

BACKGROUND

Asthma is a major public health problem in New Zealand (NZ). Prevalence rates for asthma during childhood, and for severe asthma, are amongst the highest in the world.¹⁻³

³ In NZ, one in seven children, and one in nine adults, receive treatment for asthma.^{4,5} Childhood asthma is the major determinant of subsequent asthma during adulthood. Annually in NZ over 3,500 children and over 4,600 adults are admitted to hospital with asthma exacerbations.⁴ Māori and Pacific children are disproportionately affected with relative risks (RRs) of 2.9 and 3.7, respectively, for asthma hospitalisations compared with NZ European children.⁴ The economic costs of asthma to NZ are considerable.³

Over the last 25 years, research and public health measures have seen significant advances in the assessment and management of asthma. However, progress has stalled in the last 10 years, despite increasing investment in treatment.⁶ There is an urgent need for research that leads to evidenced-based primary prevention strategies to reduce the prevalence of asthma in children.⁷

One risk factor for which there is substantive evidence for a potential role in the pathogenesis of asthma is the use of paracetamol.⁸⁻¹⁰ Paracetamol is the most commonly prescribed and over-the-counter medication dispensed to children in the first year of life. The International Study of Asthma and Allergies in Childhood (ISAAC study), conducted in 72 centres and 31 countries worldwide, led from the University of Auckland, found that administration of paracetamol to infants was associated with a 46% increased risk of current asthma symptoms at the age of 6 to 7 years.¹¹ Despite substantive non-experimental evidence of an association between paracetamol use in infancy and the presence of asthma in

later childhood,^{12,13} it remains uncertain if this association reflects true causation, or is merely subject to confounding.

To definitively answer the question of whether avoidance of paracetamol exposure in infancy will reduce the risk of developing asthma later in childhood, we will conduct the first ever randomised controlled trial of paracetamol and the risk of asthma and related allergic disorders at age six years. Because it would be unethical to give a placebo for pain or fever in infancy, paracetamol will be compared to another common anti-pyretic/analgesic drug used in children, ibuprofen, which has not been associated with allergic disease.

The findings of PIPPA Tamariki will be relevant to all parents/caregivers and health professionals who care for infants or who prescribe and/or dispense paracetamol to infants.

PURPOSE OF THE TRIAL

To determine whether paracetamol treatment, compared with ibuprofen treatment, as required for fever and pain in the first year of life, increases the risk of asthma at 6 years of age.

ENTRY CRITERIA

Inclusion Criteria:

(1) Birth within the catchment area of Auckland City, Middlemore or Wellington Hospitals; (2) Age <8 weeks.

Exclusion Criteria:

(1) Highly unlikely to remain in NZ for the first 6 years of life; (2) Chronic disease associated with limited life expectancy (i.e. less than 6 years); (3) Gestational age at birth <32 weeks; (4) Previous exposure to paracetamol or ibuprofen since birth.

STUDY GROUPS

Eligible infants are randomised into one of two study groups: 'Paracetamol Group' or the 'Ibuprofen Group'.

Caregivers are asked to give their infant(s) only the allocated medication in the first 12 months of life, if required for pain or fever. Medication will be arranged for infants and their families, based on the NZ Formulary for Children.¹⁴

Paracetamol group dosing: for ≥1 month 15 mg/kg every 4 hours as required, maximum 60 mg/kg/day; for <1 month, ONLY under advice of health professional, 15 mg/kg every 6 hours as required, maximum 60 mg/kg/day.

Ibuprofen group dosing: for 1-3 months 5 mg/kg every 6 hours as required, maximum 20 mg/kg/day; > 3 months 10 mg/kg every 6 hours as required, maximum 30 mg/kg/day; for <1 month, ONLY under advice of health professional, 5 mg/kg every 6 hours as required, maximum 20 mg/kg/day.

OUTCOMES

Primary:

- Wheeze in the last 12 months at 6 years of age

Secondary:

- Bronchiolitis or wheeze in the first year of life
- Wheeze at 3 years of age
- Eczema at 3 and 6 years of age
- Atopy at 3 and 6 years of age
- Bronchiolitis, wheeze or asthma in the first 6 years of life

SAMPLE SIZE

A sample size of 3,922 will have 90% power to detect a 20% relative difference in primary outcome between the two groups, allowing for 10% crossover and 10% loss to follow-up.



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THANK YOU FOR READING ABOUT

PIPPA TAMARIKI!

We look forward to your involvement in the PIPPA Tamariki study by:

- Discussing the choice to participate in PIPPA Tamariki with the families under your care
- Contacting the PIPPA Tamariki research team about enrolment of infants into the study
- Sharing of the results of the study



The PIPPA Tamariki Investigators:

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Paracetamol and Ibuprofen in Primary Prevention of Asthma in Tamariki



HEALTH PROFESSIONAL INFORMATION SHEET

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