

Acute lower respiratory infections (ALRI) in Indigenous and non-Indigenous children

Hannah Moore

Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, WA

Email: hannahm@ichr.uwa.edu.au

Introduction

In Australia and many other developed countries, acute lower respiratory infection (ALRI) is one of the most common reasons for hospitalisation in young children¹, and worldwide ALRI is the most common cause of death in children aged less than five years². An ALRI is any acute infection involving the lower part of the respiratory system from the trachea to the lung parenchyma. As a result, ALRI has a broad clinical spectrum incorporating whooping cough, pneumonia, bronchiolitis, bronchitis, influenza, bronchopneumonia, and croup, and the epidemiology of these clinical diagnostic categories varies. As pneumonia and bronchiolitis account for 80–91% of all ALRI admissions in children,^{3,4} and International Classification of Diseases (ICD) diagnostic coding of different ALRIs in hospitalised children is not always consistent, this review will primarily focus on ALRIs as an aggregated group of diagnoses. The aim of this review is to describe the epidemiology of ALRI in hospitalised Indigenous and non-Indigenous children, including a comparison of the burden, its aetiology and causal pathways to hospitalisation, as well as current interventions, and how data linkage studies can play a role in ongoing investigations.

Burden of ALRI in hospitalised children

The reported incidence of ALRI hospitalisations has varied between countries, geographic areas, age groups investigated and the definition of ALRI (Table 1). Children living in rural and remote areas tend to have higher hospitalisation rates, approximately 2–3 times higher than in children residing in metropolitan areas, even though they have less access to health services.³ The burden of ALRI is greater in Indigenous populations than in non-Indigenous populations. Therefore, in countries with a significant Indigenous population, like Australia, it is necessary to disaggregate hospitalisation estimates.

Non-indigenous populations

In Western Australia (WA), the highest incidence of ALRI hospitalisation is 62.9/1000 child-years in non-Aboriginal children aged 1–2 months, decreasing to 8.4/1000 in those aged 2–4 years and 3.2/1000 in those 5–9 years.⁵ As ALRI rates are highest in infants, defined as under the age of 12 months, most international comparisons are based on this age group (Table 1).

In WA during the 1990's ALRI hospitalisation rates and in particular bronchiolitis increased from 25 to 40/1000 live births

Table 1: Incidence rates of hospitalisations for ALRI for non-Indigenous and Indigenous children in developed countries

Diagnosis	Country	Year	Age	Rate per 1000	Source
Non-Indigenous children					
ALRI	USA	1999–2001	<12mths	63.2	Peck et al ⁴
ALRI	Australia – WA	1990–2000	<2yrs	45.3	Moore et al ⁵
ALRI	Australia – WA	1996–2005	<12mths	44.7	Moore et al ⁵
Bronchiolitis	UK (Rural)	1996–1998	<12mths	31.0	Deshpande et al ⁵⁸
Bronchiolitis	USA	1999–2001	<12mths	44.9	Peck et al ⁴
Pneumonia	New Zealand	1993–1996	<12mths	8.3	Grant et al ¹⁰
Pneumonia	USA	1999–2001	<12mths	20.8	Peck et al ⁴
Pneumonia	Australia – WA	1996–2005	<12mths	5.2	Moore et al ⁵
Indigenous children					
ALRI	USA	1999–2001	<12mths	116.1	Peck et al ⁴
ALRI	Australia – NT	1999–2004	<12mths	426.7	O'Grady et al ¹³
ALRI	Australia – WA	1996–2005	<12mths	276.1	Moore et al ⁵
ALRI	Canada	1997–1998	<6mths	484	Banerji et al ⁵⁹
Bronchiolitis	USA	1999–2001	<12mths	74	Peck et al ⁴
Bronchiolitis	Australia – NT	1999–2004	<12mths	352	O'Grady et al ¹³
Bronchiolitis	Australia – WA	1996–2005	<12mths	165.5	Moore et al ⁵
Pneumonia	New Zealand	1993–1996	<12mths	23.8	Grant et al ¹⁰
Pneumonia	USA	1999–2001	<12mths	54.7	Peck et al ⁴
Pneumonia	Australia – WA	1996–2005	<12mths	59.3	Moore et al ⁵

in non-Aboriginal infants.³ Increasing bronchiolitis rates were not only occurring in Australia during this time but also in Sweden,⁶ the United States of America⁴ the Netherlands⁷ and Canada.⁸ However, in WA, the increases in bronchiolitis levelled off to an estimate of 34/1000 in 2005.⁹ Hospitalisation rates for pneumonia are generally lower than those for bronchiolitis (Table 1). Influenza hospitalisations rates are again lower, and in WA children aged less than 2 years in the 1990s were 1.6/1000 live births.³ In general, ALRI hospitalisation rates for non-Indigenous Australian children are comparable to other international estimates in developed countries.

Indigenous populations

Indigenous populations around the world for which a higher burden of ALRI has been reported are American Indian and Alaskan Natives, New Zealand Maoris, Canadian Aboriginal and Australian Aboriginal.^{1, 4, 10, 11} According to the Australian Bureau of Statistics, Aboriginal Australians are hospitalised for influenza and pneumonia around 5 times more than other Australians.¹² In the Northern Territory of Australia, 1 in 5 Indigenous infants are hospitalised with ALRI before their first birthday.¹³ As seen from Table 1, the rates of ALRI, bronchiolitis and pneumonia are markedly higher in Indigenous populations than non-Indigenous populations.

Although pneumonia is associated with the largest relative disparity between Indigenous and non-Indigenous children (in the 1990s WA hospitalisation rates for pneumonia were 17.6 times higher in Aboriginal than non-Aboriginal infants³), bronchiolitis admissions are more common.

Limitation of hospitalisation studies

There are limitations to using hospitalisation data to assess the burden of ALRI caused by different pathogens. First, hospital admissions represent more severe ALRI and underestimate the true burden of ALRI. To prevent transmission and population spread of these infections, we need to investigate the burden of ALRI at the community level, but there are few such published studies. One Australian study using parent reported episodes of acute respiratory illness estimated an incidence rate of 5.8 episodes per child-year, or 0.48 per child-month with a peak of 0.87 episodes per child-month in winter.¹⁴ There are no published data documenting the out-of-hospital burden of ALRI in WA or in Aboriginal children.

The second major limitation is the lack of laboratory data to confirm the clinical diagnoses recorded on hospital morbidity databases. Numerous studies have attempted to estimate the burden of pathogen-specific ALRI using an excess hospitalisation method which involves measuring the excess rates of hospitalisation due to acute respiratory illness when circulation of a virus (e.g. influenza) is high compared with when it is low.¹⁵ A weakness of this method is the lack of confirmatory laboratory data and the reliance on ICD coding. Nicholson et al incorporated limited virology data into a hospitalisation study and reported alarming results: none of the influenza-positive cases were allocated to influenza ICD codes, only 58% were coded as acute respiratory disease and there was considerable overlap between RSV and influenza seasonal activity and a lack of distinctive clinical features.¹⁶ Another study reported a

sensitivity of influenza ICD9 codes of 65% (95%CI: 61–68%).¹⁷ These findings highlight the need to include virology data to accurately assess pathogen-specific burden of ALRI. As ALRI incidence changes with age, it is important to calculate age-specific incidence rates using an accurate denominator such as person-time-at-risk which can only be achieved by linking hospitalisation datasets with population-based birth or census data.

Aetiology

Knowledge of the causes of ALRI hospitalisations can vary according to clinical severity, age and the diagnostic methods used such as tissue culture, blood culture, direct immunofluorescence and molecular-based methods such as polymerase chain reaction (PCR). I focus here on the major known viral and bacterial pathogens of severe ALRI resulting in hospitalisation, shown in Table 2 in order of frequency of identification.

Table 2: The most common viral and bacterial pathogens associated with ALRI hospitalisations

Pathogen
Virus
Respiratory syncytial virus
Influenza virus types A and B
Rhinovirus
Parainfluenza virus types 1, 2 and 3
Adenovirus
Human Metapneumovirus
Bocavirus
Human Coronavirus
Bacteria
Streptococcus pneumoniae
Bordetella pertussis
Haemophilus influenzae
Mycoplasma pneumoniae
Chlamydia trachomatis
Chlamydia pneumoniae

Viruses

For children hospitalised with ALRI before age 2 years, tissue culture methods have yielded viral identification rates of 66%¹⁸ whereas PCR have yielded higher viral identification rates of 87%.¹⁹ Viral identification rates are higher when the clinical diagnosis of ALRI is restricted to bronchiolitis in those under 2 years, ranging from 87 to 93%.^{20–22} When the age group is extended to all children aged under 5 years, viral identification rates by PCR range from 23–78%.^{23–27} In older age groups up to 12 years, viral identification rates are approximately 50% regardless of laboratory method used.^{28, 29} The higher identification rates in younger children may reflect a higher viral load in younger children.

Respiratory syncytial virus (RSV) is the virus most commonly identified in children under 5 years hospitalised with ALRI with identification rates of 15–20%, 23–25, 30 although rates are higher in children aged under 3 years: 25–52%.^{18, 19, 31, 32} Rhinovirus has been identified more frequently than RSV in hospitalised children with community-acquired pneumonia in Brazil (21%)²⁶ and in the USA (49%),³³ although the age group

studied included children up to the age of 18 years. In view of the broader age range, the identification of RSV in this study was much lower (2%).³³ Rhinoviruses have also been identified in bronchiolitis hospitalisations with an identification rate of 28%,²¹ with speculation that rhinovirus is likely to be the second most important viral pathogen in ALRI. However, rhinoviruses are commonly identified in asymptomatic children (24% in Aboriginal and 17% in non-Aboriginal³⁴) so the attribution of rhinoviruses to causality of ALRI can not be certain. The absence of pathogens in healthy children would add more conviction to the claim of causality so it is important for studies to investigate the viral identification rates in asymptomatic children³⁵ as was done in a community-based study of non-hospital-admitted ALRI, that identified viruses in 25% of control samples, but was able to estimate an attributable risk of 32% for ALRI from rhinovirus, compared with only 10% from RSV.³⁶ Other viruses that are frequently identified in children hospitalised with ALRI are influenza virus (identification rates 3–13%), parainfluenza viruses (3–17%), adenovirus (8–14%), and more recently, human metapneumovirus and bocavirus (5–6%).^{18, 19, 23–25, 30, 31}

Viral identification rates also vary between Indigenous and non-Indigenous populations although there is a lack of recent data comparing viral identification rates in Indigenous and non-Indigenous children hospitalised with ALRI. In addition to varying rates of identification, Aboriginal children in WA have influenza infections at a significantly younger age (median 14.5 vs 26.4 months for influenza A and 10.9 vs 49.6 months for influenza B).³⁷

Bacteria

Although most hospitalised ALRI is likely to be viral, the role of bacterial infection is also important. However, the diagnosis of bacterial ALRI is more difficult than viral ALRI leading to an under-representation of bacterial pathogens in many studies. *Streptococcus pneumoniae* is an important cause of pneumonia and has been identified in 21% of specimens collected in hospitalised children in a developing country aged under 5 years with community-acquired pneumonia and *Haemophilus influenzae* in 8%.²⁶ Another important bacterial pathogen of ALRI is *Bordetella pertussis*, the agent responsible for whooping cough, which has been identified in 6% of specimens from children hospitalised with ALRI.²¹ Other bacterial pathogens implicated in ALRI are *Mycoplasma pneumoniae*, *Chlamydia trachomatis* and *Chlamydia pneumoniae*.^{26, 27} It is important to distinguish between asymptomatic bacterial carriage, most often from non-sterile sites such as nasopharyngeal aspirates and active bacterial infection, most often from sterile sites such as blood, pleural fluid and cerebrospinal fluid. Sensitive and specific molecular-based diagnostic techniques are required to detect bacterial pathogens in children hospitalised with ALRI when attributing causality, as many of these bacterial pathogens can be carried in the nasopharynx of asymptomatic children. While high levels of bacterial carriage have been noted in Aboriginal children in WA,³⁸ the proportion of children, in particular Aboriginal children, hospitalised with ALRI with active laboratory-confirmed bacterial infection is unknown.

Co-infection

The importance of co-infection and the co-occurrence of viruses and bacteria also must not be overlooked. Such viral-bacterial interactions were first identified in the 1918 influenza pandemic when bacterial superinfections with *S. pneumoniae* contributed significantly to high rates of mortality and morbidity.³⁹ Identification rates of multiple pathogens in children hospitalised with ALRI, either co-infection with multiple viruses or viral-bacteria co-infection, have ranged from 23 to 47%.^{20, 21, 33} This has implications for preventative measures such as vaccines targeting a single pathogen and highlights the importance of linking clinical data to virology and bacteriology data when investigating the epidemiology of ALRI. For example, viral vaccines, in particular influenza vaccines⁴⁰ might play a role in preventing secondary bacterial infection and subsequent bacterial diseases such as otitis media.

Seasonality

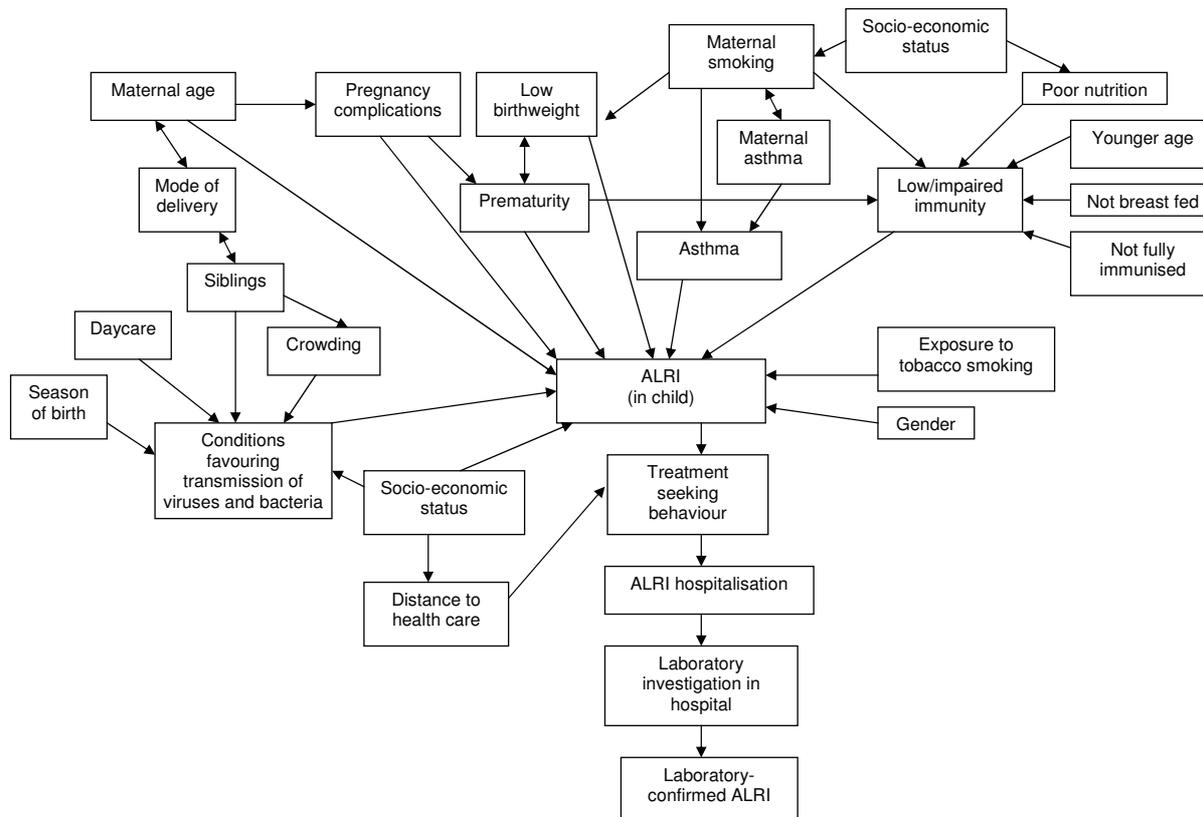
It is important to understand the seasonal characteristics of ALRI to identify the target groups for interventions and more importantly, the appropriate timing of interventions in order to maximize their impact. The identification of viruses and bacteria varies with the month of identification and there are clear seasonal patterns seen in hospitalisations with ALRI which can depend on the climate of the geographic location being studied⁴¹. Seasonal peaks of respiratory infections, in particular respiratory viruses can vary between viruses and between subgroups. Non-Aboriginal children exhibit different seasonal patterns of influenza virus identifications compared with non-Aboriginal children in metropolitan WA and seasonal peaks for RSV and adenovirus vary with age.³⁷

Causal pathways to hospitalisation

Many studies have investigated associations between single risk factors and hospitalisation of children with ALRI, but few have investigated the causal pathways to hospitalisation incorporating conditions favouring transmission, maternal factors, infant factors and socio-demographic factors. By addressing these distal factors on causal pathways to disease, implementation of more targeted interventions and the ultimate goal of prevention can be achieved.⁴² Based on previous findings, I have constructed a causal network diagram that illustrates some of the possible pathways to hospitalisation for ALRI (Figure 1). This network can be applied to Indigenous and non-Indigenous populations, although the pathways and risk factor patterns are likely to differ between the two populations.

Foetal growth measures (prematurity and birthweight) are the most commonly investigated risk factors, but with discrepant results. For example, prematurity independent of birthweight,^{43, 44} low birthweight independent of prematurity,⁴⁵ both prematurity and low birthweight⁴⁶ and extremes of birthweight⁴⁷ have been identified as risk factors for RSV infections. These conflicting reports can be addressed by using a more accurate marker of foetal growth and appropriateness of foetal growth in the form of 'proportion of optimal birthweight' or POBW, which takes into account gestational duration, foetal gender, maternal age, maternal height and parity.⁴⁸ A New Zealand study reported that being born in autumn was a risk factor for RSV hospitalisation.⁴⁴

Figure 1: Possible causal pathways to hospitalisation with ALRI



This corresponds to the child being in the high risk 1–5-month-age-group during winter when RSV is predominately circulating.³⁷ Maternal smoking during pregnancy has also been documented as an independent risk factor for hospitalisation with ALRI.⁴⁹ Few studies have investigated socio-demographic characteristics and ALRI, however Savitha et al found a clear socio-economic gradient: those families from lower socio-economic groups had significantly more ALRI episodes than those from higher groups,⁵⁰ whereas a study in New Zealand found that socioeconomic status was not an independent risk factor.⁴⁴ Low education, a proxy for low socioeconomic status is strongly associated with hospitalisations for pneumonia and influenza.⁵¹ Low education may affect treatment-seeking behaviour at the primary care level and adherence to medical regimes and therefore could result in higher hospitalisation rates.⁵¹

Few studies have investigated risk factors separately in Indigenous populations and instead have described Indigenous status as a risk factor.^{44, 52} Such research is now becoming less valuable since we know Indigenous populations are at a higher risk of ALRI and the causal pathways to hospitalisation are likely to be different. Our recent analysis highlights that 30% of ALRI hospitalisations in Aboriginal children can be attributed to low socio-economic status and limited access to health services (Moore H, 2010, unpublished data). As a result, programs designed to improve living conditions and access to education, and public health measures to reduce smoking rates could be expected to reduce ALRI hospitalisation rates in Aboriginal populations.⁵¹

Interventions for ALRI

The most effective intervention for ALRI is vaccination. Current vaccines for ALRI include Haemophilus influenzae type b (Hib), pneumococcal conjugate vaccine (7vPCV with newer higher valency vaccines now becoming available), diphtheria-tetanus-pertussis vaccine (DTPa) and influenza vaccine. The impact of vaccine programs requires constant monitoring. Vaccines could reduce hospitalisation rates for both viral and bacterial infections, and in particular the disease burden that might be prevented by a universal childhood influenza vaccination program needs to be addressed. Additionally, evaluation of the impact of pneumococcal vaccines on pneumonia and viral ALRI-associated morbidity in addition to its direct and indirect impact on invasive pneumococcal disease is needed. Although there has been a clear decline in invasive pneumococcal disease in children, there is conflicting evidence in Australia whether pneumococcal vaccination has had an impact on hospitalised pneumonia, with studies using different methodologies reporting either a decline in pneumonia hospitalisations following vaccination⁵³ or no impact.⁵⁴ Vaccination coverage rates differ for Aboriginal and non-Aboriginal populations. For example, in 2005, the coverage of 3 doses of 7vPCV was 75% for Aboriginal children and 88% for non-Aboriginal children.⁵⁵ We need to have optimal estimates of vaccination coverage, or ideally vaccination status at the individual level to monitor the impact of vaccination programs.

There is as yet no vaccine for bronchiolitis and RSV-related illness, but RSV immunoprophylaxis with the monoclonal antibody palivizumab has been found to be effective in reducing severe RSV-related illness.⁵⁶ However, monthly immunoprophylaxis is expensive and is currently aimed at high risk children during peak periods of RSV circulation. For children living in tropical climates, such as those children living in Northern Australia, where RSV seasonality differs from the traditional winter pattern, this current dosing schedule may not be appropriate.⁴¹

In addition to direct and indirect effects of vaccination, it is important to maintain adequate surveillance of ALRI hospitalisations for other factors that could influence disease trends, including changes or improvements in risk factors such as socioeconomic status.

What role can data linkage play in investigating ALRI?

It should now be apparent that in order to adequately investigate ALRI, data must be pooled from numerous resources encompassing clinical, laboratory, socio-economic and other risk factors and vaccination status data on an individual basis. Information on all aspects may not be measurable in any one study. However, population-based data (or record) linkage could address some of these limitations and is a powerful tool for research. In WA we have the rare opportunity to utilise total population-based resources through the WA Data Linkage System (<http://www.datalinkage-wa.org.au/>).⁵⁷ This system links population-level data on all births and deaths, midwives' notifications of births and hospital morbidity data for every birth in WA. Links between records from various administrative health datasets are linked by probabilistic matching on unit medical record number (unique only to metropolitan public hospitals), surname, first given name, date of birth, sex and address.⁵⁷ De-identified data are then available for researchers

to use, following ethical approval and compliance with stringent confidentiality policies. There is also the ability for data within the WA Data Linkage System to be linked to other datasets such as state-wide laboratory data or national immunisation data.

Accurate baseline data using population denominators on pathogen-specific burden of ALRI can be used as a platform for the evaluation of future and current interventions. It is important to have adequate data in order to stratify results according to age, ethnicity, and clinical and laboratory outcome, with numbers large enough for adequate statistical power. Population-based data linkage provides the necessary depth and breadth of information needed to conduct such meaningful analyses.

Conclusions

ALRI is a significant cause of paediatric morbidity with infants and Indigenous populations suffering the highest burden. With new pathogens being identified, future studies, using a causal pathway framework and pathogen-specific ALRI in Indigenous and non-Indigenous children, will inform strategies for the development of appropriate interventions to move towards the goal of ALRI prevention. Such stratified analyses will identify target groups who would benefit most from a variety of interventions. Individual level of vaccination status on total populations is needed and some of this information can be found in existing Commonwealth data collections, if it was made generally available for appropriate research projects.

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