

# BMJ Open Assessing the appropriateness of the management of upper respiratory tract infection in Australian children: a population-based sample survey

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## ABSTRACT

**Objective** To assess the proportion of Australian children aged 0–15 years that received care in line with clinical practice guidelines (CPGs) for upper respiratory tract infections (URTIs).

**Design** Retrospective medical record review using a multistage sampling strategy.

**Setting** General practices, hospital emergency departments and hospital inpatient service providers in three Australian states.

**Participants** Children aged up to 15 years who received care for URTI in 2012 and 2013.

**Primary and secondary outcome measures** The primary assessment was estimated adherence with 14 indicators of appropriate care as documented in medical records. Indicators were extracted from national and international CPGs and ratified by experts. Secondary assessment was adherence to two bundles of indicators (diagnostic symptoms and medical history taking), where all indicators must be adherent for the bundle to be scored as adherent.

**Results** There were 1653 children with one or more assessments of URTI care to CPG adherence. Over half of the children were under 3 years of age, with roughly equal numbers of males and females. Three indicators had fewer than 25 visits so were not reported. Overall adherence ranged from 0.5% for 'documented advice around antibiotics' to 88.3% for 'documentation of medical history'. Adherence with Bundle A (documentation of all three definitive symptoms) was 43.1% (95% CI 32.8% to 54.0%) and Bundle B (documentation of all four indicators of medical history) was 30.2% (95% CI 20.9% to 40.9%).

**Conclusions** URTIs in children are common, usually self-limiting, conditions that are allocated considerable resources. The results suggest that there may be a need for more thorough holistic assessment of the patient and improved documentation. Since inappropriate prescription of antibiotics for URTIs is still a known problem in Australia, there is a need for consistent, clear communication around antibiotics' lack of impact on symptoms and a high association with undesirable side effects.

## Strengths and limitations of this study

- The study used a multistage representative sample across three Australian states, generalisable to the population.
- Using medical records allowed assessment of guideline adherence in real-world settings.
- Lack of documentation of an action was interpreted as indicating the action did not occur.
- Registered paediatric nurses familiar with childhood illnesses and management extracted data from medical records.
- The patient's whole medical record was available to nurses extracting data not just the occasion of care.

## INTRODUCTION

Upper respiratory tract infections (URTIs) are characterised by nasal congestion, rhinorrhoea, cough, sore throat and fever with a median duration of symptoms of 7–15 days.<sup>1,2</sup> It is estimated that a normal child will experience five viral URTIs per year,<sup>3</sup> but more than 10% of children have 10 or more 'colds' per year.<sup>1</sup> It has been suggested that first-time parents may be surprised and concerned by this frequency and misunderstand treatment options.<sup>4</sup>

URTIs are one of the most frequent problems managed by general practitioners (GPs) in Australia.<sup>5</sup> The Bettering the Evaluation And Care of Health (BEACH) study found that URTI presentations made up 3.3% of an Australian GP's workload, being third in frequency to hypertension and immunisations/vaccinations.<sup>5</sup> Children under 15 years old made up 31% of these patients and 17% are under 5 years old.<sup>6</sup> While URTIs are self-limiting, minor ailments, this represents a considerable use of time and resources. Other costs attributed to URTIs in children are mainly due to lost work time for carers.<sup>7</sup>

National clinical practice guidelines (CPGs) for assessment and management of childhood URTIs have been developed in a number of countries such as USA,<sup>8-10</sup> Sweden,<sup>11</sup> UK<sup>12</sup> and Australia.<sup>13 14</sup> Most guidelines around assessment are consensus based as research on the clinical management on URTIs is scarce.<sup>5</sup> As URTIs are predominantly viral in origin and therefore mostly self-limiting, the clearest guidelines address the appropriate use of antibiotics and assessment for complications such as peritonsillar abscess, bacterial sinusitis or pneumonia, or differential diagnoses such as pertussis. Other guidance addresses issues of care process, such as ensuring history and comorbidities are taken into account (eg, neutropenia), and general advice to return if symptoms worsen or do not resolve.

Inappropriate management of URTIs in children can lead to overtreatment of a self-limiting condition, unnecessary antibiotic use leading to side effects, resistance of pathogenic bacteria, and increased burden for families. As one of the most frequent childhood illnesses, these considerations are significant.<sup>12-14</sup>

CareTrack Kids (CTK) assessed care of Australian children aged 0–15 years, in 2012 and 2013, to determine the proportion that received care in line with CPGs for 17 common conditions.<sup>15</sup> Across the 17 conditions, appropriate care per occasion of care was provided at an average of 59.8% (95% CI 57.5% to 62.0%), and at 53.2% (95% CI 46.6% to 59.8%) for URTI.<sup>15</sup> We present and discuss the CTK results for URTI at indicator level.

## METHODS

The CTK methods have been reported in detail elsewhere.<sup>15-17</sup> We describe some aspects specifically relevant to URTI, with a focus on indicator development.

### Development of indicators

The RAND-UCLA method was modified for indicators.<sup>18</sup> This study defined a clinical indicator as a measurable component of a standard or guideline, with explicit criteria for inclusion, exclusion, time frame and practice setting.<sup>19</sup> More details on the development of indicators have been published separately.<sup>20</sup>

Three CPGs were found following a systematic search for Australian and international CPGs for URTI relevant for the years 2012–2013. From these three, 20 recommendations were extracted. Recommendations were screened for eligibility and excluded if they: (1) contained indefinite wording (eg, ‘may’, ‘could’); (2) had a low likelihood of being documented; (3) consisted of guiding statements without recommended actions or (4) addressed aspects of care deemed out of scope of the CTK study such as ‘structure-level’ recommendations. Thirteen recommendations were excluded, with the remaining seven passed to internal review.

Candidate recommendations were ratified by experts over a two-stage multiround modified Delphi process, which comprised an email-based three-round internal

review and a collaborative, online, wiki-based two-round external review, custom designed for the study.<sup>17</sup> In total, 10 experts (comprising nine paediatricians and one GP) were recruited for the internal (n=3) and external review (n=7). An expert coordinator was appointed to lead the reviews for each condition. Reviewers completed a conflict of interest declaration<sup>17</sup> and these were managed according to an established protocol.<sup>21</sup>

In the internal review experts scored each recommendation against three criteria (acceptability, feasibility and impact)<sup>17</sup> and recommended inclusion or exclusion. External reviewers applied the same scoring criteria as internal reviewers and, in addition, used a nine-point Likert scale to score each indicator as representative of appropriate care delivered to children during 2012 and 2013.<sup>17 18</sup> Internal and external reviewers completed their assignments independently to minimise group think.<sup>22</sup> Four recommendations were ratified by this process and these were formatted into 14 medical record audit indicator questions. All indicator questions are shown in online supplementary appendix 1.

### Sample size, sampling process and data collection

A minimum of 400 medical record reviews per condition was required to obtain national estimates with 95% CIs and precision of  $\pm 5\%$ , without adjustment for design effects. CTK targeted 400 medical records for URTI and 6000 medical records for 16 other conditions. If any of the 6400 medical records we targeted and sampled contained a visit for URTI, a separate assessment of appropriateness was made for each occasion. Information about the sampling methods have been published;<sup>15</sup> additional details specific to URTI can be found in online supplementary appendix 2. Briefly, we sampled three health-care settings (hospital inpatients, emergency department (ED) presentations and consultations with GPs) in health department administrative units (health districts) in Queensland, New South Wales and South Australia, for children aged  $\leq 15$  years receiving care in 2012 and 2013. For the broader CTK study, the recruitment rate was 92% for hospitals and estimated to be 24% for GPs (see online supplementary appendix 2). Data were collected by nine experienced paediatric nurses trained to assess eligibility for indicator assessment and adherence with CPGs. Medical records for selected visits in 2012 and 2013 were reviewed on-site at each participating facility from March to October 2016. Data collectors had access to the entire medical record, not just the occasion of care.

### Analysis

At indicator level, estimates of adherence were measured as the percentage of eligible indicators (ie, indicators answered either ‘yes’ or ‘no’) which were scored as ‘yes’. Adherence results for some clinically related indicators were aggregated as bundles of care. For example, indicators URTI01-URTIO3 all relate to the documentation of symptoms of children who presented with URTI; all three of these indicators would have to be scored ‘yes’ for

the bundle to be scored as adhering to the CPG. When assessing bundles, a visit was only included if there were responses for all component indicators.

Sampling weights were constructed as specified in online supplementary appendix 2 to adjust for oversampling of states and healthcare settings and for sampling within health districts. The weighted data were analysed in SAS V.9.4 (SAS Institute), using the SurveyFreq procedure. Variance was estimated by Taylor series linearisation and the primary sampling unit (health district) was specified as the clustering unit. Stratification and, where appropriate, domain analyses were used (see online supplementary appendix 2). Exact 95% CIs were generated using the modified Clopper-Pearson method except when the point estimate was 0% or 100% where the unmodified Clopper-Pearson method was used.<sup>23</sup> In both indicator and bundle reports results were suppressed if there were <25 eligible visits, as small sample sizes could lead to misleading estimates. Differences in adherence rates between settings were restricted to comparisons between GP and the two hospital settings; as hospitals records were not sampled independently, they were not compared statistically. Statistical significance, where calculated, was based on the F-test approximation of the Rao-Scott X<sup>2</sup> test, which adjusts for the design effect.

### Ethical considerations

Australian Human Research Ethics Committees can waive requirements for patient consent for external access to medical records if the study entails minimal risk to healthcare providers and patients;<sup>16</sup> all relevant bodies provided this waiver. Participants were protected from litigation by gaining statutory immunity for CTK as a quality assurance activity from the Federal Minister for Health under part VC of the Health Insurance Act 1973 (Commonwealth of Australia). Ethical approvals included reporting by healthcare setting for URTI.

### Patient and public involvement

This study did not involve patients or the public.

## RESULTS

There were 1653 children with one or more assessable CPG indicators for URTI, with the age and sex distribution shown in table 1. Over half of the children in the CTK sample were under 3 years of age, with roughly equal number of males and females. Of 38 290 possible indicator assessments, 11 831 (30.9%) were designated as not applicable or otherwise ineligible. The field team conducted 26 459 eligible indicator assessments grouped into 2714 visits, at a median of 10 indicators per visit. Eligible URTI visits were assessed in 81 GP practices, 34 hospital EDs and 25 hospital inpatient service providers.

### Adherence

The assessed guideline adherence for each indicator is shown in table 2, presented by healthcare setting and

**Table 1** Characteristics of the eligible children with visits for URTI, 2012–2013

Characteristic	Children in the CTK Study
Age*—no. (%)	
<3 months	46 (2.8)
3–11 months	262 (15.8)
1–2 years	568 (34.4)
3–5 years	363 (22.0)
6–12 years	350 (21.2)
13–15 years	64 (3.9)
Male—no (%)	878 (53.1)

\*The child's age was calculated as the age at visit where there was only one, or the midpoint of the child's age at her first and last URTI visit, where there was more than one.  
CTK, CareTrack Kids; URTI, upper respiratory tract infection.

overall. Adherence is not reported for three of the 14 indicators because they were assessed in fewer than 25 visits and for some settings in the other 11 indicators. For the 11 reported indicators, overall adherence ranged from 0.5% (95% CI 0.1% to 1.5%) for indicator URTI09 ('Parents of children with an URTI were advised against antibiotics as they may have side effects') to 88.3% (95% CI 79.3% to 94.4%) for URTI05 ('Children who presented with an URTI had their previous medical history documented'). The IQR for overall adherence in the 11 indicators reported was 14.2%–70.3%. Large CIs on many of the indicators show substantial uncertainty in the estimates.

By healthcare setting, estimated adherence in ED and inpatient settings was generally higher than in GP settings. As shown in table 2, adherence in the GP setting was statistically significantly lower than in the ED setting for six indicators (URTI01, URTI03–04, URTI06, URTI09, URTI14), and in the inpatient setting for four indicators (URTI01, URTI05–07).

The assessed adherence for two bundles of care is shown in table 3, for all three settings and overall. Bundle A assessed the documentation of three symptoms (runny nose, cough and fever) and found 43.1% overall adherence (95% CI 32.8% to 54.0%); the component indicator with the lowest adherence was documentation of the presence of a runny nose (61.4%, 95% CI 51.4% to 70.8%; URTI01). Bundle B covered four indicators relating to the documentation of medical history and found 30.2% adherence (95% CI 20.9% to 40.9%); the component indicator with the lowest adherence was documentation of comorbidities (42.2%, 95% CI 32.0% to 52.8%; URTI04).

## DISCUSSION

This study assessed the guideline adherence of care for URTI provided to children aged 0–15 years in GP practices, EDs and inpatient services. Overall, guideline

**Table 2** Adherence by clinical indicator and by healthcare setting, 2012–2013

Indicator ID	Indicator description	Healthcare setting	No. of children	No. of visits	Proportion adherent, % (95% CI)
URTI01	Children who presented with URTI symptoms had the presence of a runny nose (rhinorrhoea) documented.	GP	1197	2073	60.8 (49.0 to 71.7)
		ED	423	530	77.5 (70.1 to 83.8)*
		Inpatient	80	89	85.0 (68.0 to 95.1)*
		Overall	1648	2692	61.4 (51.4 to 70.8)
URTI02	Children who presented with URTI symptoms had the presence of a cough documented.	GP	1197	2073	70.1 (56.4 to 81.6)
		ED	423	530	75.2 (60.9 to 86.3)
		Inpatient	80	89	76.1 (57.5 to 89.4)
		Overall	1648	2692	70.3 (58.6 to 80.3)
URTI03	Children who presented with URTI symptoms had the presence of a fever documented.	GP	1196	2071	63.2 (52.0 to 73.5)
		ED	422	529	85.2 (73.4 to 93.2)*
		Inpatient	80	89	84.1 (59.8 to 96.7)
		Overall	1646	2689	64.0 (54.3 to 73.0)
URTI04	Children who presented with an URTI had their comorbidities documented.	GP	1178	2045	40.8 (28.9 to 53.6)
		ED	417	518	78.8 (64.0 to 89.6)*
		Inpatient	79	88	63.0 (32.6 to 87.3)
		Overall	1623	2651	42.2 (32.0 to 52.8)
URTI05	Children who presented with an URTI had their medical history documented.	GP	1201	2092	88.0 (77.3 to 94.9)
		ED	423	530	95.8 (91.1 to 98.4)
		Inpatient	80	89	98.2 (92.5 to 99.9)*
		Overall	1652	2711	88.3 (79.3 to 94.4)
URTI06	Children who presented with an URTI had their current medications documented.	GP	1198	2088	45.9 (37.2 to 54.9)
		ED	422	529	82.9 (71.3 to 91.2)*
		Inpatient	80	89	87.6 (74.5 to 95.5)*
		Overall	1648	2706	47.3 (39.9 to 54.7)
URTI07	Children who presented with an URTI had a physical examination.	GP	1200	2089	83.0 (71.7 to 91.1)
		ED	422	529	94.8 (87.6 to 98.4)
		Inpatient	80	89	100.0 (95.9 to 100.0)*
		Overall	1650	2707	83.4 (73.9 to 90.5)
URTI08	Parents of children with an URTI were advised against antibiotics as they are likely to make little difference to the symptoms.	GP	1162	2013	11.0 (3.7 to 23.8)
		ED	308	386	9.4 (4.7 to 16.4)
		Inpatient	63	71	3.1 (0.1 to 15.6)
		Overall	1491	2470	11.0 (4.3 to 21.8)
URTI09	Parents of children with an URTI were advised against antibiotics as they may have side effects.	GP	1152	1993	0.4 (0.0 to 1.7)
		ED	303	381	3.6 (0.9 to 9.1)*
		Inpatient	63	71	0.0 (0.0 to 5.1)
		Overall	1475	2445	0.5 (0.1 to 1.5)
URTI10	Children with an URTI and pneumonia were prescribed antibiotics.	GP	39	41	12.0 (3.9 to 25.9)
		ED	15	16	Insufficient data
		Inpatient	4	4	Insufficient data
		Overall	57	61	14.2 (6.6 to 25.5)
URTI11	Children with an URTI and a peritonsillar abscess were prescribed antibiotics.	GP	8	8	Insufficient data
		ED	2	2	Insufficient data
		Inpatient	0	0	Insufficient data
		Overall	10	10	Insufficient data

Continued

Table 2 Continued

Indicator ID	Indicator description	Healthcare setting	No. of children	No. of visits	Proportion adherent, % (95% CI)
URTI12	Children with an URTI and <i>Bordetella pertussis</i> were prescribed antibiotics.	GP	9	9	Insufficient data
		ED	6	6	Insufficient data
		Inpatient	1	1	Insufficient data
		Overall	15	16	Insufficient data
URTI13	Children with an URTI and acute moderate/severe bacterial sinusitis were prescribed antibiotics.	GP	18	20	Insufficient data
		ED	1	1	Insufficient data
		Inpatient	3	3	Insufficient data
		Overall	21	24	Insufficient data
URTI14	Parents of children with an URTI were advised to return if the condition worsens or becomes prolonged.	GP	1183	2054	54.8 (46.8 to 62.7)
		ED	368	451	78.4 (71.1 to 84.5)*
		Inpatient	71	80	64.5 (47.0 to 79.6)
		Overall	1603	2585	55.6 (48.7 to 62.2)

\*ED/inpatient adherence statistically significantly higher than GP adherence at  $p < 0.05$ .  
ED, emergency department; GP, general practitioner; URTI, upper respiratory tract infection.

adherence was found to be suboptimal and inconsistent with indicator scores ranging from 88.3% (URTI05) to 0.5% (URTI09).

Documentation of medical history scored the highest of the indicators at 88.3% (URTI05) but is only one aspect of a holistic assessment required to make appropriate management decisions; that is, to rule out more serious underlying disease (eg, cystic fibrosis) and to limit exacerbation of chronic conditions (eg, asthma).<sup>4</sup> The second bundle of care measured documentation of medical history, comorbidities, current medications and a physical examination. All four aspects were documented in only 30.2% of patient encounters, indicating that one or more important aspects of assessment were potentially being overlooked. It could be argued that children who were seeing their usual GP or were regular presenters at the ED (eg, a well-known patient with asthma or cystic fibrosis)

may not have had these comorbidities documented at each individual episode of care. However, auditors had access to the whole medical record and were instructed to consider this when determining whether indicators were eligible for scoring (ie, to check for previous entries or summaries likely to have been referred to by clinicians).

Children under 3 months of age were included in the study and accounted for 2.8% of the cohort. We acknowledge that it is difficult at that age to differentiate URTI from early bronchiolitis.

Antibiotics are not indicated for uncomplicated viral URTI presentations and their inappropriate use may contribute to the major problem of antibiotic resistance,<sup>12</sup> and put children at risk of side effects. Other studies investigating this issue have measured inappropriate prescribing rates of 20.2% for children under 5 years of age with uncomplicated URTIs,<sup>24</sup> and 46% of patients

Table 3 Adherence by bundle of care and healthcare setting, 2012–2013

Bundle ID	Bundle description	Indicator IDs*	Healthcare setting	No. of children	No. of visits	No. of indicator assessments	Proportion adherent, % (95% CI)
A	Children who presented with URTI symptoms had the presence of symptoms documented.	01–03	GP	1196	2071	6213	42.5 (30.5 to 55.2)
			ED	422	529	1587	59.1 (46.5 to 70.9)
			Inpatient	80	89	267	60.4 (44.1 to 75.2)
			Overall	1646	2689	8067	43.1 (32.8 to 54.0)
B	Children who presented with an URTI had medical history documented.	04–07	GP	1175	2039	8156	28.8 (17.8 to 41.9)
			ED	415	516	2064	68.2 (51.4 to 82.1)
			Inpatient	79	88	352	55.6 (29.8 to 79.4)
			Overall	1618	2643	10572	30.2 (20.9 to 40.9)

\*In table 2, the indicator ID was preceded by 'URTI'.  
ED, emergency department; GP, general practitioner; URTI, upper respiratory tract infection.

of all ages with URTI in Australian general practice.<sup>25</sup> Prescribing for non-specific URTI increased fourfold in the UK between 1996 and 2006.<sup>26</sup> Pressure from parents to receive a prescription for antibiotics is a frequently mentioned issue affecting physicians' prescribing practice (eg, 25 27–29). A study in South East Wales suggested that parents of preschool children were being influenced to inappropriately seek antibiotics by the policy and social pressure exerted by day care providers, contrary to the evidence on URTI treatment.<sup>30</sup> A Canadian cluster-randomised trial which trained family physicians to engage parents in shared decision-making around treatment options demonstrated that it is possible to reduce the rate of inappropriate antibiotic use in children with acute respiratory infections by 60%.<sup>31</sup>

Two indicators were included in our study that relate to explaining to parents why antibiotics are not indicated (URTI08–09) to address this social pressure and ensure engagement with, and education of parents. These indicators were guided by the National Institute for Health and Care Excellence 2008 guidelines which recommend: 'When the 'no antibiotic prescribing strategy' is adopted, patients should be offered reassurance that antibiotics are not needed immediately because they are likely to make little difference to symptoms and may have side effects, for example, diarrhoea, vomiting and rash.' Our indicators reflect this advice yet seem infrequently given to parents in our study or were not documented. Indicator URTI09 ('Parents of children with an URTI were advised against antibiotics as they may have side effects') showed the lowest level of adherence across the indicators (0.5%) with indicator URTI08 ('Parents of children with an URTI were advised against antibiotics as they are likely to make little difference to the symptoms') scoring second lowest with 11%. There may be several reasons for this: the advice may have been given but not documented; antibiotics may have been (inappropriately) prescribed; or pressure for antibiotic prescription may not have been an issue needing to be addressed. Alternatively, discussions around the inappropriateness of antibiotics to treat an uncomplicated URTI may have been framed in a different way that auditors did not judge as equivalent; for example, focussing instead on the viral nature of URTIs and how antibiotics are only effective against bacterial infections.

Our study did assess circumstances in which antibiotic prescription was appropriate. Appropriateness of antibiotic prescription for children with concurrent pneumonia (URTI10) was only 14.2% in the aggregated data and on breakdown by setting, only GPs had a large enough number of presentations to report. GPs for this indicator scored 12.0% (95% CI 3.9% to 25.9%), which is surprisingly low. The BEACH study<sup>24</sup> measured antibiotic prescription rates for children under 5 years diagnosed with pneumonia as 65.6%. Given that 85% of children with URTI and pneumonia in our study were under 5 years of age, it is not clear why our results differ. The BEACH study relies on physician documentation of

a special form, while our study examined what was documented in the medical record. As early as 2005, we have Australian survey evidence of a high level of penetration of electronic medical record use by GPs (~90%), with 98% of users 'mostly' using the inbuilt prescribing tool, so underdocumentation seems unlikely to be the source of the discrepant results, at least for this setting.<sup>32</sup> It remains possible that the relatively small number of occasions of care surveyed (n=61), has by chance led to an unrepresentative result. Another reason may have been the lack of specificity of URTI10 which did not differentiate between bacterial and viral pneumonia. Insufficient data from EDs and inpatient settings did not allow a comparison.

Strengths of the study include the large sample of Australian children: 1653 children with one or more eligible indicator assessments were analysed. Another strength was the use of paediatric registered nurses who underwent 5 days of training and assessment in auditing the indicators before collecting data, and who were familiar with childhood illnesses and management. This increased the likelihood that records were correctly interpreted, and data recorded accurately. A weakness of the study is the use of documentation to assess actual practice; that is, if it was not documented, it was assumed it did not occur. We note, however, that from a litigation, insurance and auditing point of view, documentation is an accepted proxy measure for action and has been shown to be acceptably correlated with actual practice.<sup>33 34</sup>

Clinically, this study suggests the need for more thorough holistic assessment of the patient including consideration of all four aspects included in the indicators here (comorbidities, medical history, current medications and physical examination). Since inappropriate prescription of antibiotics for URTIs is still known to be a problem in Australia,<sup>24</sup> there is a need for consistent clear communication and patient education around antibiotics' lack of impact on symptoms and the risks of undesirable side effects.

## CONCLUSION

Uncomplicated URTIs are a common condition of childhood, with considerable time and resources expended in assessing and managing them.<sup>5</sup> This study has shown that appropriate care may not be delivered consistently and there is room for improvement. Guideline adherence for bundles of care, that require all component indicators to be addressed, was low: documentation of all three common diagnostic symptoms was only adhered to in an estimated 43.1% of visits, and holistic assessment of the patient using four indicators was only adhered to in 30.2% of visits. In a context where pressure from parents still drives inappropriate antibiotic use for children with URTI, advice to parents was infrequently reported (0.5% and 11%).

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### Contributors

JB and PDH designed the overall study. SJ and HMW contributed to design of URTI study. JB, PDH, GA, HPT and CJM carried out the collection and statistical analysis of the data. JL drafted the manuscript and was responsible for coordination of all aspects of the work. KC and LAE reviewed and made substantial contributions to earlier drafts. All authors contributed to the interpretation of results and the final manuscript.

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**Data sharing statement** All additional data are provided in online supplementary appendix.

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