitis for children 6–7 years old. ¹⁶ |
| Outcomes to be measured at mid-childhood (at 6 years of age) | |
| Hospitalisation for bronchiolitis, viral-induced wheeze or asthma in the first 6 years of life | Proportion of participants with at least one hospitalisation for bronchiolitis, viral-induced wheeze or asthma in the first 6 years of life using ICD-10 codes ³¹ and querying the New Zealand Ministry of Health datasets: 'National Non-Admitted Patient Collection' and 'National Minimum Dataset'. |

Continued

Table 1 Continued

| Outcome | Definition |
|--|--|
| Prescription for asthma medication in the first 6 years of life | Proportion of participants completing at least one prescription for ICS, SABA, LABA, montelukast or monoclonal antibodies for the treatment of asthma in the first 6 years of life by querying the New Zealand Ministry of Health dataset: 'Pharmaceutical Collection'. |
| Eczema at 6 years of age | The proportion of participants whose parent/caregiver answers 'yes' to the questions 'In the last year, has your child had an itchy skin condition—by itchy, we mean scratching or rubbing the skin?' and IF YES 'Has this skin condition ever affected the skin creases in the past—by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck or around the eyes?' using the UK Diagnostic Criteria for Eczema Questionnaire. ³² |
| Hospitalisation for eczema in the first 6 years of life | Proportion of participants with at least one hospitalisation for eczema in the first 6 years of life using ICD-10 codes ³¹ and querying the New Zealand Ministry of Health datasets: 'National Non-Admitted Patient Collection' and 'National Minimum Dataset'. |
| Prescription for eczema medications in the first 6 years of life | Proportion of participants completing at least one prescription for topical steroids in the first 6 years of life by querying the New Zealand Ministry of Health dataset: 'Pharmaceutical Collection'. |
| Atopy at 6 years of age | The proportion of participants whose parent/caregiver answers 'yes' to the question 'Has your child had wheezing or whistling in the chest in the past 12 months?' using the ISAAC Phase III Core Questionnaire for Asthma for children 6–7 years old, ¹⁶ AND/OR 'yes' to the questions 'In the last year, has your child had an itchy skin condition—by itchy, we mean scratching or rubbing the skin?' and IF YES 'Has this skin condition ever affected the skin creases in the past—by skin creases we mean fronts of elbows, behind the knees, fronts of ankles, around the neck or around the eyes?' using the UK Diagnostic Criteria for Eczema Questionnaire, ³² AND/OR 'yes' to the questions 'In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the influenza?' and IF YES 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?' using the ISAAC Phase III Core Questionnaire for Rhinitis for children 6–7 years old. ¹⁶ |

The New Zealand Ministry of Health 'National Non-Admitted Patient Collection' and 'National Minimum Dataset' provide information based on ICD-10 codes for all interactions an individual has with the public healthcare system outside of primary care including emergency department visits, secondary care outpatient visits and inpatient admissions. These interactions are coded using a unique number known as the National Health Index. As New Zealand has a universal public healthcare system, all such interactions are accounted for. The New Zealand Ministry of Health 'Pharmaceutical Collection' records all prescriptions of pharmaceuticals filled by an individual based on their National Health Index number, from both primary and secondary care.

ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; ICS, inhaled corticosteroid; ISAAC, International Study of Asthma and Allergy in Children; LABA, long-acting beta agonist; SABA, short-acting beta agonist.

Act 1996-compliant web-based application. The allocation sequence is accessible only to the trial statistician and independent data manager. Allocation will only be revealed to the research team once parental/guardian informed written consent is confirmed and participant demographic details have been entered into the trial database. In the instance of multiple birth, or subsequent birth occurring in the same household, those infants will be allocated to the same intervention as the first recruited infant.

Blinding

This is an open-label trial. After randomisation there will be no concealment of allocation from the parents/caregivers or the researchers. It is not possible to mask the trial medications due to differing concentrations, minimum dosing intervals and maximum doses per 24 hours. Furthermore, there could be risk of infant drug toxicity if administration of masked medication was unknowingly repeated by clinical staff.

Data collection and management

Data are being collected into REDCap electronic case report forms via tablet devices (enrolment), desktop computers (telephone follow-up), and/or via online follow-up questionnaires completed by parents/caregivers (accessed via a unique link for each follow-up), allowing immediate data validation with the use of logic checks and data entry ranges. Data collected by the web portal (medication diary and infant weight updates) are sent directly to the database. Hard copy back-up case report forms are available. All data will be stored securely on password-protected servers under the control of the Medical Research Institute of New Zealand, Wellington, New Zealand, and only accessible by trial staff and independent trial auditors. The trial will comply with the New Zealand Health Information Privacy Code.

Information on virology, medication prescriptions, emergency department attendance and hospital admissions will be obtained through data linkage with local and national databases using the National Health Index

Table 2 Schedule of participant enrolment, interventions and assessments

| Timepoint | Trial period | | | | | | | | |
|---|---------------|------------------------|---------|------------------|----------|----------|--------|---------|---------|
| | Pre-enrolment | Enrolment | | Post-allocation* | | | | | |
| | Antenatal | Postnatal 0–8 weeks | 1 month | 3 months | 6 months | 9 months | 1 year | 3 years | 6 years |
| Pre-enrolment | | | | | | | | | |
| Registration of interest | X | | | | | | | | |
| Enrolment | | | | | | | | | |
| Eligibility screen | | X | | | | | | | |
| Informed consent | | X | | | | | | | |
| Randomisation | | X | | | | | | | |
| Interventions | | | | | | | | | |
| Paracetamol only (as needed) | | X | X | X | X | X | | | |
| Ibuprofen only (as needed) | | X | X | X | X | X | | | |
| Provision of trial supplies | | | | | | | | | |
| Wallet cards, trial diary, sticker, fridge magnet, soft toy | | X | | | | | | | |
| Trial medication supply (as needed) | | X | X | X | X | X | | | |
| Assessments | | | | | | | | | |
| Maternal enrolment questionnaire | | X | | | | | | | |
| 1-month questionnaire | | | X | | | | | | |
| 3-month questionnaire | | | | X | | | | | |
| 6-month questionnaire | | | | | X | | | | |
| 9-month questionnaire | | | | | | X | | | |
| 1-year questionnaire | | | | | | | X | | |
| 3-year questionnaire | | | | | | | | X | |
| 6-year questionnaire | | | | | | | | | X |

*For infants born <37 weeks' gestation, follow-up is based on chronological age.

number. This information will be obtained for all participants remaining in the trial, including those that are lost to follow-up.

If parents/caregivers wish to withdraw their child from the trial, permission will be sought to use data collected up to the point of withdrawal, and via passive follow-up using their child's National Health Index number.

Statistical analysis

The primary analysis will be by intention-to-treat and will compare primary and secondary outcomes between treatment groups by generalised linear mixed model using logistic regression but also a random effect to account for clustering of children within households. A per-protocol analysis of primary and secondary outcomes will be undertaken. Secondary analysis will explore if there is a dose–response effect based on low versus high cumulative

number of doses received during the intervention period. Secondary multivariate analyses will adjust for parental history of asthma, maternal exposure to paracetamol during pregnancy, number of respiratory infections, smoke exposure, pet exposure, housing and breast-feeding status. Treatment effects will be presented as relative risks, expressed as ORs, with 95% CIs. Two-tailed alpha is set at 0.05 for primary and secondary outcomes.

Data and safety monitoring

A four-member independent Data and Safety Monitoring Committee (DSMC) has been established, comprising of experts in paediatric infectious disease, paediatric respiratory medicine, primary care, adverse event monitoring and statistics. As all trial participants will be recruited and complete the trial intervention prior to assessment of the primary outcome, there will be no interim efficacy

**Box 1 Serious adverse events of special interest**

- ▶ Death.
- ▶ Empyema or pleural effusion requiring intervention (diagnostic aspiration or drainage).
- ▶ Probable or confirmed bacterial meningitis.
- ▶ Probable or confirmed osteomyelitis.
- ▶ Confirmed septicaemia (positive microbiology and a clinical picture consistent with sepsis).
- ▶ Intensive care admission with probable or confirmed varicella, sepsis, bacterial pneumonia or cellulitis.
- ▶ Gastrointestinal haemorrhage requiring endoscopy or transfusion with blood products.
- ▶ Acute liver failure.
- ▶ Renal failure.
- ▶ Trial medication overdose (presentation to an emergency department with a diagnosis of overdose).
- ▶ Delayed diagnosis of rheumatic fever (only for household members <10 years of age provided with trial medication).

analysis. The DSMC will monitor suspected unexpected serious adverse reactions (SUSARs) to trial medication, deaths and hospitalisation due to SAESI, that is, events known to be or putatively associated with exposure to paracetamol or ibuprofen. Prespecified SAESIs are listed in **box 1**. SUSAR, deaths and SAESI will be monitored through parent report, regular screening of admission lists at each site and by linkage with national databases via the National Health Index number. Household members <10 years of age who are provided with trial medication will also be monitored for SAESIs using the same processes.

The DSMC will receive a yearly summary of all SUSAR, deaths and SAESI by masked treatment group. If required, an unblinded report will be provided. SUSARs will be reported to the national government regulatory body within the required timelines.

The Trial Steering Committee will provide oversight for all aspects of the trial and ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice and the applicable regulatory requirements.

Auditing

A study monitor has been appointed to ensure that sites adhere to Good Clinical Practice and relevant New Zealand regulatory requirements, including the Health Information Privacy Code 1994, The Health and Disability Code 1996 and the Bill of Rights Act 1990. Sites will be monitored to ensure that research staff adhere to standard operating procedures relating to recruitment, consent, confidentiality, data collection and adverse event reporting.

Patient and public involvement

Prior to designing the PIPPA Tamariki trial, two pilot studies of parents/caregivers of infants admitted with bronchiolitis, and of parents/caregivers of newborn babies, were conducted which showed that ibuprofen

was the preferred comparator arm,²⁴ and that the post-natal ward was the preferred and acceptable recruitment environment.²²

ETHICS AND DISSEMINATION

This trial has been approved by the New Zealand Northern A Health and Disability Ethics Committee (17/NTA/233). Prior to enrolling infants in this trial, informed written consent is obtained from parents/guardians. Participant Information Sheets and Consent Forms are available in English, Te Reo Māori, Samoan, Tongan and Chinese. The Language Line telephone interpreting service, or a representative from the Sign Language Interpreters of New Zealand, will be used when required.

Findings will be disseminated through publication in international peer-reviewed journals and presentation at national and international scientific meetings. The secondary outcomes of this trial will result in key manuscripts addressing outcomes in infancy (1 year) and early childhood (3 years), and will be disseminated prior to the primary outcome. Further dissemination priorities include: (1) assimilation of findings into national and international guidelines; (2) feedback to participants, communities and organisations that have supported the research in a format that meets their needs; (3) writing commentaries and editorials via established links with international journals; and (4) presenting findings to lay audiences through established media links.

DISCUSSION

Worldwide asthma represents a substantial global public health burden. Children, in particular, have high burden with 14% of the world's children experiencing asthma symptoms, and with children aged 10–14 years having the highest burden (disability adjusted life years) of any age group.^{25 26} As a chronic disease without a current cure, strategies focusing on management will always be limited in reducing the burden of disease. Recent attention has turned to the investigation of novel risk factors in the pathogenesis of asthma, and one such risk factor is the use of paracetamol in early life. While there is substantive non-experimental evidence of an association between paracetamol use in infancy and the presence of asthma in later childhood, it remains uncertain if this association reflects true causation, or is merely due to confounding, in particular respiratory tract infections.

In children with established asthma, two previous studies have compared the effect of paracetamol and ibuprofen use on asthma symptoms. Lesko *et al*,²⁷ in a *post hoc* analysis of the short-term use of paracetamol or ibuprofen for febrile illness, reported a twofold higher risk of unscheduled outpatient visits for asthma in the paracetamol group. In contrast, Sheehan *et al*²⁸ reported that among young children (12–59 months of age) with mild persistent 'asthma', as-needed use of paracetamol was not associated with a higher incidence of asthma

exacerbations or worse control than as-needed use of ibuprofen. Both the authors of this trial²⁸ and the associated editorial in the *New England Journal of Medicine*²⁹ stressed that this trial did not address whether paracetamol use can lead to the development of asthma in otherwise healthy children, and they strongly supported the need for a study designed to answer this question.

Whether a causal relationship exists between paracetamol use in infancy and the presence of asthma in later childhood can only be definitively addressed in a randomised controlled trial. PIPPA Tamariki is the first randomised controlled trial to assess the long-term risk of asthma in children who are naïve to paracetamol in early infancy.

New Zealand's healthcare environment is ideally placed to conduct this trial due to the existence of a single National Health Index number for every individual, which allows participants enrolled in studies around the time of birth to be traced and successfully contacted. Further, the National Health Index system, as well as universal public healthcare, allows easy linkage to pharmaceutical dispensing and hospital admission data, efficiencies that would not be possible in many other jurisdictions.

A potential limitation of this trial is the lack of blinding of the two interventions. This was not possible due to differing concentrations, minimum dosing intervals and maximum doses per 24 hours of paracetamol and ibuprofen. Furthermore, it is common clinical practice to prescribe a second antipyretic or analgesia agent when one alone is assumed to be insufficient,³⁰ and blinding could potentially place the infant at risk of drug toxicity. While the use of a placebo group as a comparison arm would allow for easier interpretation of the results, this was deemed unacceptable for ethical reasons in that it would not provide infants with analgesia when in pain. Our feasibility study confirmed parental non-acceptability of placebo and a clear preference for ibuprofen as the trial comparator.²⁴ Using ibuprofen as an active control also provides data which are generalisable to standard practice in New Zealand and internationally.²⁴ As with the Sheehan *et al.*²⁸ trial, our pragmatic trial will not be able to exclude the possibility that both paracetamol use and ibuprofen use may be associated with parallel increased risk of asthma. However, as paracetamol and ibuprofen have different mechanisms of action, this is unlikely.

Paracetamol is the most commonly prescribed medication, and over-the-counter medication dispensed, to children in the first year of life. The results of the PIPPA Tamariki trial will be relevant to all parents and healthcare providers who care for young infants. If this trial confirms the strong and consistent epidemiological associations between paracetamol exposure in infancy and later asthma, we will provide convincing evidence for a novel and simple public health intervention that could reduce the global prevalence of asthma. If the results of the trial fail to confirm the epidemiological associations previously found, then we will have provided a safety study of the highest quality. Thus, regardless of outcome,

the results are expected to be incorporated into all health guidelines that address analgesia and antipyretic use in young infants, including major textbooks, paediatric hospital guidelines, parent advice and WHO statements.

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REFERENCES

- Vos T, Abajobir AA, Abate KH, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet* 2017;390:1211-59.
- Bush A, Kleinert S, Pavord ID. The asthmas in 2015 and beyond: a Lancet Commission. *Lancet* 2015;385:1273-5.
- Ebmeier S, Thayabaran D, Braithwaite I, *et al*. Trends in international asthma mortality: analysis of data from the who mortality database from 46 countries (1993-2012). *Lancet* 2017;390:935-45.
- Beasley R, Semprini A, Mitchell EA. Risk factors for asthma: is prevention possible? *Lancet* 2015;386:1075-85.
- Weatherall M, Ioannides S, Braithwaite I, *et al*. The association between paracetamol use and asthma: causation or coincidence? *Clin Exp Allergy* 2015;45:108-13.
- Bertolini A, Ferrari A, Ottani A, *et al*. Paracetamol: new vistas of an old drug. *CNS Drug Rev* 2006;12:250-75.
- Beasley R, Crane J, Lai CK, *et al*. Prevalence and etiology of asthma. *J Allergy Clin Immunol* 2000;105:S466-72.
- Beasley R, Clayton T, Crane J, *et al*. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from phase three of the Isaac programme. *Lancet* 2008;372:1039-48.
- Etminan M, Sadatsafavi M, Jafari S, *et al*. Acetaminophen use and the risk of asthma in children and adults: a systematic review and metaanalysis. *Chest* 2009;136:1316-23.
- García-Marcos L, Sanchez-Solis M, Perez-Fernandez V. Early exposure to acetaminophen and allergic disorders. *Curr Opin Allergy Clin Immunol* 2011;11:162-73.
- Dimova S, Hoet PHM, Dinsdale D, *et al*. Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *Int J Biochem Cell Biol* 2005;37:1727-37.
- Peterson JD, Herzenberg LA, Vasquez K, *et al*. Glutathione levels in antigen-presenting cells modulate Th1 versus Th2 response patterns. *Proc Natl Acad Sci U S A* 1998;95:3071-6.
- Farquhar H, Stewart A, Mitchell E, *et al*. The role of paracetamol in the pathogenesis of asthma. *Clin Exp Allergy* 2010;40:32-41.
- Cheelo M, Lodge CJ, Dharmage SC, *et al*. Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis. *Arch Dis Child* 2015;100:81-9.
- Magnus MC, Karlstad Ø, Håberg SE, *et al*. Prenatal and infant paracetamol exposure and development of asthma: the Norwegian mother and child cohort study. *Int J Epidemiol* 2016;45:512-22.
- Asher MI, Keil U, Anderson HR, *et al*. International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
- New Zealand formulary for children. Available: http://www.nzfchildren.org.nz/nzf_1
- Martinez FD, Wright AL, Taussig LM, *et al*. Asthma and wheezing in the first six years of life. The group health medical associates. *N Engl J Med* 1995;332:133-8.
- Castro-Rodriguez JA, Holberg CJ, Wright AL, *et al*. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
- Taussig LM, Wright AL, Holberg CJ, *et al*. Tucson children's respiratory study: 1980 to present. *J Allergy Clin Immunol* 2003;111:661-75.
- Asher MI, Stewart AW, Clayton T, *et al*. Has the prevalence and severity of symptoms of asthma changed among children in New Zealand? Isaac phase three. *N Z Med J* 2008;121:52-63.
- Riley J, Hunt A, McDouall A, *et al*. Pilot study of feasibility of a randomised controlled trial of asthma risk with paracetamol versus ibuprofen use in infancy. *N Z Med J* 2016;129:30-42.
- Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377-81.
- Riley J, Braithwaite I, Shirtcliffe P, *et al*. Randomized controlled trial of asthma risk with paracetamol use in infancy--a feasibility study. *Clin Exp Allergy* 2015;45:448-56.
- Global Asthma Network. The global asthma report 2014. Auckland; 1994.
- Lai CKW, Beasley R, Crane J, *et al*. Global variation in the prevalence and severity of asthma symptoms: phase three of the International study of asthma and allergies in childhood (ISAAC). *Thorax* 2009;64:476-83.
- Lesko SM, Louik C, Vezina RM, *et al*. Asthma morbidity after the short-term use of ibuprofen in children. *Pediatrics* 2002;109:E20.
- Sheehan WJ, Mauger DT, Paul IM, *et al*. Acetaminophen versus ibuprofen in young children with mild persistent asthma. *N Engl J Med* 2016;375:619-30.
- Litonjua AA. Acetaminophen and asthma - a small sigh of relief? *N Engl J Med* 2016;375:684-5.
- Wong T, Stang AS, Ganshorn H, *et al*. Combined and alternating paracetamol and ibuprofen therapy for febrile children. *Evid Based Child Health* 2014;9:675-729.
- World Health Organization. *The ICD-10 classification of mental and behavioural disorders*. Geneva: World Health Organization, 1992.
- Williams HC, Burney PG, Strachan D, *et al*. The U.K. Working Party's diagnostic criteria for atopic dermatitis. II. Observer variation of clinical diagnosis and signs of atopic dermatitis. *Br J Dermatol* 1994;131:397-405.