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Prevalence of and Risk Factors for Human Rhinovirus Infection in Healthy Aboriginal and Non-Aboriginal Western Australian Children

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Abstract

Background—Human rhinovirus (HRV) species C (HRV-C) have been associated with frequent and severe acute lower respiratory infections and asthma in hospitalized children. The prevalence of HRV-C among healthy children and whether this varies with ethnicity is unknown.

Objective—to describe the prevalence of HRV species and their associations with demographic, environmental and socioeconomic factors in healthy aboriginal and non-aboriginal children.

Methods—respiratory viruses and bacteria were identified in 1006 nasopharyngeal aspirates collected from a cohort of 79 aboriginal and 88 non-aboriginal Western Australian children before 2 years of age. HRV-positive nasopharyngeal aspirates were typed for HRV species and genotypes. Longitudinal growth models incorporating generalized estimating equations were used to investigate associations between HRV species and potential risk factors.

Results—Of the 159 typed specimens, we identified 83 (52.2%) human rhinovirus species A (HrV-A), 26 (16.4%), human rhinovirus species B and 50 (31.4%) HrV-C. HRV-C was associated with upper respiratory symptoms in aboriginal (odds ratio, 3.77; 95% confidence interval: 1.05–13.55) and non-aboriginal children (odds ratio, 5.85; 95% confidence interval: 2.33–14.66). HRV-A and HRV-C were associated with carriage of respiratory bacteria. In aboriginal children, HRV-A was more common in the summer and in those whose mothers were employed prior to delivery.

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In non-aboriginal children, day-care attendance and exclusive breast-feeding at age 6–8 weeks were associated with detection of HRV-A, and gestational smoking with detection of HRV-C.

Conclusions—Factors associated with the presence of HRV differ between aboriginal and non-aboriginal children. In contrast to HRV-A, HRV-C is associated with upper respiratory symptoms suggesting that HRV-C is likely to be implicated in respiratory illness.

Keywords

human rhinovirus; aboriginal; bacterial association; environmental risk factors; upper respiratory symptoms; seasonality

Acute lower respiratory infections are the leading cause of serious childhood morbidity and mortality worldwide, accounting for an estimated 11–20 million hospitalizations and 2 million deaths each year in children <5 years of age.^{1,2} In Australia, aboriginal children bear a disproportionate burden of acute lower respiratory infections compared with non-aboriginal children.^{3–6} As many as 19 viral pathogens have been associated with respiratory infections.⁷ Of these, human rhinoviruses (HRV) are the most common worldwide and are responsible for approximately two-thirds of cases of the common cold.⁸ More recently, HRVs have been shown to infect the lower respiratory tract⁹ and are the major upper and lower respiratory pathogens in the first year of life.¹⁰

HRVs were first discovered in 1956 and were originally classified into 2 distinct species, human rhinoviruses species A (HRV-A) and human rhinoviruses species B (HRV-B), comprising 101 serotypes identified using traditional serologic and cell culture methods.^{11–13} Recent advances in the molecular detection and typing of respiratory viruses led to the identification of a third species, human rhinoviruses species C (HRV-C), which was first reported in 2006.¹⁴ Since then, over 50 new genotypes have been identified¹⁵ but cannot be formally assigned into separate serotypes as they have not yet been cultured in vitro. However, a proposed genotyping scheme has recently been published that incorporates sequence-based typing.¹⁶

Several studies worldwide investigating the prevalence of HRV species in children hospitalized with an acute lower respiratory infections have reported higher detection rates of HRV-C than HRV-A or HRV-B.^{14,17–22} HRV-C has been associated with more frequent and severe respiratory illness than HRV-A or HRV-B.^{20,22} Respiratory viruses, including HRV, are often detected not only in symptomatic but also in asymptomatic individuals.^{23,24} To date, little is known about the prevalence of HRV-C in healthy children living in the community. In the only study describing the prevalence of HRV-C in a control group of healthy children, 21 HRV-positive specimens were typed, of which 29% were HRV-C.²³ This lack of information limits the ability to determine the causal role of HRV-C in childhood respiratory illness.

The risk factors associated with the detection of HRV in the upper respiratory tract are not well understood. Day-care attendance and presence of siblings have been associated with HRV-induced wheezing among high-risk infants of atopic parents.²⁵ However, little is known about the demographic, environmental and socioeconomic risk factors associated with detection of HRV or HRV species in healthy children.

The Kalgoorlie Otitis Media research Project (KOMrP) aimed to investigate the causal pathways to otitis media in aboriginal and non-aboriginal children²⁶ and provides the opportunity to study the epidemiology of HRV in healthy children. We have previously reported on the presence of respiratory viruses and bacteria that were identified in 1006 nasopharyngeal aspirates (nPas) from 79 aboriginal and 88 non-aboriginal children who had

had at least 4 specimens collected before 2 years of age.^{24,27} HRV was the most frequently identified virus and was identified more often in aboriginal than in non-aboriginal children (24% versus 17%). HRV detection was also associated with the carriage of *Haemophilus influenzae* and *Moraxella catarrhalis* in aboriginal children. The prevalence of HRV species in aboriginal and non-aboriginal children and the risk factors associated with each species are unknown. We hypothesized that HRV-C would be less common than HRV-A among healthy children and that HRV detection would be positively associated with risk factors that may increase HRV transmission. Using a molecular method to type HRVs, we aimed to describe the prevalence of HRV species in specimens collected from healthy aboriginal and non-aboriginal children and their associations with potential demographic, environmental and socioeconomic risk factors. We also aimed to describe the associations between HRV species and concurrent carriage of respiratory bacterial pathogens.

MATERIALS AND METHODS

Setting and Study Population

Kalgoorlie-Boulder is located in the goldfields region of Western Australia, 600 km east of Perth. the population of the town is approximately 32,000 with an estimated 8% of the population being of aboriginal descent compared with 3% for Western Australia as a whole.²⁸ Kalgoorlie-Boulder has a dry climate (average rainfall of 265 mm) with minimum and maximum average temperatures ranging from 5°C to 18°C and 17°C to 34°C, respectively.²⁹ the methods and population characteristics of the KOMrP have been described in detail elsewhere.²⁶ in brief, between 1999 and 2004, 100 aboriginal and 180 non-aboriginal children living within a 1-hour drive of Kalgoorlie-Boulder were enrolled soon after birth and followed up regularly until 2 years of age. a total of 1559 NPAs were collected during routine follow-up visits conducted at ages 1–3 weeks, 6–8 weeks and at 4, 6, 12, 18 and 24 months. Some children may have experienced mild upper respiratory symptoms (blocked or runny nose) at the time of routine follow-up visits. Mothers or guardians of the children enrolled in the study were interviewed 1–3 weeks postpartum to collect demographic, socioeconomic, environmental and obstetric data as described elsewhere.³⁰ information on feeding practices and childcare attendance were collected again at subsequent follow-up visits.

Laboratory Methods

Of the 197 (19.6%) NPAs previously identified as HRVpositive, 186 were available for typing. Typing was based on a published molecular method to determine HRV genotypes and to differentiate closely related enteroviruses from HRV.^{31,32} In brief, viral RNA was extracted from the NPAs and reverse transcribed to cDNA. This was used for the semi-nested polymerase chain reaction amplification of the HRV 5' noncoding region using specifically designed primers as previously published.³¹ Polymerase chain reaction products were then sequenced commercially by the Australian genome research Facility. genotypes were assigned based on comparisons of the 5' noncoding region sequences with those of 101 classical serotypes (prefixed with r) as well as 52 newly identified genotypes (prefixed with W) using ClustalX software.^{31–33}

Statistical Analysis

NPA specimens were grouped into 7 age categories based on the average age at each of the follow-up visits. The prevalence of HRV species was defined as the proportion of specimens positive for a particular HRV species within the 1006 specimens tested for HRV. Unless otherwise stated, the² test was used to compare the prevalence of HRV species between aboriginal and non-aboriginal children in each age group.

Associations between detection of HRV species and demographic, environmental and socioeconomic risk factors were assessed using longitudinal logistic growth modeling on a complete case basis with an underlying quadratic age dependence. Generalized estimating equations with robust standard errors were used in these models to account for the within-subject dependencies in the data. Potential risk factors were first assessed in univariate models and were included as covariates in the final multivariate models if the univariate effect was significant ($P < 0.20$). Risk factors investigated were gender, presence of upper respiratory symptoms, gestational smoking, exposure to environmental tobacco smoke (indoors and/or outdoors), number of other children in the house, number of days per week spent in day care, mother's education level (postschool education/training or school only), mother's employment around the time of delivery, exclusive breast-feeding at 6–8 weeks postpartum, maternal age at delivery, crowding (>1 person/room), family history of allergy, season of NPA collection (summer, autumn, winter, spring) and simultaneous carriage of *Streptococcus pneumoniae*, *H. influenzae* or *M. catarrhalis*. Separate analyses were performed for aboriginal and non-aboriginal children. All statistical analyses were performed using SPSS, version 17 (SPSS inc, Chicago, IL).

Ethical Approval

The study design and protocol for the KOMrP were approved by the Western Australian aboriginal Health and information ethics Committee, the northern goldfields Health Service and nursing education ethics Committee in Kalgoorlie, Princess Margaret Hospital for Children ethics Committee and the Confidentiality of Health information Committee of the Health department of Western Australia.

RESULTS

Nasopharyngeal Specimens

Of the 1006 available NPAs, 19.6% were HRV-positive (23.6% in aboriginal children and 16.5% in non-aboriginal children). A total of 159 HRV-positive NPAs (85.5%) were successfully typed for HRV serotypes or genotypes. The 159 HRV-typed specimens were from 52 aboriginal children (85 specimens, average 1.50 per child, 61.2% male) and 50 non-aboriginal children (74 specimens, average 1.50 per child, 63.5% male). Of the 102 children with at least 1 HRV-typed specimen, 61 (59.8%), 25 (24.5%), 15 (14.7%) and 1 (1.0%) had 1, 2, 3 or 4 HRV-typed specimens, respectively, with no significant differences between aboriginal and non-aboriginal children.

HRV Species Identified in NPAs

Of the 159 HRV-positive typed specimens, 83 (52.2%) were HRV-A, 26 (16.4%) HRV-B and 50 (31.4%) HRV-C. Of the 436 specimens collected from aboriginal children, 47 (10.8%) were positive for HRV-A, 16 (3.7%) were positive for HRV-B and 22 (5.0%) were positive for HRV-C. In non-aboriginal children, 36 (6.3%) of the 570 specimens were positive for HRV-A, 10 (1.8%) for HRV-B and 28 (4.9%) for HRV-C. HRV-A was identified more often in specimens from aboriginal children than from non-aboriginal children, particularly in children 3–4 months of age (17.9% versus 5.1%, Fisher exact test $P = 0.017$) (Fig. 1). Although not statistically significant, HRV-C was also identified more often in specimens from aboriginal children than from non-aboriginal children 5–9 months of age (Fig. 1).

HRV Serotypes/Genotypes

Of the 159 typed HRV-positive specimens, 154 specimens had HRVs that were assigned to previously identified serotypes and genotypes. Eighty HRV-A specimens clustered into 38

known serotypes or genotypes, 24 HRV-B specimens into 11 serotypes and 50 HRV-C specimens into 28 genotypes (Table, Supplemental digital table 1 shows HRV overall and HRV species detection and Content 1, <http://links.lww.com/inF/B181>). The remaining 5 specimens (3 in HRV-a and 2 in HRV-B) could not be identified as a particular serotype or genotype as the sequences of the 2 most closely related serotypes or genotypes had equal percentage identities. No child had the same HRV serotype or genotype more than once.

Associations Between HRV Species and Demographic, Environmental and Social Factors

Table 1 shows HRV overall and HRV species detection and demographic, social and environmental predictor variables for the 79 Aboriginal children and 88 non-Aboriginal children who had at least 4 NPAs tested for respiratory viruses. Univariate and multivariate analyses of risk factors were examined for any HRV, HRV-A and HRV-C (Tables, Supplemental digital Content 2–4, <http://links.lww.com/inF/B182>, <http://links.lww.com/inF/B183> and <http://links.lww.com/inF/B184>). Analysis of risk factors was not performed on HRV-B, given the small number of HRV-B-positive specimens identified.

Respiratory Illness Symptoms

Overall, HRV detection was positively associated with the presence of a blocked or runny nose at the time of NPA collection for both Aboriginal [odds ratio (Or), 1.73; 95% confidence interval (Ci): 1.04–2.87] and non-Aboriginal (Or, 2.85; 95% Ci: 1.45–5.60) children (table, Supplemental digital Content 2, <http://links.lww.com/inF/B182>). HRV-C detection was positively associated with the presence of a blocked or runny nose in aboriginal (Or, 3.77; 95% Ci: 1.05–13.55) and non-aboriginal (Or, 5.85; 95% Ci: 2.33–14.66) children (table, Supplemental digital Content 4, <http://links.lww.com/inF/B184>), but this was not the case for HRV-a (table, Supplemental digital Content 3, <http://links.lww.com/inF/B183>).

Seasonality

The overall HRV detection rate was similar across all seasons in both Aboriginal and non-Aboriginal children (table, Supplemental digital Content 2, <http://links.lww.com/inF/B182>). However, we found different seasonal patterns for HRV-A and HRV-C (Fig. 2). In Aboriginal children, HRV-A was most likely to be detected during summer and least likely to be detected during winter (Or, 0.19; 95% Ci: 0.07–0.49) (table, Supplemental digital Content 3, <http://links.lww.com/inF/B183>), while HRV-C showed no seasonal variation (table, Supplemental digital Content 4, <http://links.lww.com/inF/B184>). In non-aboriginal children, no seasonal variation in the detection of either HRV-A or HRV-C was observed (tables, Supplemental digital Content 3 and 4, <http://links.lww.com/inF/B183> and <http://links.lww.com/inF/B184>).

Bacterial Interactions

Tables (Supplemental digital Content 2–4, <http://links.lww.com/inF/B182>, <http://links.lww.com/inF/B183>, and <http://links.lww.com/inF/B184>) show the co-occurrence of *S. pneumoniae*, *H. influenzae* or *M. catarrhalis* with any HRV, HRV-a or HRV-C in aboriginal and non-aboriginal children. after adjustment for confounders, detection of all 3 organisms was more common in aboriginal children with any HRV, but only reached statistical significance for *H. influenzae* (Or, 2.35; 95% Ci: 1.32–4.19) and *M. catarrhalis* (Or, 2.01; 95% Ci: 1.06–3.80) (table, Supplemental digital Content 2, <http://links.lww.com/inF/B182>). When analyzed by species, HRV-A was associated with carriage of *M. catarrhalis* in aboriginal children (Or, 2.65; 95% Ci: 1.16–6.07) and *S. pneumoniae* in non-aboriginal children (Or, 2.16; 95% Ci: 1.02–4.56) (table, Supplemental

digital Content 3, <http://links.lww.com/inF/B183>). HRV-C was associated with H. influenzae in aboriginal children (Or, 4.11; 95% Ci: 1.14–14.87) (table, Supplemental digital Content 4, <http://links.lww.com/inF/B184>).

Environmental and Social Factors

In non-Aboriginal children, the risk of detection of any HRV declined with an increasing number of children in the household (3 or more compared with no other children: Or, 0.39; 95% Ci: 0.16–1.00), while the number of days per week spent in day care was associated with an increased risk of HRV detection (Or, 1.71 per additional day; 95% Ci: 1.05–2.77). Increasing maternal age was associated with an increased risk of HRV detection in non-aboriginal children (compared with maternal age at delivery <25 years, Or 4.18; 95% Ci: 1.13–15.53 for maternal age 25–29 years and Or 5.18; 95% Ci: 1.48–18.23 for maternal age >30 years (table, Supplemental digital Content 2, <http://links.lww.com/inF/B182>).

In Aboriginal children, mother's employment around the time of delivery was associated with an increased risk of HRV-A detection (Or, 3.04; 95% Ci: 1.43–6.44). In non-aboriginal children, exclusive breast-feeding 6–8 weeks postpartum (Or, 3.08; 95% Ci: 1.09–8.76) and the number of days per week the child spent in day care (Or, 2.34 per additional day; 95% Ci: 1.05–5.21) were associated with an increased risk of HRV-a detection (table, Supplemental digital Content 3, <http://links.lww.com/inF/B183>). In non-aboriginal children, gestational smoking was associated with an increased risk of HRV-C detection (Or, 2.98; 95% Ci: 1.32–6.76) (table, Supplemental digital Content 4, <http://links.lww.com/inF/B184>).

DISCUSSION

This is the first study to describe the epidemiology of HRV species among aboriginal and non-aboriginal children in the community. All 3 HRV species were shown to circulate among these children in rural Western Australia, with HRV-a being the most common, followed by HRV-C. HRV-B was relatively uncommon (accounting for approximately one-sixth of all typed HRVs).

HRV-A accounted for over half of all typed HRVs in healthy aboriginal and non-aboriginal children while HRV-C accounted for one-third. This is in contrast to several studies of children hospitalized with respiratory illness, asthma or wheezing where HRV-C was the most frequently identified species.^{19–21,34–36} Furthermore, we showed that HRV-C, but not HRV-a, was significantly associated with the presence of upper respiratory symptoms in both aboriginal and non-aboriginal children. These data suggest that HRV-C is more likely than HRV-A to cause mild as well as more severe respiratory illness.

Approximately half of the 153 known serotypes or genotypes were detected, suggesting that a large number of HRV genotypes are circulating in the community and that no single HRV genotype predominates at any given time. The same HRV genotypes were identified in specimens from both aboriginal and non-aboriginal children, suggesting that they circulate between and within both ethnic groups. The fact that no child had the same HRV genotype more than once suggests that there may be genotype-specific host immune responses and limited protection against subsequent HRV exposures.

We found seasonal variations in detection of HRV-A in aboriginal children but not in non-aboriginal children. Different seasonal patterns of influenza virus infection between aboriginal and non-aboriginal children have previously been reported in urban areas of Western Australia, but to a lesser extent than seen in this study.³⁷ A review of HRV seasonality in temperate climates in the northern hemisphere found that HRV infections occurred primarily in 2 peaks, the first in April and May (late spring) and the second in

September and October (early autumn).³⁸ We found that HRV-A was most prevalent during the summer (December to February) among aboriginal children. This finding is in contrast to previous research that reported a positive correlation between relative humidity and HRV frequency³⁹ and the observation that HRV inactivates quickly at humidity levels below 50% and cannot survive in a dry environment.⁴⁰ Kalgoorlie-Boulder has a dry climate with an average relative humidity of <30% at 3 pm during summer.²⁹ Hence, other factors, including social factors such as increased social interaction over an extended period during the Christmas holidays, are likely to contribute to the high prevalence of HRV-a during summer in aboriginal children. Consistent with other studies, HRV-C was identified throughout the year, with a slightly higher incidence in autumn. Further investigation in a larger study is needed to better understand the epidemiology of these infections and their prevention.

We found statistically significant associations between HRV-A and *M. catarrhalis* in aboriginal children, HRV-A and *S. pneumoniae* in non-aboriginal children and HRV-C and *H. influenzae* in aboriginal children. HRV has previously been positively associated with *H. influenzae* and *M. catarrhalis* in aboriginal children.²⁴ In our study, nonsignificant associations were seen for other combinations of bacteria, HRV species and ethnicity. These findings suggest complex interactions between the different HRV species and bacterial pathogens and that HRV may influence the microbiome resulting in more serious diseases. Further studies are now required to investigate these interactions.

We found that aboriginal children of mothers who were employed around the time of delivery had an increased risk of HRV-A detection. The high rates of respiratory infection among aboriginal children in rural communities in Western Australia have been linked to adverse environmental and socioeconomic risk factors.⁴¹ To our knowledge; no other study has investigated the associations between HRV species and potential environmental and socioeconomic risk factors. We did not collect data regarding employment at the time of specimen collection. However, aboriginal mothers employed in late pregnancy may well return to work soon after delivery, leaving their young children with members of their extended family where HRV transmissions may be high. It is also possible that a mother's increased exposure to pathogens at work is subsequently transmitted to children at home. We also found a positive association between exclusive breast-feeding 6–8 weeks postpartum and HRV-A detection among non-aboriginal children. Generally, breast-feeding has been associated with a reduced risk of infection including respiratory infections.⁴² However, it is possible that the increased contact between mother and child as a result of breast-feeding may increase the transmission of HRV-a infection.

HRV (overall) and HRV-A infection were positively associated with the number of days per week spent at child care among non-aboriginal children, a finding which is consistent with previous studies.^{43,44} However, given that transmission of HRV is dependent on person-to-person contact, the association between a greater number of children in the household (3 or more) and a decreased risk of HRV detection among non-aboriginal children was unexpected and further studies with a greater number of participants are required to investigate this more fully. It is possible that the presence of older siblings in the household results in early transmission of HRVs and increased natural immunity in children.

Gestational smoking was positively associated with HRV-C detection among non-aboriginal children but not in aboriginal children. In our population, 41% of aboriginal children were exposed to gestational smoking compared with 18% of non-aboriginal children, which may explain why this finding was not observed in aboriginal children. Nevertheless, our findings in the non-aboriginal population suggest that efforts to reduce gestational smoking may reduce the risk of respiratory infection and specifically HRV infection in childhood.

The main limitation of this study is the relatively small sample size and the unknown potential confounders that may explain some of the unexpected results with regard to risk factors for detection of HRVs. nevertheless, this study has contributed to our understanding of the epidemiology of HRV among healthy aboriginal and non-aboriginal children and provides valuable information for future preventive strategies aimed at reducing HRV transmission and infection among young children. Further studies are now required in both healthy and sick children to understand fully the epidemiology and pathogenicity of HRV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Age-specific prevalence of HRV-A, HRV-B and HRV-C in 1006 nasopharyngeal specimens collected from healthy Aboriginal and non-Aboriginal children.

FIGURE 2.
Fitted values of the proportion of specimens positive for HRV-A and HRV-C among Aboriginal and non-Aboriginal children by season of detection.

TABLE 1

Human Rhinovirus Detection and Demographic, Environmental and Social Predictor Variables for Seventy-nine Aboriginal Children and Eighty-eight Non-Aboriginal Children who had At Least Four NPAs Tested for Viruses

Predictor Variable		Aboriginal	Non-Aboriginal
HRV at least once	Yes	58 (73.4%)	55 (62.5%)
	No	21 (26.6%)	33 (37.5%)
HRV-A at least once	Yes	37 (46.8%) *	31 (35.2%) *
	No	42 (53.2%) *	57 (64.8%) *
HRV-B at least once	Yes	14 (17.7%) *	11 (12.5%) *
	No	65 (82.3%) *	77 (87.5%) *
HRV-C at least once	Yes	19 (24.1%) *	25 (28.4%) *
	No	60 (75.9%) *	63 (71.6%) *
Gender	Male	47 (59.5%)	47 (53.4%)
	Female	32 (40.5%)	41 (46.6%)
Gestational smoking	Yes	33 (41.8%)	15 (17.0%)
	No	44 (55.7%)	73 (83.0%)
Exposure to environmental tobacco smoke	Yes	47 (59.5%)	31 (35.2%)
	No	29 (36.7%)	57 (64.8%)
Other children in house	Yes	60 (75.9%)	46 (52.3%)
	No	18 (22.8%)	42 (47.7%)
Child care ever attended	Yes	5 (6.3%)	17 (19.3%)
	No	55 (69.6%)	69 (78.4%)
Mother has postschool education	Yes	31 (39.2%)	65 (73.9%)
	No	45 (57.0%)	23 (26.1%)
Mother employed prior to delivery	Yes	24 (30.4%)	61 (69.3%)
	No	53 (67.1%)	27 (30.7%)
Exclusive breast-feeding 6–8 weeks postpartum	Yes	32 (40.5%)	61 (69.3%)
	No	34 (43.0%)	23 (26.1%)
Maternal age (years) at delivery	<25	38 (48.1%)	11 (12.5%)
	25–29	22 (27.8%)	27 (30.7%)
	30	18 (22.8%)	50 (56.8%)
Crowding (>1 person/room)	Yes	55 (69.6%)	7 (8.0%)
	No	23 (29.1%)	81 (92.0%)
Family history of allergy or atopy	Yes	43 (54.4%)	68 (77.3%)
	No	26 (32.9%)	17 (19.3%)
Crowding (>1 person/room)	Yes	55 (69.6%)	
	No	23 (29.1%)	
Family history of allergy or atopy	Yes	43 (54.4%)	
	No	26 (32.9%)	

* From 52 Aboriginal children and 50 Aboriginal children. Discrepancies between total numbers of children for different variables are the result of missing data.