The epidemiology and impact of viral respiratory infections in pre-school aged children

Stephen Bernard Lambert

Submitted in total fulfilment of the requirements of the degree of Doctor of Philosophy

December 2009

Department of Public Health
The University of Melbourne
ABSTRACT

Background

There are significant gaps in our knowledge of the epidemiology of globally endemic respiratory viruses. Current community research methods are expensive, requiring invasive specimen collection at a home visit by health-care workers.

Methods

Two cohort studies were conducted to collect better information about the epidemiology and impact of community-managed respiratory illnesses in pre-school aged children.

The pilot study recruited 121 Melbourne children aged one to four years over winter/spring of 2001. Parents collected daily respiratory symptoms and completed an impact diary, including time seeking health-care and caring for an ill child, when a pre-defined acute respiratory illness (ARI) occurred.

The Respiratory Virus Study (ReVS) followed 234 Melbourne children less than five years of age for approximately one year from January 2003. A combined nose-throat swab (NTS), collected by parents when an ARI occurred, was added to pilot study methods. NTS specimens were transported to the Victorian Infectious Diseases Reference Laboratory (VIDRL) for polymerase chain reaction (PCR) to test for influenza A, influenza B, respiratory syncytial virus (RSV), parainfluenza viruses I, II, and III, adenoviruses, and picornaviruses (rhinoviruses, enteroviruses). At the end of the study, available specimens and nucleic acid extracts were shipped on dry ice to the Queensland Paediatric Infectious Diseases (Qpid) Laboratory and tested for human metapneumovirus and human coronavirus NL63.
Results

The incidence rate for community-managed ARI in the pilot study was 0.44 episodes per child-month (95% CI 0.38 to 0.51) with an average cost per illness of $241 (95% CI $191 to $291). The key cost driver was carer time away from usual activities caring for the ill child, making up 70% of costs.

There were 730 ARIs identified in ReVS children for a rate of 0.48 ARIs per child-month (95% CI 0.45 to 0.52). At least one virus was identified in 401 of 543 ARIs (74%) with a specimen returned, and picornaviruses were identified in 269 ARIs (50%). The total cost of all illnesses with a burden diary returned was $161,454, with over one-third, $52,597, from illnesses where a picornavirus was identified in isolation. The mean cost of all ARIs was $309 (95% CI $263 to $354), and time spent caring for an ill child was again the key cost driver, responsible for 82% of all costs. The point estimate for the mean cost of influenza A illnesses ($904; 95% CI $89 to $1,719) was three times higher than RSV ($304; 95% CI $194 to $415), the next most expensive illness. Collection by a health-care worker parent, collector-reported quality, or presence of a throat swab made no difference to the proportion of specimens positive for any virus.

Discussion

Acute respiratory illnesses in community dwelling pre-school aged children are common and a virus can be detected in 74% of parent-collected specimens. Use of daily symptom diaries and parent-collected specimens were effective and efficient study methods, and provide a new model for the future conduct of community-based epidemiological studies for respiratory pathogens, including efficacy studies for new preventative vaccines and treatments.
DECLARATION

This is to certify that

(i) the thesis comprises only my original work towards the PhD except where indicated in the Preface,

(ii) due acknowledgement has been made in the text to all other material used, and

(iii) the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies, and appendices.

Stephen Bernard Lambert
PREFACE

This thesis is an original work incorporating the research that I have undertaken during my candidature and the results of that research. All components of this thesis are based on research conducted in collaboration with others. The nature and extent of my contribution for each chapter is outlined below.

Chapter 1: Introduction

This chapter is entirely my own work.

Chapter 2: Viral respiratory tract infections in children

This chapter is entirely my own work.

Chapter 3: A pilot study: epidemiology and cost of acute respiratory illness in children

All aspects of the work in this cohort study were done under the guidance and direct supervision of my PhD supervisor, Professor Terry Nolan.

I developed the protocol for this study with input from staff in the Vaccine and Immunisation Research Group (VIRGo), part of the Murdoch Childrens Research Institute and the School of Population Health, University of Melbourne, and from Dr Neil Formica at CSL Ltd. This funded research was conducted under the auspices of VIRGo. I oversaw the day-to-day running of the project, with the majority of study tasks and interactions with family performed by research assistants. Ms Susan Gabriel recruited the majority of study participants and performed most of the follow up telephone calls to families.
I designed the data collection paperwork, designed the database, entered and analysed the data, wrote progress reports for the study sponsor, and was the principal author on the two papers published from this work. Associate Professor Rob Carter provided guidance for the costing methods.

The two manuscripts from this study arose out of the analyses I performed. The initial drafts of the published work were written by me.

Chapter 4: The Respiratory Virus Study — epidemiology

Chapter 5: The Respiratory Virus Study — health economics

Chapter 6: Respiratory Virus Study — methods

The material in these three chapters presents findings from the Respiratory Virus Study conducted in the year between January 2003 and January 2004. This prospective cohort study was a collaborative project.

All aspects of the work in this cohort study were done under the guidance and direct supervision of my PhD supervisor, Professor Terry Nolan.
I wrote the applications for funding support of the project. I designed the study and wrote the study protocol, developed the data collection material, arranged and coordinated the testing of study specimens, designed the database, entered approximately half of the data, analysed the data, and am the principal author on the three publications arising from this study. Professor John Carlin provided guidance for the study analysis.

Similar to the pilot study, this project was carried out under the auspices of ViRGo. Funding for the one year of this study allowed us to hire a full-time, study-specific research assistant, Ms Kelly Allen, who supported me in the day-to-day management of the study, directly recruited approximately one-quarter of the study participants, and performed the majority of follow up contacts with all study families. Other research assistants from ViRGo assisted with recruitment of families for the study.

Staff in the Virology Laboratory at the Victorian Infectious Diseases Reference Laboratory performed the initial multiplex conventional polymerase chain reaction (PCR) testing of study specimens. Staff from Queensland Paediatric Infectious Diseases (Qpid) Laboratory, Sir Albert Sakzewski Viral Research Centre, Royal Children’s Hospital, Brisbane, Queensland, performed subsequent human metapneumovirus and human coronavirus NL63 real-time PCR testing of specimens. When I relocated to Brisbane, I performed a second round of human metapneumovirus real-time PCR testing using the Maertzdorf assay.

Associate Professor Rob Carter provided guidance for the costing methods applied to the impact data collected during the cohort study.

The three manuscripts arising from this study arose from the analyses I performed. Initial drafts of the published work were written by me.
Chapter 7: Conclusions and recommendations

This chapter is entirely my own work.
ACKNOWLEDGEMENTS

Firstly, and without hesitation, my sincere thanks go to Professor Terry Nolan for his support and guidance prior to, during, and since the life of this PhD. I was not the easiest of PhD students. I benefited enormously from his attention to detail, adherence to rigour, flexibility, and his almost tireless patience with me, even during the many times when I was more than a bit bolshie.

I am very grateful to the other members of my supervisory panel who provided time and expertise: thanks to Jonathan Carapetis, John Carlin, and Rob Carter. Kris Jamsen and Suzanna Vidmar from CEBU gave excellent Stata support.

Doing this PhD somewhere other than the Vaccine and Immunisation Research Group (VIRGo) may have been possible, but certainly nowhere near as much fun. Many thanks to Kelly Allen, the ReVS study coordinator: her hard work allowed me to have a broad PhD experience. I could not have done this without your assistance Kelly. Susie Gabriel played a similar role during the pilot study. Her support and attention to detail for that study, and during my time at VIRGo, were invaluable – your keen eye for errors is still greatly missed by me Susie. Jacinta O'Sullivan was the study coordinator when I first arrived at VIRGo in December 1999: it was a pleasure to work with her, she was welcoming, diligent, and always offered sensible advice. Marita Kefford could find solutions to the most difficult of problems, and always had time for sushi on Fridays. Thanks to my other office colleagues: Samantha Colquhoun, Kerry-Ann O’Grady, Jodie McVernon, and Jim Buttery, along with all of the research assistants and other staff at VIRGo: they were unselfish with their camaraderie and efforts to assist with these projects. Dale P Cooper helped me improve my pool game to the point where I can now beat him, occasionally. Whilst I prize my improved pool skills highly, I am most grateful to him for introducing me to Sally.

None of this work would have been possible without the families who agreed to participate in the studies, the local government Maternal and Child Health Nurses who took time out of their busy days to help with recruitment. Thanks to the National Health and Medical Research Council
Acknowledgements

for the Public Health Postgraduate Scholarship I received during my candidature. Thanks to the laboratory staff from VIDRL and Qpid who did most of the PCR tests for the main study. These projects were only possible with funding from the Victorian Department of Human Services, the Murdoch Childrens Research Institute, the University of Melbourne, and CSL Limited.

Finishing this thesis from interstate could, quite possibly, have been death of it. Thanks to my colleagues in the Queensland Paediatric Infectious Diseases Laboratory at the Royal Children’s Hospital in Brisbane: they were patient, tolerant, and greatly improved my understanding of the molecular methods and PCR used in this study. Particular thanks to Theo Sloots for his calm mentoring – I have been truly lucky to have your help Theo.

There are many more people I could thank here, though they remain unnamed, they are certainly not unappreciated — my apologies for not having the space to mention you all.

My immediate and extended family were a constant source of comfort and happiness during my time being a student, again. Mary and Lyle Hanes provided a Melbourne bed during my many transitions, and my Aunty Dot did a delicious lamb cutlet on Tuesday nights. Jane Gustus-Callanan and Robyn Cameron were generous hosts when I required a country retreat. Gratitude and much love go to my sister Cal, for the laughs and accommodation in Brisbane, but particularly for just being her. Thanks to my brother and his family, Tony and Moira, William, Tom, and Amy, for all of their loving support. My mother and father, Denise and Bernie Lambert, have been great role models for me and through their encouragement and many sacrifices, my siblings and I received, amongst other things, a good education. For these things, and much more, I will always be grateful to them.

I have been blessed beyond all imagining in meeting my now wife, Sally Jane Mapp, during the dying stages of this PhD. Sally, your boundless encouragement, support, and love are a constant source of joy to me. In our future years together, it is my solemn hope to be able to repay even a fraction of your kindness.
PUBLICATIONS, MEETINGS, AND AWARDS

Publications

First author, peer reviewed articles arising from the thesis


Other publications arising from the thesis


Meetings

Presentations: invited speaker

Lambert SB. Respiratory viruses in Australian children: conducting a community-based family study.

*Seminar at the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS), Children’s Hospital at Westmead, Sydney, New South Wales, December 2003.*

Presentations: submitted abstracts


*8th National Public Health Association of Australia Immunisation Conference, Melbourne, Victoria, May 2002.*


*5th National Public Health Association of Australia Immunisation / 1st Public Health Association of Australia Asia-Pacific Vaccine Preventable Diseases Conference, Cairns, Queensland, August 2004.*


*7th International Symposium on Respiratory Viral Infections, Curacao, Netherlands Antilles, March 2005.*


**Awards**

2001 to 2004: National Health and Medical Research Council Postgraduate Public Health Scholarship.

2005: Population Health Investing in Research Students’ Training (PHIRST) Award, University of Melbourne.
# TABLE OF CONTENTS

Abstract .................................................................................................................................................. 3

Declaration ............................................................................................................................................ 5

Preface .................................................................................................................................................. 6

Acknowledgements ............................................................................................................................ 10

Publications, meetings, and awards .................................................................................................... 12

Table of contents ................................................................................................................................. 15

List of tables and figures ...................................................................................................................... 19

Glossary and abbreviations .................................................................................................................. 26

Chapter 1: Introduction .......................................................................................................................... 28

1.1 Objective ....................................................................................................................................... 28

1.2 Background to hypothesis ............................................................................................................. 28

1.3 Hypothesis and research questions .............................................................................................. 31

1.4 Research plan ............................................................................................................................... 32

1.5 Thesis outline ............................................................................................................................... 33
Chapter 2: Viral respiratory tract infections in children

2.1 Objective

2.2 Respiratory viruses of importance in childhood

2.3 Viruses recently identified in respiratory tract specimens

2.4 Impact and health economics of viral respiratory tract infections in children

2.5 Options for prevention

2.6 Respiratory virus surveillance: an Australian context

2.7 Laboratory testing and specimen collection for respiratory viruses

2.8 Interpreting previous respiratory virus research

2.9 Conclusions

Chapter 3: A pilot study: epidemiology and cost of acute respiratory illness in children

3.1 Objectives

3.2 Introduction

3.3 Methods

3.4 Results
<table>
<thead>
<tr>
<th>3.5</th>
<th>Discussion ........................................................................................................ 99</th>
</tr>
</thead>
</table>

Chapter 4: The Respiratory Virus Study — epidemiology ........................................... 106

<table>
<thead>
<tr>
<th>4.1</th>
<th>Objective........................................................................................................ 106</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>Introduction .................................................................................................. 106</td>
</tr>
<tr>
<td>4.3</td>
<td>Methods ......................................................................................................... 107</td>
</tr>
<tr>
<td>4.4</td>
<td>Results .......................................................................................................... 124</td>
</tr>
<tr>
<td>4.5</td>
<td>Discussion .................................................................................................... 157</td>
</tr>
</tbody>
</table>

Chapter 5: The Respiratory Virus Study — health economics ........................................... 168

<table>
<thead>
<tr>
<th>5.1</th>
<th>Objective........................................................................................................ 168</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2</td>
<td>Introduction .................................................................................................. 168</td>
</tr>
<tr>
<td>5.3</td>
<td>Methods ......................................................................................................... 168</td>
</tr>
<tr>
<td>5.4</td>
<td>Results .......................................................................................................... 176</td>
</tr>
<tr>
<td>5.5</td>
<td>Discussion .................................................................................................... 187</td>
</tr>
</tbody>
</table>

Chapter 6: The Respiratory Virus Study — methods ......................................................... 196

<p>| 6.1 | Objective........................................................................................................ 196 |</p>
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.2 Introduction</td>
<td>196</td>
</tr>
<tr>
<td>6.3 Methods</td>
<td>197</td>
</tr>
<tr>
<td>6.4 Results</td>
<td>200</td>
</tr>
<tr>
<td>6.5 Discussion</td>
<td>209</td>
</tr>
<tr>
<td>Chapter 7: Conclusions and recommendations</td>
<td>214</td>
</tr>
<tr>
<td>References</td>
<td>218</td>
</tr>
<tr>
<td>Appendix</td>
<td>267</td>
</tr>
</tbody>
</table>
LIST OF TABLES AND FIGURES

Tables

Table 3.1 Defining symptoms of an acute respiratory illness .................................................. 79

Table 3.2 Univariate incidence rate ratios during the influenza season ................................. 90

Table 3.3 Mean resource use for key items in ARIs identified in the pilot study, 2001, for illnesses where a burden diary was returned (n=180) and all illnesses (n=202) ...... 91

Table 3.4 ARIs, ARI incidence rate per child-month, and average cost per episode by month 2001.................................................................................................................................................. 92

Table 3.5 Summary of resources consumed during 202 ARIs in 118 Melbourne children during winter and spring 2001 ........................................................................................................... 94

Table 3.6 One-way and multi-way sensitivity analyses for average cost of episodes ............ 97

Table 3.7 Summary of supplementary costs for the 202 ARIs in study children, incorporating costs not collected in the Respiratory Virus Study ......................................................... 99

Table 4.1 Study child, household, and time-related explanatory variables and possible values for these variables collected at enrolment visit, Respiratory Virus Study, 2003-2004121

Table 4.2 Relative contribution to study from different age groups (by year of age).. 125
Table 4.3  Family size and structure by contribution to person-time, Respiratory Virus Study, 2003-2004 ........................................................................................................................................129

Table 4.4  Comparison of proportion of study households from income brackets compared with Australian Bureau of Statistics 2001 Census data for Victorian households ..131

Table 4.5  Number and percent of days with individual symptoms, in order of frequency, Respiratory Virus Study, 2003-2004 ..........................................................................................................................136

Table 4.6  Illnesses, available swabs, and viral identification, Respiratory Virus Study, 2003-2004 ........................................................................................................................................139

Table 4.7  Pattern of virus identification in ARIs with at least one specimen collected........142

Table 4.8  Total number of ARIs by virus with at least one virus identified, the number and percent of these illnesses where at least one other virus was identified, and the percentage of all co-detections involving the virus .................................................................143

Table 4.9  Median, range, and mean duration in days of illness by specimen collection and number of viruses identified........................................................................................................148

Table 4.10  Univariate incidence rate ratios for child-specific exposures, Respiratory Virus Study, 2003 to 2004 ................................................................................................................................150

Table 4.11  Univariate incidence rate ratios for household-specific exposures, Respiratory Virus Study, 2003 to 2004 ................................................................................................................................151

Table 4.12  Acute respiratory illness impact and feature comparison by specimen return and virus identification, Respiratory Virus Study, 2003 to 2004 .......................................................154
Table 5.1 Resource item, sector responsible for bearing cost, source of applied cost, and cost applied for resources used during the Respiratory Virus Study 2003-2004 ...........173

Table 5.2 Hourly cost applied for all time on study, time seeking health-care and excess time spent caring for an ill child, by sex of carer and quarter, Respiratory Virus Study, January 2003 to January 2004 ........................................................................................................ 175

Table 5.3 Resource use for key items in ARIs identified in the Respiratory Virus Study, 2003 to 2004, for community-managed illnesses where a burden diary was returned (n=523) and all illnesses (n=725) ........................................................................................................ 177

Table 5.4 Summary of resources consumed during 725 acute respiratory illnesses in 229 Melbourne children, Respiratory Virus Study, January 2003 to January 2004....... 180

Table 5.5 Number of ARIs and average cost per episode by ARI type for all 725 ARIs, Respiratory Virus Study ........................................................................................................ 181

Table 5.6 Number of ARIs, median cost, and average cost with 95% confidence interval for all illnesses with a health cost diary returned (n=523) by virus identification............182

Table 5.7 Mean values and mean costs of components of resource use during acute respiratory illnesses, Respiratory Virus Study, Melbourne, 2003 to 2004 .......... 183

Table 5.8 Sensitivity analysis showing total cost, total duration, and cost per day, for all illnesses by virus identification and with removal of ARIs that have an outlying cost per illness greater than $1,500 ........................................................................................................ 185

Table 5.9 Average cost of ARIs by household income bracket with proportion of children in bracket and ARI rate per child-month, Respiratory Virus Study 2003 to 2004 ....... 186
Table 6.1 Specimens collected, number and percent of specimens positive by collector, Respiratory Virus Study 2003-2004 ................................................................. 201

Table 6.2 Fraction showing specimens positive for any virus in VIDRL’s multiplex PCR test over all specimens (per cent) by delay in day categories and site of delay: onset of illness to specimen collection; specimen collection to test date; and onset of illness to test date, Respiratory Virus Study 2003-2004 ................................................................. 202

Table 6.3 Specimens positive for any virus over all specimens (per cent) by site of specimen collection and collector-reported collection quality, Respiratory Virus Study 2003-2004 .................................................................................................................... 204

Table 6.4 Fraction showing specimens positive for specific viruses over all specimens (per cent) by site of specimen collection, and the p-value for difference in proportions, Respiratory Virus Study 2003-2004 ........................................................................................................ 205

Table 6.5 Mean duration of ARI and mean delay for result letter, Respiratory Virus Study, Melbourne, 2003 to 2004 ...................................................................................... 209
Figures

Figure 3.1  Schema with examples demonstrating day assignment (D1, D2, D3, D4) and duration of an ARI in relation to days with category A or category B symptoms...... 81

Figure 3.2  Map of greater Melbourne area with markers identifying the location of the 78 households which participated and submitted data for the pilot study, 2001 .......... 85

Figure 3.3  Monthly incidence rate of influenza-like illness episodes (ARIs per child-month) with 95% confidence interval bars, 01 July to 01 December 2001............................. 87

Figure 3.4  Acute respiratory illness episodes in study children by onset date in each study week and by influenza season, 01 July to 01 December 2001 ................................. 88

Figure 4.1  Cumulative enrolment of study children and child-days of symptom diary return for each study day, 17 January 2003 to 31 January 2004 ............................................. 124

Figure 4.2  Map of greater Melbourne area with markers identifying the location of the 229 households who submitted data for the Respiratory Virus Study, January 2003 to January 2004............................................................................................................. 127

Figure 4.3  Number of child-days and percent of total days (n=56,397 child-days) contributed by study children participating in no structured child care, formal care only, informal care only, or a combination of formal and informal child care.............. 128

Figure 4.4  Annual household income by number and percent of total for 229 families that provided any daily symptom data to the Respiratory Virus Study, 17 January 2003 to 31 January 2004 ......................................................................................................................... 130
Figure 4.5 Compliance with ReVS study procedures: return of specimens and burden diaries in the event of an ARI in a study child .................................................................133

Figure 4.6 Child-days by month with and without any symptoms (number and per cent), Respiratory Virus Study, January 2003 to January 2004.........................................................134

Figure 4.7 Duration of the 730 ILIs identified in the Respiratory Virus Study, 2003 to 2004 ..137

Figure 4.8 Illnesses by specimen collection and month, and percent of illnesses with specimen collected, Respiratory Virus Study .................................................................140

Figure 4.9 Illnesses by identification of any virus and month, percent of all illnesses with any virus identification, and ARI rate, Respiratory Virus Study ........................................143

Figure 4.10 Number of illnesses associated with individual viral identification by month, January 2003 to January 2004, Respiratory Virus Study..............................................145

Figure 4.11 Percent of all illnesses associated with individual viral identification by month, January 2003 to January 2004, Respiratory Virus Study..............................................146

Figure 4.12 Co-infections by pattern and number of viruses, and month of identification, Respiratory Virus Study........................................................................................................147

Figure 4.13 Compliance with return of specimens and burden diaries and subsequent illnesses in household contacts..........................................................................................156

Figure 4.14 Duration of 179 subsequent illnesses in household contacts where diaries were returned....................................................................................................................157
List of tables and figures

Figure 6.1 Specimens positive for any virus in VIDRL's RespPCR test by days of delay from onset of illness to test date, Respiratory Virus Study ................................................. 203

Figure 6.2 Parent responses to question regarding most difficult task on close-out questionnaire.................................................................................................................. 207

Figure 6.3 Parent responses to question regarding participation in an experimental vaccine study on close-out questionnaire ...................................................................................... 208
<table>
<thead>
<tr>
<th>Term, abbreviation, or symbol</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>€</td>
<td>Euros</td>
</tr>
<tr>
<td>$</td>
<td>Australian dollars</td>
</tr>
<tr>
<td>°C</td>
<td>Degrees Celsius for reporting temperature</td>
</tr>
<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
</tr>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices (US)</td>
</tr>
<tr>
<td>ARI</td>
<td>Acute respiratory illness</td>
</tr>
<tr>
<td>ARTI</td>
<td>Acute respiratory tract infection</td>
</tr>
<tr>
<td>ATAGI</td>
<td>Australian Technical Advisory Group on Immunisation</td>
</tr>
<tr>
<td>BPD</td>
<td>Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>BVDV</td>
<td>Bovine diarrhoeal disease virus</td>
</tr>
<tr>
<td>CAIV-T</td>
<td>Cold-adapted, influenza vaccine-trivalent</td>
</tr>
<tr>
<td>CDI</td>
<td><em>Communicable Diseases Intelligence journal</em></td>
</tr>
<tr>
<td>cDNA</td>
<td>Complementary DNA</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>ETS</td>
<td>Environmental tobacco smoke</td>
</tr>
<tr>
<td>H</td>
<td>Haemagglutinin surface glycoprotein of influenza viruses</td>
</tr>
<tr>
<td>hCoV</td>
<td>Human coronavirus</td>
</tr>
<tr>
<td>HMPV</td>
<td>Human metapneumovirus</td>
</tr>
<tr>
<td>HPIV</td>
<td>Human parainfluenza virus</td>
</tr>
<tr>
<td>HRSV</td>
<td>Human respiratory syncytial virus</td>
</tr>
<tr>
<td>IFA</td>
<td>Immunofluorescence antibody</td>
</tr>
<tr>
<td>ILI</td>
<td>Influenza-like illness</td>
</tr>
<tr>
<td>IV</td>
<td>Influenza virus</td>
</tr>
<tr>
<td>LAIV-T</td>
<td>Live, attenuated influenza vaccine (trivalent)</td>
</tr>
<tr>
<td>LRTI</td>
<td>Lower respiratory tract infection</td>
</tr>
<tr>
<td>MAARI</td>
<td>Medically attended acute respiratory illness</td>
</tr>
<tr>
<td>MCHN</td>
<td>Local government maternal and child health nurses</td>
</tr>
<tr>
<td>Term, abbreviation, or symbol</td>
<td>Explanation</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>MCRI</td>
<td>Murdoch Childrens Research Institute</td>
</tr>
<tr>
<td>N</td>
<td>Neuraminidase surface glycoprotein of influenza viruses</td>
</tr>
<tr>
<td>NHCDC</td>
<td>National Hospital Cost Data Collection</td>
</tr>
<tr>
<td>nm</td>
<td>Nanometre</td>
</tr>
<tr>
<td>NPA</td>
<td>Nasopharyngeal aspirate</td>
</tr>
<tr>
<td>NTS</td>
<td>Combined nose and throat swab</td>
</tr>
<tr>
<td>OM</td>
<td>Otitis media</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>Qpid</td>
<td>Queensland Paediatric Infectious Diseases Laboratory</td>
</tr>
<tr>
<td>RespPCR</td>
<td>VIDRL’s multiplex respiratory RT-PCR test</td>
</tr>
<tr>
<td>ReVS</td>
<td>Respiratory virus study</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RTI</td>
<td>Respiratory tract infection</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcription polymerase chain reaction</td>
</tr>
<tr>
<td>SARS</td>
<td>Severe acute respiratory syndrome</td>
</tr>
<tr>
<td>siRNA</td>
<td>Short inhibitory RNA</td>
</tr>
<tr>
<td>TIV</td>
<td>Trivalent, inactivated influenza vaccine</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>URTI</td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>US / USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>USSR</td>
<td>Union of Soviet Socialist Republics</td>
</tr>
<tr>
<td>VIDISCA</td>
<td>Virus discovery cDNA amplified restriction fragment length polymorphism</td>
</tr>
<tr>
<td>VIDRL</td>
<td>Victorian Infectious Diseases Reference Laboratory</td>
</tr>
<tr>
<td>VIRGo</td>
<td>Vaccine and Immunisation Research Group</td>
</tr>
<tr>
<td>VRTI</td>
<td>Viral respiratory tract infection</td>
</tr>
<tr>
<td>VTM</td>
<td>Viral transport medium</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Chapter 1

INTRODUCTION

1.1 Objective

This chapter is written to provide a research context for the studies described in this thesis.

1.2 Background to hypothesis

Respiratory tract illness caused by viruses is a leading cause of morbidity and mortality in developed and developing countries. The importance of acute respiratory tract infections in working adults and the elderly has long been recognised, and the bulk of research efforts and prevention programs have been targeted to these groups. More recently, there has been renewed attention given to the impact respiratory tract infections have in infants and children and the prospects for prevention in this group. This interest has not focused solely on influenza, the most severe of the respiratory viral infections across the childhood years, but extends to other agents such as respiratory syncytial virus, parainfluenza viruses, and adenoviruses. Other viruses, such as rhinoviruses, enteroviruses, and coronaviruses, cause acute respiratory tract infection but the impact of illness from these infections, particularly in the community, needs to be better documented. By comparison there remains limited information on the role recently identified viruses, such as human metapneumovirus and human coronavirus NL63, play in childhood respiratory disease.

Part of this growing awareness has been around the costs involved for both families and the community in managing these illnesses, and the cost-effectiveness of any potential interventions to lessen impact. It is likely the most easily measured costs, those to the health-care sector, are dwarfed by costs to the family resulting from parental time, away from work and usual activities, spent caring for an ill child. Given the importance of this component in overall resource
consumption, a more meaningful examination of the health economics of implementing a publicly-funded, population based control strategy would need to consider these costs.

The influence of these infections extends beyond their direct health effects in children. Children, particularly those attending child care and school, are the primary transmitters of viruses within communities and the introducers of viruses into households. These younger and susceptible age groups take respiratory viruses home from structured child care and social settings and infect both household contacts and their elderly and at-risk relatives, either in the household or through regular visits. These groups – the elderly and at-risk – are currently targeted for influenza and polysaccharide pneumococcal vaccination in Australia. Better control of respiratory virus transmission in younger age groups could have substantial indirect effects, including a reduction of the incidence and impact of illness in older age groups.

As well as non-pharmaceutical options, there are vaccine candidates and therapeutics against viral respiratory pathogens that may be suitable for such widespread prevention either already available, undergoing clinical trial, or in pre-clinical development. To prepare for the possibility of large scale preventative programs against childhood respiratory viral infections in Australia, similar to the recent recommendation for influenza vaccination for all children aged between six months and eighteen years of age in the United States (US) and their household contacts, local integrated data on epidemiology and health economics are required.

A small number of large community-based studies using families as the unit of observation were established, mostly in the US during the 1960s and 1970s, to examine the epidemiology of respiratory infections. These studies provided incidence estimates for clinical syndromes, information about transmission dynamics within households, and the relative importance of the aetiological agents of respiratory illness. The methods used included home visits with regular and illness-specific sampling, and laboratory testing usually involving low sensitivity viral culture, with or without assessment of seroconversion to specific agents following the respiratory season.
Similar studies have not been conducted in Australia, further highlighting the paucity of data on which to make informed decisions about local policy.

Improvements in laboratory technology and changes in the nature of family life in industrialised countries over recent decades suggest that the results could be different if similar studies were conducted today. The availability of molecular diagnostic options, such as multiplexed and real-time PCR, allows for greater sensitivity and testing for multiple pathogens at one time. The nature of family life in Australia and other countries, particularly the increasing proportion of children using child care, has changed since the original community studies were conducted, and this may have altered respiratory virus epidemiology.

The Australian Technical Advisory Group on Immunisation (ATAGI) will need to provide advice to the Pharmaceutical Benefits Advisory Committee (PBAC), the Australian government, and the Australian people regarding new vaccines against common childhood viral respiratory infections. As well as general information about the performance of any vaccine, local information about the epidemiology and burden of the illness being prevented is required in order to make an assessment about vaccine usage. This information needs to be pathogen-specific if decisions are to be made about target groups for immunisation, particularly if large and expensive population-based programs are being considered.

It has previously been suggested that research using a method of studying patients directly for the presence of specific viruses is prohibitively expensive.\(^5\) Traditionally, such studies have been conducted through the use of home visits by research staff. These visits would often be regularly scheduled, but would also occur during illness episodes making study planning difficult. The Seattle Virus Watch project used collection of respiratory specimens by a trained parent or other household member when a study nurse could not arrange a home visit.\(^6\) None of the published articles from this project provide further analysis or discussion about this method.
1.3 Hypothesis and research questions

This thesis advances the following hypothesis:

The collection of integrated epidemiology and impact data for known and emerging respiratory viruses from preschool-aged children is feasible, adequately sensitive, and acceptable using a community-based cohort approach with parents completing daily symptom diaries and collecting a combined nose-throat swab during respiratory illness episodes of interest.

This thesis aims to address the requirements for hypothesis testing by answering the following research questions:

1. Can parents be adequately trained to complete daily symptom diaries, identify respiratory illness episodes of interest, and successfully complete the collection of a combined nose-throat swab in preschool-aged children sufficient for the conduct of a community-based cohort study to describe the epidemiology and impact of virus-specific respiratory tract illness in Australian preschool-aged children?

2. What is the epidemiology and burden, assessed through resource use during illness and subsequent costing, associated with acute respiratory tract illness and virus-specific respiratory tract illness in preschool-aged Australian children?

3. What role do the recently identified viral respiratory pathogens, human metapneumovirus and human coronavirus NL63, play in the burden of community-managed viral respiratory tract infections in preschool-aged Australian children?

4. Is a method involving parent-collection from an ill child able to provide respiratory specimens that allow for the identification of viral nucleic acid by polymerase chain reaction testing in
similar proportions to historical comparison studies, where molecular diagnostic methods and home visits by study staff for specimen collection were used?

1.4 Research plan

The Vaccine and Immunisation Research Group (VIRGo), part of the School of Population Health, University of Melbourne, and the Murdoch Childrens Research Institute (MCRI), has been conducting industry-sponsored and investigator-driven research on the safety and immunogenicity of vaccines and the epidemiology and other features of vaccine preventable diseases since 1991. Mobile teams consisting of a combination of coordinating research assistant, nurse immuniser, study doctor, and phlebotomist, carrying resuscitation equipment, conduct study visits in homes of participating families. For clinical trials, study products are transported in temperature-monitored portable refrigerators. An initial screening visit is performed in the home to assess eligibility and relate study information in detail, including a point-by-point explanation of the plain language statement. VIRGo was chosen as an appropriate location for the conduct of the two studies performed to address the research questions.

The first, a pilot study, was conducted in preparation for the larger and longer prospective cohort study. The primary aim of this study was to confirm the utility of using parent-completed daily symptom diaries for study subjects. Other aims were to test printed study materials developed for the subsequent main study, and collect detailed information about the epidemiology and resources consumed during an acute respiratory illness (ARI). This study was sponsored by CSL Limited, an Australian manufacturer of trivalent, inactivated influenza vaccine (TIV).

The second study, the Respiratory Virus Study (ReVS), represented an advance on the pilot study in a number of key areas: it incorporated parent-collection of a combined nose and throat swab (NTS) from study participants when they had an acute respiratory illness (ARI); and information and specimens were also collected from household contacts with illnesses that followed on from an illness in a study child. Specimens collected from study children were tested for common
respiratory viruses using conventional, multiplexed polymerase chain reaction (PCR) assays, and subsequently real-time PCR tested for recently identified viruses, human metapneumovirus and human coronavirus NL63. In an attempt to ensure compliance and reduce loss to follow up, we reduced the complexity of the burden diary by limiting the information collected to the key cost drivers identified in the pilot study. As with all research, identifying funding for this large study was an issue. We received funding from three sources for this work: the Victorian Department of Human Services through their Public Health Research program, the Murdoch Childrens Research Institute from the Project Grant Support program, and the University of Melbourne through the Melbourne Research Grants Scheme. We originally sought to conduct this study over a three year period to observe seasonal trends in virus epidemiology. It was also our intention to test all specimens, from study children and their household contacts, as they were collected. The available funding meant the duration of the study was limited to a 12-month period, and given this, our target for subject recruitment was reduced. Our use of the respiratory multiplex PCR test was also restricted to only those specimens collected from study subjects, meaning household contact specimens remain stored in a minus 70°C freezer, waiting on further funding to complete testing.

1.5 Thesis outline

The first part of this thesis, Chapter 2, contains a review of the relevant literature. This chapter summarises key findings from and the methods of previously conducted community-based epidemiological studies on respiratory illness in children and families. The limited literature on the health economics of viral respiratory tract infections in this age group is also reviewed. Current and prospective vaccine and other preventative options available for widespread use in children in the community are examined. Previous studies on the capacity of parents to collect respiratory specimens from children are reported. This information provides the rationale for the studies undertaken.
In Chapter 3 the findings of the pilot study are outlined. Of particular interest are the outcomes of application of a detailed method for the identification of ARIs and capturing the associated burden data.

The output of the main study contributing to this thesis is described in three chapters. Chapter 4 reports the details of the main findings around epidemiology and incidence. Chapter 5 describes the cost burden associated with identified illnesses and specific viruses. Chapter 6 provides an overview of the methods used in ReVS.

The conclusions reached and brief further discussion are presented in Chapter 7. The findings of importance and limitations are reviewed and the potential impact of this work on conduct of future studies are canvassed.
Chapter 2

Viral Respiratory Tract Infections in Children

2.1 Objective

The objective of this Chapter is to report and summarise findings from a review of the literature relevant to this thesis and to identify gaps in the currently available knowledge base.

The topics reviewed include:

- Viruses found in childhood respiratory illness;
- The impact and health economics of respiratory viral infections in children;
- Currently available and future options for prevention of infection in children;
- The Australian context for the surveillance of respiratory viruses and their impact;
- Laboratory testing, specimen type, and collection method for the diagnosis of respiratory viruses; and
- The research methods used in previous population-based studies of respiratory infections, and secular societal changes that may limit current application of these findings.

These findings will be used to construct an argument for the studies that have been proposed and were conducted as part of this PhD.
2.2 Respiratory viruses of importance in childhood

There are a number of viruses that are considered primarily as pathogens of the respiratory tract; until recently, they have historically been detected using cell culture, antigen detection, or serological diagnostic panels. This group includes the influenza viruses (IVs), respiratory syncytial virus (HRSV), and the parainfluenza viruses (PIVs) – PIV I, PIV II, PIV III. Adenoviruses cause respiratory disease, but specific serotypes can affect other organ systems and produce non-specific illness, such as fever with no clear focus. There is a second line of agents, including rhinoviruses and other picornaviruses, and coronaviruses, that are relatively common, but have previously been thought of as typically associated with milder upper respiratory tract illness.8 Another group of viruses originally identified in individuals with respiratory disease, have rarely been found in conjunction with respiratory illness; these include agents such as mimivirus and Mossman virus.9 Episodic respiratory infections caused by the transmission from animals to humans of viruses that are not well adapted for human-to-human spread include avian influenza strains10 and apparent occasional episodes, such as that caused by a recently discovered reovirus, Melaka virus.11,12 A number of viruses from the herpesviruses family, including human herpes virus type 6, cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, and the herpes simplex viruses, have all been associated with respiratory tract disease, particularly in the immunocompromised.13 The vaccine preventable diseases mumps and measles are now uncommon in Australia, but where endemic, mumps can be associated with respiratory symptoms in 40-50% of cases in children under the age of five years.14 Measles continues to be a major cause of global mortality in the same age group, often due to secondary bacterial pneumonia.15 Finally, since the commencement of these projects, there have been a number of viruses identified for the first time in specimens from the human respiratory tract; human metapneumovirus (HMPV),16 a number of new coronavirus: SARS-associated coronavirus,17-20 human coronaviruses NL63 (hCoV-NL63)21 and HKU1 (hCoV-HKU1),22 human bocavirus (HBoV),23 and two human polyomaviruses: KI (KIPyV)24 and WU virus (WUPyV).25 Another new human polyomavirus, initially found in association with Merkel cell carcinoma tissue, has also been found in respiratory specimens.26-28
These viruses comprise the core group of common childhood respiratory pathogens, as well as those that may only occasionally cause illness. In the following sections, I will briefly summarise details of the common and newly detected viruses.

### 2.2.1 Influenza viruses

A virus was first identified in humans suffering from influenza during the 1933 epidemic in the United Kingdom. Influenza viruses, part of the family Orthomyxoviridae, are enveloped and contain segmented negative-sense ribonucleic acid (RNA). Three members of this family cause disease in humans: influenza A virus, influenza B virus, and influenza C virus; however, influenza C virus is not commonly sought for or detected in respiratory specimens from symptomatic individuals. Influenza is of particular interest because, unlike other respiratory viruses, it is able to cause annual epidemics in adult populations by escaping host immune defences through altering the two major surface glycoproteins, haemagglutinin (H) and neuraminidase (N), in processes called antigenic drift and antigenic shift. Antigenic drift, which occurs in influenza A, B, and C viruses, is a gradual and ongoing process that involves point mutations in the amino acid sequence of H and N. Antigenic shift, which only occurs in influenza A, results from genome reassortment usually of the H glycoprotein (rarely the N glycoprotein) with novel subtypes, sourced from waterfowl and other animals, previously or recently absent from human influenza A viruses.

Influenza can cause severe illness and death in all age groups, but, based on routinely collected data and research, hospitalisations and other complications have their highest rates in young children under the age of two years, those 65 years of age and older, and those with a predisposing risk factor from all age groups. Influenza generally causes a typical illness in susceptible adults and a variety of clinical syndromes, with or without respiratory symptoms, in children. Deaths associated with influenza infection are much less common in children than in the elderly, with five deaths recorded in Australian children less than five years of age in 2003 and 2004, compared with 85 in adults 60-years of age and older. A number of sources point to an increase in influenza mortality in the United States between the 1970s and 1990s. Annual

The annual impact of influenza on medical resource use is high, and remains unrecognised by frontline clinicians.37 The proportion of the population infected with influenza varies from year-to-year, but can be as high as 40% in children.38,39 During the influenza season even infants and children without pre-existing chronic or serious medical conditions are at increased risk for hospitalisation.40 Hospitalisation rates attributable to influenza in healthy children are similar to those for high-risk adults, and use of antibiotics increases by 10 to 30% during periods when influenza is circulating.39 Concerns about a relatively high number of paediatric influenza-associated deaths in the 2003-2004 season in the US, 153 deaths in 40 reporting states,41 led to this condition becoming a nationally notifiable disease in US from October 2004.42 Since then, annual notifications of childhood deaths have numbered 46 (2004-2005 season), 47 (2005-2006 season), and 73 (2006-2007 season) with 55% of these children having no Advisory Committee on Immunization Practices (ACIP) defined high-risk condition for complicated influenza illness.43 In Australia, annual rates of hospital admission due to influenza may be as high as 600 per 100,000 children less than one year of age.44 However, the role of influenza in childhood morbidity remains incompletely defined – there is an absence of reliable data about the community incidence of infection using laboratory confirmation of infection, rather than less specific clinical syndromic classification.

Our understanding of influenza epidemiology and impact is incomplete. One of the reasons for this is that mechanisms for identifying influenza-related illness, including routine surveillance and methods in many observational studies, lack adequate sensitivity and specificity. Syndromic definitions for influenza-like illnesses (ILIs) in all age groups are both insensitive and non-specific.37,45,46 Recent observation studies attempting to better define influenza burden in children have focused on hospitalisations, and have attempted to isolate influenza impact from
other respiratory viruses, particularly RSV,\(^5\) using administrative coding alone. Without supporting laboratory confirmation, the specificity of such a method is likely to be poor.\(^{37,45-48}\)

Whilst specificity is generally high, the laboratory methods most commonly used are older, poorly sensitive techniques, such as antigen detection or cell culture. Current best practice for identifying influenza, and other respiratory viruses, is nucleic acid amplification: these methods, properly conducted, dramatically improve sensitivity whilst maintaining high specificity. Limiting factors in more routine use of PCR include availability of the platform, staff expertise, and cost.

### 2.2.2 Human respiratory syncytial virus

Respiratory syncytial virus (HRSV) is a member of the genus *Pneumovirus*, of the family *Paramyxoviridae*.\(^{49}\) HRSV is the most important viral respiratory pathogen of infancy and early childhood,\(^{50,51}\) causing a variety of clinical syndromes including acute otitis media, acute wheezing,\(^52\) febrile upper respiratory tract infection, bronchiolitis, and pneumonia\(^53\) – either through direct effects or secondary bacterial infection.\(^54\) One in five hospitalisations that occur each year in the US for lower respiratory tract infection (LRTI) in children less than 18 years of age are due to RSV, followed by 12% from the parainfluenza viruses, and 7% to influenza viruses.\(^55\)

The documented rate of severe lower respiratory tract disease caused by HRSV in infants appears similar in developing\(^{56-58}\) and developed countries.\(^54,59\) Between 50% and 70%, of infants acquire infection in the season they are first exposed to HRSV, and more than 90% have serological evidence of infection by the end of their second season, with very few asymptomatic primary infections.\(^60\) Up to three percent of infants infected are hospitalised annually with approximately 10% of these requiring intensive care.\(^61-63\) The peak age for complicated HRSV infection is between two and six months of age.\(^54,57,64,65\)

HRSV typically causes a geographically-associated seasonal peak: occurring during winter in temperate climates and the wet season in tropical settings. Well recognised risk factors for severe LRTI with HRSV infection include children with congenital heart disease, children who
were born premature with or without chronic lung disease of prematurity, children with cystic fibrosis or other chronic lung diseases, and immunosuppressed or immunodeficient children.\textsuperscript{66} However, up to half of hospitalised patients have no identifiable risk factor.\textsuperscript{67} In children without these identified risk factors, HRSV severe LRTI is associated with male sex, being aged less than six months, birth in the first half of the HRSV season, childcare attendance, exposure to household crowding and siblings, absence of breast-feeding, tobacco smoke exposure, and race/ethnicity.\textsuperscript{66}

Reinfection with HRSV is common in both adults\textsuperscript{68} and children.\textsuperscript{69} In a 10-year prospective study of children from early infancy enrolled in a research daycare program, 98% were infected with HRSV in their first year of exposure, 74% were reinfected in their second year, and 65% during their third year.\textsuperscript{69} There were similar findings from the Houston Family Study: virtually all children had a primary infection with HRSV by their second birthday, and nearly 50% had a second infection.\textsuperscript{60}

In the US there has been a major shift in the epidemiology of HRSV over the last 30 years, as demonstrated through population-based surveillance in Houston, Texas.\textsuperscript{70} The annual duration of HRSV epidemics appears to have essentially doubled, from eight to ten weeks in the 1970s and early 1980s, to 16 to 18 weeks in the late 1990s. There was also a doubling of the annual risk of HRSV-related hospitalisation between 1979 to 1980 and 1992 to 1996, increasing from 1.2 to 2.4 per 100 infants less than six months of age.\textsuperscript{70} These data are supported by national figures which showed the annual rate of hospitalisation for bronchiolitis more than doubled between 1988 and 1996,\textsuperscript{71} with associated increases in the economic burden of illness.\textsuperscript{72} During the same period there was no equivalent change in hospitalisations for non-bronchiolitis lower respiratory tract disease, meaning annual bronchiolitis admissions as a proportion of LRTI and total admissions also doubled (from 22% to 47%) and tripled (5% to 16%), respectively.\textsuperscript{71} However, this increase was not matched by an increase in mortality due to bronchiolitis in children.\textsuperscript{73}
Chapter 2: Viral respiratory tract infections in children

No causal factors have been linked with this fundamental change in HRSV epidemiology. It is possible that a change in the structure of family life resulting in children being exposed to a cohort of other children through childcare at an earlier age and for an increasing number of hours a week may have a role to play. Increased rates of hospitalisation in the US have coincided with changes in child care attendance. At least weekly attendance at a daycare centre with more than six children present is independently associated with hospital admission for LRTI during the first two years of life.\(^7^-4\) Between 1982 and 1993, the proportion of US children less than three years of age enrolled in child care centres doubled (12% to 25%); and the same figures for children less than one year of age went from 5% to 20%.\(^7^-5\)

2.2.3 Human parainfluenza viruses

Parainfluenza viruses are medium-sized, enveloped viruses with nonsegmented, negative-strand RNA. All known human parainfluenza viruses (HPIVs), HPIV-1 to HPIV-4, were isolated in the second half of the 1950s.\(^4^-8\) In early studies HPIVs were identified as being responsible for approximately 40% of all LRTIs of childhood where a virus could be identified.\(^4^-7\) HPIV infections cause a range of syndromes similar to those caused by HRSV, but result in fewer hospitalisations.\(^7^-5\) Most HPIV infections are limited to the upper respiratory tract, with up to 50% complicated by acute otitis media, and only 15% involving the lower respiratory tract.\(^4^-8\) Almost all children have serological evidence of previous exposure to all HPIV types by their fifth birthday.\(^4^-8\)

The epidemiology of each of the HPIVs is distinct, but HPIV-1 and HPIV-3, and to a lesser extent HPIV-2, all play a role in childhood croup. The term “croup” covers a number of clinical entities, and HPIVs have a role in spasmodic croup, acute laryngotracheitis, and precipitates illnesses with secondary bacterial infection, laryngotracheobronchitis, laryngotracheobronchopneumonitis, and bacterial tracheitis.\(^7^-8\) Based on findings from population-based cohort studies in the US, in children HPIVs cause 20% of URTI, 65% of croup, and 20-40% of LRTI.\(^7^-9\)
HPIV-1 causes large, well-defined, biennial outbreaks of croup in autumn, and is the primary reason for hospitalisation in older children following a HPIV infection. HPIV-2 is less commonly identified than HPIV-1 and HPIV-3, and causes peaks in croup that tend to follow on from HPIV-1 peaks. As well as having a role in croup, HPIV-3 is a major cause of bronchiolitis and pneumonia in infants and young children, ranking second only to HRSV in importance. HPIV-3 has a longer, flatter, and less-epidemic pattern than HPIV-1 and HPIV-2 in terms of laboratory identification in community surveillance, causing disease and hospitalisations for pneumonia and bronchiolitis mainly in spring and summer. In the Houston Family Study, HPIV-3 was the most common virus identified in virus-proven ARI, more common than either RSV or influenza A infection, with two-thirds of children infected in the first year of life, and 20% of these had evidence of LRT involvement, which was more common in boys than girls. Up to 80% of children had a HPIV-3 infection in their second year of life, with one-third experiencing a reinfection. HPIV-4 epidemiology is not as clearly delineated as the other HPIVs, but it appears to have a role in URTIs in children and can occasionally cause more serious respiratory tract disease in children and adults.

### 2.2.4 Adenoviruses

Adenoviruses are non-enveloped DNA viruses between 60 to 90 nm in diameter. Adenoviruses account for 5 to 10% of URTI and LRTI in infants and children, but epidemic strains are particularly noted for causing explosive outbreaks of LRTI in communal settings, such as in newly cohorted military recruits. In immunocompetent children, adenoviral infections are self-limiting, with febrile URTI the most commonly associated clinical syndrome. However, adenoviruses may be responsible for up to 10% of early childhood pneumonias.

Adenovirus infections are common in young children, are distributed worldwide and cause hospitalisation for respiratory and gastrointestinal illness. They tend to be found in most months of the year, but their association with respiratory illness peaks in winter. Adenovirus respiratory infections can be difficult to distinguish from severe bacterial infections, with features including high fever, leukocytosis, and elevated c-reactive protein. Without rapid testing, these
features can result in hospital admission for further diagnostic testing and unnecessary antibiotic therapy.97

Transmission of adenoviruses in child care and household settings is common. In a short substudy of child care attendees, 14 of 21 (67%) well contacts exposed to an index child with adenovirus isolated from respiratory tract specimens developed febrile respiratory tract illness and shedding of the same serotype within two weeks.98 During a four to six week follow-up period in 18 families with an index case diagnosed with adenovirus infection by indirect enzyme-linked immunosorbent assay (ELISA), 94% of siblings and 56% of parents had clinical syndromes consistent with acute infection, and 63% and 20%, respectively, had adenovirus confirmed.99

2.2.5 Picornaviruses

Picornaviruses – meaning literally very small (pico) RNA viruses – are approximately 30 nm in diameter, having a simple capsid and a single strand of RNA which encodes for production of a single, multi-domain, proteolytically-processed polyprotein.100 As a group, the picornaviruses are the most common causes of human infection, infecting nearly all children by their second birthday.101 The major contributors to human respiratory disease from this group are the rhinoviruses, although, in some regions, enteroviruses also play a substantial role.

Compared to the other respiratory viruses under active research since the 1960s, the rhinovirus literature had been relatively quiescent for some decades. Until recently, these viruses were considered mostly as causative agents in benign upper airways disease, such as the common cold. Recent discoveries have changed the way we think about rhinoviruses in two key aspects: rhinoviruses cause a broader spectrum of illness than uncomplicated upper respiratory tract disease and can replicate in the lower airways causing lower airways disease; and rhinoviruses appear more prevalent than previously suggested based on culture methods alone.

The expanded role played by rhinoviruses has been driven by recognition of their routine involvement of the sinuses102 and the middle ear103,104 in rhinovirus infections of the upper
airways; the key role rhinoviruses play in exacerbation of wheezing and asthma in children; and from this, strong evidence they are important lower airways pathogens, including being responsible for pneumonia in immunocompetent individuals of all ages. The recognition of rhinoviruses as LRTI pathogens developed despite the hypothesis that they would not, in normal circumstances, infect the lower airways due to temperature restrictions on viral replication. It was thought any LRTI symptoms associated with rhinovirus infection may be due to biological features, including the release of inflammatory mediators. However, initial support for their involvement in more than upper airways disease came from evidence that illness-causing rhinoviruses can replicate effectively at 37°C, that is lower respiratory tract temperatures, some preferentially so. Further and direct evidence then became available from laboratory work and clinical research showing that rhinoviruses can and do cause lower airways disease.

More sensitive laboratory methods based on nucleic acid detection aided routine identification of these viruses and allowed for the recent description of previously unknown rhinoviruses. In fact, using rhinovirus-specific (or picornavirus) PCR in community-based studies in different countries, using different populations and indications for specimen collection has consistently yielded point prevalences in specimens from ill subjects of over 50%. Molecular methods have meant that rhinovirus prevalence can often outstrip the virus of interest in published papers, causing up to 80% of upper respiratory tract illness in seasonal peaks, but even in the middle of winter, the rhinovirus nadir, when we typically think of other viruses predominating, rhinoviruses are now the most commonly detected pathogen in infants. Whilst some of the improved detection has to do with PCR’s improved sensitivity over traditional methods of known virus detection, it appears as though PCR is also detecting a range of rhinoviruses not detectable by traditional methods. In 2007, there were a number of reports of previously uncharacterised rhinovirus strains detected by molecular methods alone and, to date, not able to be cultured.

Using picornavirus specific primers in PCR reactions does not allow, in the first instance, for rhinovirus and enterovirus discrimination. Whilst it is generally considered that most
picornaviruses identified in respiratory tract specimens are likely to be rhinoviruses, depending on the population and the season testing is done, there can be evidence for enterovirus predominance. In a group of 179 Australian children with a history of asthma and acute respiratory illness, 40% of NPAs collected were positive for enteroviruses. Further, in two groups of Finnish children enteroviruses were found in one quarter of NPAs: community-dwelling children with upper respiratory tract symptoms, and children hospitalised with acute expiratory wheezing.

2.2.6 Human coronaviruses

Coronaviruses, members of the family *Coronaviridae*, are enveloped viruses with a positive-sense single-stranded RNA genome and a helical symmetry. Prior to the identification of the SARS coronavirus, human coronaviruses (hCoVs) were recognised as having a wide range of antigenic variation and generally thought of as causing simple, uncomplicated viral upper respiratory tract infections. Despite being first discovered in 1965, the full epidemiology of these viruses has been slow to come to light due to difficulty growing these viruses in cell culture systems from clinical specimens. These difficulties are highlighted in more recent studies where traditional methods of identification and PCR are compared: in inner-city adults with asthma, 71% of all coronavirus infections were identified by RT-PCR only.

There are now five coronaviruses recognised as having the capacity to cause disease in humans: two of these viruses have been known about since they were identified in the 1960s, hCoV-229E and hCoV-OC43, and the initial reports for the remaining three, SARS-CoV, hCoV-NL63, and hCoV-HKU1, were made only in 2003, 2004, 2005, respectively. As well as these five, there are a number of forgotten coronaviruses that were pathogenic in humans, including the first human coronavirus described, B814, hCoV-OC16, hCoV-OC37, and hCoV-OC48. None of these viruses grew well in tissue culture and were without a suitable animal model, meaning all lacked a reliable method for subsequent study from the time of their identification. The absence of stored material from these early studies means it is possible the newly described
coronaviruses, hCoV-NL63 and hCoV-HKU1, are just rediscoveries of these previously recognised viruses.

Human coronavirus 229E and hCoV-OC43 are prototype representatives of group one and two coronaviruses, respectively. Findings from historical studies using serology and more recent studies using molecular techniques make it clear that, as well as causing relatively minor respiratory illness in all age groups, they also cause more serious disease in a wide range of populations: the young, infants and children in neonatal and paediatric intensive care units, institutionalised military recruits and institutionalised and frail elderly, and the immunocompromised.

Recent improvements in identification have come with the development and application of PCR methods for identifying coronaviruses. Using molecular methods these viruses have been identified in a not insignificant proportion of upper respiratory tract infections: for example, they were found in one-quarter of URTI in a recent UK study of community-living elderly, they were more common than influenza as a cause for hospital presentation of inner-city adults with asthma, and, in children, they were found in 17% of middle ear fluid or NPAs from children with acute otitis media. An RT-PCR study on routinely collected specimens from staff and patients in paediatric and neonatal intensive care units in France showed a high prevalence of hCoV-229E in community-acquired (9%) and nosocomial infections (17%). Coronaviruses were relatively uncommon in Finnish children less than two years of age, being present in 2.4% of NPAs and middle ear fluid specimens from children with ARI and otitis media. Serological studies in Finland show that by two years of age, 40% of children have antibodies to hCoV-OC43 and that by six years of age nearly all have antibodies.

2.3 Viruses recently identified in respiratory tract specimens

Since commencing these cohort studies, there has been a small explosion in the detection of previously unidentified viruses in respiratory specimens, with the likelihood of more to come.
These new viruses have been identified using a variety of molecular techniques: virus discovery cDNA amplified restriction fragment length polymorphism technique (VIDISCA),\textsuperscript{21} pan-viral DNA microarrays,\textsuperscript{147} consensus PCR primers,\textsuperscript{22} and high-throughput sequencing.\textsuperscript{24,25} In this section, human metapneumovirus (HMPV),\textsuperscript{16} new hCoVs: SARS coronavirus,\textsuperscript{17-20} hCoV-NL63,\textsuperscript{21} and hCoV-HKU1,\textsuperscript{22} human bocavirus (hBoV),\textsuperscript{23} and new hPyVs: KIPyV\textsuperscript{25} and WUPyV\textsuperscript{25} will be reviewed briefly.

2.3.1 Human metapneumovirus

The discovery of a newly identified respiratory pathogen, human metapneumovirus (HMPV), was announced by a group of Dutch researchers in 2001.\textsuperscript{16} This virus is the first mammalian virus member of the family \textit{Paramyxoviridae}, subfamily \textit{Pneumovirinae}, genus \textit{Metapneumovirus}, and is an enveloped virus with a single strand of negative polarity RNA.\textsuperscript{13} The key epidemiological features of HMPV described in that original paper still hold true: namely, that similar to other respiratory viruses, HMPV is more common in children than adults, and the range of clinical illness extends from minor upper respiratory tract illness to severe bronchiolitis and pneumonia.\textsuperscript{16} Early reports of studies on stored respiratory specimens confirmed children were the most commonly affected group.\textsuperscript{148-150} HMPV is a common and geographically ubiquitous virus, having been detected on every populated continent.\textsuperscript{16,105,117,148-163} Though only recently described HMPV could not be considered a newly emerging pathogen: 100% of 72 sera collected in 1958 from individuals aged from eight to 99 years old were positive for HMPV by indirect immunofluorescence antibody (IFA) testing, implying virus circulation for more than 45 years.\textsuperscript{16} Since its discovery HMPV has proved to be a respiratory pathogen that can cause moderate to severe respiratory disease in normal healthy children at a rate somewhat less than HRSV, but more commonly than infection due to parainfluenza viruses.\textsuperscript{164,165}

Given the variety in each of these elements in the papers reporting HMPV to date, it appears as though HMPV is the causative agent in approximately 5 to 10% of children hospitalised for respiratory illness.\textsuperscript{166} Depending on the patient population used, this value can be as low as no specimens positive for HMPV from children hospitalised with moderate or severe HRSV disease.
at a time when the virus was known to be circulating in the wider community;\textsuperscript{167} and has been as high as 52\% (25 of 48 patients) in the first group to be diagnosed with SARS in Hong Kong.\textsuperscript{168} Season and age of the patients studied play a major role in the likelihood of finding HMPV: for example, the proportion of specimens from hospitalised children less than two years of age positive for HMPV was as high as 43\% between January and May 2002 in an Italian study.\textsuperscript{169}

There have been limited studies looking at the true community incidence of HMPV. A US prospective study by Falsey and colleagues\textsuperscript{170} which enrolled healthy and chronically ill adults and obtained specimens by home visit when subjects had respiratory illness, identified HMPV in 6.6\% of illnesses in healthy young adults using a combination of PCR and serology. In an early UK study, only 1.3\% of virus-negative specimens tested from a mainly adult population presenting to general practice with an ILI were positive for HMPV.\textsuperscript{171} But the Dutch group who identified the virus reported a lower proportion of specimens from patients with ILI were positive for HMPV compared with specimens from patients with RTI,\textsuperscript{172} meaning the figure of 1.3\% may well be an underestimate of HMPV's role in ARI.\textsuperscript{173}

Human metapneumovirus causes a spectrum of clinical illness similar to HRSV, ranging from apparently uncommon asymptomatic infections\textsuperscript{170} through to severe respiratory disease in healthy young children, individuals from all age groups with predisposing illnesses or who were immunocompromised,\textsuperscript{150,174} and young adults and the elderly.\textsuperscript{170} In children, the elderly and the immunocompromised, illness usually ranges from mild URTI through to bronchiolitis, croup, or pneumonia. Whilst most studies to date, including those examining the epidemiology of lower respiratory tract illness, have relied on identification of HMPV from specimens collected from the upper respiratory tract, the virus has been identified in post mortem lung tissue.\textsuperscript{168,175} By testing respiratory specimens from children under the age of five-years collected during a 25-year prospective study for HMPV, US researchers have shown the most common clinical manifestation in 49 infected children was bronchiolitis (59\%), followed by croup (18\%), exacerbation of asthma (14\%), and pneumonia (8\%).\textsuperscript{176} Accompanying acute otitis media was common being reported in 37\% of HMPV cases.\textsuperscript{176} HMPV has been associated with wheeze\textsuperscript{117} and acute exacerbations in
Chapter 2: Viral respiratory tract infections in children

children with asthma. HMPV infection, in the absence of other pathogens, has resulted in death in immunocompromised children, immunocompromised adults, a previously healthy young adult, and the elderly.

2.3.2 Human coronaviruses

Of the three newly identified human respiratory coronaviruses, one, the SARS-associated hCoV, produced a short-lived global epidemic in 2003 associated with severe respiratory illness and a high mortality rate. SARS will not be dealt with in any detail here, as it is not continuing to circulate in human populations. The other two viruses – hCoV-NL63 and hCoV-HKU1 – share similarities with the previously known coronaviruses: they appear to circulate globally and cause a varying proportion of a broad spectrum of clinical respiratory syndromes.

First recognised in February 2003, the outbreak caused by SARS-associated coronavirus in humans appears to have begun in November 2002 in Guangdong province, China. Global spread of the disease was facilitated in early February 2003 when an infected physician who had been treating SARS-affected patients in China stayed in a Hong Kong hotel whilst symptomatic. Spread from this focus resulted in more than 8,000 cases and 774 deaths in 26 countries. The identification of the causative agent resulted from a collaborative effort led by the World Health Organization, allowing for complete genomic sequencing and the development of diagnostic tests to guide treatment and public health management within a matter of months. Since the initial outbreak, there have been a small number of inadvertent laboratory releases of the SARS-coronaviruses. Unlike the other four human coronaviruses known to cause respiratory illness in humans, there is no evidence of continued epidemic or endemic transmission of SARS-CoV in human populations.

In 2004 and 2005, three separate papers were published that described apparently the same, previously unreported human coronavirus — labelled variously as hCoV-NL63 by the group from the Netherlands who published first in 2004, hCoV-NL by the other group from the Netherlands who published shortly after their compatriots, and controversially given the available
data do not provide evidence of a new virus, New Haven coronavirus (hCoV-NH) by the American group who published in 2005.193 These initial reports identified the virus and went some way to describing its epidemiology, and it has since been found globally.194-199

The first published paper described the virus was initially isolated from a seven-month-old child suffering from bronchiolitis and conjunctivitis.21 This paper went on to describe that hCoV-NL63 was found in 7% of specimens collected from hospitalised individuals and outpatients in January 2003; a total of eight specimens collected between December 2002 and February 2003 were positive; and the virus was identified in none of 306 specimens collected between March and August 2003.21 The virus was strongly associated with specimens from children with croup later by the same group,195 and bronchiolitis in Australian children.200

The other group from the Netherlands first found the virus in a specimen collected from an eight-month-old boy with pneumonia in 1988, providing a temporally distinct identification of the virus.189 Specimens negative for other respiratory viruses, including other coronaviruses, collected between November 2000 and January 2002 from hospitalised patients, were tested for hCoV-NL63, with four (2.9%) of 139 positive, all from children.189

The US group used a novel screening method to identify previously undocumented coronavirus RNA sequences from pooled respiratory samples from hospitalised patients and outpatients less than five years of age.193 The specimens, collected between January 2002 and February 2003, were initially negative for common respiratory pathogens, with 79 (8.8%) of 895 children positive for hCoV-NH.193 Interestingly, one of the positive cases had Kawasaki disease, leading to a case-control study which demonstrated an association between the virus and this disease — eight of 11 cases hCoV-NH positive, compared with one of 22 age and season-matched controls (OR 16.0, 95%CI 3.4 to 74.4).201 Although, subsequent findings have not provided any support for this association.202,203
Findings to date show hCoV-NL63 has a prevalence of usually less than 5%, was present in all age groups but clustered around the very young and the elderly, and had a geographically diverse pattern of distribution being found in tropical and temperate climates (although perhaps with different seasonal patterns). Human coronavirus NL63 was present in hospitalised and outpatient groups and could cause URTI, LRTI, and febrile illness, could also cause gastrointestinal symptoms (when reported), and it appears a more common pathogen than either hCoV-OC43 or hCoV-229E where testing for all three viruses was performed on the same population.194-199

The most recent addition to the collection of coronaviruses known to cause respiratory illness in humans is hCoV-HKU1. Human coronavirus HKU1 is a group two coronavirus, sitting alongside hCoV-OC43. This virus was identified in Hong Kong in nasopharyngeal aspirates collected in January 2004 from a 71-year-old man with pneumonia, who had returned from Shenzhen, China, three days prior to admission.22 The virus was subsequently identified by RT-PCR in one of 400 SARS-negative specimens from patients with ARTI during the SARS outbreak period.22 The patient was a previously healthy 35-year-old woman with pneumonia of unknown aetiology in March 2003. To date, further publications include identification of hCoV-HKU1 from specimens in Sweden described in the first report of human bocavirus (hBoV).204 Other reports of hCoV-HKU1 suggest it has a global presence, being found in Australia,205 France,206 United States,207 Italy,208,209 and mainland China.210 From these papers, hCoV-HKU1 appears to be somewhat less prevalent than hCoV-NL63, occurs mainly in winter-spring, can be found in stool specimens from patients with acute gastrointestinal symptoms, is found in upper and, less commonly, lower respiratory tract illness, and is often found in the presence of an underlying condition, such as: birth prematurity, older age, and immunocompromised states.

### 2.3.3 Human bocavirus

In mid-2005 a paper from Sweden outlined another novel technique for the identification of respiratory tract pathogens, and reported a previously unknown human parvovirus, human bocavirus (hBoV).204 Full-length genome sequence analysis showed the virus to be closely related to bovine parvovirus and canine minute virus and is a member of the genus *Bocavirus*, subfamily
Parvovirinae, family Parvoviridae. The researchers went on to screen stored clinical respiratory specimens and identified the virus in a further 17 patients (3.1%) from 540 NPA samples collected from hospital wards between November 2003 and October 2004. Three specimens (18%) were positive for another virus by immunofluorescence or virus culture, and hBoV was more common in winter, matching the pattern of specimen collection. Fever greater than 38.5°C was a common symptom (59%), and asthma was a common comorbidity (41%).

Human bocavirus has a global distribution having been found in Australia, Europe, the UK, North and South America, and Asia. There is no apparent seasonal variation to hBoV detection. The virus has its highest detection prevalences in children less than three years of age, and when detected in adults, is usually associated with immunocompromise. There remains uncertainty whether hBoV is causally associated with clinical illness involving the respiratory and the gastrointestinal tract. One reason for this is the high rate of codetection with other viruses. A number of studies have found the virus is more common in subjects with disease than controls, but there remain issues about the appropriateness of the controls used, in particular, specimen type and age group.

2.3.4 Human polyomaviruses

In 2007 came reports of two new human polyomaviruses in respiratory samples: KI polyomavirus (hPyV-KI) and WU polyomavirus (hPyV-WU). Polyomaviruses are small DNA viruses with circular, covalently closed double-stranded genomes; they can infect a wide range of mammalian and avian species.

Both of these new polyomaviruses have been found to have a global distribution, with prevalence in respiratory specimens from symptomatic patients of around or below 5%. The issues of showing a causal association with virus identification and respiratory illness discussed for hBoV, are even more acute with hPyV-KI and hPyV-WU with high levels of codetection with other viruses in specimens from symptomatic subjects, up to 74% for hPyV-KI and 68% to 79% for hPyV-WU, relatively high levels detection in asymptomatic controls: 4.2%, 5.4%, and 52%.
and 6.4%\textsuperscript{231} for hPyV-WU, and 5.4% for hPyV-KI.\textsuperscript{232} Issues about the control subjects used make it difficult to interpret some of these data,\textsuperscript{228} but it may be that these new polyomaviruses are only transmitted via the respiratory route and may be subsequently detected following persistence or reactivation.

### 2.4 Impact and health economics of viral respiratory tract infections in children

#### 2.4.1 Impact of respiratory viruses

Acute respiratory tract infections are the most common illness experienced by all age groups and, globally, it is estimated they are responsible for approximately four million of the 14 million deaths every year in children under the age of five years.\textsuperscript{235} These deaths occur disproportionately in children in developing countries. Rates of lower respiratory tract infection as high as 240 per 1,000 children per year have been found in population based studies.\textsuperscript{50} In 1999 lower respiratory tract infections were identified as the leading cause of global disability-adjusted life-years (DALYs), and will remain in the top ten causes of DALYs to 2020 and beyond.\textsuperscript{236} This prominent role for ARIs in mortality and morbidity persists in updated burden of disease calculations.\textsuperscript{237} Despite this, global expenditure on health research into acute respiratory diseases is low in relative terms compared to other diseases where the annual research investment per DALY is much higher.\textsuperscript{238} Reasons for this may be that such infections disproportionately affect children, and that the serious consequences of such infections are more common in developing country settings; both relatively disenfranchised in relation to the selection of priority areas for spending on global medical care and medical research.

Whilst deaths are uncommon, significant morbidity associated with ARIs occurs in industrialised countries. ARI incidence is highest in the first two years of life, with up to eight episodes per year, and during the winter peak averaging close to one infection per child-month.\textsuperscript{1} Whilst illnesses can often be managed in the community with supportive care from parents or other caring adults, complications requiring a medical visit and antibiotic therapy, such as otitis media (30%) and
sinusitis (8%), are common. In pre-school aged children, nearly 50% of general practitioner visits are for ARI. Further, up to 5% of all infants are hospitalised for viral lower respiratory tract infections (LRTI) such as croup, bronchiolitis, and pneumonia, or from secondary bacterial pneumonia. Rapid identification of respiratory viruses in children can reduce the duration of hospital admission, antibiotic use, and number of investigations performed, and has been shown to be cost-effective in busy diagnostic settings.

2.4.2 Burden of non-influenza respiratory viruses

Estimates of the cost impact of respiratory viruses, and in particular, non-influenza viruses are rare – particularly compared to their relative frequency – but there are some US data. The quality of these data is questionable given the methods used, and these studies have limited applicability to Australia. In the absence of data from better quality research or from Australian studies, they are presented here, but should be interpreted with caution.

Using a telephone survey of over 4,000 households, the researchers collected self-reported incidence of and resource use during non-influenza, viral respiratory infections. These figures were extrapolated to the US population and costs attached to resource use. The direct costs associated with viral respiratory infections were US$17 billion annually, with these being outweighed by the indirect cost burden of US$22.5 billion. The indirect cost component was made up of missed workdays due to illness totalling 70 million days, and missed workdays whilst caring for a household member totalling 189 million days. The annual cost burden of antibiotic use for acute respiratory tract illness in the US is over US$1.3 billion alone. Even more impressive is an estimate of US$112 billion for the total cost to employers alone in 1997, including medical treatment and time lost from work, due to respiratory infections.

Information about HRSV impact is more common than other non-influenza viruses, but pertains mainly to those groups of children who are currently eligible for preventive interventions: those born prematurely with associated lung disease, or with specific congenital cardiopulmonary malformations.
A US study using three national databases and an assumption that 15% of all acute OM was due to HRSV calculated direct medical costs from HRSV to be over US$1.3 billion (2002 dollars) per annum, with 98% of these costs associated with illness in the less than five age group. Figures from Canada, with a population size approximately one-tenth of the US, seem to be somewhat lower, with a 1997 study that included indirect costs finding that for the same age group, the annual cost was US$18 million (1993 US dollars). Data on indirect costs associated with HRSV illness are scant. For infants in the US, substantial indirect costs accumulated before, during, and after HRSV-related hospitalisation with the burden being twice as high per episode for premature infants, with the greatest contributor to overall costs (85-90%) being lost carer productivity.

2.4.3 Influenza

A recent modelling assessment of seasonal influenza suggested annual costs of US$87.1 billion, with 83% of this cost due to annual deaths. Influenza is the respiratory virus about which most cost-of-illness and cost-effectiveness work has been done. This is due to the availability of preventive and therapeutic options, with most of the research being done in the US. Influenza vaccination of children may yield both health and economic benefits during epidemic and pandemic periods.

Direct medical costs, particularly those that are more easily measured such as influenza-associated hospitalisations, play an integral role in cost-effectiveness evaluations of these interventions. There have been a number of studies in recent years that have examined this central cost, and the findings are compared and summarised in a 2006 paper by Keren and colleagues. In this paper, they estimate the cost of an influenza-related hospitalisation in those less than 21 years of age to be $13,159 (2004 US dollars) by specifically examining admissions due to laboratory-confirmed influenza over four consecutive influenza seasons.
Prior to this, there were three studies that calculated the cost of hospitalisation by using less-specific coding to identify influenza cases, rather than laboratory confirmation. Meltzer and colleagues\textsuperscript{256} used health-insurance claim form data with influenza related (non-specific) coding to calculate a mean cost of admission of US$4,129 (2004 US dollars).\textsuperscript{257} Using a 1995 US-wide inpatient sample, Luce and colleagues\textsuperscript{255} used non-specific coding to calculate a mean cost of influenza-associated hospitalisation of $2,964 (2004 US dollars) in a paper published in 2001.\textsuperscript{257} As highlighted by Keren,\textsuperscript{257} Cohen and Nettleman took an even more indirect approach to calculate a cost of hospitalisation for their assessment of the economic impact in influenza in pre-school aged children.\textsuperscript{253} They used incidence figures from the US National Hospital Discharge Survey and applied a mean daily cost for asthma hospitalisations in an older age group to calculate a mean cost of hospitalisation of $3,643 (2004 US dollars).\textsuperscript{253,257} Making it clear they deliberately aimed for a conservative estimate, the applied daily cost is noted to be less than the median charge for an inpatient stay for all respiratory illness in children, and lower than the cost of HRSV-related admission.\textsuperscript{253}

Keren and colleagues further make the point that other estimates that are similar to their figure come from papers that also used laboratory-confirmed influenza.\textsuperscript{257} Hall and Katz examined the medical notes of 35 children with and without ACIP high-risk conditions and found weighted mean hospitalisation costs to be $19,117 and $6,072, respectively.\textsuperscript{258} The equivalent figures in the Keren paper were $15,269 and $9,107, respectively.\textsuperscript{257} Finally, a paper providing costs using laboratory-confirmation and chart review by Ampofo and colleagues published in 2006 also shows a cost per admission in the higher range of $6,124 (2001 US dollars).\textsuperscript{259} Whilst each of these studies is based on national data, it is worth noting that there is marked regional variation in healthcare costs in the US,\textsuperscript{260} meaning general findings may not be applicable to specific states or locations.

For any illness the cost of hospitalisation is of great interest, particularly to governments as third-party payers. However, most economic evaluations of influenza vaccine in children highlight the central role of indirect costs. Whilst there have been a number of health economic evaluations
performed on influenza vaccine use in children, in different settings, different health-care structures, and for different populations; they have generally been characterised by a number of key findings. Firstly, cost-effectiveness is enhanced, not surprisingly, by taking a societal perspective through the inclusion of some indirect costs, such as carer time away from work. Secondly, the potential cost-effectiveness of implementing universal childhood influenza immunisation is improved by flexible or non-individual based delivery programs. This is the case when inactivated vaccine or live intranasal vaccine is used in calculations. Relative cost-effectiveness of the two vaccine types has been compared using results from a large, multinational head-to-head efficacy trial in children. For those in the 24 to 59 month age group, the live vaccine, despite higher vaccine costs, was cost saving (US$45.80) relative to the inactivated vaccine due to higher efficacy in preventing laboratory-confirmed infection.

The effect logistic and delivery issues may have on cost-effectiveness of a publicly funded, universal recommendation for annual childhood influenza vaccination may be substantial. In the US it was estimated that, assuming only well child visits were used for vaccination and that the delivery period covered three months, 39% of children would require one additional visit and 35% would require two additional visits to a health-care provider to be fully immunised. Further, a wider recommendation would mean more than half the children over the age of two years would need an extra healthcare visit during the influenza vaccine delivery period, and this increased to two-thirds in those children over the age of five years. Most of the time at such general practice visits would be spent waiting for vaccination, with a median duration of visits in the US being 14 minutes with only one to two minutes used for hands-on vaccination. More flexible mechanisms of vaccine delivery would be required with a universal childhood recommendation in Australia: such settings for vaccine delivery in children can include mass immunisation of cohorts, such as in day care centres or schools. Pharmacy delivered programs are used in the US, but only deliver adult programs. Barriers to vaccinating US children at pharmacies and other non-traditional settings include that changes to the laws of every state would be required, and the lack of profit for delivering such programs. The ease of overcoming such barriers in Australia may make this form of delivery more straightforward.
Researchers in other countries have undertaken cost evaluations of influenza and other viruses. In a German study reporting the cost of LRTI in children less than three years of age, the inclusion of indirect costs, such as lost work time caring for a sick child, had the largest impact on community-managed influenza, as compared with HRSV and hPIV infections. For non-hospitalised illness, mean costs in 2002 Euros (€) were highest for influenza with a higher proportion of total cost being made up of indirect costs: influenza €223, 65%; HRSV €163, 43%; hPIVs €100, 27%; and other pathogens €111, 30%. Unlike in the US, the cost associated with hospitalisation did not appear to be different for laboratory confirmed influenza and other infections. The mean cost associated with hospitalised cases also did not show any variation in the proportion of total costs made up of indirect costs: influenza €2,597, 4%; HRSV €2,772, 6%; hPIVs €2,374, 6%; and other pathogens €2,267, 6%.

An Italian group, led by Nicola Principi, have done much work in delineating the burden and impact imposed by influenza in children. Their work has shown that inactivated influenza vaccination of children aged two to five years old has clinical and economic impacts on the children themselves and their extended household. Further, household contacts of otherwise healthy children presenting to outpatient settings with influenza were more likely to have a similar illness, require medical attention themselves, received antibiotics, and lose work days for their child’s and their own illness, compared to household contacts of children with ARTI who were influenza negative.

2.5 Options for prevention

2.5.1 Methods for controlling respiratory viral infections

The broad headings for preventive options in dealing with respiratory virus infections are: non-pharmaceutical options, such as hand washing, use of face masks, and social distancing; preventive pharmaceutical options, including passive and active immunisation, and use of other therapeutic preventive agents, such as antivirals and, possibly, in the future, short inhibitory RNAs (siRNAs); and similarly, antivirals, and potentially siRNAs, may be used to prevent duration
and effectiveness of transmission when infection has already occurred. Prophylaxis and
treatment with a number of anti-viral medications are available in Australia for influenza,277,278
but their use is currently not widespread in children.

Whilst other preventive options will be discussed briefly, the following section will focus mostly
on the only specific agents available for widespread, population-based prevention of a
respiratory viral infection, namely influenza vaccine.

2.5.2 Non-pharmaceutical preventive options

Non-pharmaceutical preventive options were implemented as public health interventions in
affected countries during the 2003 SARS outbreak. In Hong Kong, community hygiene measures,
including hand and respiratory hygiene, appeared to significantly reduce the incidence of a
number of other respiratory viruses.279 Evidence from the 1918-1919 influenza pandemic in the
US shows that cities that implemented non-pharmaceutical interventions early, particularly social
distancing through bans on public gathering and school closure, delayed peak mortality, lowered
peak mortality rates, and resulted in lower overall mortality, which was also independently
associated with duration of non-pharmaceutical interventions.280 The World Health Organization
(WHO) recommends the implementation of nonpharmaceutical interventions at the
international,281 and the national and community levels282 in the event of an influenza pandemic.
In a more routine setting, for children attending child care, an intervention consisting primarily of
hand washing for staff and attendees resulted in a significant reduction in respiratory illness in
children less than two years of age, but not older age groups.283 Welliver suggests that over the
time studies of HRSV antibody-based preventive strategies were conducted, improved education
of parents in non-pharmaceutical household infection control measures, such as hand-washing
prior to contact with an infant and isolating household contacts who have respiratory symptoms
from an infant, resulted in a reduction of hospitalisation in control groups.284

In non-pandemic or epidemic settings, social distancing or international quarantine measures
would not be implemented, but more widespread implementation of simple non-pharmaceutical
interventions, such as hand washing, and potentially the use of face masks, could reduce the communitywide burden of respiratory viral infections.

2.5.3 Options for non-influenza respiratory virus illness prevention in children

The risk of severe HRSV disease outcomes can be reduced in high-risk children through the use of HRSV-specific antibody prophylaxis. Severe HRSV outcomes were reduced in high-risk children by 62% in a US study in the early 1990s using monthly intravenous delivery of immune globulin with high-titre HRSV neutralising antibody. A subsequent study showed hospitalisation due to HRSV was reduced by 41% in children with bronchopulmonary dysplasia (BPD) or prematurity with monthly application of HRSV intravenous immune globulin. A monoclonal antibody, palivizumab, that binds to the F-protein of HRSV was developed to allow reduced administration time via the intramuscular route and to avoid the use of human blood derived products. Palivizumab reduced HRSV hospitalisation in high-risk children by 55%, with post-marketing surveillance showing it to be safe and effective. Other observational studies suggest its use has reduced hospitalisations in at-risk groups. Further refinement of the monoclonal antibody (motavizumab), to make it more potent via affinity maturation, has increased HRSV F-protein binding in vitro and this product is now undergoing clinical trials. Widespread use of immune globulin prophylaxis, other than in those children at highest risk of severe HRSV outcomes, is limited by the need for monthly intramuscular injections during HRSV season. The single feature that most limits wider antibody prophylaxis in high-risk groups is prohibitive cost: a single course over winter costs tens of thousands of dollars in Australia, and even in high-risk children, its use may not be cost-effective.

Despite decades of work on a HRSV vaccine, efforts to date have not resulted in a licensed product. Safety problems, resulting in exaggerated disease and deaths in children following administration of a formalin-inactivated vaccine in the 1960s, have impacted on the development of all HRSV vaccines, particularly other inactivated and subunit vaccines. The development of a live, attenuated vaccine has been hampered by the difficulty of balancing immunogenicity with attenuation, particularly in young infants, the target population for such a
vaccine. The early peak in serious disease requires that any vaccine against HRSV would need to be delivered to HRSV-naïve infants within the first months of life. Recent developments in reverse genetics have seen the possibility of producing live, infectious HRSV through cloned cDNA, with highly specific mutations producing a desired attenuation phenotype.\textsuperscript{292,293} Other live vaccine options include structures developed using reverse genetics with HRSV components. A chimeric construct consisting of bovine PIV3 backbone, expressing hPIV3 fusion protein, hPIV3 haemagglutinin-neuraminidase, and HRSV F-protein\textsuperscript{294} is one of the more promising live virus vaccine candidates currently undergoing clinical trial, including in young children.\textsuperscript{295,296}

Evidence-based treatment options for HRSV infection are currently limited: ribavirin continues to be a somewhat controversial treatment option for those children with severe disease.\textsuperscript{247,285-287,297} A meta-analysis of randomised, placebo-controlled trials failed to demonstrate significant benefits with its use.\textsuperscript{298} The concept of inhibiting HRSV infection by silencing gene expression using short interfering RNA (siRNA)\textsuperscript{299} has been demonstrated.\textsuperscript{300} Early clinical studies in adults show one such product to be safe and well tolerated when delivered intranasally.\textsuperscript{301}

Vaccine candidates for other respiratory viruses, developed using chimeric constructs or engineered through reverse genetics, have been developed but are yet to reach wider clinical testing.\textsuperscript{302-309}

2.5.4 Prevention using influenza vaccine in children

There is current controversy about the use of TIV for the prevention of death in older age groups,\textsuperscript{310} however, use of TIV and LAIV-T for the prevention of influenza infection in children is more soundly based in evidence. Concerns about high rates of hospitalisation in young children in the US due to influenza led to a the introduction of a childhood influenza immunisation program with the recommendation that children aged six to 23-months of age in 2004 and their close contacts receive annual influenza vaccination,\textsuperscript{311} which has gradually expanded to now cover universal immunisation for all aged six months to 18-years.\textsuperscript{312}
In this section, the evidence for benefits of influenza vaccine use in children will be reviewed: benefits will be divided into direct – that is the prevention of influenza and its complications in the children vaccinated – and indirect – non-influenza specific benefits in vaccinated children or benefits in the non-vaccinated and wider community. Safety of TIV and CAIV-T in children will not be discussed here in detail. TIVs are licensed in Australia and the US for administration to children down to six months of age, and there is some evidence to support safety and immunogenicity in even younger children. CAIV-T is licensed for use in the US in children down to two years of age. Use in younger children has been associated with an increased risk of wheezing, particularly in younger age groups, and also with an increased risk of hospitalisation during the six months after vaccination. This makes future use of LAIV-T in a younger age group unlikely.

2.5.4.1 Direct effects

The efficacy and effectiveness of influenza vaccine depends on the population being studied, the vaccine used, the match between vaccine and the circulating influenza strains, and the outcome measure being assessed. As a general rule, the vaccine has higher efficacy and effectiveness estimates when used in younger and more immunocompetent populations, when the vaccine and circulating strains are well matched, and when the outcome being assessed is more specifically caused by influenza. For example, vaccine efficacy and effectiveness should be higher against laboratory-confirmed influenza infection compared with ILI. However, having laboratory confirmation may not always be possible, and routinely collected, but less specific, outcome measures may still provide useful information about vaccine effectiveness.

Recently, there have been three systematic reviews covering influenza vaccine use in children published. The Negri and Jefferson reviews were meta-analyses and included papers that met pre-specified criteria. The Manzoli review further used metaregression techniques to accommodate the method quality of the studies included.
Despite using different methods for selecting papers (Jefferson: no language restriction, no date restriction; Negri: English only, published after 1990; Manzoli: no language or date restrictions) the results of all three reviews were favourable for use of vaccines in older age groups. The Jefferson Cochrane Review\textsuperscript{317} examined the efficacy (prevention of laboratory-confirmed influenza) and effectiveness (prevention of ILI) of influenza vaccine in children: updated figures show live attenuated vaccines had 82% efficacy and 33% effectiveness in children over two years of age; equivalent figures for TIVs were 59% and 36%, respectively.\textsuperscript{316} The review highlighted the need for improved information about the vaccine, particularly its effectiveness in younger age groups.\textsuperscript{316,317} Results from the Negri review were very similar: against culture-confirmed illness, live attenuated vaccines had 80% efficacy and TIVs 65%, with figures against serologically-confirmed illness being 54% and 63%, and against clinical illness, 34% and 33%, respectively.\textsuperscript{314} The authors also noted the scanty nature of available data for infants and young children, stating that this prevented separate assessment for these age groups.\textsuperscript{314} The Manzoli meta-analysis, using regression techniques to account for study quality, provided an efficacy against laboratory confirmed illness of 67%, acute otitis media of 51%, and clinically diagnosed illness of 36% (but potentially as high as 61% if USSR studies were excluded).\textsuperscript{315} The metaregression analysis also showed improved vaccine efficacy against laboratory-confirmed influenza with increasing age, and again the authors commented that the lack of data for children two years of age or younger prevented them from drawing firm conclusions. All reviews noted that insufficient power and data meant that conclusions could not be drawn about vaccine outcomes in this age group: this was reported, somewhat controversially,\textsuperscript{318,319} in the Jefferson reviews as the vaccine having “similar effects to placebo”.\textsuperscript{317} Despite the small numbers, in studies where infants and children less than two years of age are included or are the sole subjects, there is evidence to support influenza vaccine efficacy in this age group,\textsuperscript{320,321} particularly in epidemic years,\textsuperscript{322} even though there may be insufficient power to show a significant effect.\textsuperscript{323}

Data from a variety of interventional studies in healthy children show inactivated influenza vaccines have efficacy in significantly reducing laboratory-confirmed influenza infection;\textsuperscript{322,324,325} antigen-positive respiratory specimens;\textsuperscript{326} influenza positive serology or culture,\textsuperscript{327,328} influenza-
like illness and daycare absenteeism, acute febrile illness, and ILI and pneumonia/influenza visits to primary care. However, there have been some equivocal results from studies not sufficiently powered to demonstrate end point differences successfully, particularly in subanalyses in younger age groups. The live, intranasal vaccine has demonstrated effectiveness in reducing laboratory-confirmed influenza illness (including years where vaccine and circulating virus are not well matched) and medically attended acute respiratory illness (MAARI).

Given the high incidence in young children, there has been research interest in any impact influenza vaccine may have on acute otitis media, particularly in those attending daycare. Depending on the season and circulating strain, influenza vaccine may also have a role in reducing acute otitis media in daycare attending children. In a variety of studies, there has been a reduction in either all-cause otitis media or laboratory-confirmed influenza associated otitis media during the influenza season, particularly in children attending daycare.

In summary, the available data and meta-analyses, despite differences in tone and interpretation, show vaccine efficacy for both live attenuated vaccines and TIVs in preventing a range of clinical syndromes associated with influenza in children: culture-confirmed, laboratory-confirmed, and serologically-confirmed illness, any clinical illness, and acute otitis media. Whilst more data were available for assessment in older age groups, there was no information to suggest the vaccines were not effective, or no better than placebo, in children aged six months to two years. Getting better efficacy data to support widespread use of vaccine in this younger age group is a priority.

2.5.4.2 Indirect effects

Indirect effects of vaccinating children using influenza vaccine include non-influenza specific effects in vaccinated children, benefits from improved influenza control extending to non-vaccinated individuals, and community-wide benefits not accrued by individuals.
There are a number of preclinical and human observational studies showing that vaccinated children may be protected against not only influenza, but potentially serious bacterial infections. Influenza, or other viral infection, may be a causal precursor to invasive or severe mucosal bacterial infection. Preclinical studies show that *Streptococcus pneumoniae* is more adherent to human epithelial cells previously infected with a variety of viruses. Correlation studies show a temporal association between invasive pneumococcal disease and influenza and HRSV outbreaks and seasons. Severe pneumococcal and meningococcal disease has also been associated with outbreaks and increased influenza A seroconversion in cases compared to controls. Finally, in a double-blind, randomised placebo-controlled trial in South African children nine-valent conjugate pneumococcal vaccine prevented 31% of virus-associated pneumonias, confirming the importance of viral/bacterial interactions in respiratory tract illness.

Widespread use of influenza vaccine in children may have a role in preventing secondary bacterial illness.

The concept of herd protection extending from vaccinated children now has strong observational study support following the introduction of conjugate pneumococcal vaccine for children in the US with striking reductions in invasive disease seen in older, non-targeted age groups. There is evidence for a similar indirect effect through using influenza vaccine in children.

A recent systematic review of indirect effects in non-vaccinated individuals identified general issues around study quality but found the trend for indirect effects of vaccinating children against influenza is present. A single dose of inactivated, monovalent influenza A (H3N2) vaccine delivered to 86% of school children in Tecumseh, Michigan, significantly reduced ILI for all age groups when compared with a neighbouring community where the intervention was not available. In Australia, in 1969 an effort to immunise as many people as possible in Northern Territory remote Indigenous communities in 1969 was interrupted by the appearance of influenza A/Hong Kong: communities where no vaccination had taken place had significantly higher community disease rates, fewer disease free communities, and influenza related deaths. In Japan, from 1962 to 1994 vaccinating most school aged children resulted in
reductions in all cause mortality and deaths attributed to influenza and pneumonia, with one death averted for every 420 children vaccinated.\textsuperscript{360} Use of inactivated vaccine in daycare attending children resulted in 42% fewer febrile respiratory illnesses amongst all household contacts, compared with controlled households where children received hepatitis A vaccine.\textsuperscript{335} In school aged household contacts this figure was 80%, and greater than 70% reduction in missed school, an adult carer missing work, physician visits, and antibiotic prescriptions.\textsuperscript{335} A Russian study in which more than 50% of preschool and school aged children in treatment communities were vaccinated showed significant reductions in ILI in community-dwelling elderly compared with control communities.\textsuperscript{329} Use of an intranasal, inactivated virosomal vaccine in Milan, Italy, in children with recurrent respiratory tract illness resulted in significant reductions of a number of outcomes in household contacts compared with control household contacts: respiratory tract illness, medical visits for respiratory illness, antipyretic and antibiotic use, and missed school and work.\textsuperscript{361} For three years from 1998 in Texas, open label, community-based use of CAIV-T well-matched to circulating strains in children aged 18 months to 18 years with up to 25% coverage, resulted in significant reductions of MAARI in adults aged 35 years and older.\textsuperscript{362} In the same community, the 2003-2004 season saw a poor match between vaccine and circulating H3N2 strains: use of CAIT-V in healthy children and TIV aged five to 18 years resulted in significant reductions in MAARI in those aged five to 11 years and 35 to 44 years, compared with non-intervention communities.\textsuperscript{363} In the US, countywide vaccination of younger school going children using LAIV-T resulted in significant reductions in absenteeism in targeted age groups during influenza season compared with a control county, but also reduced absenteeism in the non-targeted high school aged group.\textsuperscript{364}

Indirect effects extending from children to older age groups are of more than academic interest. The recent controversy surrounding influenza vaccine in the elderly suggests that previous observational studies supporting prevention of hospitalisation and deaths may have been subject to previously unrecognised bias, meaning that use of TIV in older people may have little to no effect on serious morbidity and mortality in this high-risk age group.\textsuperscript{310,365-367} Modelling studies show one way to reduce hospitalisation and deaths in the elderly may be through the use of
vaccine in children. Weycker and colleagues work suggests vaccination of 20% of US children aged six months to 18 years would reduce influenza cases in all age groups by 46%, and improving coverage to 80% would see that figure climb to 91%. Of particular note is the effect in the elderly: even a modest increase in childhood coverage from 5% to 20% could reduce hospitalisation and deaths in those aged 65 years and older by 42%, with 18,200 admissions and 14,600 deaths averted. Further modelling efforts suggest that vaccinating just 20% of school aged children would be more effective in reducing overall mortality in those 65 years of age and older, than vaccinating 90% of this same older age group. Whilst waiting for vaccines with improved immunogenicity in older adults and, hopefully, an enhanced direct protective effect, current efforts would be better directed to maximising any indirect protection through improved coverage using existing vaccines in children.

Finally, vaccinating children may have community-wide benefits not accrued by individuals. Developing and implementing a universal influenza vaccination program for children can be seen as an important part of public health capacity building. Skills used in delivering a community or school based childhood program would have application in influenza pandemic preparation, preparing for potential bioterrorism related incidents, and for the control of unrelated epidemic emerging epidemic diseases.

2.5.4.3 Potential benefits of intranasal live vaccine over injected inactivated vaccine

An intranasal vaccine has clear logistic benefits over injected vaccine, and there is evidence that the live mucosally-delivered vaccine has improved efficacy compared with inactivated vaccines, and also provides heterotypic protection against drift variants.

The implementation of a universal childhood influenza vaccination program delivered primarily through general practice in Australia may not be feasible or desirable. Given current pressures on general practice in Australia it is unlikely high coverage rates could be achieved through this option alone: delivery through alternate mechanisms will be needed. Intranasal vaccine delivered
in the school setting could be an important complementary administration path to improve childhood coverage at a reasonable delivery cost.\textsuperscript{373,374} Other non-traditional delivery mechanisms are currently being used in large parts of the US: appropriately trained healthcare workers in pharmacies and supermarkets are administering adult vaccinations.\textsuperscript{273,375,376} Compliance with the initial two dose TIV recommendation in the US varies by season and age group: second dose delivery in two to eight year olds, who have received a first dose, occurs in less than one quarter.\textsuperscript{377} Pre-season delivery to children of the previous season’s vaccine is one possible means of alleviating the pressure to achieve coverage in autumn and winter.\textsuperscript{378} In Australia, using non-traditional sites of delivery and intranasal vaccine for childhood programs may be better options to deliver the most current vaccines.

CAIV-T provides protection in children against drifted influenza strains. In the second year of the pivotal efficacy study by Belshe and colleagues,\textsuperscript{336} despite the dominant circulating strain (influenza A/Sydney) not being well matched to vaccine strains, CAIV-T was 86\% effective in preventing laboratory-confirmed disease by the drifted strain.\textsuperscript{337,340} Efficacy was also seen against a drift variant circulating in Texas during the 2003/2004 season.\textsuperscript{379} The basis for improved efficacy in children is the development of mucosal immunity and production of heterotypic, cross-protective antibodies,\textsuperscript{380} but this effect may not be seen in adults.\textsuperscript{381,382}

There have been a number of studies where TIV and LAIV-T have been compared in head-to-head randomised, double-blind studies. Belshe and colleagues showed that in children six to 59 months of age, the live vaccine had an efficacy of 54.9\% for preventing culture confirmed influenza when compared with TIV as the baseline intervention: this improved efficacy was present for virus well matched to vaccine strains, but also drifted variants.\textsuperscript{265} A similar, improved efficacy of 53\% for two doses of CAIV-T over two doses of TIV was seen in children aged six to 71 months.\textsuperscript{383} With a single dose of either vaccine in children six to 17 years of age with a diagnosis of asthma, CAIV-T had a superior relative efficacy for preventing culture confirmed influenza of 35\% over TIV.\textsuperscript{384} In a systematic review for the prevention of influenza in healthy children, CAIV-T had 82\% efficacy against laboratory-confirmed influenza and 33\% against ILI compared with no
treatment or placebo; with equivalent figures for TIV being 59% and 36%, respectively.316 Where indirect effects have been compared, CAIV-T provides better protection in non-targeted age groups than TIV.363 Despite higher vaccine costs, CAIV-T was more cost-effective than TIV due to improved relative efficacy in disease prevention.266

CAIV-T has clear logistic benefits over TIV, and this along with improved heterotypic and mucosal immunity resulting in enhanced relative efficacy leading to improved cost-effectiveness makes it a logical choice for use in delivering a universal childhood immunisation recommendation.

2.6 Respiratory virus surveillance: an Australian context

Having identified potential issues for implementation of a universal influenza vaccination program for any age group in childhood, it is worthwhile considering what data are needed to support this, or any other respiratory virus intervention, in Australia.

There is a paucity of reliable population-based data regarding incidence or costs of respiratory virus infections in Australian children. The Laboratory Virology and Serology Reporting Scheme (LabVISE), commenced in 1977, collates information on a range of viruses that cause infection,385,386 but interpretation is difficult for a number of reasons. There is a lack of age-specific and population or submitted specimen denominator data, and sources of potential bias include changing trends in diagnostic practices and the use of referral or public health laboratories to source data. Such a system is also slow to provide data about newly identified and emerging viruses. The National Influenza Surveillance Scheme summarises data from a number of sources, and covers virus epidemiology, morbidity and mortality, and virology.387 Whilst of some value for local seasonal epidemic detection, response, and temporal comparison, the individual state-based systems that provide these data are fragmented, use different case definitions for ILI, and have varying presence and quality of laboratory support.388 Laboratory-confirmed influenza became notifiable at a national level for the first time in January 2001,389 but similar to other surveillance systems it is likely the data under-represent true disease incidence and are subject to
secular and regional variations in disease identification and diagnostic testing. National influenza notification, hospitalisation, and mortality data are also reported retrospectively in the biennial vaccine preventable diseases and coverage report. Other than these existing surveillance structures, which overwhelming focus on counting influenza cases, information about all respiratory viruses is supplemented by specific research projects. Integrated data about epidemiology and burden of disease, of the sort required to make the case for preventative interventions, are limited.

2.7 Laboratory testing and specimen collection for respiratory viruses

Individual viruses have distinct temporal, epidemiologic, and syndromic patterns that may assist clinical diagnosis without laboratory testing. Despite this, clinical identification of virus-specific syndromes is necessarily associated with false negatives and false positives. All respiratory viruses can cause the broad spectrum of respiratory syndromes in children, and by corollary, any ARI, from mild upper respiratory tract illness through to fatal lower respiratory tract disease, can be caused by any virus, or virus combination. Even in studies reporting complex modelling, the predictive values for syndromic identification of specific viruses are inadequate for their routine use. This feature of respiratory tract illness is highlighted by concerns of potential bias when interpreting research based on discharge or administrative coding: particularly in children, such methods are unable to adequately differentiate between influenza and illnesses caused by HRSV and other viruses. Whilst common things occur commonly, specificity of a viral diagnosis can only be assured through laboratory confirmation of virus presence.

The advent of nucleic acid amplification primarily through PCR has manifestly altered the detection of viruses and other fastidious organisms. Compared with cell culture and antigen detection techniques, PCR is a more sensitive technique. Improvements in PCR methods have included reverse transcription, allowing for the detection of RNA, and development of the real-time platforms, even further enhancing sensitivity and specificity compared with conventional
assays. The development of commercial or in-house multiplex techniques has allowed the simultaneous detection of a number of viruses.

Despite the enhanced sensitivity offered by molecular testing, there remains a substantial diagnostic gap: a proportion of specimens remain pathogen negative, even after exhaustive testing. This size of the diagnostic gap varies depending on the nature and handling of the specimens being tested, the age group of the patients, time from illness onset to specimen collection, the range of pathogens being tested, and the detection method employed. Although the gap is commonly between 20 to 30% of specimens negative for any pathogen, it can be higher than 50%. Since commencement of these projects, a number of viral discoveries have eaten into this virus-negative diagnostic gap: HMPV, hCoV-NL63, hCoV-HKU1, hBoV, hPyV-KI, and hPyV-WU, although a causal association with illness for some of these viruses has not been established.

A number of studies have suggested that use of nasal swabs for the collection of respiratory virus specimens may have suboptimal sensitivity, compared to more invasive collection methods like nasopharyngeal aspirates. Swabs are generally inferior for most viruses but this problem appears most acute for the detection of the major viral respiratory pathogen of early childhood, HRSV. Nasal swab collection is preferred by parents and is less painful for children, but when used in combination with non-amplification detection methods, such as immunofluorescence or culture for the detection of HRSV, up to one-third of cases are missed. It has been suggested for larger epidemiologic studies, the benefits of reduced costs and the ability to collect from a population-based sample might outweigh lower sensitivity. The combination of a less invasive specimen collection method with no loss of sensitivity would clearly be more acceptable.

2.8 Interpreting previous respiratory virus research

Interpretation and external validity of research findings depends on the environment studies are performed in and the methods used. Secular changes since the conduct of large, community-
based studies on respiratory viral infections may pose limitations on applying those data to modern communities. These changes include the methods for identifying respiratory viruses and the nature of family life.

The absolute and relative contribution individual viruses make to ARI burden depends on the nature of the study from which the values are reported. Factors which play a role in the proportion of specimens or subjects positive for a particular virus include: where the study was conducted; the year and season of study conduct; the age of the study participants and whether or not they had predisposing factors for a serious outcome with viral respiratory infection; whether only moderate to severe disease is considered, such as those illnesses prompting hospitalisation, or whether the study includes outpatients, general practice patients, or community-managed illness; whether all available specimens were tested or whether testing was limited to those specimens negative by previous testing for other respiratory pathogens; the nature and handling of the specimen collected; and the nature of the laboratory test used. Even when studies use modern platforms for virus identification, such as PCR, sensitivity cannot be assured, particularly for previously poorly characterised viruses. For example, primer sets used in early studies of HMPV may have missed a significant proportion of serotype B infections,\textsuperscript{408} thereby underestimating HMPV’s overall contribution to respiratory illness.

Previous respiratory virus research has involved healthcare worker specimen collection. This occurred either with routine diagnostic specimen collection in a hospital or clinic setting or at study specific visits that either required subjects to present to a study clinic or be available for a home visit. Such methods were used in a number of pivotal studies conducted in the second half of last century. Most of this research has taken place in the US: examples include Tecumseh, Michigan;\textsuperscript{4,358} Houston, Texas;\textsuperscript{2,47,50} Chapel Hill, North Carolina;\textsuperscript{69} Tucson, Arizona;\textsuperscript{397} and Seattle, Washington State.\textsuperscript{3,6,409,410} These and similar studies provide our current understanding of respiratory virus epidemiology in the community, particularly household transmission of viruses. The continued use of household transmission parameters for influenza\textsuperscript{411} from such studies in current modelling to contain an influenza pandemic\textsuperscript{412} demonstrates the durability of the
findings, but also the lack of any subsequent similar research using more sensitive molecular methods. Complexity and expense have shifted the practice of studying respiratory viruses from prospective, longitudinal research to cross-sectional studies using administrative data rather than information collected directly from subjects.\(^{5,413}\) This can be seen in recent observational studies examining the impact of respiratory pathogens which have focussed on hospitalisation episodes for clinical syndromes, rather than a specific laboratory diagnosed illness, during the winter respiratory illness season.\(^{39,40}\)

Employing study staff to conduct home visits is one of the major expenses in conducting a prospective, longitudinal study. Alternative options, such as non-healthcare worker collection of specimens, were described in the methods of the Seattle Virus Watch study, but were not part of any other community-based research project. In that study, when a nurse was unavailable for a home visit during the day, the mother or another trained household member would collect the specimen.\(^6\) In the papers reporting results of this study there were no data on the number of specimens collected by non-study staff or comparing the proportion of specimens positive by study staff or household member collection. Streptococcal research provides the only published comparisons available: these studies were typically a direct comparison of two throat swab results collected in the same child, one by a healthcare worker and the other by a parent. In each of these settings, including mailed-back specimens, the sensitivity for bacterial detection by parent collection overall was the same or very similar to healthcare worker collection.\(^{414-417}\)

Laboratory techniques used to identify respiratory viruses are not the only secular changes that have occurred since these earlier pivotal studies: the nature of family life has also undergone dramatic change. Driven by increasing adult workforce participation, the proportion of Australian children under 12 years of age using formal and/or informal child care has increased in the last two decades, from 38% in 1984 to 48% in 2005; with the increase most marked in children aged less than two years.\(^{418,419}\) Acute respiratory infections are common in children who attend child care, particularly those less than two years of age.\(^{283}\) Therefore, increased child care use may have led to previously undocumented increases in individual and household incidence of acute
respiratory infections. Data from the United States show a more than doubling of the rate of hospitalisations for bronchiolitis in infants less than 12 months of age between 1980 and 1996, and the authors of this paper suggest changes in child care patterns may be a contributing factor. The increased number of families with both parents in the paid workforce is also likely to increase the costs of viral respiratory tract infections to the household and community, with leave time required to care for a sick child. Published Australian data are limited: a New South Wales study reported an increase in age-specific rates for admissions due to acute bronchiolitis between 1990 and 1995.71

2.9 Conclusions

Respiratory viral infections in children and the capacity for children to act as reservoirs of infection for all other age groups are underappreciated, with the large proportion of community-managed infections uncounted and unrecognised. Better data about these infections are required to drive interest in large scale, population-based interventions to reduce their impact. Australian surveillance mechanisms for respiratory viruses are fragmented and incomplete. They largely focus on influenza in the older age groups targeted for publicly funded vaccination: this is to the exclusion other respiratory viruses and childhood disease. Substantial gaps exist in our knowledge of the epidemiology and burden of childhood respiratory viral infections in Australian children, making any assessment of impact, based on available data, difficult and likely to be conservative. Surveillance data can contribute to our understanding, but findings from targeted and specific research will be required.

There is strong evidence of direct and indirect effects from influenza vaccine use in children, and that childhood programs can be either cost saving or, at least, cost effective. With this option for influenza prevention in children available now and future options for control of influenza and other viruses in clinical trials, data necessary to support large scale prevention programs in Australian children should be collected without delay.
Secular changes may have altered the epidemiology of respiratory viruses and the sensitivity of their laboratory detection since the large, community-based studies conducted mostly in the US in the second half of last century. Firstly, these studies were conducted using viral culture: whilst highly specific, culture lacks the sensitivity of now available molecular amplification diagnostic techniques. Incidence and transmission rates in these studies are likely to be underestimated. Currently available multiplex PCR provides increased sensitivity for multiple pathogens in a single test. Furthermore, due to changes in the nature of employment, increasing proportions of children are exposed to child care and are started at an earlier age. From many studies, childcare is an independent risk factor for the acquisition of respiratory viral infections and early exposure to child care may be one causal reason for lengthening of the annual HRSV epidemic and doubling of HRSV-related hospitalisations. These factors combined may mean the findings from previously performed studies, conducted using less sensitive diagnostics in households where preschool-aged children were less likely to be attending childcare, are no longer relevant or age group specific.

Three pieces of information are required in assessing whether to recommend or implement a publicly-funded vaccination program, or any intervention, against respiratory viruses: epidemiology of the targeted illness, the efficacy of the intervention, and the cost-effectiveness of the intervention. At present there is a lack of Australian data to meet the requirements of this triad. Improved and integrated epidemiology and cost data for respiratory viral infections in children are required to guide the local decision making process and improve awareness of the current uncontrolled nature of endemic and epidemic disease caused by these agents. In following Chapters, results from two cohort studies, a pilot study and a larger subsequent study, designed to provide such data, are reported.
Chapter 3

A PILOT STUDY: EPIDEMIOLOGY AND COST OF ACUTE RESPIRATORY ILLNESS IN CHILDREN

3.1 Objectives

The work presented in this Chapter was undertaken to describe the epidemiology of winter respiratory tract illness in Melbourne children and to collect comprehensive resource use associated with these illnesses. An attempt was made to capture the burden information associated with these illnesses in a detailed and comprehensive fashion. This study was done, in part, as preparatory work for the planned larger and longer cohort study. We wanted to obtain initial epidemiology and burden estimates of acute respiratory illness in community-dwelling children. This process involved trialling two diary cards: one for the collection of daily symptom information and the other for resource use during illness. We used the resource data to identify the key cost drivers of these illnesses, with the aim of simplifying the data collection process for the main study, the Respiratory Virus Study (Chapter 4).

3.2 Introduction

In 1998 Belshe and colleagues published data for a cold-adapted, influenza vaccine-trivalent (CAIV-T) which showed the vaccine was well-tolerated and had an efficacy of 93% (95% CI 88 to 96%) for the prevention of culture-confirmed influenza.\textsuperscript{336} In this pilot study, we used the same definitions and classification of illness as the Belshe study to allow application of efficacy estimates for the prevention of not only laboratory-confirmed influenza infection (up to 95%) in influenza-like illnesses (ILIs) identified using this method, but also any febrile ILI (21%, 95% CI 11 to 30%) and ILI with febrile otitis media (30%, 95% CI 18 to 45%).\textsuperscript{336}
3.3 Methods

A prospective cohort study of healthy children in metropolitan Melbourne, Victoria, was conducted between 01 July and 01 December 2001. The Royal Children’s Hospital Ethics in Human Research Committee approved the study and written informed consent was obtained from parents or guardians prior to study procedures being conducted.

Children were eligible to participate if they were generally healthy and between 12 and 71 months of age at the time of enrolment. Children between 12 and 23 months of age were recruited, largely via maternal and child health nurses (MCHNs) and immunisation providers in 23 local council areas across the greater Melbourne area. Families with older children who had previously participated in a (non-respiratory pathogen) vaccine study conducted by our group were invited to participate, and flyers and posters were distributed through child care centres in greater Melbourne. More than one child per family could be enrolled. Children at increased risk of respiratory infection or increased risk of severe disease following infection, such as those with chronic pulmonary or cardiovascular disorders, immune system disorders, or other chronic illnesses, were excluded. Similarly, children with asthma were not eligible for enrolment.

All study visits were conducted in the home of participating families. This included a pre-study visit where a research assistant explained the study to one or more parent or guardian went through the plain language statement and all study documents in detail. The family was left with these materials for a few days to consider and discuss, after which they were recontacted to see if they had made a decision about participating. If they did agree to participate, a mutually convenient time was arranged for the home enrolment visit.

At the enrolment visit, demographic information on the child and the household was collected. This included gross household income which was collected in four brackets: bracket 1, ≤ $21,000; bracket 2, $21,101 to $33,000; bracket 3, $33,001 to $56,000; and bracket 4, > $56,000. These
income brackets were chosen to match the household income category structure used by the Australian Bureau of Statistics.422

Parents/guardians completed a tick-box symptom diary card for each day the child was on the study. This diary card required either marking the “no symptoms” box, or marking those symptoms that were present on that day. Each symptom diary card collected information for one week. Regular telephone contact, every two to three weeks, from a research assistant during the influenza season assisted parents/guardians to identify illnesses and complete documentation. Symptoms were taken as documented by parents on the diary card. It was beyond the scope of this study to validate the data recorded by parents in the daily diary or the burden diary, either through health-care provider or other source.

An acute respiratory illness (ARI) was defined according to the criteria used by Belshe et al for an ILI in the pivotal vaccine efficacy study conducted in the United States during 1996 and 1997.336 This definition was selected to allow for comparison with the Belshe paper and because it should be sensitive for even minor illnesses. This would mean a broad range of ARIs from mild to severe would result in the case definition being met. All information about symptoms was from parental report; no symptom or illness was validated by study staff with medical practitioners or through a home visit. An illness episode was based on symptoms in two categories: category A and category B (Table 3.1).
Chapter 3: A pilot study: epidemiology and cost of acute respiratory illness in children

Table 3.1  Defining symptoms of an acute respiratory illness

<table>
<thead>
<tr>
<th>Category A symptoms</th>
<th>Category B symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (either identified without measurement or a measured temperature of 37.6°C or higher by axillary thermometer)</td>
<td>Runny nose/nasal congestion</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Sore throat</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Cough</td>
</tr>
<tr>
<td>Pulmonary congestion (moist cough)</td>
<td>Muscle aches</td>
</tr>
<tr>
<td>Pneumonia (diagnosed by a health-care provider)</td>
<td>Chills</td>
</tr>
<tr>
<td>Ear infection (suspected by parent/guardian or diagnosed by health-care provider)</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
</tr>
<tr>
<td></td>
<td>Decreased activity (lethargy/weakness)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
</tr>
</tbody>
</table>

Identified ARIs were then classified as follows:

a)  ARI: at least one category A symptom OR at least two category B symptoms;

b)  Febrile ARI: ARI with a parental report of fever (with or without a recorded temperature) during the episode;

c)  ARI with otitis media: ARI with parental suspicion of, or parental report of health-care provider diagnosed, otitis media during the episode; and

d)  Febrile ARI with otitis media: ARI with a parental report of both fever (with or without a recorded temperature) and parental suspicion of, or parental report of health-care provider diagnosed, otitis media during the episode.

The number and duration of ARI episodes were ascertained. To calculate duration of illness, individual episodes commenced on the first date of any symptoms in the illness period (D1) and
concluded on the last date of any symptoms associated with the illness (D4). The duration included both of these days. A new episode was deemed to have commenced if there were three or more consecutive symptom-free days since the last day with symptoms of the previous episode. Hence, there could not be more than two consecutive symptom-free days between the first day of an ARI and the first day on which there were sufficient symptoms for the illness to meet the ARI definition. As defined, an ARI can have duration of one day only, for example if a child had adequate symptoms to meet the definition of an ARI, for example a parent-reported fever, that occurred on one day only.

Four dates were defined in the course of an ARI:

Date 1 (D1): The first date on which the study child had any symptoms in an illness that went on to meet the definition of an ARI.

Date 2 (D2): The first date on which the illness met the definition of an ARI.

Date 3 (D3): The last date on which the illness met the definition of an ARI.

Date 4 (D4): The final date on which the study child had any symptoms. This date must be followed by at least three symptom free days for the ARI to be concluded on this date.

A schema of how these dates relate to ARI days and the duration of illness is provided (Figure 3.1). The mean, median, and range for the differences between date 1 and date 2, date 2 and date 3, and date 3 and date 4 are reported. If symptoms of an ARI were recorded on the last day of data collection, 01 December 2001, this was deemed to be the final date of the illness.

Incident rates, using child-months (person-time) as the denominator, and 95% confidence intervals (95% CIs) were calculated. Child-months person time was calculated by dividing the
available child-days by 30.4375, and this figure is the average number of days per year (365.25) divided by the 12 months of the year. Crude (unadjusted) incidence rate ratios were calculated for specific exposures and the corresponding 95% CIs were produced.

Figure 3.1  Schema with examples demonstrating day assignment (D1, D2, D3, D4) and duration of an ARI in relation to days with category A or category B symptoms

Legend
- Day with no symptoms (neither category A nor category B symptoms)
- Day with symptoms, but insufficient to meet the definition of an ARI in own right (a day with only one category B symptom)
- Day with sufficient symptoms to meet the definition of an ARI (a day with at least one category A symptom or at least two category B symptoms)
- Days included in the ARI, length depicts duration
Of particular interest were the ARI episodes occurring within the local influenza season, as these were more likely to represent currently preventable illnesses using available efficacy estimates for laboratory-confirmed influenza infection, febrile illness, and febrile otitis media. Incidence rates during the influenza season and the non-influenza season were compared. The timing of the local influenza season was identified using the Victorian influenza surveillance system, managed by the Victorian Infectious Diseases Reference Laboratory and the Department of Human Services. The local influenza season was defined prior to study commencement, based on figures from previous years, with the start being the beginning of the first fortnight in which there were five or more laboratory identifications of influenza viruses (type A or B), in the presence of an increasing number of ARIs being notified by the Victorian general practice surveillance scheme. The end of the local influenza season was defined as the end of the fortnight preceding the first fortnight in which there were less than 15 laboratory identifications of influenza viruses (type A or B), in the presence of a declining number of ARIs being notified by the Victorian general practice surveillance scheme.

Once a child developed an ARI an extra diary (burden diary) collected information on health-care use, medication usage, investigations performed, and time spent on health-care visits for the episode. For this diary, parents also estimated any excess time spent caring for a sick child — time over and above that normally required for the care of the child when well. Parents were not given instructions about when or how frequently they should capture time data during an ARI. Completed daily symptom diary cards and burden diaries were mailed back to the study team by the participating family on a monthly basis.

Incident-based costing was used to calculate an average cost of community-managed ARI episodes. Summary figures including episodes where a child was hospitalised are provided, but as the focus of this study was community-managed ARIs, detailed costing figures are provided with information from hospitalised cases removed.
Cost data were calculated from a societal perspective using 2001-2002 financial year Australian dollar values (Table 3.5). Discounting was not performed as costs were collected within a single year. Direct and indirect costs were included, and costs were allocated as being borne either by the patient and family, the health-care sector, or by another sector. Details of sources and values for all applied costs are provided (Table 3.5, Table 3.6). An average cost per episode was calculated using the total number of illnesses, not just those where burden information was available, as the denominator, more likely making estimates conservative if at all biased.

As well as an average cost of illness for all illnesses, calculations were performed to produce an average cost of illness by stratum level for a number of variables. Cost figures were calculated by month, whether or not they occurred in the influenza season, ARI type, febrile and afebrile ARIs, and by household income bracket.

Carer time spent seeking health-care and excess time spent caring for an ill child were collected in three categories: time away from work with pay lost; time away from work with no pay lost; and time away from usual activities. A sex-weighted hourly rate derived from the Australian Bureau of Statistics (ABS) average weekly earnings in 2001 (females: $19.69 per hour; males: $22.44 per hour) was applied to reported times. Time away from work with pay lost and time away from usual activities was allocated as a cost to the patient and family sector; and time away from work with no pay lost was allocated to the employer (other sector), who was paying for working hours not performed.

Key cost drivers for illness were identified and an average resource unit used per episode and 95% CIs were calculated. Where information was not available for an illness, a zero value for missing data was applied when calculating means and CIs. One-way sensitivity analyses were undertaken by using the 95% confidence limits for the key cost drivers, and an average cost for all episodes was calculated by including those illnesses identified, not just community-managed illness, where there was a hospitalisation. Confidence limits of the key cost drivers were also
used to perform multi-way sensitivity analyses, with a least expensive and most expensive scenario for community-managed episodes.

For time seeking health-care for an ill child and excess time caring for an ill child, the proportion of the time away from work (and therefore costs) classified as time with lost pay and time with no pay lost in this study were identified. The division of carer time away from work as either being with pay intact or pay lost for both time seeking health-care and excess time spent caring for the ill child were documented. Some burden data collected in this pilot study and not collected in the Respiratory Virus Study were:

- The use of prescription medication (other than antibiotics, with the number of courses of antibiotics per illness collected in ReVS);

- Use of over-the-counter and other medications (including natural or herbal remedies);

- Travel costs seeking health-care; and

- Child care arrangements for other children whilst the study child was ill.

In order to calculate an average cost for illnesses in the Respiratory Virus Study incorporating a value for the costs of these items, an average cost per illness incorporating only the costs of these non-included items, was calculated for all community-managed illnesses where any costs were recorded. The average cost for these items are labelled supplementary costs, and the proportion each of the cost elements contributed to the total is also provided. All of the components of the supplementary cost were borne by the patient and family sector.

As this was a pilot study undertaken to examine the feasibility and practicality of instituting the Respiratory Virus Study (ReVS) a sample size calculation was not performed. Collected data were initially stored on a Microsoft Excel spreadsheet and subsequently analysed using Microsoft Excel
(Microsoft, Redmond, Washington, USA) and Intercooled Stata 8.2 for Windows (StataCorp, Houston, Texas, USA).

3.4 Results

One hundred and twenty one children from 80 households in 23 local council areas in greater Melbourne were enrolled; complete data about 118 children (98%) from 78 households (97.5%) were available and these are included in this analysis. The locations of participating households were spread over the greater Melbourne region (Figure 3.2).

![Map of greater Melbourne area with markers identifying the location of the 78 households which participated and submitted data for the pilot study, 2001]

The first date any subject provided data was Sunday 01 July 2001 and the final date of data submission was Saturday 01 December 2001. Participants were recruited gradually with the last study subject recruited on and providing data from 09 September 2001. If all study participants had provided daily information from their first date of data contribution through to 01 December
2001, there was a maximum possible person-time for analysis of 15,260 child-days. Daily symptom diary cards were received from the 118 study subjects for 14,161 child-days — 93% of maximum possible days for analysis.

Of the 118 children, 52 (44.1%) were female and 66 were male. On enrolment eight (6.8%) children were one year of age, 62 (52.5%) were two years old, 19 (16.1%) were three years old, 18 (15.3%) were four years old, and 11 (9.3%) were five years old. Sixty-seven children (56.8%) attended child care, 23 (19.5%) preschool, and 5 (4.2%) school, leaving 22 (18.6%) children with no structured exposure of this type to other children outside the home. No child had previously received an influenza vaccine.

A majority of households had four people living in them: 14 households (18%) with three people, 44 households (56%) with four people, 17 households (22%) with five people, two households (3%) with six people, and one household (1%) with seven people. Almost three-quarters of study households were in the highest total household annual income band: >$56,000 band, 57 households (73%); $33,001 to $56,000 band, 12 households (15%); $21,001 to $33,000 band, five households (6%); and ≤$21,000 band, four households (5%). Over three-quarters of study households had private health insurance, with 36 households (46%) having hospital and ancillary cover, 24 households (31%) having hospital only cover, and 18 households (23%) reporting no private health insurance.

There were 205 ARI episodes (including three episodes with a hospitalisation) identified in 465.2 child-months (14,161 child-days) between 01 July and 01 December 2001, giving an incidence rate of 0.44 ARI episodes per child-month (95% CI 0.38 to 0.51). The incidence rate of ARI episodes varied by month, with the rate highest in July and gradually declining after this (Figure 3.3, Table 3.4).
The local influenza season commenced on 15 July and ended on 06 October 2001. The season encompassed 258.4 child-months (7,865 child-days) of observation, with 137 ARI episodes documented (Figure 3.4), giving an incidence rate of 0.53 ARI episodes per child-month (95% CI 0.45 to 0.63). The non-influenza season encompassed 206.9 child-months (6,296 child-days) with 68 observations, for an incidence rate of 0.33 ARI episodes per child-month (95% CI 0.26 to 0.42). The incidence rate ratio for ARI episodes in the influenza season versus the non-influenza season was 1.61 (95% CI 1.20 to 2.19).
The 137 episodes occurred in 89 (75.4%) children from 65 (83.3%) households. For all 118 children, this equates to a mean of 1.16 ARI events per child during the season (median: 1 event, range 0 to 4). Of the 137 events, 69 (50.4%) were ARI only, 54 (39.4%) were ARI with fever, 7 (5.1%) were ARI with otitis media, and 7 (5.1%) were ARI with febrile otitis media. These events resulted in a total of 1,592 illness days (20% of observed days) with an average duration of 10.4 days per episode (median: 8 days, range 1 to 95). Thirty-nine ARIs (28.5%) continued for more than two weeks. There were 160 (10.1%) illness days on which a fever was reported, and 270 (17.0%) illness days with decreased activity (mean: 1.97 days of decreased activity per episode).

Risk factors for ARI episodes during the influenza season were explored by calculating incident rate ratios for a number of exposures (Table 3.2). Point estimates for the rates of ARI fell with increasing age and increasing number of children per household. Rate ratios were also higher for
Chapter 3: A pilot study: epidemiology and cost of acute respiratory illness in children

children who had structured exposure to other children outside the home (child care, preschool, or school) or came from a household with a higher annual income level.

Burden diary cards were available for 122 (89.1%) of the 137 ARIs that occurred during the influenza season. These 122 episodes resulted in 77 visits to a health-care provider: 64 general practitioner (GP) visits, five hospital visits, and eight visits to other providers (chiropractors, naturopaths). Twenty-seven courses of an antibiotic were prescribed in 24 (17.5%) ARI episodes: 22 events with a single course, one event with two courses, and one event with three courses. There were 20 prescriptions for other medications in 13 episodes (9.4%). Over-the-counter medicines were used 182 times in 119 episodes. Four episodes resulted in diagnostic tests being performed: two chest radiographs, two haematological and biochemical blood examinations, and two urine microscopy, culture, and sensitivity.

Of the five hospital visits, two were managed as emergency department outpatients and three resulted in overnight admissions: a four-year-old male admitted for rehydration following an ARI with cough and vomiting; a five-year-old female with a history of febrile seizures who was taken to hospital by ambulance following a prolonged febrile seizure at home during an ARI; and a two-year-old male admitted for intravenous antibiotics to treat pneumonia.

The resources used for all illnesses, not just those in the influenza season, were examined. In order to focus on community-managed illness and provide cost estimates for these illnesses alone, we excluded the three episodes that resulted in hospitalisation of the study child from general calculations (all occurred in the influenza season).
Table 3.2  Univariate incidence rate ratios during the influenza season

<table>
<thead>
<tr>
<th>Exposure and value</th>
<th>Incidence rate (ARI episodes per child month)</th>
<th>Incidence rate ratio (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.71</td>
<td>1.98 (0.76 to 5.20)</td>
</tr>
<tr>
<td>2</td>
<td>0.56</td>
<td>1.56 (0.80 to 3.40)</td>
</tr>
<tr>
<td>3</td>
<td>0.48</td>
<td>1.32 (0.60 to 3.13)</td>
</tr>
<tr>
<td>4</td>
<td>0.54</td>
<td>1.51 (0.69 to 3.56)</td>
</tr>
<tr>
<td>5</td>
<td>0.36</td>
<td>referent rate</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.49</td>
<td>1.12 (0.79 to 1.57)</td>
</tr>
<tr>
<td>Male</td>
<td>0.56</td>
<td>referent rate</td>
</tr>
<tr>
<td><strong>Number of children in the household</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.62</td>
<td>1.91 (0.56 to 6.45)</td>
</tr>
<tr>
<td>2</td>
<td>0.53</td>
<td>1.62 (0.51 to 5.15)</td>
</tr>
<tr>
<td>3</td>
<td>0.50</td>
<td>1.54 (0.48 to 4.96)</td>
</tr>
<tr>
<td>4</td>
<td>0.33</td>
<td>referent rate</td>
</tr>
<tr>
<td><strong>Structured exposure to other children outside the home</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.43</td>
<td>referent rate</td>
</tr>
<tr>
<td>Child care</td>
<td>0.58</td>
<td>1.35 (0.82 to 2.21)</td>
</tr>
<tr>
<td>Preschool</td>
<td>0.47</td>
<td>1.09 (0.60 to 1.97)</td>
</tr>
<tr>
<td>School</td>
<td>0.48</td>
<td>1.12 (0.45 to 2.81)</td>
</tr>
<tr>
<td>Any</td>
<td>0.55</td>
<td>1.27 (0.78 to 2.06)</td>
</tr>
<tr>
<td><strong>Family private health insurance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.56</td>
<td>1.42 (0.91 to 2.20)</td>
</tr>
<tr>
<td>No</td>
<td>0.40</td>
<td>referent rate</td>
</tr>
<tr>
<td><strong>Household income per annum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ $56,000</td>
<td>0.36</td>
<td>referent rate</td>
</tr>
<tr>
<td>&gt; $56,000</td>
<td>0.57</td>
<td>1.57 (0.98 to 2.53)</td>
</tr>
</tbody>
</table>
Burden information was available for 180 (89%) of these illnesses. The illnesses where burden data were not available were shorter (median duration: 6.5 days versus 8 days) and less likely to have parent-reported fever or ear infection (proportion with uncomplicated illness: 77% versus 48%), compared to those illnesses where burden data were available.

Table 3.3  
Mean resource use for key items in ARIs identified in the pilot study, 2001, for illnesses where a burden diary was returned (n=180) and all illnesses (n=202)

<table>
<thead>
<tr>
<th>Resource item</th>
<th>Mean use in illness with diary returned</th>
<th>Mean use in all illnesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practice visits</td>
<td>36 visits per 100 ARIs</td>
<td>32 visits per 100 ARIs</td>
</tr>
<tr>
<td>Emergency department presentations</td>
<td>2.2 per 100 ARIs</td>
<td>2.0 per 100 ARIs</td>
</tr>
<tr>
<td>Courses of antibiotics</td>
<td>23 courses per 100 ARIs</td>
<td>21 courses per 100 ARIs</td>
</tr>
<tr>
<td>Time seeking health care</td>
<td>69 hours per 100 ARIs</td>
<td>61 hours per 100 ARIs</td>
</tr>
<tr>
<td>Excess time caring for ill child</td>
<td>1079 hours per 100 ARIs</td>
<td>962 hours per 100 ARIs</td>
</tr>
</tbody>
</table>

Using the total costs from these 180 ARIs gave an average cost for the 202 illnesses of $241 per ARI (95% CI $191 to $291). The average cost using only those illnesses we had information on was $270.

Along with the incidence rate of illness, the average cost per episode varied by influenza season and month during the study. The mean cost of an ARI was higher in the influenza season at $264 (95% CI $194 to $334) compared with a mean cost in the non-influenza season of $198 (95% CI $137 to $259). Whilst the rate of ARIs peaked in July, the mean cost per episode was highest in August at $303, falling progressively in September, October, and November (Table 3.4).
Table 3.4  ARIs, ARI incidence rate per child-month, and average cost per episode by month 2001

<table>
<thead>
<tr>
<th>Month</th>
<th>ARI events</th>
<th>ARI incidence rate (95% CI)</th>
<th>Average cost per episode (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>July</td>
<td>39</td>
<td>0.88 (0.65 to 1.21)</td>
<td>$280 ($178 to $382)</td>
</tr>
<tr>
<td>August</td>
<td>73</td>
<td>0.75 (0.59 to 0.94)</td>
<td>$303 ($209 to $397)</td>
</tr>
<tr>
<td>September</td>
<td>38</td>
<td>0.35 (0.25 to 0.48)</td>
<td>$218 ($66 to $369)</td>
</tr>
<tr>
<td>October</td>
<td>33</td>
<td>0.30 (0.21 to 0.42)</td>
<td>$148 ($70 to $227)</td>
</tr>
<tr>
<td>November</td>
<td>19</td>
<td>0.19 (0.12 to 0.30)</td>
<td>$131 ($45 to $217)</td>
</tr>
<tr>
<td>December*</td>
<td>0</td>
<td>0 (—)</td>
<td>— (—)</td>
</tr>
<tr>
<td>Total</td>
<td>202</td>
<td>0.43 (0.38 to 0.50)</td>
<td>$241 ($191 to $291)</td>
</tr>
</tbody>
</table>

* Data were only collected on 01 December for that month and no ARIs started on that day

The presence of reported fever increased the average cost per illness. During the study, the 104 ARIs without fever or otitis media had an average cost of $195. The average cost for illnesses with fever alone (n=75), otitis media alone (n=14), or febrile otitis media (n=9) was $287, $212, and $433, respectively. Categorising illnesses by whether or not they had fever, the average cost of illness for an afebrile ARI (n=118) was $197 compared with $303 for febrile illness (n=84).

The key cost driver for ARI in children was carer time spent caring for the ill child away from usual activities, making up 70% of total costs (Table 3.5). Females spent an average of 6.38 hours per episode (95% CI 4.61 to 8.15) caring for the ill child away from their usual activities, and males an average of 1.95 hours per episode (95% CI 1.05 to 2.84). The next most important non-carer time related drivers were use of non-prescription medication (5.4% of total costs: 244 episodes of use, 95% CI 215 to 273), and general practitioner visits (5.0% of total costs: 89 visits, 95% CI 68 to 110 visits).

The resources used during illness were predominantly provided by the patient and family sector, being responsible for meeting 87% of total costs (mean cost per episode: $209). The health-care sector met 5% of costs ($12), and other sectors met 8% of costs ($20).
The average cost per episode was lowest for those illnesses occurring in households from the highest income bracket: bracket 4, $208; bracket 2, $290; bracket 1, $377; and bracket 3, $449. These rankings remained the same when illnesses where there was no information available were removed from average calculations (bracket 4, $235; bracket 2, $327; bracket 1, $431; and bracket 3, $474).

The key costs drivers, carer time away from usual activities, non-prescription medication, and general practice visits, were individually varied in one-way sensitivity analyses, according to the upper and lower 95% confidence limits. The average cost per episode varied little for the sensitivity analyses involving non-prescription medication and general practice visits (Table 3.6), but ranged from $186 to $296 when carer time away from usual activities was varied. The one-way sensitivity analysis which included the three illnesses with hospitalisations increased average cost per episode to $287 (Table 3.6). For the multi-way sensitivity analysis, two scenarios were tested producing a least expensive average cost per episode of $177, and a most expensive average cost per episode of $304 (Table 3.6). Unsurprisingly, these values varied little from those generated in the one-way analyses of carer time away from usual activities.

The total supplementary cost and average for all illnesses, incorporating those resource items not included in the Respiratory Virus Study, was $3,310.29 and $16.39, respectively (Table 3.7). All of these cost items were borne by the patient and family sector. The cost of these items combined made up 6.8% of the total cost of all illnesses. The average supplementary cost for illnesses where any cost was recorded was $19.59 (95% CI $17.32 to $21.86).
Table 3.5  Summary of resources consumed during 202 ARI episodes in 118 Melbourne children during winter and spring 2001

<table>
<thead>
<tr>
<th>Resource</th>
<th>Units consumed</th>
<th>Patient and family sector</th>
<th>Health-care sector</th>
<th>Other sectors</th>
<th>% ARI cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practice visits(^s)</td>
<td>89</td>
<td>$255.43</td>
<td>$2,174.94</td>
<td>—</td>
<td>5.0%</td>
</tr>
<tr>
<td>Other health-care provider visits(^s)</td>
<td>10</td>
<td>$156.42</td>
<td>$115.00</td>
<td>—</td>
<td>0.2%</td>
</tr>
<tr>
<td>Hospital emergency department visit (no admission)(^s)</td>
<td>4</td>
<td>—</td>
<td>$160.00</td>
<td>—</td>
<td>0.3%</td>
</tr>
<tr>
<td>Diagnostic tests(^s)</td>
<td>1</td>
<td>$5.00</td>
<td>$28.31</td>
<td>—</td>
<td>0.1%</td>
</tr>
<tr>
<td>Antibiotics(^s)</td>
<td>42</td>
<td>$579.47</td>
<td>—</td>
<td>—</td>
<td>1.2%</td>
</tr>
<tr>
<td>Other prescription medication(^s)</td>
<td>24</td>
<td>$336.92</td>
<td>—</td>
<td>—</td>
<td>0.7%</td>
</tr>
<tr>
<td>Over-the-counter and other medication(^s)</td>
<td>244</td>
<td>$2,617.40</td>
<td>—</td>
<td>—</td>
<td>5.4%</td>
</tr>
<tr>
<td>Paid child care for other children(^s)</td>
<td>11 episodes</td>
<td>$133.00</td>
<td>—</td>
<td>—</td>
<td>0.3%</td>
</tr>
<tr>
<td>Travel costs seeking health-care(^s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Car</td>
<td>460.6 kms</td>
<td>$209.96</td>
<td>—</td>
<td>—</td>
<td>0.4%</td>
</tr>
<tr>
<td>Parking</td>
<td>3 episodes</td>
<td>$13.00</td>
<td>—</td>
<td>—</td>
<td>0.0%</td>
</tr>
<tr>
<td>Time seeking health-care(^s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time away from work, pay lost</td>
<td>34.50 hours</td>
<td>$679.31</td>
<td>—</td>
<td>—</td>
<td>1.4%</td>
</tr>
<tr>
<td>Time away from work, no pay lost</td>
<td>22.25 hours</td>
<td>—</td>
<td>—</td>
<td>$438.10</td>
<td>0.9%</td>
</tr>
<tr>
<td>Time away from usual activities</td>
<td>67.04 hours</td>
<td>$1,329.18</td>
<td>—</td>
<td>—</td>
<td>2.7%</td>
</tr>
</tbody>
</table>
### Table 3.5  Summary of resources consumed during 202 influenza-like illnesses in 118 Melbourne children during winter and spring 2001, continued

<table>
<thead>
<tr>
<th>Resource</th>
<th>Units consumed</th>
<th>Patient and family sector</th>
<th>Health-care sector</th>
<th>Other sectors</th>
<th>% ARI cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess time caring for ill child</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time away from work, pay lost</td>
<td>81.50 hours</td>
<td>$1,604.74</td>
<td>$ —</td>
<td>$ —</td>
<td>3.3%</td>
</tr>
<tr>
<td>Time away from work, no pay lost</td>
<td>178.60 hours</td>
<td>$ —</td>
<td>$ —</td>
<td>$3,609.03</td>
<td>7.4%</td>
</tr>
<tr>
<td>Time away from usual activities</td>
<td>1682.54 hours</td>
<td>$34,212.06</td>
<td>$ —</td>
<td>$ —</td>
<td>70.3%</td>
</tr>
<tr>
<td><strong>Sector total</strong></td>
<td></td>
<td><strong>$42,131.87</strong></td>
<td><strong>$2,478.24</strong></td>
<td><strong>$4,047.14</strong></td>
<td><strong>100%</strong></td>
</tr>
<tr>
<td><strong>Sector cost per ARI</strong></td>
<td></td>
<td><strong>$208.57</strong></td>
<td><strong>$12.27</strong></td>
<td><strong>$20.04</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sector per cent</strong></td>
<td></td>
<td>86.6%</td>
<td>5.1%</td>
<td>8.3%</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>$48,657.25</strong></td>
<td><strong>Total cost per ARI</strong></td>
<td><strong>$240.88</strong></td>
<td></td>
</tr>
</tbody>
</table>

* Based on 2001 Medicare Benefits Schedule rates for health-care sector costs\(^6\) – 85% of code 23 ([$38.75]) – and mean patient cost per GP / vocationally registered GP visit for 2001 [$2.87] for patient and family cost\(^7\)

† Based on parent-reported costs for visits to naturopaths (2 visits) and chiropractors (6 visits), and 2001 Medicare Benefits Schedule\(^6\) fee rates for 2 specialist visits – 85% of MBS code 104 ([$57.50]) – and mean patient cost per specialist visit for 2001 [$15.71] for patient and family cost\(^7\)

‡ Hospital emergency department (ED) visits based on the cost for emergency department presentation for the Australian Ambulatory Classes group 23: Other respiratory diseases without procedure ([$40]).\(^8\)

§ Actual cost paid by parent charged not uniformly available. Government cost based on 85% of 2001 Medicare Benefits Schedule\(^6\) fees for one chest x-ray (MBS code 58600 [$33.30]). The cost allocated to patient and family was the difference between the Medicare rebate and the schedule fee (15% of the Medicare Benefits Schedule Fee).\(^6\)
Table 3.5  Summary of resources consumed during 202 influenza-like illnesses in 118 Melbourne children during winter and spring 2001, continued

|| Given the high proportion of households in the study from the highest income bracket, we have costed all prescription medication for general PBS beneficiaries (no concessional beneficiaries); we have also assumed they were purchased without a Safety Net Entitlement Card. Prescription medication costs were the maximum recordable value for the Safety Net from the Schedule of Pharmaceutical Benefits for Approved Pharmacists and Medical Practitioners.\textsuperscript{429} None of these individual costs exceed the maximum cost for a pharmaceutical benefit item ($21.90), so all costs were allocated to the patient and family sector.

\textsuperscript{¶} Over-the-counter medication from pharmacies is the MIMS Australia cited cost,\textsuperscript{430} and other medication (for example, natural therapies) based on parent-report.

\textsuperscript{**} Parent-reported child care costs for other children whilst seeking care for ill child.

\textsuperscript{††} Car running costs per kilometre (business cost) from the Royal Automobile Club of Victoria (RACV) based on type, age, and engine size of car used.\textsuperscript{431} Parking costs as report by parents in seeking health-care.

\textsuperscript{‡‡} All time based on parent-reported hours. Cost applied from sex-weighted Australian Bureau of Statistics (ABS) average weekly earnings, November 2001: male ($852.70 per 38 hour week) and female ($748.20 per 38 hour week). Cost allocated to the employer (other sector) for time away from work, no pay lost, and to patient and family sector for time away from work, pay lost and time away from usual activities.

\textsuperscript{§§} Columns do not add exactly to total due to rounding.
### One-way and multi-way sensitivity analyses for average cost of episodes

<table>
<thead>
<tr>
<th>Sensitivity analyses</th>
<th>Modification</th>
<th>Values used</th>
<th>Average cost per episode</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One-way analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General practice visits</td>
<td>Number of general practice visits and dependent variables</td>
<td>Lower value: 68 visits</td>
<td>$233.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper value: 110 visits</td>
<td>$247.94</td>
</tr>
<tr>
<td>Over-the-counter and other medication use</td>
<td>Number of episodes of over-the-counter and other medication use</td>
<td>Lower value: 215 episodes</td>
<td>$239.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper value: 273 episodes</td>
<td>$242.42</td>
</tr>
<tr>
<td>Carer time away from usual activities</td>
<td>Time spent caring from ill child away from usual activities</td>
<td>Lower value: 5.67 hours (4.61 female, 1.05 male)</td>
<td>$186.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper value: 10.99 hours (8.15 female, 2.84 male)</td>
<td>$295.73</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>Addition of three ARIs with a hospitalisation</td>
<td>All costs for these ARIs added to total costs</td>
<td>$287.03</td>
</tr>
<tr>
<td><strong>Multi-way analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least expensive scenario</td>
<td>General practice visits</td>
<td>68 visits</td>
<td>$177.17</td>
</tr>
<tr>
<td></td>
<td>Over-the-counter and other medication</td>
<td>215 episodes of use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carer time from usual activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female carers: 4.61 hours per episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male carers: 1.05 hours per episode</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3.6  One-way and multi-way sensitivity analyses for average cost of episodes, continued

<table>
<thead>
<tr>
<th>Sensitivity analyses</th>
<th>Modification</th>
<th>Values used</th>
<th>Average cost per episode</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multi-way analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most expensive scenario</td>
<td>General practice visits*</td>
<td>110 visits</td>
<td>$304.33</td>
</tr>
<tr>
<td></td>
<td>Over-the-counter and other medication</td>
<td>273 episodes of use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carer time from usual activities</td>
<td>Female carers: 8.15 hours per episode</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male carers: 2.84 hours per episode</td>
<td></td>
</tr>
</tbody>
</table>

* Changes in the number of general practice visits included proportionate changes in the cost of other variables that rely on a general practice visit: diagnostic tests, antibiotics and other prescription medication, travel seeking health-care, parking, and time seeking health-care.

† Costing for non-hospital related costs in three additional ARIs as per Table 3.5. Extra diagnostic tests performed outside of hospital: urine microscopy, culture, and sensitivity (MBS code 69312 [$13.00] with 2 performed), full blood evaluation (MBS code 65070 [$16.70] with 2 performed), and serum biochemistry (MBS code 66515 [$19.20] with 2 performed). Health-care sector cost based on 85% of 2001 Medicare Benefits Schedule; the cost allocated to patient and family for diagnostic tests was the difference between the Medicare rebate and the schedule fee (15% of the Medicare Benefits Schedule Fee). Ambulance cost from Victorian Ambulance Service for emergency transport to hospital less than 10kms away (one transfer). Public hospital admission National Hospital Cost Data Collection code E62C [$2,395]. Private hospital admission costs as reported by the two private hospitals: overnight admission for respiratory infection $228 paid by patient and family to private hospital; overnight admission for febrile convulsion $400 paid by health insurance company (other sector cost), and $222 paid by patient and family to private hospital. Private health insurance fees not included.
Table 3.7  Summary of supplementary costs for the 202 ARIs in study children, incorporating costs not collected in the Respiratory Virus Study

<table>
<thead>
<tr>
<th>Resource</th>
<th>Total cost</th>
<th>Per cent of total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-antibiotic prescription medication</td>
<td>$336.92</td>
<td>10.2</td>
</tr>
<tr>
<td>Over-the-counter and other medication</td>
<td>$2617.40</td>
<td>79.1</td>
</tr>
<tr>
<td>Paid child care for other children</td>
<td>$133.00</td>
<td>4.0</td>
</tr>
<tr>
<td>Travel costs seeking health-care</td>
<td>$222.97</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$3,310.29</strong></td>
<td><strong>100.0</strong></td>
</tr>
<tr>
<td><strong>Average supplementary cost per illness</strong></td>
<td><strong>$16.39</strong></td>
<td></td>
</tr>
</tbody>
</table>

The proportion of time away from work made up of time away with pay lost and time away with no pay lost varied depending on whether that time was spent seeking health-care or excess time spent caring for an ill child (Table 3.5). There were a total of 56.75 carer hours spent away from work seeking health-care, with 34.50 hours (61%) being time with pay lost, and 22.25 hours (39%) being time with no pay lost. For excess time caring for an ill child, there were a total of 260.10 hours with 81.50 hours (31%) resulting in lost pay and 178.60 hours (69%) with no pay lost.

### 3.5 Discussion

This pilot study provided important information for the planning of the larger, subsequent community-based study and new information on the epidemiology of acute respiratory illnesses in preschool aged children.

The key practical findings included evidence that parents, with minimal training and support, can maintain and return a daily respiratory symptom diary for young study children – 93% of possible study days of data were returned. Further, parents identified an average of 0.44 ARI episodes per child-month and when an ARI was reported they had an excellent rate of completing and returning a burden diary – 89% of identified ARIs during the influenza season had a burden diary returned. This information was invaluable for planning our approach to the Respiratory Virus...
Study. Given the paucity of local data on ARIs in children, the study also provided important epidemiological information about the frequency, burden, and costs associated with winter respiratory illnesses in Australian children. As this was a pilot study designed to plan methods for a larger study, the study was not sufficiently powered for comparisons in some outcomes of interest.

We found the rate of respiratory illness highest in younger children and in those that had structured exposure to other children outside of the home through day care, preschool, or school attendance. In previous studies in developed settings, the rate of infection within households has increased with decreasing household income, thought to be a reflection of greater crowding, but in this study we found the opposite. Also in contrast to previous studies, having fewer people in the household increased the rate of infection for study children. It may be that modifications in lifestyle make previously gathered data less meaningful in today’s context. The nature of family life in Australia and other countries has changed substantially since community respiratory illness studies conducted in the United States from the 1950s to 1980s, and these changes may have impacted on respiratory virus epidemiology. The proportion of Australian children under 12 years of age using formal and/or informal child care has increased in the last two decades, from 38% in 1984 to 51% in 1999, and 49% in 2002, with the increase most marked in children aged less than two years. ARIs are common in children who attend child care, particularly those less than two years of age, and increased child care utilisation may have led to previously undocumented increases in individual and household incidence of ARI. In the past, children from relatively higher income households may have not only avoided overcrowding in the home but may have also had a caregiver remain at home with them, thereby avoiding exposure to respiratory viruses at child care. With the increasing expense of raising a family and the need for both parents to work outside of the home, these children may have lost their previously held advantage due to an increasing likelihood and younger age of attending child care.

More than 50% of the identified ARIs in study children had duration greater than one week, with more than a quarter lasting beyond two weeks. A United Kingdom study showed that 56% of
children with upper respiratory tract infections had not recovered one week from onset, and 26% had not recovered by day 10. A Melbourne community-based study that used a more sensitive case definition for a respiratory episode (one day of runny nose, sore throat, or cough) found children less than two years of age shared the longest mean duration of illness (6.8 days) with those aged 31 to 40 years, with the duration for all illnesses ranging from 1 to 70 days. Respiratory problems are one of the most common reasons for a GP visit in Australia, accounting for 14.2% of problems managed, and antibiotics are the most commonly administered group of medications with 13.8 prescriptions written for every 100 consultations.

There was substantial resource use associated with the identified ARIs, with the major impact on families likely to be the excess time spent caring for a sick child. These findings have implications for preventive strategies in Australian children, particularly vaccine use. The impact carer time away from usual activities has on the average cost per episode can be seen in a number of ways: the proportion of total costs made up by this single variable (70%), and in the multi-way sensitivity analyses producing least and most expensive cost per episode scenarios varying little from the one-way sensitivity analysis of this variable alone. Not including carer time away from usual activities, as recommended for submissions to have drugs listed on the Pharmaceutical Benefits Scheme, would substantially under-estimate the true impact of community-managed disease of this nature. In this regard, these illnesses may be similar to chickenpox, being common and usually community-managed, with the direct costs of a proposed infant vaccination program in Australia outweighing the direct costs associated with not implementing such a program.

Recorded ARI events in our study consumed considerable resources, both in societal and family terms. Urban children who were subjects on this study experienced, on average, at least one ARI episode during the 2001 respiratory virus season. A significant proportion of the illnesses identified in this study are likely to have been caused by respiratory viral infections, including respiratory syncytial virus, influenza virus, parainfluenza viruses, human metapneumovirus, coronaviruses, adenoviruses, and rhinoviruses. The Victorian Infectious Diseases Reference Laboratory identifies 2001 as a year of normal seasonal activity for influenza from the
collaborative sentinel influenza surveillance scheme. Influenza A(H1N1) was predominant circulating virus in 2001 making up 72% of viable viruses submitted to the WHO Collaborating Centre for Reference and Research on Influenza for typing. All sequenced H1N1 viruses in Australia being A/New Caledonia/20/99-like strains; H3N2 isolates were antigenically similar to the vaccine strain, A/Panama/2007/99. Injectable influenza vaccine is licensed in Australia for children down to six months of age. The increasing use of intranasal CAIV-T vaccine in the US provides the possibility of better access, acceptability, and delivery of public influenza vaccination programs, especially if the license for use extends to a lower age group. The price of the vaccine, though falling to US$23.50 for the 2004/2005 influenza season in the United States, will remain an impediment to its wider use. Vaccines against other respiratory viruses are under development, but still likely to be some way off; the possibility for preventing such illnesses at present is limited to influenza.

Beginning in 2004 the Advisory Committee on Immunisation Practices (ACIP) in the US have made injectable influenza vaccine part of the routine childhood immunisation schedule — for children from six months up to two years of age. This recommendation extends to household contacts (including older children) and out-of-home caregivers of all children less than two years of age. Interest in this recommendation was driven by the US Centers for Disease Control and Prevention initiating national surveillance for paediatric influenza-associated deaths. It is also possible that use of vaccine in this age group may lead to reduced incidence of disease in other age groups due to herd protection, similar to effects seen from vaccinating school-aged children against influenza, and more recently, in vaccinating US infants with conjugate pneumococcal vaccine.

Vaccination programs against illnesses that are largely managed in the community may not appear cost-effective if the impact of lost productivity is ignored. Vaccines against influenza and other viral respiratory pathogens may be recommended for young children in the near future, but may not pass the cost-effectiveness hurdle for public funding in Australia. There are few published studies looking at the cost-effectiveness of influenza vaccine specifically in children.
Given the findings of our study, it will not be surprising that a childhood influenza vaccine program could be potentially cost-saving if indirect costs are included.\textsuperscript{264} Indirect costs were major findings in other ARI costing studies,\textsuperscript{442} potentially surpassing direct costs.\textsuperscript{243} The reduction in indirect costs is central to the economic benefits of vaccination,\textsuperscript{253,254,266} with previous studies showing that these benefits are greatest when parents are prevented from missing work to care for an ill child.\textsuperscript{253} For this reason, cost effectiveness evaluations of any intervention to prevent these illnesses should be from a societal perspective and include family and patient costs.

There are some issues which need to be considered when interpreting the findings of this study. The study was conducted over one winter season only and respiratory specimens were not obtained to confirm the aetiology of the illness. The incidence and cause of respiratory infections change from year-to-year. Only a proportion of all illness identified would be preventable, or modifiable, through the use of influenza vaccine. Even in years when influenza virus is circulating in the community, RSV is responsible for more hospitalisations in young children.\textsuperscript{54} RSV was more common than influenza in a community study of Sydney infants, being detected by polymerase chain reaction testing in 16 of 101 specimens collected, compared with only one specimen positive for influenza A, but both were less common than rhinovirus, found in 35 specimens.\textsuperscript{120} Despite this and whilst we were unable to link these ARIs with a viral cause, the increasing incidence and cost of ARIs during the defined influenza season suggests a potential role for preventative efforts in healthy children using vaccine.

Convenience sampling was employed in this study as it is not feasible to randomly select a representative sample of children for a community-based study of this nature. This may mean, depending on sample representativeness, point estimates of rates are biased. Given the nature of the family structures involved in this community-based study, and the number and relatedness of the events under observation, a convenience sample may be no less likely to produce a valid result than a randomly selected sample. However the rates of ARI we identified were comparable to those seen in the placebo-controlled arm of the CAIV-T study.\textsuperscript{120} The inclusion of more than one child from each household may have been expected to have a clustering effect on the
identification of ARIs, although this would not seem to be the case as incidence rates of illness fell with increasing numbers of children in the household.

We did not get universal diary card return, either for the daily symptom diary or the burden diary, which may have resulted in information biases. ARIs with no burden diary returned, but identified by study staff on review of the daily symptom diary, were shorter and less likely to involve fever and/or otitis media. Parents may have been less likely to report burden information for illnesses they felt were less serious or resulted in no excess resource consumption. The absence of complete burden information about these illnesses means our estimates are likely to be biased away from the null.

The majority of households (73%) in our study came from the highest income bracket. This compares with approximately 40% of Victorian family households being in this income range, according to 2001 Census data. Members of lower income households have been shown to have a higher incidence of respiratory viral infections, thought to be due to the impact of crowding; but in this study we did not find a lower rate of illness in children from high income families. It could be argued that parents from relatively higher income households might be more likely to expend more resources in caring for a sick child, as compared with those from a lower income household; but we found that the average cost per episode was lowest in households from the highest income bracket. The hourly rate applied to costs in this study was deliberately not varied by household income. As time away from usual activities was captured in this study, to value this differentially according to household income would imply the leisure time of high income households should be valued more highly than the same time from other households. In this study, high-income households were more likely to have both parents spending some time working outside the home. Parents in these households might have different thresholds for seeking medical attention or using medication for illnesses that are perceived to be mild or of minor significance. If anything, due to the lower average cost per episode in higher income households, the over-representation of such households in our study may have made our cost estimate conservative.
Costing studies such as this, together with studies that measure the relative role of specific pathogens, will not only inform local cost-effectiveness studies, but failing public funding of programs, will provide important information for vaccine providers to give parents about the likely benefits of paying for available vaccines themselves. There is a need for pathogen-specific baseline data to quantify the epidemiology and impact of respiratory viruses in children so that cost-effective decisions about interventions can be made. Information from this study was used to assist in the planning of the larger, community-based study of children with the addition of multiplex polymerase chain reaction (PCR) testing for common respiratory viruses — influenza, respiratory syncytial virus, parainfluenza viruses, adenovirus, and picornaviruses — at the time of an ARI episode. The ability to provide integrated pathogen-specific epidemiological and cost-of-illness data should assist in assessment of preventative and therapeutic interventions in the future.
Chapter 4

THE RESPIRATORY VIRUS STUDY – EPIDEMIOLOGY

4.1 Objective

The work presented in this Chapter was undertaken to collect virus-specific epidemiology and burden information about respiratory viral infection in healthy Australian children less than five years of age.

4.2 Introduction

Influenza vaccination use in Australia is the subject of evolving recommendations. Future changes to extend the publicly funded component of this program to include a universal childhood recommendation, similar to recent US and Canadian recommendations, are a possibility. As such, local information on the epidemiology and cost-of-illness for influenza in Australian children are required.

In order to gain some insight into the year-by-year variation of the circulation of the respiratory viruses of importance in children, it was originally planned to conduct this study over a three year period. The primary outcome for this study with respect to the initial sample size calculation was an estimate of the proportion of enrolled infants who would acquire infection with a specific viral agent in a given year, with the assumption that this proportion would be 0.5 or 50%. Using the usual formula for the standard error of proportions, a sample size of 384 would allow this proportion to be estimated with a precision no less than ± 5% (where this is the width of a 95% confidence interval). Using this approach would mean smaller or larger proportions would be estimated with greater precision. Based on this, we sought funding to conduct a prospective cohort study of 400 infants and children in the greater Melbourne area over a three year period. This was both and ambitious and expensive undertaking, and applications to competitive funding
bodies to conduct such a study were not successful, but funding that allowed the conduct of a smaller study over a 12 month period was received.

4.3 Methods

4.3.1 Recruitment and enrolment procedures

A prospective cohort study of healthy children in metropolitan Melbourne, Victoria, was conducted between 17 January 2003 and 31 January 2004. The Royal Children’s Hospital Ethics in Human Research Committee approved the study and written informed consent was obtained from parents / guardians prior to enrolment. As a secondary aim of the study involved attempting to identify intra-household transmission of viruses from the primary study subject to other household members, by participating in the study families were consenting to the all household members undergoing illness surveillance and specimen collection sometime during study participation.

Amassing a sample of children from this age group using a simple random or other systematic sampling strategy is not logistically possible or likely to be unbiased for a number of reasons. Firstly, no readily accessible sampling frame exists for Melbourne children of this age. The Medicare database, or the Australian Childhood Immunisation Register (ACIR) which is linked to the Medicare database, could potentially act as a universal sampling frame from which to randomly or systematically sample children of this age, with more than 98% of Australian children having Medicare registration by 12 months of age. However, previous attempts by our research group to use identifying information from the Australian Childhood Immunisation Register (ACIR) have not been successful due to legal and privacy limitations. There are no other complete or near complete sampling frames for Melbourne children available. Other lists, such as those children registered at local council for either immunisation services or MCHN care, or a list of births from either the Victorian Registry of Births, Deaths, and Marriages or from Melbourne maternity hospitals, similarly have privacy issues that would preclude their use, but also suffer from not being updated with new household address information (particularly a problem for
families with older children in our age target) and not containing information about children who have moved into or away from the greater Melbourne area. Even if a universal or near universal sampling frame were available, random sampling would not ensure a representative and unbiased study population, due to refusal to participate. As seen from the pilot study, despite using local council areas with a wide range of socioeconomic indicators, families who participated were more likely to come from a higher income band and did not appear fully representative of the general community.

Given this, study children were a sample of convenience. Children were eligible to participate if they were generally healthy, born between 36 and 42 weeks gestational age, and less than five years of age at the time of enrolment. The objective of this study was to collect epidemiological and burden information about illnesses in healthy children. So, to avoid recruiting children who may have infections complicated by pre-existing illness, and therefore be more likely to come to attention of healthcare professionals and be more costly, we did not enrol:

- Children with chronic pulmonary or cardiovascular disorders (including diagnosed asthma, or frequent use of asthma medication);

- Children with chronic metabolic disorders (such as diabetes mellitus, renal dysfunction, haemoglobinopathies);

- Children with immune system disorders (such as HIV/AIDS or receiving immune system suppressing medications); and

- Children with other chronic illnesses whose enrolment was deemed to be inappropriate due to potential upward biasing of the mean cost-of-illness associated with higher use of medical services and medication when ill.
Funding was not available to translate study documents and other material into languages other than English, or for the use of interpreter services. For this reason only children with a parent or guardian with sufficient English language skills to understand the informed consent process and complete study documents were enrolled.

Only one child per family was enrolled in the study as the primary study subject. If more than one child met the enrolment requirements, a study participant was randomly selected from the available participants.

The method for recruiting study subjects took a number of forms. Similar to the pilot study, families with infants and younger children less than two years of age were identified through maternal and child health nurses (MCHNs) and immunisation providers in local council areas across the greater Melbourne area. In an effort to avoid the socioeconomic clustering of families seen in the pilot study, we expanded the number of council areas we used for recruiting children to include extra councils with lower socioeconomic indicators, and asked our research staff to ensure they spent time recruiting from all council areas.

MCHNs identified children who were age eligible for the study and offered their parent or guardian a brochure containing information about the study and contact details if they were interested in learning more about the study. Families who used the services of a MCHN often also had another child or children less than five years of age, who were eligible for selection as the primary study subject chosen from the family. Older children were also specifically targeted for recruitment by the distribution of promotional material for the study to sites where such children congregate: play and other recreational centres, and child care centres. The study promotional material consisted of a poster with contact information for study staff and a brochure outlining the study in more detail. The promotional material about the study and a call for subjects was made on the web-based bulletin board and the daily e-mail staff bulletin at the Royal Children’s Hospital campus, Melbourne, and the Royal Women’s Hospital campus, Melbourne. The study
promotional material was also placed at various sites, general areas, outpatients and wards, around the Children’s and Women’s hospitals.

Research staff involved in recruiting and interviewing families for this study went through a uniform training process which included explaining the study, reviewing the study documents including the plain language statement and consent form, explaining and demonstrating the procedure for specimen collection and arrangements for transport to the Victorian Infectious Diseases Reference Laboratory (VIDRL), practising specimen collection on other staff members, and the subsequent handling of collected specimens. Research staff attended meetings in councils that had agreed to participate in the study to explain the rationale and methods for the study to the MCHNs.

Parents or guardians interested in learning more about the study were directed by the study material or by MCHNs to make telephone contact with a member of the study team. This telephone contact provided the caller with more detail about the study procedures (including diary keeping and swab collection) and allowed for an initial check of the inclusion and exclusion criteria. If appropriate, during the telephone interview arrangements were then made for a research staff member to visit the family in their home to go through the plain language statement and study documents in detail, and explain and demonstrate the procedure for swab collection. At the end of this home visit, parents were offered the option of providing written informed consent or having more time to think about the study and discuss it with family members. If more time was required but the family eventually agreed to participate, another home visit was organised to obtain written informed consent and deliver the study diaries and material required for collecting and transporting a specimen.

Once written informed consent was obtained, documentation that the primary study child was eligible to participate in the study, by virtue of having met all of the inclusion criteria and none of the exclusion criteria was made in the study workbook. The study workbook, completed at the informed consent visit, collected contact details for the family, the best method for contacting
the family and times when this was convenient, and information about the study child and all household members. The information from the study child included basic demographic details such as date of birth and sex, household structure, breast feeding history, current or previous influenza vaccination, child care details, and details about bedroom sharing. Household members were asked to provide their sex and date of birth, whether they had received an influenza vaccine in the last 12 months or anytime prior, and whether they were a cigarette smoker, and if so, whether they smoked in the home or car in the presence of the study child.

Definitions of child care were from Australian Bureau of Statistics classifications. There are two main categories used, informal and formal care:

- Informal care is non-regulated care, arranged by a child's parent/guardian, either in the child's home or elsewhere. It comprises care by (step) brothers or sisters, care by grandparents, care by other relatives (including a parent living elsewhere) and care by other (unrelated) people such as friends, neighbours, nannies or babysitters. It may be paid or unpaid.

- Formal care is regulated care away from the child's home. The main types of formal care are before and/or after school care, long day care, family day care, occasional care, and preschool.

There were some children who turned five years of age whilst on the study and were eligible to attend school. For the purposes of this study, school was included as a category of formal care, along with preschool. It was felt reasonable to include school under the category of formal child care as the process of mingling with other children at school most likely makes this environment equivalent to other formal child care settings in terms of exposure to the agents of respiratory infections. It is worth noting child care information was collected as a general categorical variable, and not on a day-by-day basis. This information was updated upon contact with the family during the course of the study. The collection of day-by-day child care participation status
from study subjects, along with daily symptom data, was felt to be requiring too much of participating parents and may have inhibited recruitment.

Details collected about the entire household included the annual household income, working details of caregivers (usually the parents or guardians of the study child) including occupation and hours worked per week, whether the family had private health insurance and, if so, what type (hospital cover only, ancillary cover only, or both). Household income was collected in nine bands based on those used in the national census by the Australian Bureau of Statistics: <$10,400; $10,400 to $20,799; $20,800 to $31,199; $31,200 to $41,999; $42,000 to $51,999; $52,000 to $62,399; $62,400 to $77,999; $78,000 to $103,999; and >$103,999. Variations in information, such as child care arrangements, bedroom sharing, and new additions to or departures from the study household, were updated during regular family contact, and all details and changes were confirmed at the end of the study using a closeout study questionnaire.

At the home visit where informed consent was obtained, families were also given the following study material:

- A copy of the plain language statement and informed consent document;

- Contact information for the study team;

- Daily respiratory symptom diary for the primary study subject, containing day-by-day symptom check box for each month;

- Burden diaries for the primary study subject;

- Combined symptom and burden diary for household contacts for use if they developed a respiratory illness within seven days of illness in the primary study child;
Brief written instructions for completing all study documentation and for the collection of a combined nose-throat swab;

Pre-addressed postage paid envelopes for monthly return of completed study diaries and documents;

A digital thermometer; and

Two sets of specimen collection material (which could be used for collection a specimen from either the primary study subject or a household member): a labelled container of viral transport medium, two wood shaft, sterile soft rayon-tipped swabs each in a tamper-evident tube (one each for nose specimen and throat specimen collection), wooden tongue depressor, specimen collection form, specimen carrier (biohazard) bag, ice brick (to be stored in freezer), a small esky (polystyrene transport container), masking tape for sealing the esky, a multipurpose cloth for placing between the ice brick at the base of the esky and the specimen carrier bag during transport, and an esky sticker label.

4.3.2 Study conduct, logistics, and compliance

Parents were asked to mark any relevant symptoms experienced by the study subject on a day-by-day basis on the daily respiratory symptom diary card. The respiratory symptom diary was specific for each month the child was on the study, and parents were asked to return the monthly diary, along with any other completed paperwork, to the study team in the provided pre-addressed postage paid envelope. It was recognised that for a lot of families there may be reasons where uninterrupted return of daily symptom and other study material, whilst strongly encouraged, would not always be possible; such as family holidays away from Melbourne. Families were encouraged, at enrolment and through regular telephone or email contact, to participate in the study and return all study material or as much material as possible.
For all children on the study, the maximum possible daily symptom data that could have been submitted for that child was calculated. This was done using the first day data were submitted for all children where any data were available and from the date of enrolment for children where no data were submitted, up until the last day of data collection (31 January 2004).

If an acute respiratory illness (ARI) was identified in a study child (Section 4.3.3) parents were asked to do a number of things:

- Collect a combined nose-throat swab from the study child as soon as practical, and contact the study team to make arrangements for the specimen to be couriered to the laboratory;

- Complete a burden diary and wait for the illness to be finished (three clear symptom-free days after the last day of the illness with symptoms) before this was returned; and

- Undertake surveillance for any respiratory illness in any household contacts for the duration of the illness in the study child and seven days after cessation of illness.

Sometimes it was not practical or parents were unable to collect a specimen and complete a burden diary for a given illness. In these circumstances we asked parents to provide us with as much detail about the illness as possible, meaning that for some illnesses specimens were sent without a corresponding burden diary, a burden diary was returned without a corresponding specimen, or neither a specimen or burden diary were sent.

For the duration of a family’s participation, the study team made an attempt to contact a parent every two weeks, to encourage the return of paperwork, clarify any uncertainties about study procedures, identify a hospitalisation, deal with any problems that had arisen, and ask if any further diaries or specimen collection material were required. Parents who requested study contact to be made via email were asked to reply to their first email contact to confirm its receipt.
A number of pieces of study information were used to assess completeness of reporting and compliance with study procedures by study families. The possible total of daily symptom contribution to the study was calculated from the first day of data return up to and including 31 January 2004, representing the maximum number of days for which data could be provided by each study child. The sum of the actual contributed days of daily symptom data for the whole study population was expressed as a per cent of the sum of the maximum possible days for each study child.

For each ARI identified in a study child, parents were asked to collect a combined nose-throat specimen and complete a burden diary. Completeness of collecting at least one nose-throat specimen or returning a complete burden diary or returning at least one nose-throat specimen and the burden diary are reported for all ARIs. Illnesses in household contacts were identified either through the return of a completed combined symptom and burden diary, or the submission of a specimen collected from a household contact, with the total number of household contact ARIs being illnesses where at least one of these was returned. As a measure of completeness, the per cent of illnesses missing a swab or missing a diary are reported.

4.3.3 Daily symptoms and acute respiratory illness

The method of symptom collection and identification remained unchanged from the pilot study. The daily respiratory symptom diary captured the same information, but the paperwork was structured to capture this information for one month, as opposed to one week in the pilot study. This method for identifying respiratory illness is the same as that used by Belshe et al in the seminal efficacy study of CAIV-T, and was used without modification during this study. Symptoms were classified as belonging to either category A (fever regardless of whether the temperature was documented with a thermometer, wheezing, shortness of breath, pulmonary congestion or moist cough, pneumonia diagnosed by a health-care provider, and ear infection suspected by parent/guardian or diagnosed by health-care provider) or category B (runny nose or nasal congestion, sore throat, cough, muscle aches, chills, headache, irritability, decreased activity including lethargy or weakness, and vomiting).
Symptoms were taken as documented by parents on the diary card and no attempt was made at validation through health-care provider or other source. Diary cards included a “no symptoms” option to confirm days on which the child was not experiencing any potentially respiratory illness related symptoms. An option for recording a maximum daily temperature during an illness was also provided on the diary card, but parents were asked not to modify their routine temperature-measuring practice during the study.

Parents were asked to identify when an acute respiratory illness (ARI), which could encompass a collection of relatively minor respiratory symptoms, occurred in the study subject. This definition, being quite sensitive for a range of respiratory illnesses from relatively minor to serious, was used to detect all but trivial illnesses and asymptomatic viral respiratory infection in the study population. The threshold for identifying an ARI was the presence of at least one category A symptom or at least two category B symptoms in the study child on the same day (Figure 3.1). To make the process of identifying an ARI in real time as simple as possible for parents, as they were responsible for identifying illnesses that met the threshold without routine support on a daily basis, we used a colour coded diary card. Category A symptoms were coded yellow, and Category B symptoms blue.

4.3.4 Specimen collection, handling, and transport

Parents were given verbal and written instructions and a demonstration of collecting a combined nose-throat swab at the home visit where written informed consent was obtained and study enrolment occurred. When collecting a swab, parents were asked to complete the collection details on the viral transport medium (VTM) tube provided, and use the two swabs provided to collect the nose and throat swabs separately. The VTM tubes were stored in the household freezer and defrosted for approximately ten minutes prior to swab collection. The nose swab was collected first and with the one swab used for collecting a specimen from both nostrils, and then placed in the VTM. The throat swab was collected using a second swab, and then also placed in the VTM along with the nose swab. Parents were encouraged to collect the nose swab first; collecting the throat swab was potentially more intrusive, and a failed initial attempt at throat
swabbing in the first instance may have resulted in no usable specimen being collected during the illness. Parents were always encouraged to collect a throat swab, but in an attempt to reduce family dropout and ensure ongoing specimen collection, they were told it was acceptable to send only a nose swab if collecting a throat swab would be too distressing, particularly for an ill child. The type of specimen collected, either a nose or a throat swab, or both, was identified on the specimen collection form. Parents were asked to delay collecting the swabs until they were able to get assistance if required. After collecting the specimens, the specimen collection form was completed with details of who the specimen was collected from, the identity of the collector, the type of specimen collected (nose alone, throat alone, or both), the collector’s subjective perception of the quality of specimen collection, and the date and time of collection. If specimens were collected overnight or on the weekend, they were stored in the household refrigerator until ready for collection the next working day.

When a swab was collected from either the study child or a household contact, parents were asked to contact the study team to arrange for couriering to VIDRL. Study staff could arrange for collection via the courier company’s secure website, or, if this was not available, over the telephone. For transport, an ice brick was placed in the bottom of the esky and covered with the multipurpose cloth. The specimen carrier bag, containing the labelled VTM tube with swabs and completed specimen collection form, was placed on top of the multipurpose cloth. The esky was closed and sealed with masking tape, and an esky sticker label was placed on the lid with directions for the courier for transport to VIDRL.

Parents were asked to leave the VTM with specimens in the refrigerator until just prior to collection by the courier. If there was going to be nobody at home during the day of collection, the esky was to be packed and left at the front door for collection. In these circumstances, instructions were given to the courier that nobody would be at home and that the esky could be collected from an arranged site.
The swabs from study subjects were tested using VIDRL’s multiplex respiratory PCR, RespPCR (Section 4.3.6.1), either on the day of receipt at the laboratory or, if they arrived after commencement of the PCR run for that day, on the next working day. Due to a lack of funding, specimens from household contacts were not tested using RespPCR at VIDRL. The original specimens from both study subjects and household contacts, whether tested for viruses or not, were stored in a minus 70 degree Celsius freezer. Any cDNA available for storage after testing had been completed at VIDRL was stored in a minus 20 degrees Celsius freezer. At the conclusion of the data and specimen collection phase of the study, all available original specimens (study subject and household contact specimens) and stored cDNA were transported to the Queensland Paediatric Infectious Diseases (Qpid) Laboratory (Section 4.3.6.2).

VIDRL provided results for study subjects by automatically generated facsimile on the day that testing was performed. These results were used to generate a form letter which was posted to parents detailing what viruses, if any, had been detected.

Laboratory-confirmed influenza became a notifiable condition by both diagnosing clinician and laboratory in Victoria on 16 May 2001. All laboratory-confirmed cases of influenza in study subjects, and household contacts where testing was inadvertently performed, were notified to the Victorian Department of Human Services.

4.3.5 Epidemiological methods

The number, duration, and type of acute respiratory illnesses were identified by review of the daily symptom diaries. Identified ARIs were classified as being uncomplicated (fever or ear infection not recorded in symptoms for the duration of the ARI), a febrile ARI (fever and no ear infection recorded in symptoms), an ARI with otitis media (ear infection and no fever recorded in symptoms), and a febrile ARI with otitis media (fever and ear infection recorded in symptoms).

The duration of each ARI was calculated using the first and last days (inclusive) of any symptoms of the discrete illness. This means there could have been days within the illness where no
symptoms were reported, but these could not amount to three or more consecutive days without symptoms, as subsequent symptoms following these days would define a new illness. If symptoms of an ARI were recorded on the last day of data collection, 31 January 2004, this was deemed to be the final date of the illness. For monthly rate calculations, illnesses were assigned to the month in which the first day of illness fell, regardless of the duration of the illness.

In published papers on respiratory illness, incidence has been reported using the number of events per 100 children during the winter respiratory illness season\(^4\) or an incident rate using person-time as the denominator.\(^4\) There is usually no reference to the removal of days from the denominator where subjects were not at risk of illness to calculate a true at-risk incident rate.\(^4\) The rates of illness and virus identification in this study were calculated using only at-risk days in the denominator.\(^4\)

Non-at-risk days are those days for any study subject where they are refractory to the development of a new ARI episode, that is, a new ARI episode cannot be commenced on that day. Non-at-risk days are therefore those days any symptoms recorded on the symptom diary would be incorporated into an existing ARI. As well as days already incorporated in ARIs, such days also include the three symptom-free days immediately following an ARI, as symptoms on any of these days will mean that day, and preceding symptom-free days are incorporated in the preceding ARI. This means non-at-risk days are made up by two distinct day types: those days that are already part of an ARI, and the three symptom-free days immediately following the end of an ARI.

For the purposes of calculating an at-risk incidence rate, the data from each ARI are collapsed into a single event with remaining days in the ARI and subsequent three symptom-free days (non-at-risk days) removed from the dataset. Removing non-at-risk days leaves each ARI represented as a single day in both the denominator and the numerator, regardless of duration.
Incident rates, using child-months (person-time) as the denominator, and 95% confidence intervals were calculated. Child-months person time was calculated by dividing the available child-days by 30.4375 – this figure is the average number of days per year (365.25) divided by the 12 months of the year.

Risk factor information for the development of ARIs and respiratory viral infections (Table 4.1) was collected, as described (Section 4.3.1) at the visit where informed consent was signed by a parent. Univariate incident rate ratios and associated 95% confidence intervals for the development of ARIs and infections were calculated for various risk factors, including time-related variables, such as season and month of the year.

All data from the study were initially entered in a Microsoft Access relational database (Microsoft, Redmond, Washington, USA). The final datasets were combined and analysed using Stata 8.2 (StataCorp, Houston, Texas, USA). In Stata, the data were treated as survival time data (multiple failure-per-subject data) allowing for calculation of stratum specific incidence rates and incidence rate ratios with 95% confidence intervals.

The burden diary details and costing methods and results are presented in detail in Chapter Five.
### Table 4.1
Study child, household, and time-related explanatory variables and possible values for these variables collected at enrolment visit, Respiratory Virus Study, 2003-2004

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Details, range of possible values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child variables</strong></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male or female</td>
</tr>
<tr>
<td>Age</td>
<td>Age in years (calculated on a daily basis)</td>
</tr>
<tr>
<td>Breast feeding history</td>
<td>Report of exclusive or any breast feeding: current, previous, or never</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>A history of study child having received any doses of influenza vaccination for the current season, or previously</td>
</tr>
<tr>
<td>Childcare attendance</td>
<td>Type of care, if any, attended (see text)</td>
</tr>
<tr>
<td>Bedroom sharing</td>
<td>The number of other people sharing the study child's bedroom</td>
</tr>
<tr>
<td><strong>Household variables</strong></td>
<td></td>
</tr>
<tr>
<td>Household size</td>
<td>Combined number of adults and children</td>
</tr>
<tr>
<td>Household income</td>
<td>Collected in nine brackets matching Australian Bureau of Statistics classification</td>
</tr>
<tr>
<td>Private health insurance</td>
<td>Whether the family has private health insurance</td>
</tr>
<tr>
<td>Household smoker</td>
<td>Whether a cigarette smoker lives in the household</td>
</tr>
<tr>
<td>Environmental tobacco smoke exposure</td>
<td>Whether the study child is directly exposed to environmental tobacco smoke either in the home or car</td>
</tr>
<tr>
<td>Household influenza vaccination</td>
<td>Presence of household members who have received influenza vaccine for the current season, or in previous years</td>
</tr>
<tr>
<td>Primary carer employed</td>
<td>Whether the primary carer works outside of the home</td>
</tr>
<tr>
<td>Parent education level</td>
<td>Highest level of education achieved by mother / father; Australian Bureau of Statistics classification</td>
</tr>
<tr>
<td><strong>Time-related variables</strong></td>
<td></td>
</tr>
<tr>
<td>Month of year</td>
<td>Calendar month of the year</td>
</tr>
<tr>
<td>Season</td>
<td></td>
</tr>
<tr>
<td>Summer 1</td>
<td>17 January 2003 to 28 February 2003</td>
</tr>
<tr>
<td>Autumn</td>
<td>01 March 2003 to 31 May 2003</td>
</tr>
<tr>
<td>Winter</td>
<td>01 June 2003 to 31 August 2003</td>
</tr>
<tr>
<td>Spring</td>
<td>01 September 2003 to 30 November 2003</td>
</tr>
<tr>
<td>Summer 2</td>
<td>01 December 2003 to 31 January 2004</td>
</tr>
</tbody>
</table>

* For time-related variables, influenza-like illnesses are assigned to the day when the illness first occurred (date 1)

### 4.3.6 Laboratory methods

#### 4.3.6.1 Victorian Infectious Diseases Reference Laboratory

The development, testing, validation, and implementation for diagnostic use of the multiplex PCR detection of respiratory viruses (RespPCR) by the Victorian Infectious Diseases Reference Laboratory have been published in detail. The testing of ReVS specimens occurred in parallel
with specimens received for diagnostic testing or as part of general practice sentinel influenza surveillance.439

Preparing and testing ReVS specimens involved a number of processes, including:

- Spiking the specimen with a non-human virus, bovine diarrhoeal disease virus (BVDV), for the purpose of acting as an internal control for the nucleic acid extraction process;

- Viral nucleic acid extraction was performed using two commercially available methods in a hierarchical fashion, with the second process being performed if inhibitors of PCR were present, as shown by the failure of the BVDV control to amplify;

- Reverse transcription for RNA viruses; and

- Conventional polymerase chain reaction testing, including amplicon detection by agarose gel electrophoresis, for the identification of respiratory virus nucleic acid.

A panel of nested PCR assays, using primers reported by others or developed at VIDRL, were used to test all study subject specimens for influenza A virus (H1 and H3 subtypes), influenza B virus, adenoviruses, human respiratory syncytial virus, picornaviruses (primers specific for all enteroviruses and picornaviruses), and parainfluenza virus types 1, 2, and 3. This represents tubes 1, 2, and 3 in the article describing the VIDRL RT-PCR method.448 A negative and positive control specimen were used for each round of PCR.

4.3.6.2 Queensland Paediatric Infectious Diseases Laboratory, Sir Albert Sakzewski Virus Research Centre, Royal Children’s Hospital, Queensland

Available material, both the original study specimens and available extracted cDNA from study subjects and household contacts were couriered overnight on dry ice to the Queensland
Paediatric Infectious Diseases Laboratory, Sir Albert Sakzewski Virus Research Centre, Royal Children’s Hospital, Brisbane, Queensland, where they were tested for HMPV and hCoV-NL63.

A published real-time assay was used to detect HMPV\(^{408}\) and two previously described nested assays were used to detect hCoV-NL63.\(^{21}\) For hCoV-NL63, testing of RNA consisted of a single-tube RT-PCR amplification followed by a nested PCR using 1 μl of the first round product (HotStarTaq, QIAGEN, Australia). Positive results from assay one were confirmed using assay two. Specimens were considered positive when the two assays were in agreement. In testing samples from this study, there was no assay disagreement.

All RT-PCR assays were performed using the OneStep RT-PCR kit (QIAGEN, Australia) incorporating 0.6 μM of each primer and subjecting the reaction mixes to a 20 minute incubation at 50°C followed by 15 minutes at 95°C. PCR was performed for 45 cycles at 94°C for 30 seconds; 55°C for 30 seconds; and 72°C for 30 seconds.

### 4.3.7 Household contact illnesses

Parents were asked to perform household surveillance from the beginning of the illness in the study child, up to seven days after the illness had resolved. If a respiratory illness was identified in a household contact, we asked that symptom and burden data were recorded (on a separate, household contact specific diary card) and a combined nose-throat swab was collected. The diary card was mailed back with other study documentation at the end of each month.

The household contact diary card collected the same daily symptom details as those collected from the study subject for the life of the illness. Truncated burden data were also collected: health-care visits for the illness, including general practice, hospital, and other health-care provider visits; whether antibiotics were taken to treat the illness; time away from work or school for the household contact because of their illness; and excess time spent by a carer looking after the household contact because they were ill.
4.4 Results

4.4.1 Recruitment of study subjects and enrolment

Informed consent was provided by a parent of 234 children eligible to participate in the study. These children were enrolled from 17 January 2003 to 05 November 2003 (Figure 4.1), and were recruited from 26 local council areas around greater Melbourne (Figure 4.2).

Figure 4.1  Cumulative enrolment of study children and child-days of symptom diary return for each study day, 17 January 2003 to 31 January 2004

Of the 234 children enrolled, there were no daily symptom diaries submitted for five, leaving 229 (98%) children for whom at least one symptom diary had been returned. The final day for data collection for all children on the study was 31 January 2004. The maximum possible days for all children on the study was 68,400 child-days (mean: 292 days per child). The actual number of child-days for which daily symptom data were submitted was 56,397 days, representing 82% of the maximum possible days (Table 4.2). The widest margin between possible child-days and
received data occurred in December 2003 and January 2004 (Figure 4.1); this time of year is traditionally a period where families go away on holidays in Australia, and many families gave this as a reason for non-return of study material over the Christmas and New Year period. Other reasons for non-return of study paperwork included the arrival of a new baby in the household making study participation a lower priority, significant illness in a family member, and not finding time to complete paperwork due to general busyness of family life. A small number of families moved away from Melbourne, either interstate or overseas, during the study.

Table 4.2 Relative contribution to study from different age groups (by year of age)

<table>
<thead>
<tr>
<th>Age *</th>
<th>Number of children in age group at enrolment †</th>
<th>Maximum possible child-days contribution from age group ‡</th>
<th>Actual child-days contribution from age group (%) §</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65</td>
<td>9,649</td>
<td>8,661 (90%)</td>
</tr>
<tr>
<td>1</td>
<td>56</td>
<td>20,087</td>
<td>16,003 (80%)</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>14,641</td>
<td>11,835 (81%)</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>12,779</td>
<td>10,343 (81%)</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>9,421</td>
<td>8,112 (86%)</td>
</tr>
<tr>
<td>5</td>
<td>0†</td>
<td>1,823</td>
<td>1,443 (79%)</td>
</tr>
<tr>
<td>Total</td>
<td>234</td>
<td>68,400</td>
<td>56,397 (82%)</td>
</tr>
</tbody>
</table>

* Year of age

† Includes five children for whom no daily symptom diaries were submitted

‡ Calculated as the difference between the first day of data submission (where no data submitted, enrolment date used) and the last date of the study (31 January 2004), and disaggregated into year of age categories — value calculated on a daily basis from 234 children enrolled in the study

§ The number of child-days of daily symptom data submitted (daily symptom diary) from 229 study subjects, disaggregated into year of age categories (value calculated on a daily basis), and this figure shown as a percentage of the maximum possible child-days for that age group

†† Children had to be not yet five years of age to enrol in the study, but could turn five year during the course of the study
Of the 229 children from whom data were submitted, 118 (52%) were female and 111 (48%) were male. At the time of study entry 63 children (27.5%) were less than one year of age, 55 (24.0%) were one or more but less than two years of age, 44 (19.2%) were two or more but less than three years of age, 45 (19.7%) were three or more but less than four years of age, and 22 (9.6%) were four or more but less than five years of age.

The 229 children and their families were not obviously geographically clustered, coming from 111 postcodes in 26 local council areas of greater Melbourne (Figure 4.2). Of 111 postcode areas represented by children enrolled in the study, 41 contained one study child, 20 contained two children, 34 contained three children, eight contained four children, four contained five children, two contained six children, two contained seven children, and an individual postcode area contained eight, nine, and eleven children each.
Nearly all (220/229, 96%) study children had been breastfed for a period after birth. Study subjects who were being breastfed during the study contributed 15% (8,395 child-days) of the study time compared with 4% (2,434 child-days) contributed by never-breastfed children, and 81% (45,568 child-days) from previously breastfed children.

Influenza vaccination was uncommon in the study group. Only four children (1.7%) were reported to have ever received influenza vaccine, with three of those reporting vaccination for the influenza season covered by this study. No adults in the study households where study subjects had been immunised reported ever having received influenza vaccine. There were another seven households (3%) where an adult ever had received an influenza vaccine. Parents of study children
did not fall into the 65 years and over age group who are eligible for free influenza vaccination recommended for routine annual influenza vaccination by the National Health and Medical Research Council\textsuperscript{49} and provided free of charge under the National Immunisation Program in Australia. The age range of study parents was 20 to 46 years at child enrolment for mothers, and 24 to 51 years for study fathers.

More than two-thirds of study children (154/229, 67\%) were attending child care of some description at study enrolment. Of those children in care, 111 (72\%) were in formal child care only, 21 (14\%) were in informal care only, and 22 (14\%) were receiving a combination of both formal and informal child care. These figures reflect the overall contribution to study time by child care usage and type of care provided (Figure 4.3).
For over a quarter of study time (16,112/56,397, 29%), participants shared their bedroom, with most of this time spent sharing with only one other person (12,391/56,397, 22%). Two was the highest number of other people a study child shared with, and when this occurred (3,721/56,397, 7%) the child was always sharing with his or her parents.

Children from a single parent household provided nearly five per cent of all study time (Table 4.3). Two parent, two child households were the most common (43% of study time), flanked by two parent, one child households (27%) and two parent, three children households (19%). Children from these three household types provided 90% of total study time.

<table>
<thead>
<tr>
<th>Family type</th>
<th>Child-days (% of total study time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single parent, one child</td>
<td>683 (1.2%)</td>
</tr>
<tr>
<td>Single parent, two children</td>
<td>283 (0.5%)</td>
</tr>
<tr>
<td>Single parent, three children</td>
<td>1,644 (2.9%)</td>
</tr>
<tr>
<td>Two parents, one child</td>
<td>15,423 (27.4%)</td>
</tr>
<tr>
<td>Two parents, two children</td>
<td>24,249 (43.0%)</td>
</tr>
<tr>
<td>Two parents, three children</td>
<td>10,958 (19.4%)</td>
</tr>
<tr>
<td>Two parents, four children</td>
<td>2,166 (3.8%)</td>
</tr>
<tr>
<td>Two parents, five children</td>
<td>991 (1.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>56,397 (100%)</td>
</tr>
</tbody>
</table>

Children enrolled in the study were unlikely to be exposed to environmental tobacco smoke (ETS) from other household members. One hundred and ninety-six households (86%) reported having no household members who smoked tobacco products. Only three (1% of all households) of the remaining 33 households (14% of all households) reported children were routinely directly
exposed to ETS resulting from a household member smoking inside the house, or in an automobile whilst children were present.

Annual household income was collected in brackets based on Australian Bureau of Statistics (ABS) household income data, and, similar to the pilot study, ReVS participants more commonly came from higher income households (Figure 4.4). The highest annual income bracket, greater than $103,999, was the modal income range for study households. Less than five per cent of all households come from the lowest three brackets covering an annual household income of less than $31,200. A comparison of study households in each income bracket with similar figures for all of Victoria from the 2001 Census shows that the state figures have a more gradual and stepwise increase in cumulative percent (Table 4.4).

![Figure 4.4](image-url)

**Figure 4.4** Annual household income by number and percent of total for 229 families that provided any daily symptom data to the Respiratory Virus Study, 17 January 2003 to 31 January 2004
In keeping with these findings, 79% of study households reported having private health insurance at enrolment. The mother of the study child worked outside of the home in just over half (117/229, 51%) of the participating households.

<table>
<thead>
<tr>
<th>Annual household income</th>
<th>Study households (%)</th>
<th>Victorian households (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bracket %</td>
<td>Cumulative %</td>
</tr>
<tr>
<td>&lt; $10,400</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>$10,400 to $20,799</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>$20,800 to $31,199</td>
<td>3.1</td>
<td>4.4</td>
</tr>
<tr>
<td>$31,200 to $41,999</td>
<td>9.2</td>
<td>13.6</td>
</tr>
<tr>
<td>$42,000 to $51,999</td>
<td>10.0</td>
<td>23.6</td>
</tr>
<tr>
<td>$52,000 to $62,399</td>
<td>10.5</td>
<td>34.1</td>
</tr>
<tr>
<td>$62,400 to $77,999</td>
<td>17.5</td>
<td>51.6</td>
</tr>
<tr>
<td>$78,000 to $103,999</td>
<td>23.1</td>
<td>74.7</td>
</tr>
<tr>
<td>≥ $104,000</td>
<td>25.3</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

* Victorian households containing children; column total and final cumulative per cents may not equal 100% due to rounding

4.4.2 Study compliance

The return rate of specimens and burden diaries was examined to assess compliance with study procedures. From review of 56,397 child-days of daily symptom surveillance, 730 acute
respiratory illnesses were identified (Figure 4.5). For these illnesses, approximately three-quarters (74%) had at least one specimen returned, and a similar proportion (72%) had burden data returned. Two-thirds of illnesses (66.7%) had the combination of at least one specimen and burden data returned (Figure 4.5).
Figure 4.5  Compliance with ReVS study procedures: return of specimens and burden diaries in the event of an ARI in a study child

234 children enrolled in the Respiratory Virus Study

Maximum possible symptom data: 68,400 child–days

56,397 child–days of daily symptom data returned

730 acute respiratory illnesses identified in study subjects during study

187 ILIs (26%) with no specimens returned
543 ILIs (74%) with at least one specimen returned

202 ILIs (28%) with no burden data returned
528 ILIs (72%) with burden data returned

Return of data for ARIs:

- no specimens and no burden diary 146 (20.0%)
- burden diary, no specimens 41 (5.6%)
- at least one specimen, no burden diary 56 (7.7%)
- at least one specimen with burden diary 487 (66.7%)
4.4.3 Daily symptoms and acute respiratory illness in study children

Of the 56,397 child-days of symptom data, children had at least one of the solicited symptoms (including a maximal daily measured temperature greater than 37.5°C) on 12,720 days (23%). The proportion of days with any symptom varied by month of study, reaching a peak in August 2003 at 24% (Figure 4.6).

Figure 4.6 Child-days by month with and without any symptoms (number and per cent), Respiratory Virus Study, January 2003 to January 2004

---

Runny nose and any cough (combined Category A symptom: pulmonary congestion/moist cough; and Category B symptom: cough) were the most commonly reported symptoms, occurring on 16.0% and 10.2% of days, respectively (Table 4.5). There were 21% of child-days (11,615/56,397) on which either a runny nose or any cough was reported in a study child (Table 4.5). Parent-reported fever or temperature greater than 37.5°C was recorded on 870 days (1.5%) with a monthly range of 0.1% (January 2004) to a high of 3.2% (August 2003).
There were 4,697 (8.3%) child-days on which the definition for an ARI (at least one Category A symptom or at least two Category B symptoms) was met. Because an ARI could include days that did not meet this definition (Figure 3.1), with either insufficient symptoms to met the definition (such as having only one Category B symptom) or no symptoms, the number of days that fell within an ARI is greater than the number of days that a child had sufficient symptoms to met the ARI definition. There were 8,926 child-days that fell within the boundaries of the 730 ARIs identified, giving an average duration 12.2 days per ARI. This means just over half the days (53%, 4,697/8,926) contained within all ARIs met the ARI definition, with the average number of days per ARI that met the ARI definition being 6.4 days.
Table 4.5  Number* and percent of days with individual symptoms, in order of frequency, Respiratory Virus Study, 2003-2004

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Child-days (% of total study time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>43,677 (77.5%)</td>
</tr>
<tr>
<td>Runny nose (nasal congestion)</td>
<td>9,024 (16.0%)</td>
</tr>
<tr>
<td>Cough</td>
<td>5,027 (8.9%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>1,671 (3.0%)</td>
</tr>
<tr>
<td>Decreased activity (lethargy/weakness)</td>
<td>918 (1.6%)</td>
</tr>
<tr>
<td>Pulmonary congestion (moist cough)</td>
<td>905 (1.6%)</td>
</tr>
<tr>
<td>Fever†</td>
<td>870 (1.5%)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>568 (1.0%)</td>
</tr>
<tr>
<td>Ear infection</td>
<td>428 (0.8%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>354 (0.6%)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>248 (0.4%)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>132 (0.2%)</td>
</tr>
<tr>
<td>Chills</td>
<td>119 (0.2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>72 (0.1%)</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>46 (0.1%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>20 (0.0%)</td>
</tr>
</tbody>
</table>

* Child-days with symptoms do not add to total child-days with any symptoms as more than one symptom could be present on a given day

† Parent-reported fever or documented temperature > 37.5°C
4.4.4 The epidemiology of acute respiratory illnesses and virus detection in study children

There were 730 acute respiratory illnesses identified occurring over 8,926 ARI days (mean: 12.2 days; median 10 days), with illnesses ranging in duration from one to 99 days (Figure 4.7).

Figure 4.7 Duration of the 730 ILIs identified in the Respiratory Virus Study, 2003 to 2004

Nearly half (49.9%, 364/730) of all ARIs were uncomplicated, occurring without fever or otitis media. Another 39.5% (288/730) were febrile ARIs (with fever but without otitis media), 6.3% (46/730) were febrile otitis media, and the remaining 4.4% (32/730) were otitis media without fever. The median duration of illness varied by type of ARI: uncomplicated ARIs had median duration of 9 days (mean 10.8 days); febrile ARIs 10 days (mean 12.6 days); otitis media 12 days (14.8 days); and febrile otitis media 17 days (mean 19.0 days). Illnesses without fever (uncomplicated ARI and otitis media without fever) had a median duration of nine days (mean
11.2 days) and illnesses with fever (febrile ARI and febrile otitis media) had a median duration of 11 days (mean 13.5 days).

There were no specimens collected for 187 ARIs (26%) with at least one specimen collected for the other 543 (74%). There were 563 specimens collected from study children during the 730 ARIs: one specimen for 524 ILIs (72%); two specimens for 18 ILIs (2%); three specimens for one ARI (0%) (Table 4.6). The proportion of illnesses where a specimen was collected dropped during the course of the study: being a maximum in January 2003 when each of the four ILIs that month had a specimen collected, and reaching a minimum of 40% (6/15) in January 2004 (Figure 4.8).
Table 4.6  Illnesses, available swabs, and viral identification, Respiratory Virus Study, 2003-2004

<table>
<thead>
<tr>
<th>Illnesses, swabs, and viral identification</th>
<th>Number of illnesses (% of all illnesses)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of illnesses identified from daily symptom diaries during study</td>
<td>730 ARIs (100.0%)</td>
</tr>
<tr>
<td>ARIs with no specimens collected</td>
<td>187 ARIs (25.6%)</td>
</tr>
<tr>
<td>ARIs with one specimen collected</td>
<td>524 ARIs (71.8%)</td>
</tr>
<tr>
<td>No viruses detected</td>
<td>142 ARIs (19.5%)</td>
</tr>
<tr>
<td>One virus detected</td>
<td>336 ARIs (46.0%)</td>
</tr>
<tr>
<td>Two viruses detected</td>
<td>42 ARIs (5.8%)</td>
</tr>
<tr>
<td>Three viruses detected</td>
<td>4 ARIs (0.5%)</td>
</tr>
<tr>
<td>ARIs with two specimens collected</td>
<td>18 ARIs (2.5%)</td>
</tr>
<tr>
<td>No viruses detected</td>
<td>1 ARI (0.1%)</td>
</tr>
<tr>
<td>One virus detected</td>
<td>13 ARIs (1.8%)</td>
</tr>
<tr>
<td>Two viruses detected²</td>
<td>4 ARIs (0.5%)</td>
</tr>
<tr>
<td>ARIs with three specimens collected</td>
<td>1 ARI (0.1%)</td>
</tr>
<tr>
<td>Two viruses detected²</td>
<td>1 ARI (0.1%)</td>
</tr>
</tbody>
</table>

¹  Per cents do not add exactly to 100% due to rounding

²  In ARIs with multiple swabs collected and with more than one virus identified were all co-infections with the multiple viruses identified simultaneously in the same swab
Of the 543 illnesses with at least one specimen collected, 400 (74%) ARIs were associated with a positive PCR test for at least one of the tested viruses (Table 4.7). No viruses were identified in 143 ARIs (26%); one virus in 349 ARIs (64%); two viruses in 47 ARIs (9%); and three viruses in four ARIs (1%). All associations of multiple viruses with an illness were due to co-infections with the simultaneous identification of more than one virus from the same swab.

Picornaviruses were the most commonly identified virus type in this study, present in 49.5% (269/543) of illnesses where at least one specimen was collected. They were followed, in order of frequency of detection in illnesses with at least one specimen available, by adenoviruses: 7.9% (43/543); RSV: 7.4% (40/543); parainfluenza viruses: 6.1% (33/543); HMPV: 5.2% (28/543); influenza A virus: 4.4% (24/543); and hCoV-NL63: 3.3% (18/543). Influenza B virus was not identified in any specimen from a study child, despite being present in low numbers in diagnostic
and surveillance specimens submitted to VIDRL during March, April, August, September, and October 2003.\textsuperscript{450}

Some viruses were more likely to be involved in co-infections than their relative presence in all ARIs with a positive specimen suggested (Table 4.8). Adenoviruses, hCoV-NL63, PIVs, and HMPV, in particular, had a high proportion of their illnesses involved in co-infection — 58%, 50%, 33%, and 32%, respectively. In addition, three of these were also involved in a relatively high proportion of all co-infections — adenoviruses 49%, hCoV-NL63 30%, HMPV 30%, respectively — compared with their presence in all illnesses where a virus was identified — 11%, 5%, and 7%, respectively (Table 4.8).
Table 4.7  Pattern of virus identification in ARIs with at least one specimen collected

<table>
<thead>
<tr>
<th>Pattern of virus identification</th>
<th>Number of ARIs</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No viruses identified</td>
<td>143</td>
<td>(26.3%)</td>
</tr>
<tr>
<td>Single virus detection</td>
<td>349</td>
<td>(64.3%)</td>
</tr>
<tr>
<td>Picornaviruses</td>
<td>225</td>
<td>(41.4%)</td>
</tr>
<tr>
<td>RSV</td>
<td>36</td>
<td>(6.6%)</td>
</tr>
<tr>
<td>PIVs</td>
<td>22</td>
<td>(4.1%)</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>20</td>
<td>(3.7%)</td>
</tr>
<tr>
<td>HMPV</td>
<td>19</td>
<td>(3.5%)</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>18</td>
<td>(3.3%)</td>
</tr>
<tr>
<td>hCoV-NL63</td>
<td>9</td>
<td>(1.7%)</td>
</tr>
<tr>
<td>Co-detection: two viruses</td>
<td>47</td>
<td>(8.7%)</td>
</tr>
<tr>
<td>Picornavirus / adenovirus</td>
<td>19</td>
<td>(3.5%)</td>
</tr>
<tr>
<td>Picornavirus / hCoV-NL63</td>
<td>7</td>
<td>(1.3%)</td>
</tr>
<tr>
<td>Picornavirus / PIV</td>
<td>7</td>
<td>(1.3%)</td>
</tr>
<tr>
<td>Picornavirus / HMPV</td>
<td>4</td>
<td>(0.7%)</td>
</tr>
<tr>
<td>Picornavirus / influenza A</td>
<td>2</td>
<td>(0.4%)</td>
</tr>
<tr>
<td>Adenovirus / HMPV</td>
<td>2</td>
<td>(0.4%)</td>
</tr>
<tr>
<td>Picornavirus / RSV</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>Adenovirus / PIV</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>Adenovirus / RSV</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>RSV / hCoV-NL63</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>RSV / HMPV</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>Influenza A / hCoV-NL63</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>Co-detection: three viruses</td>
<td>4</td>
<td>(0.7%)</td>
</tr>
<tr>
<td>Picornavirus / PIV / adenovirus</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>Picornavirus / PIV / HMPV</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>Picornavirus / PIV / influenza A</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>Picornavirus / adenovirus / HMPV</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>543</td>
<td>(100%)</td>
</tr>
</tbody>
</table>

* Per cents do not add to 100% due to rounding
Table 4.8  Total number of ARIs by virus with at least one virus identified, the number and percent of these illnesses where at least one other virus was identified, and the percentage of all co-detections involving the virus

<table>
<thead>
<tr>
<th>Virus identified</th>
<th>Number of ARIs (%)</th>
<th>Number of ARIs with co-detection (%)</th>
<th>Percentage of all co-detections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picornaviruses</td>
<td>269 (68%)</td>
<td>44 (16%)</td>
<td>86%</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>43 (11%)</td>
<td>25 (58%)</td>
<td>49%</td>
</tr>
<tr>
<td>RSV</td>
<td>40 (10%)</td>
<td>4 (10%)</td>
<td>8%</td>
</tr>
<tr>
<td>PIVs</td>
<td>33 (8%)</td>
<td>11 (33%)</td>
<td>15%</td>
</tr>
<tr>
<td>HMPV</td>
<td>28 (7%)</td>
<td>9 (32%)</td>
<td>30%</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>24 (6%)</td>
<td>4 (17%)</td>
<td>8%</td>
</tr>
<tr>
<td>hCoV-NL63</td>
<td>18 (5%)</td>
<td>9 (50%)</td>
<td>30%</td>
</tr>
<tr>
<td>Total</td>
<td>400 (100%)</td>
<td>51 (13%)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Figure 4.9  Illnesses by identification of any virus and month, percent of all illnesses with any virus identification, and ARI rate, Respiratory Virus Study
The presence of respiratory viruses, individually and collectively, varied month-by-month over the course of the study (Figure 4.9; Figure 4.10; Figure 4.11).

Picornaviruses were detected from specimens during every month of the study, but reached peaks in May and October 2003 (Figure 4.10). PIVs were present at low levels in most months the year and adenoviruses through all months of the year, peaking in August with seven identifications and September with nine identifications. RSV, HMPV, and hCoV-NL63 with monthly baseline levels of zero identifications, peaked in June, with smaller increases from baseline in the adjacent months. Similarly, influenza A virus was absent for most of the year — nine months without identification — peaking in August, and July and September being the only other months of influenza identification (Figure 4.10). Influenza B was not identified from any specimen collected during the study.

The number of specimens collected in the warmer months of the year was lower compared with mid-year months, meaning the absolute number of viral identifications was lower (Figure 4.9; Figure 4.10). The association with illness, expressed as a percent of all illnesses (Figure 4.11), shows the relative presence of the respiratory viruses, month-by-month. Whilst picornaviruses were detected in relatively low numbers in the warmer months of the year, this was related to the number of specimens collected, with these viruses detected in approximately 80% of all specimens collected in January 2003 and January 2004.

Co-detections were identified in 51 illnesses: seven per cent of all illnesses; nine per cent of illnesses where at least one specimen was collected; and 13% of illnesses where any virus was detected (Table 4.7). Co-detections clustered during the cooler months of the year, when many viruses were prevalent (Figure 4.12). There were 16 patterns of co-infection: 12 associated with two viruses and four associated with three viruses. Picornaviruses were involved in 44 (86%) co-detections, including each of the co-detections involving three viruses.
Figure 4.10  Number of illnesses associated with individual viral identification by month, January 2003 to January 2004, Respiratory Virus Study

Note: Due to co-infections, individual illnesses can be associated with more than one virus.
Figure 4.11  Percent of all illnesses associated with individual viral identification by month, January 2003 to January 2004, Respiratory Virus Study

Note: Due to co-infections, individual illnesses can be associated with more than one virus
Illnesses where no specimen was collected were shorter, having a median duration of six days (mean 7.7 days), compared to a median duration of 11 days (mean 13.8 days) for illnesses where at least one specimen was collected (Table 4.9). For illnesses where a specimen was collected, co-detections with either two or three viruses was associated with a longer median duration (16 days) compared with illnesses where only one virus was identified (11 days). The range of median durations by different virus type (Table 4.9) was only three days, with HMPV and hCoV-NL63 positive illnesses having the minimum median duration of 10 days and RSV positive illnesses
having the maximum of 13 days. The minimum mean duration occurred in PIV positive illnesses (11.0 days). The mean duration of illness was highest in adenovirus positive illnesses (19.4 days) and hCoV-NL63 positive illnesses (15.7 days), but both values dropped considerably with the removal of the single highest outlier: to 14.7 days and 12.3 days, respectively.

Table 4.9  Median, range, and mean duration in days of illness by specimen collection and number of viruses identified

<table>
<thead>
<tr>
<th>Specimen and virus pattern</th>
<th>Median duration (range)</th>
<th>Mean duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>All illnesses (n=730)</td>
<td>10 (1 to 99)</td>
<td>12.2</td>
</tr>
<tr>
<td>No specimen collected (n=187)</td>
<td>6 (1 to 57)</td>
<td>7.7</td>
</tr>
<tr>
<td>Illnesses with at least one specimen collected (n=543)</td>
<td>11 (1 to 99)</td>
<td>13.8</td>
</tr>
<tr>
<td>No viruses identified (n=143)</td>
<td>10 (1 to 97)</td>
<td>12.7</td>
</tr>
<tr>
<td>Single virus identifications (n=349)</td>
<td>11 (1 to 99)</td>
<td>13.7</td>
</tr>
<tr>
<td>All co-infections (n=51)</td>
<td>16 (2 to 58)</td>
<td>17.5</td>
</tr>
<tr>
<td>Co-infection: two viruses (n=47)</td>
<td>17 (2 to 58)</td>
<td>17.9</td>
</tr>
<tr>
<td>Co-infection: three viruses (n=4)</td>
<td>13 (9 to 17)</td>
<td>13.0</td>
</tr>
<tr>
<td>Illness positive for picornavirus only (n=225)</td>
<td>11 (1 to 69)</td>
<td>13.1</td>
</tr>
<tr>
<td>Illness positive for RSV only (n=36)</td>
<td>13 (3 to 99)</td>
<td>14.7</td>
</tr>
<tr>
<td>Illness positive for PIV only (n=22)</td>
<td>11 (3 to 30)</td>
<td>11.0</td>
</tr>
<tr>
<td>Illness positive for influenza A only (n=20)</td>
<td>12.5 (6 to 37)</td>
<td>15.1</td>
</tr>
<tr>
<td>Illness positive for HMPV only (n=19)</td>
<td>10 (6 to 37)</td>
<td>13.9</td>
</tr>
<tr>
<td>Illness positive for adenovirus only (n=18)</td>
<td>12 (3 to 99)</td>
<td>19.4</td>
</tr>
<tr>
<td>Illness positive for hCoV-NL63 only (n=9)</td>
<td>10 (4 to 43)</td>
<td>15.7</td>
</tr>
</tbody>
</table>
ARIs with fever and otitis media were more likely than other illnesses to have a specimen collected, 87% compared with 74% of all other illnesses combined. But only marginally more of these were likely to be positive: 80% of ARIs with fever and otitis media were positive for at least one virus, compared with 73% of other illnesses where a specimen was collected.

Parents completing the burden diaries were asked to identify a source of infection for their child’s illness. In nearly one-third (162, 31%) of the 528 ILIs where a burden diary was available, a household contact was identified as having experienced a respiratory illness in the seven days preceding the subject’s ARI. A sibling was the most commonly suspected source of infection with a preceding illness in a brother identified in 59 episodes (36%), a sister in 49 episodes (30%), in the mother for 37 episodes (23%), the father in 16 episodes (10%), and from a grandmother in one case (0%). In a further 114 (22%) ARIs, a non-household contact was suggested as the source of infection, leaving nearly half (252, 48%) of all illnesses, where information was available, without a suspected preceding source identified. For the 114 non-household suspected sources of infection, contact for transmission was reported as exposure to other children (child care, crèche, kindergarten, preschool) in 52 cases (46%).

The 730 acute respiratory illnesses identified occurred in a total observation period of 46,063 at-risk days, giving an overall incidence rate of 0.48 ARIs per child-month for the entire study period (95% CI 0.45 to 0.52) or an annual figure of 5.8 ARI episodes per child. The peak rate of ARIs was in June at 0.87 ARIs per child-months (Figure 4.9).

Univariate incidence rate ratios and 95% confidence intervals were calculated for stratum levels of key exposure variables (Table 4.10). There was little change in incidence rates by sex. The incidence rate peaked for children aged one year at 0.44 ILIs per child-month, and fell with each increase in year of age to 0.19 ILIs per child-month for five year olds.
Exposure to child care was associated with an increase in the risk of ILI by 31% (95% CI 11 to 55%) in study children, with formal care alone increasing the risk by 34% (95% CI 12 to 60%). Bedroom sharing had no impact on incidence rates.

Table 4.10  Univariate incidence rate ratios for child-specific exposures, Respiratory Virus Study, 2003 to 2004

<table>
<thead>
<tr>
<th>Exposure and value</th>
<th>Incident rate (ARI episodes per child-month)</th>
<th>Incident rate ratio (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.400</td>
<td>1.03 (0.89 to 1.20)</td>
</tr>
<tr>
<td>Male</td>
<td>0.387</td>
<td>referent rate</td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.408</td>
<td>referent rate</td>
</tr>
<tr>
<td>1</td>
<td>0.441</td>
<td>1.08 (0.86 to 1.36)</td>
</tr>
<tr>
<td>2</td>
<td>0.411</td>
<td>1.01 (0.79 to 1.29)</td>
</tr>
<tr>
<td>3</td>
<td>0.368</td>
<td>0.90 (0.70 to 1.17)</td>
</tr>
<tr>
<td>4</td>
<td>0.330</td>
<td>0.81 (0.61 to 1.08)</td>
</tr>
<tr>
<td>5</td>
<td>0.190</td>
<td>0.47 (0.21 to 0.91)</td>
</tr>
<tr>
<td><strong>Any breast feeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0.300</td>
<td>referent rate</td>
</tr>
<tr>
<td>Previously</td>
<td>0.399</td>
<td>1.33 (0.89 to 2.09)</td>
</tr>
<tr>
<td>Current</td>
<td>0.392</td>
<td>1.31 (0.83 to 2.12)</td>
</tr>
<tr>
<td><strong>Current exclusive breast feeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.276</td>
<td>0.70 (0.30 to 1.38)</td>
</tr>
<tr>
<td>No</td>
<td>0.396</td>
<td>referent rate</td>
</tr>
<tr>
<td><strong>Previous influenza vaccination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.404</td>
<td>1.03 (0.51 to 1.85)</td>
</tr>
<tr>
<td>No</td>
<td>0.394</td>
<td>referent rate</td>
</tr>
<tr>
<td><strong>Child care</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.326</td>
<td>referent rate</td>
</tr>
<tr>
<td>Any care</td>
<td>0.427</td>
<td>1.31 (1.11 to 1.55)</td>
</tr>
<tr>
<td>Informal care only</td>
<td>0.377</td>
<td>1.16 (0.88 to 1.51)</td>
</tr>
<tr>
<td>Formal care only</td>
<td>0.436</td>
<td>1.34 (1.12 to 1.60)</td>
</tr>
<tr>
<td>Both types of care</td>
<td>0.447</td>
<td>1.37 (1.03 to 1.80)</td>
</tr>
<tr>
<td><strong>Bedroom sharing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.392</td>
<td>referent rate</td>
</tr>
<tr>
<td>No</td>
<td>0.399</td>
<td>1.02 (0.86 to 1.20)</td>
</tr>
</tbody>
</table>
Table 4.11  Univariate incidence rate ratios for household-specific exposures, Respiratory Virus Study, 2003 to 2004

<table>
<thead>
<tr>
<th>Exposure and value</th>
<th>Incident rate (ARI episodes per child-month)</th>
<th>Incident rate ratio (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children in the household</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.376</td>
<td>referent rate</td>
</tr>
<tr>
<td>2</td>
<td>0.392</td>
<td>1.04 (0.87 to 1.24)</td>
</tr>
<tr>
<td>3</td>
<td>0.438</td>
<td>1.16 (0.94 to 1.44)</td>
</tr>
<tr>
<td>4</td>
<td>0.253</td>
<td>0.67 (0.39 to 1.09)</td>
</tr>
<tr>
<td>5</td>
<td>0.614</td>
<td>1.63 (0.98 to 2.58)</td>
</tr>
<tr>
<td>Number of parents in the household</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.662</td>
<td>referent rate</td>
</tr>
<tr>
<td>2</td>
<td>0.390</td>
<td>0.59 (0.38 to 0.96)</td>
</tr>
<tr>
<td>Number of younger siblings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.402</td>
<td>1.24 (0.75 to 2.23)</td>
</tr>
<tr>
<td>1</td>
<td>0.379</td>
<td>1.17 (0.69 to 2.13)</td>
</tr>
<tr>
<td>2</td>
<td>0.325</td>
<td>referent rate</td>
</tr>
<tr>
<td>Number of older siblings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.372</td>
<td>referent rate</td>
</tr>
<tr>
<td>1</td>
<td>0.407</td>
<td>1.09 (0.92 to 1.29)</td>
</tr>
<tr>
<td>2</td>
<td>0.457</td>
<td>1.23 (0.98 to 1.52)</td>
</tr>
<tr>
<td>3 or more</td>
<td>0.349</td>
<td>0.94 (0.57 to 1.47)</td>
</tr>
<tr>
<td>Household size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.758</td>
<td>referent rate</td>
</tr>
<tr>
<td>3</td>
<td>0.364</td>
<td>0.48 (0.29 to 0.84)</td>
</tr>
<tr>
<td>4</td>
<td>0.402</td>
<td>0.53 (0.33 to 0.92)</td>
</tr>
<tr>
<td>5</td>
<td>0.403</td>
<td>0.53 (0.32 to 0.94)</td>
</tr>
<tr>
<td>6</td>
<td>0.253</td>
<td>0.33 (0.16 to 0.69)</td>
</tr>
<tr>
<td>7</td>
<td>0.614</td>
<td>0.81 (0.40 to 1.65)</td>
</tr>
<tr>
<td>Household income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; $10,400</td>
<td>no households</td>
<td></td>
</tr>
<tr>
<td>$10,400 to $20,799</td>
<td>0.315</td>
<td>referent rate</td>
</tr>
<tr>
<td>$20,800 to $31,199</td>
<td>0.436</td>
<td>1.38 (0.48 to 5.44)</td>
</tr>
<tr>
<td>$31,200 to $41,999</td>
<td>0.333</td>
<td>1.06 (0.40 to 3.95)</td>
</tr>
<tr>
<td>$41,200 to $51,999</td>
<td>0.375</td>
<td>1.19 (0.44 to 4.27)</td>
</tr>
<tr>
<td>$52,000 to $62,399</td>
<td>0.412</td>
<td>1.31 (0.49 to 4.91)</td>
</tr>
<tr>
<td>$62,400 to $77,999</td>
<td>0.340</td>
<td>1.08 (0.41 to 4.03)</td>
</tr>
<tr>
<td>$78,000 to $103,999</td>
<td>0.443</td>
<td>1.41 (0.54 to 5.23)</td>
</tr>
<tr>
<td>≥ $104,000</td>
<td>0.430</td>
<td>1.37 (0.53 to 5.07)</td>
</tr>
<tr>
<td>Median income of study households</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below</td>
<td>0.358</td>
<td>referent range</td>
</tr>
<tr>
<td>Above</td>
<td>0.436</td>
<td>1.22 (1.05 to 1.41)</td>
</tr>
</tbody>
</table>
### Table 4.11
Univariate incidence rate ratios for household-specific exposures, Respiratory Virus Study, 2003 to 2004, continued

<table>
<thead>
<tr>
<th>Exposure and value</th>
<th>Incident rate (ARI episodes per child-month)</th>
<th>Incident rate ratio (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median income of Victorian households</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below</td>
<td>0.346</td>
<td>referent range</td>
</tr>
<tr>
<td>Above</td>
<td>0.410</td>
<td>1.18 (0.99 to 1.42)</td>
</tr>
<tr>
<td><strong>Private health insurance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.399</td>
<td>1.07 (0.89 to 1.30)</td>
</tr>
<tr>
<td>No</td>
<td>0.373</td>
<td>referent rate</td>
</tr>
<tr>
<td><strong>Household smoker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.274</td>
<td>referent rate</td>
</tr>
<tr>
<td>No</td>
<td>0.413</td>
<td>1.51 (1.18 to 1.95)</td>
</tr>
<tr>
<td><strong>Environmental tobacco smoke exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.321</td>
<td>referent rate</td>
</tr>
<tr>
<td>No</td>
<td>0.396</td>
<td>1.23 (0.74 to 2.58)</td>
</tr>
<tr>
<td><strong>Household member with previous influenza vaccination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.491</td>
<td>1.26 (0.84 to 1.81)</td>
</tr>
<tr>
<td>No</td>
<td>0.391</td>
<td>referent rate</td>
</tr>
<tr>
<td><strong>Primary carer employed outside the home</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.431</td>
<td>1.23 (1.06 to 1.44)</td>
</tr>
<tr>
<td>No</td>
<td>0.349</td>
<td>referent rate</td>
</tr>
<tr>
<td><strong>Highest education level achieved by mother</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 10 or below</td>
<td>0.360</td>
<td>referent rate</td>
</tr>
<tr>
<td>Year 11 or year 12</td>
<td>0.322</td>
<td>0.89 (0.57 to 1.45)</td>
</tr>
<tr>
<td>Diploma, certificate</td>
<td>0.385</td>
<td>1.07 (0.67 to 1.78)</td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>0.386</td>
<td>1.07 (0.70 to 1.73)</td>
</tr>
<tr>
<td>Graduate, postgraduate degree</td>
<td>0.470</td>
<td>1.30 (0.85 to 2.09)</td>
</tr>
<tr>
<td><strong>Highest education level achieved by father</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 10 or below</td>
<td>0.324</td>
<td>referent rate</td>
</tr>
<tr>
<td>Year 11 or year 12</td>
<td>0.328</td>
<td>1.01 (0.76 to 1.36)</td>
</tr>
<tr>
<td>Diploma, certificate</td>
<td>0.407</td>
<td>1.25 (0.93 to 1.70)</td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>0.408</td>
<td>1.26 (0.95 to 1.68)</td>
</tr>
<tr>
<td>Graduate, postgraduate degree</td>
<td>0.478</td>
<td>1.47 (1.12 to 1.95)</td>
</tr>
</tbody>
</table>
4.4.5 Impact of acute respiratory illnesses and virus detection in study children

Features and impact of illnesses by virus and specimen return are summarised (Table 4.12). Influenza A (95%) and adenoviruses (76%) most commonly had fever, whilst picornaviruses were least likely to have fever identified (36%). Influenza A (61%) and RSV (47%) illnesses in study children were most likely to be followed by one or more respiratory illnesses in a household contact. The rate of general practitioner (GP) consultations was highest for adenoviruses (12.9/10 ARIs) and influenza A (10.6) and lowest for picornaviruses (4.6) and hCoV-NL63 (5.0). Co-detection was most common with adenoviruses (60%) and hCoV-NL63 (56%) and least common with RSV (10%).

There were 29 presentations to a hospital emergency department during an ARI, with five of these resulting in admission (Table 4.12). Of the 24 presentations that did not result in admission, eight (33%) had no specimen collected during the ARI, four had a specimen collected but no virus identified (17%), six (25%) had picornavirus identified, one (4%) had PIV identified, two (8%) had adenovirus identified, and two (8%) had influenza A virus identified; there were no co-infections identified in this hospital outpatient group.

All hospitalisation admissions resulted from a febrile respiratory illness, including two episodes of pneumonia; four had specimens collected (Table 4.12) with one RSV infection (pneumonia, admission duration three days), one influenza A virus infection (fever, dehydration, two days), one picornavirus infection (fever, wheeze, rash illness, two days), and one adenovirus/picornavirus co-infection (pneumonia, three days). The admission without a specimen collected was for fever, wheeze, cough, and shortness of breath and had admission duration of two days.
### Table 4.12  
Acute respiratory illness impact and feature comparison by specimen return and virus identification, Respiratory Virus Study, 2003 to 2004

<table>
<thead>
<tr>
<th>ARI feature</th>
<th>Picornaviruses</th>
<th>RSV</th>
<th>PIVs</th>
<th>Influenza A</th>
<th>HMPV</th>
<th>Adenoviruses</th>
<th>hCoV-NL63</th>
<th>Co-detections</th>
<th>No virus</th>
<th>No specimen</th>
<th>All ARIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIs with single virus</td>
<td>224</td>
<td>36</td>
<td>22</td>
<td>20</td>
<td>20</td>
<td>17</td>
<td>8</td>
<td>54</td>
<td>142</td>
<td>187</td>
<td>730</td>
</tr>
<tr>
<td>% of all ARIS</td>
<td>30.7</td>
<td>4.9</td>
<td>3.0</td>
<td>2.7</td>
<td>2.7</td>
<td>2.3</td>
<td>1.1</td>
<td>7.4</td>
<td>19.5</td>
<td>25.6</td>
<td>100</td>
</tr>
<tr>
<td>% of ARIs with specimen</td>
<td>41.3</td>
<td>6.6</td>
<td>4.1</td>
<td>3.7</td>
<td>3.7</td>
<td>3.1</td>
<td>1.5</td>
<td>9.9</td>
<td>26.2</td>
<td>0.0</td>
<td>74.4</td>
</tr>
<tr>
<td>Mean age (months)</td>
<td>26.2</td>
<td>27.3</td>
<td>19.5</td>
<td>29.5</td>
<td>28.3</td>
<td>24.6</td>
<td>25.0</td>
<td>24.6</td>
<td>28.9</td>
<td>30.1</td>
<td>27.6</td>
</tr>
<tr>
<td>% female</td>
<td>51</td>
<td>56</td>
<td>59</td>
<td>50</td>
<td>60</td>
<td>41</td>
<td>63</td>
<td>43</td>
<td>56</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>% in child care</td>
<td>68</td>
<td>67</td>
<td>68</td>
<td>65</td>
<td>80</td>
<td>65</td>
<td>88</td>
<td>74</td>
<td>72</td>
<td>81</td>
<td>73</td>
</tr>
<tr>
<td>Mean duration (days)</td>
<td>13.1</td>
<td>14.7</td>
<td>11.0</td>
<td>15.1</td>
<td>13.6</td>
<td>18.6</td>
<td>17.0</td>
<td>17.5</td>
<td>12.8</td>
<td>7.7</td>
<td>12.2</td>
</tr>
<tr>
<td>Median duration (days)</td>
<td>11.0</td>
<td>13.0</td>
<td>11.0</td>
<td>12.5</td>
<td>10.0</td>
<td>12.0</td>
<td>12.0</td>
<td>16.0</td>
<td>10.0</td>
<td>6.0</td>
<td>11.0</td>
</tr>
<tr>
<td>% ARIs with fever</td>
<td>36</td>
<td>50</td>
<td>50</td>
<td>95</td>
<td>55</td>
<td>76</td>
<td>50</td>
<td>45</td>
<td>44</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Months virus identified</td>
<td>13</td>
<td>6</td>
<td>9</td>
<td>3</td>
<td>7</td>
<td>13</td>
<td>6</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Peak month*</td>
<td>May</td>
<td>June</td>
<td>August</td>
<td>August</td>
<td>June</td>
<td>September</td>
<td>June</td>
<td>June</td>
<td>August</td>
<td>June</td>
<td>June</td>
</tr>
<tr>
<td>ARIs with impact diary</td>
<td>198</td>
<td>34</td>
<td>21</td>
<td>18</td>
<td>15</td>
<td>17</td>
<td>6</td>
<td>52</td>
<td>126</td>
<td>41</td>
<td>528</td>
</tr>
<tr>
<td>% subsequent illness in ≥1 contact†</td>
<td>30</td>
<td>47</td>
<td>33</td>
<td>61</td>
<td>13</td>
<td>24</td>
<td>33</td>
<td>38</td>
<td>21</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>GP visits/10 ARIs†</td>
<td>4.6</td>
<td>7.4</td>
<td>6.2</td>
<td>10.6</td>
<td>8.7</td>
<td>12.9</td>
<td>5.0</td>
<td>7.9</td>
<td>6.3</td>
<td>8.0</td>
<td>6.4</td>
</tr>
<tr>
<td>ARIs with hospitalisation†</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>ARIs with ED presentation†</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>Total ARIs with virus identified‡</td>
<td>269</td>
<td>40</td>
<td>33</td>
<td>24</td>
<td>33</td>
<td>43</td>
<td>18</td>
<td>54</td>
<td>142</td>
<td>187</td>
<td>730</td>
</tr>
<tr>
<td>% of virus IDs with co-detections</td>
<td>17</td>
<td>10</td>
<td>33</td>
<td>17</td>
<td>39</td>
<td>60</td>
<td>56</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>10%</td>
</tr>
</tbody>
</table>

* All peak months in 2003  
† Data from 528 ARIs with impact diaries returned  
‡ Row sums to more than the total number of ARIs (730) because figures include coinfections, which means that individual ARIs may be represented in 2 or 3 columns  
§ Data include the percentage of all illnesses with ≥1 specimen returned where ≥1 virus was identified (54 of 543)
4.4.6 Subsequent illnesses in household contacts

The epidemiology of subsequent illnesses in household contacts will only be examined briefly as specimens from these remain frozen awaiting testing.

Of the 730 illnesses in study subjects, 164 (22%) were followed by a respiratory illness in a household member (Figure 4.13). Of these 164 study child ARIs, 137 (84%) were followed by a subsequent illness in one household contact, 27 (15%) were followed by illnesses in two household contacts, and three (2%) were followed by illnesses in three household contacts; a total of 194 subsequent illnesses in household contacts. Of the 194 illnesses in household contacts, 173 (89%) had a specimen collected and 179 (92%) had a burden diary returned (Figure 4.13).

Where a household contact burden diary had been returned (n=179), there were 112 uncomplicated ARIs (63%); 50 febrile ARIs (28%); 12 (7%) ARIs with otitis media; and 5 (3%) ARIs with fever and otitis media. The mean duration of the 179 illnesses was 10.1 days, and median duration 10 days (Figure 4.14). Individual household contact diaries collected symptom data for 10 days, and although participants were asked to complete as many diaries as necessary for each illness, it is clear from the clustering for duration at day 10 (Figure 4.14) that this instruction was not always followed. The clustering of illness duration at ten days means that mean and median durations are likely to be conservative estimates.
730 acute respiratory illnesses identified in study subjects during study

164 illnesses (22%) were followed by at least one illness in a household contact

137 episodes of illness in one household contact only
24 episodes of illness in two household contacts only
3 episodes of illness in three household contacts only

194 subsequent illnesses in household contacts

Return of data for subsequent illnesses in household contacts:
- burden diary, no specimens 21 (10.8%)
- specimen, no burden diary 15 (7.7%)
- specimen and burden diary 158 (81.4%)
Chapter 4: The Respiratory Virus Study — epidemiology

Figure 4.14 Duration of 179 subsequent illnesses in household contacts where diaries were returned

Note: The clustering of illness durations at 10 days is likely due to diary card collecting symptoms had initial space for recording 10 days only; study families were encouraged to report continuing symptoms on further diaries.

4.5 Discussion

In this Chapter, the key findings of the community-based study examining the role of respiratory viral illness in 234 pre-school aged children are presented. The conduct and results of this work make a number of novel contributions to our knowledge about these infections in children.

There were 234 children recruited to the study, providing 56,397 child-days of symptom data – 82% of the maximum possible 68,400 days. Of these 56,397 days, at least one of the solicited symptoms was present on 23% of days. The most commonly reported symptoms were runny nose and any cough (category A option: pulmonary congestion/moist cough or category B option: cough) with either or both of these occurring on 21% of child-days. Fever was present on 1.5% of days, peaking in the mid-winter months.
There were 730 acute respiratory illnesses identified in study children with 46,063 at-risk days, giving an overall incidence rate of 0.48 ARIs per child-month (95% CI 0.45 to 0.52) or an annual number of 5.8 ARI episodes per child. The peak incidence month was June 2003 with 0.87 episodes per child-month. There were a number of child-specific and household exposures that were significantly associated with an increased rate of ARIs:

- Childcare outside of the home, with the highest risk for those children receiving a combination of both formal and informal care;

- Having the primary carer employed outside the home;

- Having a father with a graduate or post-graduate degree;

- Coming from a single parent household or a household with only two occupants (parent and child); and

- Having a household income above the median of all study households.

A number of variables that increase the risk of ARI are potentially related to each other and further analysis using a method to control for confounding would be required to determine if these interacted with each other. However, as shown from the results of virus testing and will be shown in Chapter 5, these illnesses do not represent a homogenous collection of related outcomes.

At least one specimen was returned in 543 (74%) of ARIs, and at least one virus could be detected by PCR testing in 74% of illnesses with a specimen available. Co-detections occurred in 10% of ARIs.
Chapter 4: The Respiratory Virus Study — epidemiology

The most common virus group identified in specimens from study subjects were the picornaviruses – they were found in 41% of ARIs with a specimen returned, and in 31% of all ARIs. Picornavirus-related ARIs were at the milder end of the spectrum. Associated illnesses had a relatively shorter median duration of 11 days and subsequent respiratory illness followed in at least one household contact in 30% of ARIs. They were associated with GP visit rate of 4.6/10 ARIs and were responsible for the highest absolute number of illnesses and emergency department presentations.

RSV was the next most common virus found in 5.5% of returned specimens; when present as the only agent it was associated with the longest median duration of illness at 13 days and subsequent respiratory illness in at least on household contact occurred after 47% of ARIs. Influenza A and adenovirus-related ARIs were less common, being found in 24 and 43 ARIs overall or 20 and 17 ARIs as a single agent, respectively. Influenza A ARIs had fever identified 95% of the time, and for adenoviruses 76% of ARIs. For influenza A, household contact illness followed in 61% of ARIs, and every 10 cases generated 10.6 GP visits; matching figures for adenoviruses were 24% and 12.9 visits. Whilst associated with relatively few ARIs, this study demonstrated the community circulation of two viruses recently identified at the time of study conduct: HMPV and hCoV-NL63.

For some viruses, the data in the impact table are generated from small numbers of infections, and point estimates should be interpreted with caution. Despite this caution, it is reassuring that, for individual viruses, the variety of impact data, such as the presence of fever, GP visits, and likelihood of subsequent illness in a household contact, are generally all in agreement.

Picornaviruses are the most common cause of human infection, with essentially all children infected by their second birthday. In recent years, picornavirus research has led to an increasing awareness that these viruses, particularly rhinoviruses, have an important role in complicated upper respiratory tract infections with involvement of sinuses and the middle ear. Contrary to accepted orthodoxy, it is now recognised that their influence extends to the
lower airways with a predominant role in asthma exacerbations and wheezing in children,\textsuperscript{52,105} as well as pneumonia in immunocompetent individuals of all ages.\textsuperscript{106-108} More sensitive molecular detection, compared to conventional techniques,\textsuperscript{115} has driven much of this improved understanding. Use of rhinovirus or picornavirus-specific PCR suggests this group may be responsible for over 50\% of acute respiratory illness.\textsuperscript{111-116} As well as documenting prevalence, molecular techniques have also identified the previously unknown group C rhinoviruses.\textsuperscript{9,122,451} Since their identification group C rhinoviruses have been identified in children with lower respiratory tract infection,\textsuperscript{452,453} and asthma and wheezing in particular.\textsuperscript{454} Based on sequence details of this new group, the primers used for generic picornavirus identification in this study were capable for detecting the group C rhinoviruses.\textsuperscript{448} To assist our understanding of the epidemiology of the rhinoviruses, further typing of the picornavirus positive specimens in this study is required.

Whilst new molecular methods have consolidated the role of rhinoviruses in acute respiratory illness, they bring with them issues of interpretation. Using molecular methods, rhinoviruses have been serially identified in children for weeks following an initial positive result, and shown to be highly prevalent in both symptomatic and asymptomatic children. When this study was being planned, the manuscripts that have identified rhinovirus nucleic acid in serial specimens following initial identification during symptomatic illness and in asymptomatic individuals, had not been published.\textsuperscript{455-458} There are now a number of papers which reinforce the need for specimens to be collected from a control population or specimens to be collected from study subjects during asymptomatic periods in respiratory virus research.

In a paper published in 2002, rhinovirus nucleic acid was found in 20\% of 107 Finnish children having elective surgery without preceding or subsequent respiratory symptoms.\textsuperscript{455} In a Dutch study, the same proportion of children without nasal symptoms also had rhinovirus RNA detected.\textsuperscript{456} In another Finnish study, 16\% of asymptomatic children were PCR positive for rhinovirus, 50\% of initially rhinovirus-positive, symptomatic children were still PCR positive at two weeks, and 4\% were still positive at five weeks.\textsuperscript{457} In a clinical trial for respiratory virus vaccines,
rhinovirus RNA was found in 22% of specimens collected from participants when they had no symptoms, and in 36% of specimens when symptoms were present. Along with these data, the high proportion of adenoidal and tonsilar tissue positive for rhinovirus RNA, persisting throughout most months of the year, has also been cited as supporting the concept of rhinovirus persistance. However, this interpretation of generic rhinovirus or picornavirus-positive PCR results from prevalence studies became more complicated with a recent paper from Finland confirming different rhinovirus strains can co-circulate and rapidly replace each other in households, causing both symptomatic and asymptomatic infections. This paper also showed that new strains of rhinovirus can appear within days of an initial strain-specific positive PCR test. An unresolved question remains about disease attributable to rhinoviruses in studies such as this one, and even in others where control specimens are collected. The high prevalence of these viruses combined with co-circulation of the many different and expanding strains means that, in terms of incident infections, it may not be possible to reliably interpret published studies to date. Further limitations on interpreting PCR results are required as current molecular methods are not specifically designed to be able to identify co-detection of different strains of picornaviruses. Given these viruses are the most prevalent identified in this and other studies, this mean there are currently no methods for identifying the most probable virus co-detection event: two different picornavirus strains present in the same sample.

This highlights an issue with the data from this study: control specimens were not collected from children at study entry nor were any specimens collected during asymptomatic periods. Furthermore, to date, positive specimens have not been typed to allow a more specific description of picornavirus epidemiology. To better interpret PCR findings for this group of viruses, a large family cohort study with systematic collection of specimens at regular time points regardless of symptoms, along with symptomatic sampling, is required. When rhinoviruses are identified in such studies, they need to be typed so that presence of other strains and rapid strain replacement can be differentiated from what was believed to be persisting nucleic acid.
All molecular assays performed at VIDRL were conventional PCR tests, meaning amplification and visualization of assay product took place as separate steps. Amplicon detection was performed by agarose gel electrophoresis. Using these methods it has been demonstrated that conventional PCR is somewhat less sensitive than real-time PCR, and it is likely that estimates for virus detection using this manner in this study, may be somewhat conservative.

Although conducted during a season with higher-than-normal influenza activity, influenza A was associated with fewer illnesses than RSV. Influenza A illnesses were more severe than those associated with RSV, having 95% of infections associated with fever, the highest figure for subsequent illness in ≥1 household contact, and, on average, ≥1 GP physician visit per illness. Adenoviruses were identified in all months of the study, and when identified in isolation, caused illness at the more severe end of the spectrum, often involving fever with a prolonged duration, and having the highest GP consultation rate (12.9 visits/10 ARIs). However, adenoviruses were the viral group with the highest proportion involved in co-detections. It is possible that a proportion of the adenoviruses identified in co-detections represent persistence rather than acute infection. This study demonstrated, soon after their discovery, that HMPV and hCoV-NL63 were involved in community-wide transmission in pre-school aged children. HMPV was as common as influenza A in this group and caused moderate disease; findings in keeping with other publications since this study.

Large community-based studies have become increasingly uncommon in recent times, most likely because of cost. Such studies have been replaced by hospital or diagnostic specimen bank-based retrospective studies. From our pilot study, we knew parents could recognize and document ARIs of interest, and reports in the literature suggested that parents could be trained to collect an adequate respiratory specimen. Previous community-based work on respiratory viral infections has required research staff to collect a specimen. This has the benefit of allowing for the collection of clinical information, but entails additional expense. As well as cost, there is also some evidence to suggest that using parent collection at home may be more likely to result in a specimen being collected, compared with requiring parents to be available for a home visit or to
present for a clinic visit with a child with symptoms.\textsuperscript{471} This study showed that although parent collection and home-visited households identified a similar number of symptomatic periods during the study (47 and 49, respectively), the illness periods in parent collection households were approximately twice as likely to result in specimen collection, although this finding did not reach statistical significance (43% and 24%, respectively; \(p=0.07\)). Parent-collected specimens may also be more likely to be positive for a virus, possibly by virtue of being collected at an earlier point in illness. Home-collected specimens were positive for any virus 80% of the time, compared with 67% of clinic-collected specimens (\(p=0.44\)).\textsuperscript{471}

Other recent studies have used molecular methods for virus identification in specimens from community-based children. An English home-visit study, which followed 88 infants with \(\geq 1\) atopic, asthmatic parent during their first winter, tested for respiratory viruses, some bacterial pathogens, hCoV-OC43, and hCoV-229E, but not HMPV or hCoV-NL63, and identified a respiratory pathogen in 103 (83%) of 123 episodes.\textsuperscript{119} A similarly designed Western Australian study followed ARIIs in 263 infants (with \(\geq 1\) parent having a diagnosis of asthma, hay fever, or eczema) during their first year (including testing for HMPV, hCoV-OC43, and hCoV-229E) and identified a virus in 69% of illnesses.\textsuperscript{472} This study had an unexplained low rate of HMPV detection, being present in only 1.8% of specimens collected during illnesses. Our figure of 74% fits between these two values without having the expense of home visits or difficulty of more invasive testing.

Different overall detection rates in our study and these English and Western Australian studies may be due to a number of factors: seasonality, the relative presence of the different pathogens, the different ages and inclusion criteria for the studies, different methods for virus identification, and the nature of specimen collection (nose-throat swab versus nasal lavage or nasopharyngeal aspirate). The further identification of new agents from respiratory specimens, hCoV-HKU1,\textsuperscript{22} human bocavirus,\textsuperscript{23} and a number of new polyomaviruses,\textsuperscript{24-26} may also have an impact on relative proportions of virus identification, particularly in future studies. As well as new virus gaps in testing algorithms, we did not test for hCoV-OC43 and hCoV-229E, and this may account for
some of the virus-negative specimens we received. In the English and Western Australian studies, these viruses were identified in 9.0%\textsuperscript{119} and 5.5% (including from 4.4% of control subjects)\textsuperscript{472} of specimens, respectively. In Victorian hospital and influenza sentinel surveillance specimens, these two coronaviruses (primarily hCoV-OC43) were a reasonably common cause of influenza-like illness in children. They were found in 6% of influenza surveillance specimens and 12% of hospital specimens overall and peaked in August 2003,\textsuperscript{448} possibly accounting for the increase in virus-negative specimens that we found in August and September (Figure 4.9). As respiratory virus epidemiology was the focus of this study, we did not test for any bacterial pathogens. As well as pathogen gaps in our testing, it may be that combined NTS specimens, alone or in combination with the transport method used, reduced our sensitivity for detecting viruses – these issues are discussed further in Chapter 6.

As with all studies, the results obtained rely on the methods used. In this study, there were a number of features of study design and practice that may have influenced the results we obtained. Firstly, following our experience with recruitment for the pilot study, we sought to enrol study subjects that were more representative of the general population. The outcome of our attempts to avoid over-recruiting from higher income households is discussed in Chapter 5.

The definition used for identifying ARIs of interest in this study was the same as that used in the pivotal randomised placebo-controlled trial of cold-adapted, live attenuated, intranasal trivalent influenza vaccine to identify influenza-like illness.\textsuperscript{136} This definition could be met by having either one more severe symptom, coming from Category A, or at least two less severe symptoms from Category B. For example, fever in the absence of any other symptom met the definition, as did the combination of lethargy and irritability. This definition was used to capture the broadest range of illnesses and to make the definition easy for parents to follow without the need for ongoing instruction or training in how to recognise specific syndromes or differentiate between upper and lower respiratory tract symptoms. It may be argued that because of its high sensitivity, this definition captures illnesses of a minor nature. ARIs with no specimen returned appeared to have a mixture of severity features: duration and likelihood of subsequent illness in a household
contact were the lowest observed for any category of illness and a relatively low presence of fever; however GP visits were eight for every 10 ARIs and this category also had the highest number of emergency department presentations (Table 4.12). It is likely this category combined a mix of mild illness, but also illnesses where parents were either too concerned or too busy caring for a sick child to collect a specimen. If milder illnesses predominate in the category of ARIs without specimens returned, it may cause estimates of impact for virus-specific ARIs are biased toward being more severe than the true value.

This study was not free of missing data or loss to follow up: both represent a potential form of information bias in cohort studies. This study required a reasonable commitment from the primary care giver of study participants, usually the mother, who was responsible for completing the study diary and collecting study specimens. As many primary care givers also work out of the home, we made participation as flexible as possible by allowing families to temporarily withdraw from this study as required. This allowed study re-entry on return from family holidays or following other significant events, such as death of a family member or arrival of a new infant, that may have seen the family withdraw from the study completely. This concept is not dissimilar to seminal community-based respiratory illness studies conducted last century where cohort members could leave the study after a period of enrolment.2,4,47,50,358 The proportion of maximum possible study days we had daily symptom data for was 82%. Without an indication of the number or timing of ARIs during the non-reported child-days, it was not possible to assess the presence or direction of any bias. The proportion of missed days, compared with maximum possible days, increased as the study progressed (Figure 4.1). Given the later months of the study had lower rates of ARI (Figure 4.9), missing data from this period is likely to have had a lower rate of ARIs, and absence of these data may have biased the overall study ARI rate in a positive direction.

As well as missing daily symptom data, there were also ARIs with specimens and burden diaries not returned. The absence of specimens is likely to have led to an underestimation of the number of illnesses caused by all respiratory viruses. The proportion of ARIs with a specimen returned fell
during the final months of the study (Figure 4.8) when picornaviruses, and to a lesser extent, adenoviruses, were prevalent (Figure 4.11). It is unclear why the rate of specimen return fell during the final months of the study, but it may have been a combination of participation fatigue for some families, and difficulty returning specimens during summer holidays in December and January. Failure to have specimens returned in this period may have led to an underestimation of the count but not necessarily the proportion of ARIs in those months due to the viruses.

Burden diaries were available for 72% of ARIs identified. Parents received details of PCR testing, including negative results, by mail as they became available, and receipt of this information may have introduced an information bias. Knowledge of the viral cause of an illness may have altered the way parents sought healthcare or reported resource use, particularly for influenza, which is more prominent in the media. One factor would suggest that the impact of such a bias, if it occurred, is likely to be minimal: ARIs where no virus was identified seemed no less severe, in terms of impact, than other illnesses where viruses were identified. The impact of any bias this study procedure may have caused is discussed in Chapter 5.

There is a clear and unmet need for accurate and timely information about the community-based epidemiology of previously known and recently identified respiratory viruses in all age groups. Hospital-based studies and even community studies based around primary care have the potential to miss most illnesses: primary care physicians were consulted in only 45% of ARIs in this study. Options are currently available for the prevention and treatment of influenza with possibilities for other viruses, including vaccines and intranasal short interfering RNAs.

Despite the limitations discussed, in this Chapter I have shown that it is feasible to conduct large, community-based studies with personal or parent specimen collection using sensitive molecular techniques for diagnosis. There is a need for further work: continuing studies are required to develop the most appropriate method for symptom identification, specimen collection, and specimen transport. New molecular techniques have dramatically increased sensitivity for common viral agents as well as allowed for the detection of numerous previously unidentified
viruses. It is now time for these techniques to be further exploited in community-based work. Future studies should preferably be conducted in all ages at centres with concurrent hospital-based surveillance of respiratory viruses for comparison. Specimens should be tested for known viruses and stored for retesting when new pathogens are recognised. This approach also provides an efficient way of conducting vaccine or treatment efficacy studies requiring hundreds or thousands of participants.
Chapter 5

THE RESPIRATORY VIRUS STUDY — HEALTH ECONOMICS

5.1 Objective

The aim of this chapter is to present detailed and comparative burden information from community-managed illnesses caused by a range of known and recently identified respiratory viruses.

5.2 Introduction

Given the frequency and seriousness of childhood respiratory infections there are relatively few studies that document the economic impact of these illnesses on families and society. Such studies have tended to focus on influenza, being the only respiratory virus for which a relatively cheap and effective preventive strategy exists, particularly in healthy working adults. Recent studies that have looked at the economic impact of influenza in children have used estimates rather than actual values for key cost drivers, such as productivity loss. Little detailed information has been published about the comparative impact and burden of different respiratory viruses.

The addition of molecular testing in this study offered the prospect of calculating virus-specific average cost of illness, along with a comparison of the costs of illness where more than one virus was identified.

5.3 Methods

The methods for the costing component of the Respiratory Virus Study should be read in conjunction with the Methods section in Chapter 4.
5.3.1 Lessons incorporated from the pilot study

In the pilot study we attempted to collect detailed cost data, incorporating every identifiable resource used when a child had an acute respiratory illness. The pilot study showed that ARIs occur frequently in some children, and that non-prescription medication, in particular, was commonly used to treat symptoms. Given this, it was felt that asking parents to collect detailed information on use of these items for the duration of a cohort study, the planned duration of which at the outset was years, would be unnecessarily onerous and may have posed an obstacle to recruitment and ongoing participation. As well as non-prescription medication, there were other resources used that it was felt did not warrant the effort required to fully document: non-antibiotic prescription medication; paid child care for other children required when the study child was unwell; and travel and time costs involved in seeking health-care for the ill child. The average supplementary cost for all of these items for all illnesses in the pilot study was $16.39 (Table 3.7). All of these cost items were borne by the patient and family sector. The cost of these items combined made up 6.8% of the total cost of all illnesses. Given their modest impact, these data were not considered further in the analysis for this study. Use of antibiotics for the treatment of these illnesses was the only prescription medication collected, due to their importance beyond economic issues, including inducing antibiotic resistance in bacteria.

In the pilot study, the distinction was made between time away from work with pay lost (cost borne by the patient and family sector) or time with no pay lost (cost borne by the employer — other sector). To simplify diary keeping, this distinction was not made in ReVS. For the purpose of classifying time away from work and the associated cost as being borne either by the patient and family sector or the other sector (employer), the proportions of costs for time away from work for each sector from the pilot study were applied. Such distribution would have no impact on total and averages costs of illness, but only on the proportion of costs borne by the patient and family sector and the employer (other sector). For time seeking health-care for the ill child away from work, costs were apportioned as follows: 61% time with pay lost (patient and family sector) and 39% time with no pay lost (employer — other sector). For excess time spent caring for the ill
child away from work, costs were apportioned as follows: 31% time with pay lost (patient and family sector) and 69% time with no pay lost (employer — other sector). For the purposes of assessing the maximum variability around the division of costs across the sectors caused by variations in work time distribution, one-way sensitivity analyses were performed by assigning all time away from work, including time seeking health-care and excess time spent caring for the ill child, to either the patient and family sector, or to the employer (other sector).

5.3.2 Data collection in acute respiratory illnesses using burden diaries

When parents identified an ARI in a study child, they were asked to complete a burden diary. The burden diary for the respiratory virus study contained two distinct sections. The first section collected information about a possible source of infection for the study child’s illness: the results of this data collection have been presented in the epidemiology chapter (Chapter 4). The second section collected data about resource use associated with the ARI, using a similar method as the pilot study.

Study families were asked to mail back completed burden diaries, along with other completed study material (including the daily symptom diary, paperwork from collecting specimens, and household contact ARI diaries), to the study team on a monthly basis.

The resource items collected in ReVS were:

- Health-care visits — number and details of general practice, hospital, and other provider visits;
- Admissions to hospital;
- Use of prescribed antibiotics;
- Laboratory tests performed to investigate the illness;
• Carer time consumed during the illness seeking health-care; and

• Excess carer time during the illness spent caring for the ill study child.

Resource use in study children during the identified illnesses is described, as are the rates of key cost driver events per illness.

Time is appropriated in a similar manner to the pilot study. Time spent seeking health-care and caring for an ill study child were collected. Similar to the pilot study, parents were asked to record excess time spent caring for the ill child during the ARI; time over and above the usual time spent caring for the child when well. All carer time, either seeking health-care or excess time caring for a sick child, was collected as either time off work or as time off the carer’s usual activity.

5.3.3 Costing methods and applied costs

The costing methods used in ReVS were similar to those used in the pilot study. Incident-based costing was used in the calculation of an average cost for ARI episodes.

As a general approach to costing, where options were available for incorporating a range of costs, the most conservative value was used. This was done to ensure that calculated values represent minimum costs, and, where appropriate, sensitivity analyses have been performed to include a range of cost values.

Applied costs were sourced in a similar way to the pilot study, and the details of sources of all applied costs are provided (Table 5.1; Table 5.2). Health-care costs for both the patient and family sector and the health-care sector were sourced from the Medicare Benefits Schedule and other government statistics, and costs applied to time were from the Australian Bureau of Statistics’ values for male and female average weekly earnings.
For those illnesses where a burden diary was returned, the total cost of ARIs and the mean cost of all ARIs with the corresponding 95% confidence interval were calculated. Costing totals were calculated from a societal perspective using 2003 and 2004 Australian dollar values. All costs were incurred over a 380 day period between 17 January 2003 and 31 January 2004. The time preference for adjusting costs is not routinely considered for periods of time less than 12 months, and as this study period barely exceeds this time frame, none of the costs applied have been discounted for time preference.

Costs were allocated to the sector that was responsible for meeting them: the patient and family sector, health-care sector, or other sectors. Where applied costs were used from the pilot study — including the mean cost per illness of antibiotics and attending alternative health-care providers — they were kept at the 2001 values, and not inflated to reflect equivalent 2003 and 2004 costs.
### Table 5.1 Resource item, sector responsible for bearing cost, source of applied cost, and cost applied for resources used during the Respiratory Virus Study 2003-2004

<table>
<thead>
<tr>
<th>Resource item</th>
<th>Sector</th>
<th>Applied cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practice visits</td>
<td>Patient and family</td>
<td>Mean patient cost per GP / vocationally registered GP visit by quarter&lt;sup&gt;427&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$4.03 January to March 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$4.08 April to June 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$4.34 July to September 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$4.61 October to December 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$4.64 January 2004</td>
</tr>
<tr>
<td>General practice visits</td>
<td>Health-care</td>
<td>85% of code 23, Medicare Benefits Schedule</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$25.05 January to October 2003&lt;sup&gt;474&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$25.70 November 2003 to January 2004&lt;sup&gt;475&lt;/sup&gt;</td>
</tr>
<tr>
<td>Specialist visits</td>
<td>Patient and family</td>
<td>Mean patient cost per specialist visit by quarter&lt;sup&gt;427&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$19.30 January to March 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$19.56 April to June 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$19.74 July to September 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$20.36 October to December 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$21.65 January 2004</td>
</tr>
<tr>
<td>Specialist visits</td>
<td>Health-care</td>
<td>85% of code 104, Medicare Benefits Schedule</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$58.95 January to October 2003&lt;sup&gt;474&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$60.45 November 2003 to January 2004&lt;sup&gt;475&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other health-care provider visits</td>
<td>Patient and family</td>
<td>Application of mean other health-care provider visit cost from pilot study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$15.63 per visit to allied and alternative health professionals</td>
</tr>
<tr>
<td>Hospital emergency department visits</td>
<td>Health-care</td>
<td>Australian Ambulatory Classes group 23: Other respiratory diseases without procedure&lt;sup&gt;428&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$40 per visit</td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>Patient and family</td>
<td>15% of the Medicare Benefits Scheduled fee</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$4.95 Chest x-ray (MBS code 58500) January 2003 to January 2004&lt;sup&gt;474,475&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2.50 Full blood examination (MBS code 65070) January to October 2003&lt;sup&gt;474&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2.55 Full blood examination (MBS code 65070) November 2003 to January 2004&lt;sup&gt;475&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2.85 Urea, electrolytes, creatinine, liver function tests (MBS code 66515) January to October 2003 Medicare Benefits Schedule Book&lt;sup&gt;474&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$2.95 Urea, electrolytes, creatinine, liver function tests (MBS code 66515) November 2003 to January 2004&lt;sup&gt;475&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$3.00 Urine microscopy, culture, identification, and sensitivity (MBS code 69333) January to October 2003&lt;sup&gt;476&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$3.10 Urine microscopy, culture, identification, and sensitivity (MBS code 69333) November 2003 to January 2004&lt;sup&gt;476&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>427</sup> Mean patient cost per GP / vocationally registered GP visit by quarter.<sup>428</sup> Mean patient cost per specialist visit by quarter.<sup>474</sup> 85% of code 23, Medicare Benefits Schedule.<sup>475</sup> 85% of code 104, Medicare Benefits Schedule.<sup>476</sup> Application of mean other health-care provider visit cost from pilot study.
<table>
<thead>
<tr>
<th>Resource Item</th>
<th>Sector</th>
<th>Source and applied cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic tests</td>
<td>Health-care</td>
<td>85% of the Medicare Benefits Scheduled fee $28.35 Chest x-ray (MBS code 58500) January 2003 to January 2004[^4][^5]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$14.20 Full blood examination (MBS code 65070) January to October 2003[^4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$14.65 Full blood examination (MBS code 65070) November 2003 to January 2004[^7][^5]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$16.35 Urea, electrolytes, creatinine, liver function tests (MBS code 66515) January to October 2003[^1]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$16.85 Urea, electrolytes, creatinine, liver function tests (MBS code 66515) November 2003 to January 2004[^7][^5]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$17.10 Urine microscopy, culture, identification, and sensitivity (MBS code 69333) January to October 2003[^7][^4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$17.60 Urine microscopy, culture, identification, and sensitivity (MBS code 69333) November 2003 to January 2004[^7][^5]</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Patient and family</td>
<td>Application of mean antibiotic cost from pilot study $13.80 per course of antibiotics</td>
</tr>
<tr>
<td>Time[^*]</td>
<td>Patient and family</td>
<td>Time seeking health-care, 61% of time away from work (representing time away from work, pay lost; percent from pilot study)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excess time caring for ill child, 31% of time away from work (representing time away from work, pay lost; percent from pilot study)</td>
</tr>
<tr>
<td>Time[^*]</td>
<td>Other</td>
<td>Time seeking health-care, 39% of time away from work (representing time away from work, no pay lost; percent from pilot study)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Excess time caring for ill child, 69% of time away from work (representing time away from work, pay lost; percent from pilot study)</td>
</tr>
<tr>
<td>Hospitalisation (sensitivity analysis)</td>
<td>Health-care</td>
<td>$2,395 Hospitalisations resulting from an ARI in a study child. Applied cost from the National Hospital Cost Data Collection code E62C for public hospital admissions: respiratory infections/inflammations without complications.^[2]</td>
</tr>
</tbody>
</table>

[^*]: Applied costs for all time expended on study detailed in Table 5.2
Table 5.2  Hourly cost applied for all time on study, time seeking health-care and excess time spent caring for an ill child, by sex of carer and quarter, Respiratory Virus Study, January 2003 to January 2004

<table>
<thead>
<tr>
<th>Sex</th>
<th>Period</th>
<th>Weekly earnings*</th>
<th>Hourly cost applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>January 2003</td>
<td>$760.00</td>
<td>$20.00</td>
</tr>
<tr>
<td>Female</td>
<td>February to April 2003</td>
<td>$768.40</td>
<td>$20.22</td>
</tr>
<tr>
<td>Female</td>
<td>May to July 2003</td>
<td>$778.20</td>
<td>$20.48</td>
</tr>
<tr>
<td>Female</td>
<td>August to October 2003</td>
<td>$791.70</td>
<td>$20.83</td>
</tr>
<tr>
<td>Female</td>
<td>November 2003 to January 2004</td>
<td>$805.80</td>
<td>$21.21</td>
</tr>
<tr>
<td>Male</td>
<td>January 2003</td>
<td>$917.10</td>
<td>$24.13</td>
</tr>
<tr>
<td>Male</td>
<td>February to April 2003</td>
<td>$930.70</td>
<td>$24.29</td>
</tr>
<tr>
<td>Male</td>
<td>May to July 2003</td>
<td>$950.90</td>
<td>$25.02</td>
</tr>
<tr>
<td>Male</td>
<td>August to October 2003</td>
<td>$972.10</td>
<td>$25.58</td>
</tr>
<tr>
<td>Male</td>
<td>November 2003 to January 2004</td>
<td>$988.40</td>
<td>$26.01</td>
</tr>
</tbody>
</table>

* Weekly earnings based on Australian Bureau of Statistics average weekly, full-time adult total earnings for females and males. Responsibility for meeting time costs by sector outlined in Table 5.1.

A one-way sensitivity analysis was performed including the five episodes where a child was admitted to hospital, and, as with the pilot study, this included all costs relating to that illness, not just the cost of hospitalisation.

Virus-specific mean costs were calculated using illnesses where a positive specimen and burden diary data were available.

To gain a better understanding of the impact of illness duration on cost, the cost per day of specific virus infections was calculated. For some viruses where identification occurred only in
small numbers of illnesses, a single illness with an extreme cost could have a dramatic impact on
the mean cost of illness. A one-way sensitivity analysis was performed by recalculating cost of
illness per day by removing individual illnesses where the total cost was more than $1,500.

Details of household income were collected at the enrolment visit and, similar to the pilot study,
households from upper income bands were over-recruited (Figure 4.4). For the purposes of
comparing mean illness cost by income, we collapsed income bands into four brackets that
roughly divided the study population into income quartiles: bracket 1, <$52,000; bracket 2,
$52,000 to $77,999; bracket 3, $78,000 to $103,999; and bracket 4, ≥$104,000. The proportion of
the study population in each bracket was compared to the approximate proportions of Australian
households in the same categories.477 To allow for a direct comparison with the pilot study of
mean cost by household income, the ReVS households were placed in similar categories: bracket
1, ≤$20,800; bracket 2, $20,800 to $31,199; bracket 3, $31,200 to $51,999; and bracket 4,
>$52,000.

Data from the study were initially collated in a Microsoft Access relational database and then
collapsed into a single Stata spreadsheet as previously described. All calculations in this chapter
were performed using Intercooled Stata 8.2 for Windows.

5.4 Results

5.4.1 Diary return and the burden of acute respiratory illnesses

For the 730 ARIs identified in the Respiratory Virus Study, burden data were available for 528
(72%) of this total (Figure 4.5). Five of the illnesses where data were available resulted in an
admission to hospital: these illnesses have been removed from general calculations and are dealt
with in a sensitivity analysis, leaving 523 community-managed illnesses with a burden diary
returned.
For those illnesses where a burden diary was returned, the overall resource use associated with the community-managed ARIs identified in this study show similar patterns to those identified in the pilot study, with some key differences (Table 3.3; Table 5.3). Despite the different time frames and study populations, excess time caring for an ill child, the key cost driver in the pilot study, was remarkably consistent across both studies: 1079 hours per 100 ARIs in the pilot study and 1089 hours per 100 ARIs in ReVS — representing a difference in the mean value of only 6 minutes per ARI between the studies. There were 355 general practice (GP) visits arising from the ARIs in ReVS where burden data were available, giving a rate of 64 GP visits per 100 ARIs; compared to a rate of 36 visits per 100 ARI in the pilot study. The amount of time spent seeking health-care per illness in ReVS was twice that of the pilot study: 140 hours per 100 ARIs and 69 hours per 100 ARIs, respectively. Of time spent seeking health-care in ReVS, 45% (329.20 hours of 730.20 hours) was spent as time away from work; the same was seen in the pilot study: 46% (56.75 hours of 123.79 hours).

Table 5.3 Resource use for key items in ARIs identified in the Respiratory Virus Study, 2003 to 2004, for community-managed illnesses where a burden diary was returned (n=523) and all illnesses (n=725)

<table>
<thead>
<tr>
<th>Resource item</th>
<th>Use in illnesses with diary returned</th>
<th>Use in all illnesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practice visits</td>
<td>64 visits per 100 ARIs</td>
<td>46 visits per 100 ARIs</td>
</tr>
<tr>
<td>Emergency department presentations</td>
<td>4.4 visits per 100 ARIs</td>
<td>3.2 visits per 100 ARIs</td>
</tr>
<tr>
<td>Courses of antibiotics</td>
<td>30 courses per 100 ARIs</td>
<td>22 courses per 100 ARIs</td>
</tr>
<tr>
<td>Time seeking health care</td>
<td>140 hours per 100 ARIs</td>
<td>101 hours per 100 ARIs</td>
</tr>
<tr>
<td>Excess time caring for ill child</td>
<td>1089 hours per 100 ARIs</td>
<td>786 hours per 100 ARIs</td>
</tr>
</tbody>
</table>
5.4.2 The cost of acute respiratory illness

The total cost of the 523 non-hospitalised, community-managed illnesses, applying costs as described, was $161,454 (Table 5.4); giving an average cost for illnesses where burden data were available of $309 (95% CI $263 to $354).

One reason burden data may not have been returned was that an illness resulted in no or very little resource use. Illnesses where no burden data were returned were shorter than illnesses where a diary was returned (median duration: 6 days versus 11 days) and were less likely to have parent-reported fever or ear infection (proportion with uncomplicated illness: 57% versus 47%).

The cost of excess time spent caring for an ill child, either away from work or usual activities, was the key cost driver making up 82.2% of the total cost of illnesses (Table 5.4). The major component of this was excess time spent caring for the ill child away from the carer’s usual activity, being responsible for 63% of all costs. Female carers spent an average of 5.11 hours per ARI (95% CI 3.90 to 6.32 hours) away from usual activity caring for an ill child, whilst male carers spent an average of 0.96 hours per ARI (95% CI 0.75 to 1.16 hours) away from usual activities.

For this study the data around the distribution of time away from work as occurring with or without pay lost, either for time seeking health-care or excess time caring for the ill child, were not collected. For the purposes of sector attribution, this time was distributed across sectors in the same proportions as the pilot study: being borne by the patient and family (time off work with pay lost) or other sectors — the employer (time of work with no pay lost). With these conditions, the costs of illness were overwhelmingly borne by the patient and family sector, meeting 79.2% of all costs incurred. Other sectors (employers) met 14.5% of costs with the health-care sector, or government as a third party provider, meeting 6.2% of costs. Sensitivity analyses performed by varying the distribution of costs associated with time away from work showed the following proportion of all costs met by each sector: patient and family sector 71%, health-care sector 7%, other sector 22% when 0% of costs for time away from work assigned to the patient and family sector and 100% to the other sector; patient and family sector 93%,
health-care sector 7%, other sector 0% when 100% of costs for time away from work assigned to the patient and family sector and 0% to the other sector.

Female subjects had a mean ARI cost point estimate that was $67 greater than their male counterparts: female mean cost $341 (95% CI $265 to $418), male mean cost $274 (95% CI $228 to $319).
**Table 5.4**  Summary of resources consumed during 725 acute respiratory illnesses in 229 Melbourne children, Respiratory Virus Study, January 2003 to January 2004

<table>
<thead>
<tr>
<th>Resource</th>
<th>Units consumed</th>
<th>Patient and family sector</th>
<th>Health-care sector</th>
<th>Other sectors</th>
<th>% ARI cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practice visits</td>
<td>335</td>
<td>$1,425.04</td>
<td>$8,411.90</td>
<td>—</td>
<td>6.6%</td>
</tr>
<tr>
<td>Specialist visits</td>
<td>7</td>
<td>$136.68</td>
<td>$412.65</td>
<td>—</td>
<td>0.4%</td>
</tr>
<tr>
<td>Other health-care provider visits</td>
<td>26</td>
<td>$406.8</td>
<td>—</td>
<td>—</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hospital emergency department visit (no admission)</td>
<td>24</td>
<td>—</td>
<td>$960.00</td>
<td>—</td>
<td>0.6%</td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>10</td>
<td>$46.40</td>
<td>$265.40</td>
<td>—</td>
<td>0.2%</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>158</td>
<td>$2,180.40</td>
<td>—</td>
<td>—</td>
<td>1.5%</td>
</tr>
<tr>
<td><strong>Time seeking health-care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time away from work</td>
<td>329.20 hours</td>
<td>$3,239.34</td>
<td>—</td>
<td>$2,071.06</td>
<td>3.3%</td>
</tr>
<tr>
<td>Time away from usual activities</td>
<td>401.00 hours</td>
<td>$9,116.39</td>
<td>—</td>
<td>—</td>
<td>5.6%</td>
</tr>
<tr>
<td><strong>Excess time caring for ill child</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time away from work</td>
<td>1300.83 hours</td>
<td>$9,621.04</td>
<td>—</td>
<td>$21,414.58</td>
<td>19.2%</td>
</tr>
<tr>
<td>Time away from usual activities</td>
<td>4398.00 hours</td>
<td>$101,746.70</td>
<td>—</td>
<td>—</td>
<td>63.0%</td>
</tr>
<tr>
<td><strong>Sector total</strong></td>
<td></td>
<td>$127,918.37</td>
<td>$10,049.95</td>
<td>$23,485.64</td>
<td>100.0%</td>
</tr>
<tr>
<td>Sector cost per ARI</td>
<td>$176.44</td>
<td>$13.86</td>
<td>$32.39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sector per cent</td>
<td>79.2%</td>
<td>6.2%</td>
<td>14.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>$161,453.96</td>
<td>Total cost per ARI</td>
<td>$308.71</td>
<td></td>
</tr>
</tbody>
</table>
Similar to the pilot study, the presence of fever had an impact on the cost of illness, with all febrile illnesses having an average cost of illness of $303 (95% CI $246 to $360) compared with afebrile illnesses, $127 (95% CI $96 to $158). The reported presence of otitis media in the absence of fever increased the average cost of illness to a similar level as the presence of fever alone, $275, with the reported presence of both resulting in an incremental increase in mean cost per illness of over $200 (Table 5.5).

<table>
<thead>
<tr>
<th>ARI type</th>
<th>ARI events</th>
<th>Average cost per ARI</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated ARI</td>
<td>364</td>
<td>$114</td>
<td>$82 to $146</td>
</tr>
<tr>
<td>Febrile ARI</td>
<td>284</td>
<td>$275</td>
<td>$213 to $337</td>
</tr>
<tr>
<td>ARI with OM</td>
<td>32</td>
<td>$274</td>
<td>$147 to $401</td>
</tr>
<tr>
<td>Febrile, OM ARI</td>
<td>45</td>
<td>$481</td>
<td>$340 to $622</td>
</tr>
</tbody>
</table>

In nearly all circumstances, the median cost of illness is less than the average cost of illness (Table 5.6) demonstrating the influence of high cost illnesses have on the average.

The point estimates for the average cost, either identified in isolation or with another virus, and the median cost of influenza A infections managed in the community, are more than two and one-half times that of any other virus studied (Table 5.6). The order from highest average cost of single virus in isolation illnesses was: influenza A ($904), RSV ($304), picornaviruses ($267), hCoV-NL63 ($251), adenoviruses ($248), PIVs ($229), and HMPV ($219).
Table 5.6  Number of ARIs, median cost, and average cost with 95% confidence interval for all illnesses with a health cost diary returned (n=523) by virus identification

<table>
<thead>
<tr>
<th>Pattern of virus identification</th>
<th>Number of ARIs (%)</th>
<th>Total costs</th>
<th>Median cost (interquartile range)</th>
<th>Average cost (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No specimen submitted</td>
<td>40 (7.6%)</td>
<td>$12,281</td>
<td>$216 ($88, $434)</td>
<td>$307 ($212 to $402)</td>
</tr>
<tr>
<td>No virus identified</td>
<td>126 (24.1%)</td>
<td>$39,853</td>
<td>$151 ($44, $364)</td>
<td>$316 ($208 to $425)</td>
</tr>
<tr>
<td>Single virus identified</td>
<td>306 (58.5%)</td>
<td>$91,817</td>
<td>$148 ($44, $357)</td>
<td>$300 ($241 to $359)</td>
</tr>
<tr>
<td>Picornaviruses</td>
<td>197 (37.7%)</td>
<td>$52,597</td>
<td>$124 ($32, $337)</td>
<td>$267 ($211 to $323)</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>17 (3.3%)</td>
<td>$15,366</td>
<td>$571 ($162, $1,023)</td>
<td>$904 ($89 to $1719)</td>
</tr>
<tr>
<td>RSVs</td>
<td>33 (6.3%)</td>
<td>$10,047</td>
<td>$198 ($60, $398)</td>
<td>$304 ($194 to $415)</td>
</tr>
<tr>
<td>PIVs</td>
<td>21 (4.0%)</td>
<td>$4,804</td>
<td>$112 ($84, $291)</td>
<td>$229 ($104 to $354)</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>17 (3.3%)</td>
<td>$4,212</td>
<td>$185 ($90, $341)</td>
<td>$248 ($140 to $356)</td>
</tr>
<tr>
<td>HMPV</td>
<td>15 (2.9%)</td>
<td>$3,284</td>
<td>$204 ($57, $324)</td>
<td>$219 ($109 to $328)</td>
</tr>
<tr>
<td>hCoV-NL63</td>
<td>6 (1.1%)</td>
<td>$1,508</td>
<td>$83 ($30, $625)</td>
<td>$251 (-$77 to $580)</td>
</tr>
<tr>
<td>Co-detection</td>
<td>51 (9.8%)</td>
<td>$17,503</td>
<td>$185 ($72, $431)</td>
<td>$343 ($212 to $475)</td>
</tr>
<tr>
<td>All ARIs</td>
<td>523 (100.0%)</td>
<td>$161,454</td>
<td>$156 ($45, $376)</td>
<td>$309 ($263 to $354)</td>
</tr>
</tbody>
</table>
Table 5.7  Mean values and mean costs of components of resource use during acute respiratory illnesses, Respiratory Virus Study, Melbourne, 2003 to 2004

<table>
<thead>
<tr>
<th>ARI type</th>
<th>ARIs</th>
<th>GP visits</th>
<th>All other healthcare costs</th>
<th>Seeking healthcare time off work</th>
<th>Seeking healthcare time off usual activity</th>
<th>Excess care time off work</th>
<th>Excess care time away from usual activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean count</td>
<td>Mean cost</td>
<td>Mean male time</td>
<td>Mean female time</td>
</tr>
<tr>
<td>Influenza A</td>
<td>17</td>
<td>1.11</td>
<td>$2.85</td>
<td>$12.84</td>
<td>0.00</td>
<td>0.12</td>
<td>$2.65</td>
</tr>
<tr>
<td>Others single virus</td>
<td>289</td>
<td>0.57</td>
<td>$16.73</td>
<td>$7.19</td>
<td>0.02</td>
<td>0.55</td>
<td>$12.83</td>
</tr>
<tr>
<td>Co-detections</td>
<td>51</td>
<td>0.76</td>
<td>$22.46</td>
<td>$3.79</td>
<td>0.00</td>
<td>0.38</td>
<td>$8.43</td>
</tr>
<tr>
<td>No virus</td>
<td>126</td>
<td>0.63</td>
<td>$18.65</td>
<td>$7.07</td>
<td>0.02</td>
<td>0.22</td>
<td>$5.58</td>
</tr>
<tr>
<td>No specimen</td>
<td>40</td>
<td>0.80</td>
<td>$23.72</td>
<td>$25.70</td>
<td>0.00</td>
<td>0.48</td>
<td>$10.64</td>
</tr>
<tr>
<td>All ARIs</td>
<td>523</td>
<td>0.64</td>
<td>$18.81</td>
<td>$8.43</td>
<td>0.02</td>
<td>0.44</td>
<td>$10.15</td>
</tr>
</tbody>
</table>
The mean cost per ARI for non-influenza single virus illnesses was $265 (95% CI $223 to $306). Excess carer time was a key cost driver for all illnesses, particularly taken from usual activity (Table 5.7). For influenza A only illnesses the cost of excess carer time from usual activity was $706 per ARI – 78% of the total mean cost for all illnesses, compared with $164 and 62% for other single virus identified ARIs (Table 5.7).

When the costs of the five hospitalised ARIs were included, the total cost of all illnesses increased from $161,454 to $178,209, and the average cost of illness went from $309 to $341.

In order to assess the impact of duration of illness on resource use during an ARI, the average cost of illness per day was calculated using the total costs for illnesses divided by the total number of child-days involved (Table 5.8). A sensitivity analysis was also performed looking at the impact of outlying, high cost illnesses on the cost of illness per day, using the arbitrary cut-off of $1,500. There were 14 illnesses — 2.7% of 523 illnesses with a burden diary returned — with a total cost of illness greater than $1,500: ten of these occurred in illnesses where at least one virus was identified (Table 5.8). If all illnesses are included in calculations, ARIs where influenza A was identified had the highest average cost per day of $55. The next most expensive illness in terms of cost per day was caused by PIVs at $19, closely followed by RSV ($19) and picornaviruses ($19), HMPV ($15), adenoviruses ($13), and hCoV-NL63 ($12).

There was one influenza A illness that had an outlying total cost — $6,296 — with a duration of 25 days. The next most expensive influenza A positive illness had a total cost of $1,457. Of the total cost of this outlier illness, 99% ($6,249) was made up by reported excess time by a carer spent looking after an ill child away from usual activities, given as 300 hours (12.5 days), over the 25 day illness.
Table 5.8  Sensitivity analysis showing total cost, total duration, and cost per day, for all illnesses by virus identification and with removal of ARIs that have an outlying cost per illness greater than $1,500

<table>
<thead>
<tr>
<th>Virus</th>
<th>Number of ARIs</th>
<th>Total cost</th>
<th>Total duration</th>
<th>Cost per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>No specimen</td>
<td>40</td>
<td>$11,474.39</td>
<td>419</td>
<td>$27.39</td>
</tr>
<tr>
<td>No virus identified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all ARIs</td>
<td>126</td>
<td>$36,996.35</td>
<td>1,529</td>
<td>$24.20</td>
</tr>
<tr>
<td>ARIs &lt; $1,500</td>
<td>122</td>
<td>$26,022.84</td>
<td>1,466</td>
<td>$17.75</td>
</tr>
<tr>
<td>Picornaviruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all ARIs</td>
<td>198</td>
<td>$49,324.84</td>
<td>2,633</td>
<td>$18.73</td>
</tr>
<tr>
<td>ARIs &lt; $1,500</td>
<td>194</td>
<td>$41,314.04</td>
<td>2,509</td>
<td>$16.47</td>
</tr>
<tr>
<td>Influenza A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all ARIs</td>
<td>17</td>
<td>$14,264.23</td>
<td>259</td>
<td>$55.07</td>
</tr>
<tr>
<td>ARIs &lt; $1,500</td>
<td>16</td>
<td>$7,968.49</td>
<td>234</td>
<td>$34.05</td>
</tr>
<tr>
<td>RSV</td>
<td>33</td>
<td>$9,301.90</td>
<td>494</td>
<td>$18.83</td>
</tr>
<tr>
<td>PIVs</td>
<td>21</td>
<td>$4,463.83</td>
<td>234</td>
<td>$19.08</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>18</td>
<td>$4,550.42</td>
<td>349</td>
<td>$13.04</td>
</tr>
<tr>
<td>HMPV</td>
<td>15</td>
<td>$3,058.67</td>
<td>208</td>
<td>$14.71</td>
</tr>
<tr>
<td>hCoV-NL63</td>
<td>7</td>
<td>$1,388.99</td>
<td>117</td>
<td>$11.87</td>
</tr>
<tr>
<td>Co-infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all ARIs</td>
<td>48</td>
<td>$15,016.51</td>
<td>840</td>
<td>$17.88</td>
</tr>
<tr>
<td>ARIs &lt; $1,500</td>
<td>47</td>
<td>$12,628.18</td>
<td>782</td>
<td>$16.15</td>
</tr>
<tr>
<td>All ARIs with a virus identified</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>all ARIs</td>
<td>483</td>
<td>$138,365.70</td>
<td>6,663</td>
<td>$20.77</td>
</tr>
<tr>
<td>ARIs &lt; $1,500</td>
<td>473</td>
<td>$110,697.40</td>
<td>6,393</td>
<td>$17.32</td>
</tr>
</tbody>
</table>

The removal of illnesses with a total cost greater than $1,500 affected cost per day values for illnesses where no virus was identified, illnesses where picornavirus or influenza A was detected, and illnesses where more than one virus was identified (Table 5.8). The removal of four outlier illnesses from 126 ARIs dropped cost per day from $24 to $18 in ARIs where no virus was
identified. The removal of four outlier illnesses from 198 ARIs where picornavirus alone was identified resulted in cost per day dropping from $19 to $16. Removing one co-infection from 48 ARIs where more than one virus was identified moved the cost per day from $18 to $16. Removing the outlier illnesses for influenza A resulted in a fall in the cost per day value from $55 to $34. Even at $34, the cost of influenza A illness per day approaches being twice the next most expensive viral ARI.

The income brackets divided study household into approximate quartiles: bracket 1 (<$52,000), 24% of households; bracket 2 ($52,000 to $77,999), 28%; bracket 3 ($78,000 to $103,999), 23%; and bracket 4 (≥$104,000), 25%. This compares with the proportion of the Australian population in equivalent income brackets of: bracket 1, 54%; bracket 2, 20%; bracket 3, 13%; and bracket 4, 13%. The average cost per ARI was highest in the second income bracket, followed in order by the third bracket, the fourth bracket, and the first bracket (Table 5.9), with confidence intervals overlapping.

<table>
<thead>
<tr>
<th>Income bracket</th>
<th>% of study children</th>
<th>ARI rate</th>
<th>Average ARI cost (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bracket 1</td>
<td>(&lt;$52,000)</td>
<td>24%</td>
<td>0.35</td>
</tr>
<tr>
<td>Bracket 2</td>
<td>($52,000 to $77,999)</td>
<td>28%</td>
<td>0.37</td>
</tr>
<tr>
<td>Bracket 3</td>
<td>($78,000 to $103,999)</td>
<td>23%</td>
<td>0.44</td>
</tr>
<tr>
<td>Bracket 4</td>
<td>(≥$104,000)</td>
<td>25%</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Household income in the pilot study was collected in four brackets: bracket 1, ≤$21,000; bracket 2, $21,101 to $33,000; bracket 3, $33,001 to $56,000; and bracket 4, >$56,000. For that study, mean costs were lowest in the highest bracket, with an order of bracket 4, $208; bracket 2, $290;
bracket 1, $377; and bracket 3, $449. Placing ReVS households in similar brackets using the categories collected resulted in: bracket 1, ≤$20,800 (4 ARIs); bracket 2, $20,800 to $31,199 (18 ARIs); bracket 3, $31,200 to $51,999 (99 ARIs); and bracket 4, >$52,000 (402 ARIs). Using this classification in ReVS, cost of illness was highest in the highest income bracket: bracket 4, $335; bracket 3, $241; bracket 2, $141; and bracket 1, $109.

5.5 Discussion

In this Chapter, key findings relating to the cost data collected in the Respiratory Virus Study are summarised. This is the first time results derived from a unique combination of methods such as those used in this study have been presented: a sensitive definition for ARI, parent-collected specimens collected without the need for a healthcare worker home visit, laboratory testing for respiratory viruses using sensitive molecular methods, and, based on findings from the pilot study, comprehensive collection of costs, including the previously neglected indirect cost, time away from a usual, non-work activity.

The total cost of the 523 non-hospitalised, community-managed illnesses, applying costs as described, was $161,454; giving an average cost for illnesses where burden data were available of $309 (95% CI $263 to $354). Applying a conservative zero-value cost to the 202 illnesses (28% of all ARIs) with no burden diary increases the number of illnesses in the denominator to 725 and returns an average cost per ARI of $207 (95% CI $175 to $238). The total cost of all illnesses increased with the addition of the five hospitalised cases from $161,454 to $178,209, and the average cost of illness went from $309 to $341. Picornavirus ARIs were associated with the highest overall costs of any viral group totalling just over $50,000 for the 12-month study period.

From a societal perspective, community-managed influenza A ARIs in healthy preschool aged children cost approximately three times more than similar illnesses caused by RSV and the other common respiratory viral infections of childhood. The order from highest average cost of single virus in isolation illnesses was: influenza A ($904), RSV ($304), picornaviruses ($267), hCoV-NL63
($251), adenoviruses ($248), PIVs ($229), HMPV ($219). The presence of fever and/or otitis media increased the point estimate of the mean cost of illness; but despite having a high prevalence of fever, a longer mean duration, and higher primary care usage, adenoviral infections, by comparison, did not have the cost burden of influenza infections. This highlights the pivotal contribution of excess carer time away from usual non-work activity to total costs, making it the key cost driver for all ARIs in children and, in this study, differentially amplifying the total costs of influenza illnesses. Whilst the confidence intervals for mean cost of influenza A ARIs and other single virus ARIs overlap, due to the relatively small number of influenza illnesses available for costing, it is unlikely that chance could account for such an extreme difference.

The proportion of costs met by each sector was similar to the values seen in the pilot study: costs were overwhelmingly borne by the patient and family sector, meeting 79.2% of all costs incurred. Other sectors (employers) met 14.5% of costs with the health-care sector, or government as a third party provider, meeting 6.2% of costs. Excess carer time away from usual non-work activity made a pivotal contribution to total costs, making it the key cost driver for ARIs in children. The cost of excess time spent caring for an ill child, either away from work or usual activities, was the key cost driver responsible for all illnesses and is met in full by the patient and family sector. For influenza A, mean excess carer time away from usual activity cost was $706 per ARI (78% of the total mean cost for all illnesses). For other single virus illnesses, these values were $164 and 62%.

The point estimate for the mean cost of all ARIs ($309; 95% CI $263 to $354) was not dissimilar to the mean value calculated from the pilot study ($241; 95% CI $191 to $291) with only minor modifications to the impact diary. Changes to the impact diary for this study, with the removal of some minor supplementary items, should have moved the mean cost slightly lower compared to the pilot study. PCR testing was used to assign impact and costs to specific viral agents. For all but influenza A illnesses, the cost of community-managed ARIs in healthy preschool aged children fell within a relatively narrow $85 range.
The availability of preventive vaccines and specific therapeutic options makes influenza the most studied of respiratory viruses in all age groups; no other virus is more predictably disruptive year-on-year than annual interpandemic influenza.\textsuperscript{261,276,478,479} Studies conducted in the second half of last century\textsuperscript{358,480-482} and recent observation\textsuperscript{39,40} and intervention\textsuperscript{329,335,361} studies show children have comparatively higher rates of influenza infection and are the most important transmitters of infection within households and communities. Whilst dollar amounts may not directly translate, impact data from this study may be transferable to other countries with developed economies, and similar disease epidemiology and healthcare systems. Ideally further studies in other countries should be conducted to allow for an examination of how impact and cost data vary with the nature of the healthcare system, local virus epidemiology, and other societal factors, including household structure.

Despite lower mean costs than influenza illnesses and the lack of population-based prevention options, the importance of working towards the prevention of other respiratory viral infections is obvious. Of particular note, picornavirus ARIs, though typically milder and more difficult to be certain of a causal association with illness,\textsuperscript{455,456} were associated with the highest overall costs of any viral group totalling over $50,000 or one-third of all costs, for the 12-month study period. In the absence of specific vaccines and therapies for other viruses, the application of nonpharmaceutical interventions at a population level, such as improved hand and respiratory hygiene, may have an important place in reducing illness due to respiratory viruses.\textsuperscript{282} Whilst there is difficulty in assessing the attributable contribution when a picornavirus is identified by PCR in the presence of symptoms, as discussed in Chapter 4, it is clear they have a major role in respiratory illness in medically-attended respiratory illnesses in children and adults.

These findings reinforce the importance of virus testing in such studies to accurately estimate epidemiology and costs.\textsuperscript{483} These data add to accumulating evidence that laboratory confirmation of influenza, in particular, is required, rather than less specific influenza-like illness (ILI) definitions or hospital coding. Other recent studies have found laboratory-confirmed
influenza hospitalisations were two to four times more costly than shown in previous studies using coding-based estimates. When ILI definitions or coding are used, rather than laboratory confirmation, a lack of specificity results in influenza illnesses being mixed with other agents, thereby considerably diluting cost differences. A direct comparison of parent-collected NTS specimens with collection of a more invasive specimen, such as a nasopharyngeal aspirate, by a healthcare worker at the time of an ARI was beyond the scope of this study. Any reduction in sensitivity caused by the type of specimen used is likely to minor: the finding that 74% of all specimens collected from children in this study were positive for at least one virus is within the range of values from recent home visit studies which also used PCR for diagnosis and nasopharyngeal aspirates (69%) or nasal lavages (83%). Since this study, further work has been done comparing the sensitivity of NTS specimens with the more invasive nasopharyngeal aspirate in a cohort of symptomatic, hospital-presenting children. A combined nose-throat swab had a sensitivity of 92% for influenza A, 100% for influenza B, and 93.1% for RSV. PCR is likely to be highly specific for the identification of these viruses, meaning that, in combination with NTS specimens, it is a suitable method for virus-specific attribution for impact and costs.

There are clearly some issues about the cost of illnesses caused by respiratory viruses in children unresolved by this study, and these other issues that need to be considered before interpretation. Despite being a relatively large cohort the number of illnesses on which to make costing estimates for some virus types is quite small. Further community-based estimates are required to not only confirm these findings but to improve precision around point estimates.

For all illnesses where a specimen was tested, parents received a result letter by mail. The delay between illness onset and posting the letter was shortest for influenza illnesses, but for most illnesses parents would have been aware of the result before illness end. This issue will be explored further in Chapter 6 (Table 6.5), but receiving a letter prior to the end of an illness may bias either behaviour or recording impact data.
The finding of mean ARI costs being lowest in the highest income households, seen in the pilot study, did not persist in this study. Using a classification that divided household income into quartiles, the mean ARI cost order from highest to lowest was: bracket 3, bracket 2, bracket 4, and bracket 1. When a similar income structure as the pilot study was applied, there were very few low income households and associated ARIs. The mean cost of ARIs in the highest income households went from lowest (pilot study) to highest (ReVS with similar income categories). The ordinal classification of mean cost by household income is a value that shows variability in these two studies – conducted in different years using different populations. Neither study collected specific further data that would allow further exploration to explain this variability. It may be that this value is inherently unstable, or other factors may come into play: such as the role and mean cost of different viruses and their relative presence year-to-year in households with different incomes. It is not possible to compare these findings with similar studies as there are no other published data that provide cost-of-illness information by household income. Assessments of cost-effectiveness for vaccine and other interventions generally treat the population as a homogeneous group using a single mean cost of illness, without considering what impact variations in category values, such as household income, may have on mean cost of illness. Further research is needed to clarify the role household income may have on mean cost of ARI and what impact different household income structures in different communities and countries may have on overall effectiveness of a preventative or therapeutic intervention.

Recruiting a broadly representative sample for community-based studies is challenging. In Australia there is no easily identifiable sampling frame, where availability is not constrained by privacy laws, from which to randomly solicit participation. Given participation in such studies is voluntary, the purpose of using such a sampling frame – enrolling a truly representative study population – is likely to be unsuccessful. Nearly three-quarters of the 121 children in the pilot study came from households in the highest income bracket, >$56,000. In an attempt to avoid a similar recruitment issue in this study, nurses from council areas that, according to the Australian Bureau of Statistics, had a lower mean household income were actively sought to assist with
recruitment. Compared with the Australian population, households with lower incomes were under-represented in this study sample, and, despite overlapping confidence intervals around income band point estimates of mean costs, this may have lead to an overestimation of total costs. However, this may be balanced somewhat by the over-representation of households from the top income band which had a relatively lower mean ARI cost ($272). This pattern of household income distribution was similar to that found in the pilot study. Attempts to better recruit from local council areas with a higher proportion of lower income households appeared to make little difference to the composition of the study population. It may be the case that lower income households are under-represented as they do not have the spare capacity required, in time or other resources, to allow for study involvement. In this study, no empiric data were collected that would allow the quantification of any bias resulting from this skewed sample. Other recent burden studies do not report similar household level income data to allow for comparison.\textsuperscript{275,467,488} To allow better interpretation of how mean cost of ARIs may be affected, future studies should collect household income.

Impact diaries were received for just over 70% of all ARIs identified by daily symptom surveillance. ARIs without a diary were more likely to be shorter and without fever or otitis media; any information bias resulting from this would likely be in the direction of inflating mean illness costs. This study only captured information from a single season with higher than normal influenza activity with H3N2 influenza A (drifted strain subtype A/Fujian/411/ 2002-like) being the predominant circulating type.\textsuperscript{464} Variations in incidence and severity year-by-year for all respiratory viruses make it difficult to directly translate these findings to other years.

To accurately and adequately characterise ARIs in children, documenting all time spent on caring for an ill child is important, even when taken away from a usual activity. Applying standard wage rates to leisure time is not a straightforward issue in economics. This approach values carer leisure time and non-paid working time in a similar way to a worker’s time consistent with neoclassical theories of labour economics.\textsuperscript{488} Attaching value to leisure time and using sex-
weighted wage rates, as in this Chapter, is done with the associated assumptions made explicit, and these values are provided in sufficient detail so that others can adjust unit prices using different approaches or for the purposes of cost-effectiveness calculations. As discussed in Chapter 3, the hourly rate applied to costs in this study was deliberately not varied by household income as to do so would imply the leisure time of high income households should be valued more highly than the same time from other households. Previous burden data have been used to assess the cost-effectiveness of using influenza vaccine in children. If these cost values, incorporating these indirect costs, were used in the numerator of cost effectiveness calculations, there is a distinct possibility of double counting. Double counting is likely where the denominator is a utility measure that incorporates a quality assessment (such as the quality adjusted life year or QALY), and most economists would see leisure time as a logical component of the QALY. There is also debate about the inclusion, measurement, and valuation of lost working time in economic evaluations, with the debate centring on whether in practice QALY instruments capture income effects related to absenteeism. Given the issues, incorporation of these findings into a formal cost-effectiveness analysis of the type performed by pharmaceutical companies and required by the PBAC, would be problematic. PBAC will consider indirect cost data collected in a rigorous fashion from well-conducted randomised, controlled trials. If data from observational research with indirect costs are to be included, such as data from this study, modification to the fundable threshold for drugs and vaccines may be required, with prevention of a higher burden of disease required prior to funding. Funding of a single-dose of varicella vaccine at 18-months of age for the prevention of chickenpox, a childhood illness with largely indirect costs, was achieved in the pre-PBAC era of vaccine approval in Australia. Despite the limitations of this study, it provides an initial, and previously not attempted, method for calculating virus-specific cost values.

Despite the impact of respiratory viral infections in children there are relatively few burden comparisons available that collect primary data from ill children. An Italian study examining the impact of HMPV, RSV, and influenza in children less than 15-years of age presenting to an
emergency department found HMPV illnesses to be significantly more burdensome than RSV, having a similar impact to influenza. In this study HMPV was the least expensive single-virus illness. This finding may be due to the different nature of illnesses that result in hospital presentation or hospital admission, compared with community managed illness. Of the 730 ARIs in this study only 4.0% (n = 29) prompted hospital presentation, with less than 1% (n = 5) requiring admission. A community- based Finnish study describing the burden of influenza in children 13-years of age or younger over two seasons, with 2231 child-seasons of data, also contrasts this imbalance between community-managed and hospitalized cases of influenza, with only three emergency department referrals and one hospital admission in 131 children less than three years of age with influenza. ReVS differed from this study in that whilst it used laboratory confirmation, the Finnish study did not employ more sensitive molecular diagnostics, families were required to visit the study clinic when the study child had fever or signs of respiratory infection, indirect costs did not include nonwork time away from a usual activity, and the study did not provide a comparison with other viral acute respiratory illnesses. The findings from the Finnish study reinforce the need to follow children for ARIs over more than one season, with different rates of influenza infection from year-to-year in each age group. These differences extended to changes in likelihood of infection between age groups: for example, the rate of laboratory-confirmed influenza increased by one-third from season one (2000– 2001) to season two (2001–2002) for children less than three years of age, but the rates for three to six year olds and seven to 13 year olds fell 47% and 86%, respectively. A German study, recruiting children less than three years of age with lower respiratory tract infection (LRTI) through office and hospital-based paediatricians, collected cost of illness from a societal perspective, including loss of work days by caregivers. This study showed that non-hospitalized cases of influenza LRTI had twice the cost of PIV LRTI and were one-third more costly than RSV LRTI, with this difference made up entirely by indirect costs.

Whilst methods vary, previous cost effectiveness studies of influenza vaccine in children are characterised by two findings: first, that cost-effectiveness is unsurprisingly enhanced by taking a
societal perspective through the inclusion of indirect costs.\textsuperscript{253,255,261-264} These findings reinforce the importance of indirect costs,\textsuperscript{275} and highlight a previously inadequately measured layer of burden – carer time away from a usual, non-work activity. Second, the potential cost-effectiveness of implementing a vaccination program is improved by flexible or non-individual based delivery programs.\textsuperscript{253,255} Vaccine delivered through pharmacies for a small service fee – improving access and negating the time and costs associated with a primary care visit – or large school-based programs, are likely to be acceptable to parents and providers. It is likely that the cost benefits of preventing influenza in children would extend beyond the targeted age-group,\textsuperscript{362} similar to the indirect effects in older age groups seen following the introduction of childhood conjugate pneumococcal vaccination in the US.\textsuperscript{491}

This study highlights the costly impact of all respiratory viruses, but particularly interpandemic influenza, on children, their families, and society. Efforts to further explore the costs associated with community-managed illness over a number of seasons for all respiratory infections are needed. Similar to recent hospital-based findings, using laboratory-confirmation to specifically identify influenza appears to increase the cost of illness many fold; a finding that may make population-based vaccination programs a more cost-effective proposition.

The use of parent-collected specimens may have important effects in reducing bias in both the epidemiologic and impact data collected. Not requiring parents to either present with their ill child to a health clinic or host a home visit by study staff may result in enhanced ARI surveillance and also allows for the reporting of impact data uncontaminated by compliance with study procedures, thereby reducing any impact a Hawthorne effect may have. Further studies that collect primary, integrated epidemiologic and economic data, particularly indirect costs, directly from families about community-managed ARIs in children, are required. Such data would allow for a more informed exploration of the cost-effectiveness of vaccine programs and other interventions designed to reduce the morbidity associated with ARIs in children.
Chapter 6

THE RESPIRATORY VIRUS STUDY — METHODS

6.1 Objective

The aim of this chapter is to examine the methods used, including specimen collection, of the Respiratory Virus Study data for items that could have influenced the results obtained, and to identify strengths and limitations for use in future community-based respiratory virus studies.

6.2 Introduction

In planning for the implementation of the Respiratory Virus Study, initial thoughts were to combine the methods of previous community-based respiratory illness research and the structure of community-based industry sponsored vaccine trials conducted at our site since the early 1990s. The sponsored study structure used previously has ensured excellent cohort retention and compliance with study procedures, including specimen collection. However, such an approach would be a relatively expensive way of conducting this study, compared with a clinic or hospital based approach. Preliminary examination of the costs involved in using a research nurse to conduct home visits for specimen collection in the event of an ARI in a study child, even without including subsequent illnesses in household contacts, showed this approach to be prohibitively expensive.

The aim was for a study design that would meet the research requirements – identifying the incidence of community-managed respiratory viral infections in children – and was methodologically sound and affordable. The methods used in the Respiratory Virus Study were a combination of the known: a community-based cohort study, the novel, parent-collected specimens, and the modern: nucleic acid amplification for virus identification.
6.3 Methods

This Section should be read in conjunction with the Methods sections of Chapter 4 and Chapter 5. This Chapter will focus on methods that may have had an impact on study interpretation: specimen collection and virus positivity, study procedures, and the findings from the study conclusion questionnaire.

6.3.1 Specimens

Specimens, rather than illnesses, are the unit of analysis in this Section. A number of factors were assessed for their impact on whether each a specimen was positive for any virus. Firstly, the impact of the person who collected the specimen and whether they were a health-care worker was examined; secondly, the delays between illness onset and specimen collection, specimen collection and PCR testing, and illness onset and PCR testing; thirdly, the type of specimen collected — a nose-only specimen or a specimen containing a throat swab; and finally, the subjective collector reported quality of specimen collection — very good, good, or poor.

Recruitment of study families took place in a variety of settings, including hospitals and through MCHNs. A number of parents involved in the study worked in a health-related field. A parent was classified as a health-care worker if they gave as their occupation suggesting relevant experience at performing health-related procedures, including the collections of specimens. They were not specifically asked about prior experience in collecting respiratory specimens. Occupations classified as health-care work included doctor, nurse, ambulance officer, paramedic, scientist in medical research or health-related service delivery, and allied health professional, such as occupational, speech, or physical therapist.

Three delays were examined, with each calculated as the difference in days between both dates; where events occurred on the same day, for example illness onset and specimen collection, the delay value was zero days.
Specimens were classified as being nose swabs only (nose swab) or a specimen including a throat swab (throat swab). There were only two specimens submitted that were throat-only swabs, with the remaining specimens classified as throat swabs being combined nose-throat swabs. Two-sided, two-sample tests of proportion were performed to compare virus positivity and a $\chi^2$ test for trend was performed to compare proportions of specimens positive for any virus with reported quality of collection.

6.3.2 Study conclusion questionnaire

A close-out questionnaire was mailed out to study households to finalise the study, for the administrative task of identifying any changes to child and household exposure variables during the study, and to assess parents’ response to and attitudes about the study. In order to maximise the response questions were kept brief and simple, the number of questions asked was limited, and questionnaires were sent with a return-addressed, free-post envelope. If a response had not been received at the end of one month, families were contacted by telephone and prompted to respond, with an offer to send another questionnaire and return envelope. If no response was forthcoming at the end of another month, another questionnaire and return envelope were sent to study households encouraging them to complete and return.

On the questionnaire, parents were asked to identify the one task they found most difficult to perform whilst on the study, and were given seven options:

- Keeping the daily symptom diary;

- Collecting the nose swab from the study child;

- Collecting the throat swab from the study child;

- Completing the burden diary for the study child;
Taking swabs from other household members;

Completing the burden diary for other household members; or

Another option (parents were given free-text space to nominate a non-listed most difficult task).

It was originally intended for the study to continue for at least three years, with parents given the option to continue at annual intervals. All parents were asked what their response would have been if asked to continue with the study for another year beyond the first year.

To assess the implications for using household-based research in community vaccine trials, such as those our research group performs, parents were asked to consider their possible participation in a vaccine trial with methods similar to the Respiratory Virus Study. Parents were asked to give an indication of intent by selecting one of the following responses to the question:

In the future, there is the possibility that the way we have conducted the Respiratory Virus Study may be used to test new vaccines against respiratory viruses.

If you were asked to be involved in an experimental respiratory virus vaccine study and you were then asked to do the same things you have done in ReVS (complete diaries and collect swabs from the study child) over the winter season (up to five months), what would your response be following your experience with ReVS?

Yes, I would definitely consider putting my child on the study;
• Maybe, but I would need to hear more about the study before deciding;

• Definitely not, I wouldn’t want my child to receive a study vaccine but would be happy to keep diaries and collect swabs;

• Definitely not, I would be happy for my child to receive a study vaccine but I wouldn’t want to keep diaries and collect swabs; or

• Definitely not, I wouldn’t want my child to receive a study vaccine AND I also wouldn’t want to keep diaries and collect swabs.

6.3.3 Result notification

Results of the RespPCR were sent by facsimile to the study site from VIDRL at the end of every working day. These were used to generate a form letter to the parents of the study subject reporting the result. The delay in days between ARI onset and the date the results letter was sent was calculated for influenza A, other single virus detection, co-identifications, no virus detected, and all ARIs, and compared to the mean duration of ARIs by each category.

6.4 Results

6.4.1 Specimens

There were 563 specimens collected for 543 of the 730 influenza-like illnesses that occurred during the study: 187 ARIs (26%) with no specimens; 524 ARIs (72%) with one specimen; 18 ARIs (2%) with two specimens; and one ARI (0%) with three specimens. Of the 563 specimens collected, 409 (73%) were positive for at least one virus.

The majority of specimens (88.5%) were collected by the study child’s mother, with 8.7% collected by the study child’s father. At the time of the enrolment study visit, 11 children met the definition of an ARI and had a specimen collected by a research assistant demonstrating the
process of swab collection (2.0%), and five children had a specimen collected by their general practitioner when having a consultation about the illness (0.9%). A higher proportion of the specimens collected by fathers were virus-positive (84%) compared with those collected by other groups (Table 6.1).

The mothers of 60 study children (26%) were classified as health-care workers, along with 20 (9%) fathers. One-third of study specimens, 185 (33%) were collected by a parent classified as a health-care worker, a general practitioner, or a study research assistant. Specimens collected by a health-care worker were positive for at least one virus 75% of the time (138/185), compared with 72% (271/378) of specimens collected by non-health-care workers (p=0.468).

<table>
<thead>
<tr>
<th>Specimen collector</th>
<th>Number of specimens collected</th>
<th>Number (%) positive for at least one virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>498 (88.5%)</td>
<td>368 (74%)</td>
</tr>
<tr>
<td>Father</td>
<td>49 (8.7%)</td>
<td>41 (84%)</td>
</tr>
<tr>
<td>Research assistant</td>
<td>11 (2.0%)</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>Doctor</td>
<td>5 (0.9%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Total</td>
<td>563 (100%)</td>
<td>419 (74%)</td>
</tr>
</tbody>
</table>

There were two areas where a delay could have impacted on the sensitivity of the PCR testing: from onset of illness to collection of a specimen, and collection of a specimen to testing (Table 6.2). Both of these periods sum to give the delay from onset of illness to date of testing (Figure 6.1). For the period between onset of illness and specimen testing, there is a gradual trend to a decreasing proportion of specimens positive with increasing delay (Figure 6.1). To further explore the relative contribution of the delays from onset to collection, and collection and testing, these
Delays were cross-tabulated (Table 6.2). When the delay from illness onset to specimen collection was less than five days, positivity of specimens was not reduced. The delay from collection to testing is more challenging to interpret; however the combination of six or more days delay from onset to collection combined with even minor delays in testing appears to reduce the likelihood of virus identification using PCR.

Table 6.2  Fraction showing specimens positive for any virus in VIDRL’s multiplex PCR test over all specimens (per cent) by delay in day categories and site of delay: onset of illness to specimen collection; specimen collection to test date; and onset of illness to test date, Respiratory Virus Study 2003-2004

<table>
<thead>
<tr>
<th>Onset to collection (days)</th>
<th>Collection to test (days)</th>
<th>≤1</th>
<th>2</th>
<th>≥3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td></td>
<td>41</td>
<td>40</td>
<td>48</td>
<td>129 (75%)</td>
</tr>
<tr>
<td>2 to 3</td>
<td></td>
<td>45</td>
<td>47</td>
<td>39</td>
<td>131 (73%)</td>
</tr>
<tr>
<td>4 to 5</td>
<td></td>
<td>25</td>
<td>15</td>
<td>31</td>
<td>71 (74%)</td>
</tr>
<tr>
<td>≥6</td>
<td></td>
<td>35</td>
<td>20</td>
<td>23</td>
<td>78 (68%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>146</td>
<td>122</td>
<td>141</td>
<td>409 (73%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Onset to collection (days)</th>
<th>Collection to test (days)</th>
<th>≤1</th>
<th>2</th>
<th>≥3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td></td>
<td>58</td>
<td>53</td>
<td>61</td>
<td>172 (75%)</td>
</tr>
<tr>
<td>2 to 3</td>
<td></td>
<td>60</td>
<td>63</td>
<td>57</td>
<td>180 (73%)</td>
</tr>
<tr>
<td>4 to 5</td>
<td></td>
<td>34</td>
<td>22</td>
<td>40</td>
<td>90 (74%)</td>
</tr>
<tr>
<td>≥6</td>
<td></td>
<td>45</td>
<td>32</td>
<td>38</td>
<td>115 (68%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>197</td>
<td>170</td>
<td>196</td>
<td>563 (73%)</td>
</tr>
</tbody>
</table>
There were 169 specimens (30%) that consisted of a nose swab only, and 394 specimens (70%) contained a throat swab, including two throat-only swabs (Table 6.3). Neither collector-reported quality of specimen collection nor whether the specimen included a throat swab had a great impact on the likelihood a specimen would be positive for any viruses (Table 6.3). Specimens that included a throat swab were less likely to be positive for a virus than specimens that included a nose swab only (71% versus 78%, p=0.090). The range of proportions of specimens positive by collector-reported specimen quality (Table 6.3) was similar for specimens containing a throat swab and varied more for nose-only swabs. For nose-only swabs, those reported as being of very good quality had an 82% likelihood of being positive for any virus, compared to 72% for specimens that included a throat swab. It was not possible to demonstrate that very good quality collection (76%) resulted in a higher likelihood of specimen positivity compared to good (71%, p=0.223) or poor (71%, p=0.511) quality of specimen collection (χ² test for trend: p=0.29).
There was some variation in individual virus identification by specimen type (Table 6.4). Although based on small numbers, PIVs were the only virus type where there was a measurable difference between the proportion of specimens positive by specimen type: nose-only 9% vs throat 5% (p=0.046). The proportion of specimens positive by specimen type was similar for picornaviruses. Adenoviruses, HMPV, and hCoV-NL63 were found more commonly in specimens containing a throat swab, and PIVs, RSV, and influenza A were more commonly found in specimens without a throat swab.
### Table 6.4

<table>
<thead>
<tr>
<th>Virus</th>
<th>Site of specimen collection</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nose only</td>
<td>Throat</td>
<td></td>
</tr>
<tr>
<td>Picornaviruses</td>
<td>83/169 (49%)</td>
<td>191/394 (49%)</td>
<td>274/563 (49%)</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>9/169 (5%)</td>
<td>36/394 (9%)</td>
<td>45/563 (8%)</td>
</tr>
<tr>
<td>PIVs</td>
<td>15/169 (9%)</td>
<td>18/394 (5%)</td>
<td>33/563 (6%)</td>
</tr>
<tr>
<td>RSV</td>
<td>15/169 (9%)</td>
<td>26/394 (7%)</td>
<td>41/563 (7%)</td>
</tr>
<tr>
<td>Influenza A</td>
<td>8/169 (5%)</td>
<td>16/394 (4%)</td>
<td>24/563 (4%)</td>
</tr>
<tr>
<td>HMPV</td>
<td>9/169 (5%)</td>
<td>25/394 (6%)</td>
<td>34/563 (6%)</td>
</tr>
<tr>
<td>hCoV-NL63</td>
<td>5/169 (3%)</td>
<td>14/394 (4%)</td>
<td>19/563 (3%)</td>
</tr>
<tr>
<td>Any virus</td>
<td>131/169 (78%)</td>
<td>278/394 (71%)</td>
<td>409/563 (73%)</td>
</tr>
</tbody>
</table>

### 6.4.2 Study conclusion questionnaire

Of the 229 families who provided any daily symptom diary data, 183 (80%) returned the close-out questionnaire. In response to the question about the most difficult task during the study, the most common response (58.5%) was collecting the throat swab from the study child (Figure 6.2). This was followed by completing the burden diary in the event of an ARI (20.8%) and keeping the daily symptom diary (10.9%). By year of age at time of enrolment on the study, the parents of children less than one-year of age were least likely to nominate collecting a throat swab from the study child as the most difficult task (46%).
One-hundred and fifty-nine (87%) families who returned a questionnaire reported they would have continued with the study if asked. This represents 69% of all study families who participated in ReVS.

When asked if they would allow their child to participate in an experimental vaccine study, a combined total of 80% of parents said yes or maybe (Figure 6.3). Of the 20% who gave a definite no answer to participating, two-thirds gave the experimental vaccine as the sole reason for not wishing to participate, saying they would be happy to keep diaries and take swabs (Figure 6.3).
Figure 6.2  Parent responses to question regarding most difficult task on close-out questionnaire

What was the most difficult task you were asked to do on this study? (n=183)

- No task nominated: 7 (3.8%)
- Keep the daily symptom diary: 20 (10.9%)
- Nose swab from study child: 5 (2.7%)
- Throat swab from study child: 107 (58.5%)
- Burden diary for study child: 38 (20.8%)
- Take swabs from household contacts: 4 (2.2%)
- Burden diary for household contact: 2 (1.1%)

By year of age of study child at time of enrolment (relative proportions):

- 0 years (n=50)
- 1 year (n=47)
- 2 years (n=33)
- 3 years (n=35)
- 4 years (n=18)
Figure 6.3  Parent responses to question regarding participation in an experimental vaccine study on close-out questionnaire

Would you allow your child to participate in an experimental vaccine study against respiratory viruses?
(n=183)

- Definite yes: 64 (35.0%)
- Maybe, need more information: 83 (45.4%)
- Definite no to vaccine, would keep diaries / take swabs: 24 (13.1%)
- Definite no to diaries / swabs, yes to vaccine: 5 (2.7%)
- Definite no to vaccine / diaries / swabs: 7 (3.8%)

6.4.3  Result notification

For all illnesses where a specimen was tested, parents received a result letter by mail. The delay between illness onset and posting the letter was shortest for influenza illnesses at least two days shorter compared with all other illness categories, but for most illnesses parents would have been aware of the result before illness end (Table 6.5).
Table 6.5  Mean duration of ARI and mean delay for result letter, Respiratory Virus Study, Melbourne, 2003 to 2004

<table>
<thead>
<tr>
<th>ARI type</th>
<th>Mean duration (days)</th>
<th>Mean delay: ARI onset to letter sent (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A</td>
<td>15.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Other single virus</td>
<td>13.8</td>
<td>8.9</td>
</tr>
<tr>
<td>Co-identifications</td>
<td>17.4</td>
<td>8.8</td>
</tr>
<tr>
<td>No virus detected</td>
<td>12.2</td>
<td>8.4</td>
</tr>
<tr>
<td>No specimen returned</td>
<td>10.5</td>
<td>—</td>
</tr>
<tr>
<td>All ARIs</td>
<td>13.5</td>
<td>8.7</td>
</tr>
</tbody>
</table>

6.5 Discussion

In this Chapter, findings relating to the conduct and methods used in the Respiratory Virus Study for three areas – specimens, general conduct issues, closeout questionnaire – are presented. This project combines, for the first time, a large, community-based respiratory illness study with parent-collected specimens tested using highly sensitive molecular techniques.

With the number of specimens available in this study it was not possible to show a difference in the likelihood of a virus-positive specimen by whether or not the collector was a healthcare worker, the subjective specimen quality as reported by the collector, or whether the specimen included a throat swab. For all viruses other than adenovirus, nose-only specimens had an equivalent or higher point estimate for the likelihood of virus identification. Overall, nose-only swabs had a 78% virus positive rate compared to 71% for NTS specimens. In study specimens, a delay from ARI onset to specimen collection of six days or longer reduced the likelihood of a virus being detected. This decrease in positivity was highest for those specimens where there was even a minor delay from specimen collection to testing.
Parents most commonly identified collecting the throat swab from an ill child as the most difficult study task. Despite difficulties, 87% of families that returned the questionnaire (69% of study households) reported they would have been happy to continue the study if it had continued for a further year and 80% reported they would have enrolled or considered enrolling their child in an experimental vaccine study using similar methods for outcome follow-up.

Prior to, and with this study, NTS specimens have not been validated as a sample collection method for the respiratory tract. The proportion of specimens that were positive for any virus fell within the range of virus identification of other recent community-based studies using more invasive specimen collection methods combined with PCR techniques.\(^{119,472}\) These values are similar to hospital-based findings using mainly NPAs and a comprehensive panel of respiratory virus PCR assays.\(^9\)

Since this study, NTS specimens have been validated against the more invasive nasopharyngeal aspirate in a hospital-presenting population in Queensland.\(^{487}\) Whilst rhinoviruses were not included as part of the testing panel, this study showed that detection of the key viruses of early childhood was very good, with sensitivities for influenza A of 92%, RSV 93%, and PIV III 85%.

Interestingly, a throat swab did not increase the likelihood of virus identification from study children. This study did not include a simultaneous, head-to-head comparison of nose-only versus nose-throat swabs, but in this setting, nose-only specimens had a non-significant higher rate of positivity. This finding may obviously have been confounded by illness severity and virus shedding: a child with more severe illness may have been shedding more virus at the time of specimen collection. In sicker children, parents may have been less likely to attempt collection of the additionally invasive throat specimen.

The only viral group where throat swabs appeared to improve detection was the adenoviruses. A throat swab may have been more likely to capture adenoviral persistence in the oropharynx.
rather than acute infection, particularly in the age group under study.  

In the Queensland study, sensitivity for adenoviruses using the NTS was only 65%. A recent study showed that detecting adenoviral persistence one to 12 weeks after initial positivity was not possible using nose swabs alone in children six months to four years of age. These findings, in combination with reduced adenoviral detection in this study using nose-only swabs, support the need for further work using molecular methods to document adenovirus kinetics in throat and nose swabs from children.

RSV detection using nose-only, throat, and nasopharyngeal swabs and antigen-based techniques have not performed as well as nasopharyngeal aspirates (NPAs) or nasal washes, with a reduction in sensitivity of up to one-third. The use of PCR and collection of specimens in the early stages of illness in this study may have minimised differences caused by site of collection, with nose-only swabs performing as well as specimens with a throat swab for virus positivity. The use of molecular methods for virus detection may also make any improvement in sensitivity for virus detection when using a nasopharyngeal specimen over an NTS or a nose-only swab, marginal.

Virus positivity was not affected by whether or not the collector was a healthcare worker, or worked in a health-related field. Similarly, collector subjective reporting of specimen quality did not appear to affect positivity. These findings, in combination with the high virus prevalence in collected specimens, suggest parent-collected nose-throat specimens are a robust method for identifying viral nucleic acid in the respiratory tract of community-dwelling children. A recently reported small study from the Netherlands compared ARI identification and specimen collection in households randomised to with healthcare worker visiting and collection and parent specimen collection when an ARI occurred. Whilst ARI identification was similar in both groups, children from parent collection households were almost twice as likely to have a specimen collection when an ARI occurred (43% vs 24%, respectively; p=0.07). Further, the likelihood of virus identification in parent collected specimens was higher than healthcare worker collected specimens (80% vs 67%, p=0.44). Whilst not reported, it may be that earlier timing in collection and testing of parent collected specimens was responsible for the higher virus identification.
Findings from studies conducted before the advent of cell culture diagnostics had clinical syndromes, rather than viral diagnoses, as the primary endpoint.492 These studies showed that the rate of minor respiratory illness identification was dependant on study methods. Illness identification increased with increasing frequency of visits to record such illnesses, and further, for individuals in families having monthly home visits, the rate of illness reporting was highest in the week prior to the visit and fell week-by-week regardless of the season.493

It has been suggested that using upper respiratory tract infection or even febrile upper respiratory tract infection would be an unsatisfactory outcome measure for a respiratory virus vaccine trial, due to the frequency of the outcome and a lack of pathogen specificity.54 It was argued that culturing all cases of URTI would be burdensome and, for individual agents such as RSV, would have a low yield.54 This discussion took place in a different context to this study: prior to the ready availability of nucleic acid testing for respiratory viruses at a time when viral culture or antigen detection was the insensitive standard.54 Since that time a large efficacy study for intranasal influenza vaccine has been reported, using largely upper respiratory tract symptomatology end points to prompt specimen collection.336

For all illnesses where a specimen was tested, parents received a result letter by mail. For influenza A illnesses, the mean time taken from ARI onset to a result letter being sent from study site was two days shorter than any other illness category. Whilst the delay between illness onset and posting the letter was shortest for influenza illnesses, for most illnesses parents would have been aware of the laboratory testing result before illness end. Pandemic influenza was not being widely discussed in Australia during 2003, but interpandemic influenza does receive media coverage annually encouraging vaccine uptake, and this may have caused parents to overestimate key parameters associated with their child's influenza-positive illness, including those reported in previous sections of this thesis (Section 4.4.5; Chapter 5). However, if such a bias was in operation it might also be expected that time values for illnesses where no virus was identified may be relatively understated when compared to ARIs with one or more viruses.
present. Such a phenomenon was not observed; ARIs with no virus identified had a higher mean
cost than those with a single virus present, and for the key cost driver of excess carer time away
from a usual activity, no cause illnesses had higher values than both single and multiple virus
ARIs.

Previous streptococcal research has shown that parents can collect an adequate respiratory
specimen from an ill child with brief training.414-417 ReVS was the first, large-scale implementation
of a community-based study solely reliant on parents collecting respiratory specimens. Parents
were generally positively disposed to the study, and it is of interest that a high proportion of all
study families reported they would have been happy to continue for another year. The most
difficult part of the study was reported as being the collection of a throat specimen from an ill
study child, but, based on the swab positivity results for all but adenoviruses, it may not be
required – a well collected nose swab may suffice. Available strands of evidence now suggest
that, far from being a suboptimal method for conducting community-based respiratory research,
parent-collected specimens should now be the considered the method of choice for such studies.
CONCLUSIONS AND RECOMMENDATIONS

The work presented in this thesis has made a number of novel contributions to the understanding of respiratory virus epidemiology and impact, and the methods used to conduct community-based research.

The key lessons from these studies, as they relate to the hypothesis and research questions outlined in Chapter 1, are:

- Both the pilot study and ReVS provided estimates of acute respiratory illness incidence in community-dwelling children, and for ReVS these data included virus-specific incidence values for children collected over a one year period;

- The virus-specific cost-of-illness information are the first data of their kind to be available about respiratory illness in children;

- Along with already known viruses, HMPV and hCoV-NL63 were identified in our cohort, demonstrating that these study methods can quickly and successfully confirm community circulation and relative importance of newly identified respiratory viruses; and

- ReVS provided proof-of-concept for the conduct of large scale, community-based illness studies with parent collection of respiratory specimens as the key methodological feature. The key study participants in households were mothers, and they could be relied upon to collect daily respiratory symptoms, identify acute respiratory illnesses that met pre-defined criteria, take a combined nose-throat swab, and capture burden data about the illness.
Autonomous household units could be enrolled and trained in study procedures, including the collection of a simple respiratory sample, at a single home visit. Continuing study participation by enrolled households required minimal ongoing maintenance. These features combine to make for a simple, cost-efficient, and effective study method which can be used for generalised, community-based research or would be suitable for research in a specific target group.

Picornaviruses were identified in half of the specimens returned for this study, confirming their ubiquitous circulation in pre-school aged children. Whilst questions remain about their attributable role, it is clear they are major contributors to respiratory illness, including asthma exacerbations and other lower respiratory tract syndromes. Rhinovirus and picornavirus publications since the conduct of ReVS have highlighted the need for future studies to collect control specimens during asymptomatic periods, as well as typing all positive specimens to better identify rapid rhinovirus replacement, as opposed to prolonged shedding.

Influenza A had three times the cost-of-illness of RSV and other viruses. This finding is in keeping with other research showing that the cost of hospitalisation for laboratory-confirmed influenza infection is multiple times higher than those identified using less specific discharge codes associated with influenza-like illness. There were few influenza A illnesses, even during a year with higher than expected seasonal activity, from which to calculate the cost-of-illness figure meaning confidence intervals were wide. It will be important to confirm these findings in Australian and other settings to aid decision making about more widespread use of influenza A vaccine and treatment.

As with all observational research, consideration of potential biases and other design weaknesses is these studies is required during interpretation. For both the pilot study and ReVS, households from higher income brackets were over-represented in the study populations. This is despite targeting recruitment efforts in council areas with lower than average mean household incomes for ReVS. Higher household income could have a dual impact on values from this research, with
both incidence of ARIs and associated costs potentially being biased. Other published respiratory illness research does not routinely report income or socioeconomic status of participating households. These findings identify the importance of collecting, reporting, and considering income as a potential source of bias in similar studies in the future.

The simplicity and efficient conduct of these studies meant cohorts could be enrolled and maintained with a relatively small staffing investment. This design for respiratory illness studies does mean there is no doctor or healthcare worker verified data on syndromic illness. For example, it is not possible to be definitive about lower respiratory tract involvement in an illness without formal examination. Whilst of interest, it may be that in future research such data are not always required, with the cost benefits of an easily maintained study cohort outweighing the need for confirmed clinical data, particularly with the ability to get pathogen identification and impact data unbiased by study staff visits. Work done in Queensland since the conclusion of these studies has confirmed the sensitivity of nose-throat specimens for the major viral pathogens of childhood when compared to more invasive nasopharyngeal aspiration. Other work from the Netherlands suggested that home visiting may be much less efficient in terms of capturing a specimen for every illness. This is possibly due to the increasing proportion of families with both parents working outside the home. Parent monitoring of illness and collection of specimens from household members during illnesses meeting pre-defined criteria could soon become the obvious choice for cost efficient and methodologically pure research. Further evolution of this method, including the return of specimens through surface mail, could make the system even less expensive without loss of laboratory testing sensitivity.

Studies to assess the efficacy of prophylactic vaccines, other prophylactic agents (such as targeted antibody preparations), and therapeutic agents under development will be required in the near future. Whilst an important component of action for all of these agents will be to limit the occurrence and degree of severe infections, real prospects for population control rest with the capability of a product to eliminate or greatly reduce the burden associated with community-
managed illness. Control of illness in the later group could be achieved through direct or indirect effects of large scale prevention programs. Evidence from this thesis supports the notion that community-managed illness is an appropriate and realistic efficacy end point for future research, and should be assessed in conjunction with more serious, but less common, end points, such as hospitalisations.
References


303. Skiadopoulos MH, Vogel L, Riggs JM, Surman SR, Collins PL, Murphy BR. The genome length of human parainfluenza virus type 2 follows the rule of six, and recombinant viruses recovered from non-polyhexameric-length antigenomic cDNAs contain a biased distribution of correcting mutations. *J Virol* 2003; 77:270-279.


References


Appendix

FIRST AUTHOR, PEER REVIEWED PUBLICATIONS ARISING FROM THIS THESIS

A.1


*Communicable Diseases Intelligence* 2004; 28:509-516.
The cost of seasonal respiratory illnesses in Australian children: the dominance of patient and family costs and implications for vaccine use

Stephen Lambert,1,2 Kerry-Ann O’Grady,1 Susan Gabriel,1 Robert Carter,3 Terry Nolan1,2

Abstract
Respiratory viral infections are one of the next group of diseases likely to be targeted for prevention in childhood by the use of vaccines. To begin collecting necessary epidemiology and cost information about the illnesses caused by these viruses, we conducted a prospective cohort study in 118 Melbourne children between 12 and 71 months of age during winter and spring 2001. We were interested in calculating an average cost per episode of community-managed acute respiratory disease, in identifying the key cost drivers of such illness, and to identify the proportion of costs borne by the patient and family. There were 202 community-managed influenza-like illnesses identified between July and December 2001, generating 89 general practitioner visits, and 42 antibiotic prescriptions. The average cost of community-managed episodes (without hospitalisation) was $241 (95% CI $191 to $291), with the key cost drivers being carer time away from usual activities caring for the ill child (70% of costs), use of non-prescription medications (5.4%), and general practice visits (5.0%). The patient and family met 87 per cent of total costs. The lowest average cost occurred in households from the highest income bracket. Acute respiratory illness managed in the community is common, with the responsibility for meeting the cost of episodes predominantly borne by the patient and family in the form of lost productivity. These findings have implications for preventive strategies in children, such as the individual use of, or implementation of public programs using, currently available vaccines against influenza and vaccines under development against other viral respiratory pathogens. Commun Dis Intell 2004;28:509–516.

Keywords: vaccine use, respiratory illnesses

1. Murdoch Childrens Research Institute, Royal Children’s Hospital, Parkville, Victoria
2. School of Population Health, University of Melbourne, Melbourne, Victoria
3. Program Evaluation Unit, School of Population Health, University of Melbourne, Melbourne, Victoria

Corresponding author: Dr Stephen Lambert, School of Population Health, Level 5/207 Bouverie Street, University of Melbourne Victoria 3010. Telephone: +61 3 8344 9330. Facsimile: +61 3 9348 1827. Email: s.lambert@unimelb.edu.au
Introduction

For some time now there has been a divergence between what vaccines the National Health and Medical Research Council (NHMRC), more recently on the advice of the Australian Technical Advisory Group on Immunisation (ATAGI), recommends Australians should receive, and what is paid for by the National Immunisation Program (NIP). The NIP is a Commonwealth, State and Territory Governments’ initiative that provides certain vaccines free of charge to Australians.

This divergence previously only applied to recommendations for older Australians, in particular, influenza and 23-valent polysaccharide pneumococcal vaccines. Influenza vaccine was first recommended for older Australians in the third edition of, what is now called, the Australian Immunisation Handbook in 1986 but was only funded nationally in 1999. A general recommendation for use of polysaccharide pneumococcal vaccine in older Australians was first made in the fifth edition of the immunisation handbook (1994). and the Commonwealth Government has announced funding for a national program to commence in 2005.

But as Burgess and McIntyre reported recently, the release of the eighth edition of the handbook has seen this divergence between recommended and funded vaccines extend to children. Varicella vaccine is on the Australian Standard Vaccination Schedule at 18 months of age; there is a universal recommendation for a primary course of the relatively expensive seven-valent conjugate pneumococcal vaccine; and inactivated poliomyelitis vaccine is recommended when appropriate combination vaccines become available. An infant program and a catch-up program for children under the age of two years for pneumococcal vaccine commenced at the beginning of 2005, but there is currently no provision to fund either universal childhood varicella vaccination or a transition to inactivated poliomyelitis vaccine.

This emerging discrepancy between recommended and funded vaccines is only likely to widen. One of the next major groups of diseases preventable by use of vaccines is likely to be the respiratory viral infections of childhood. Injectable influenza vaccines are currently licensed for Australian children down to the age of six months, but are currently recommended only for children in high-risk groups. A trivalent, cold-adapted, influenza vaccine (CAIV-T), containing live-attenuated virus and delivered intranasally, was licensed in the United States of America (USA) in 2003 for healthy five to 49-year-olds, with the likelihood of younger and older age indications in the future. Other vaccines against respiratory viral infections, including respiratory syncytial virus and parainfluenza viruses, are currently under development. Information about the epidemiology and costs of acute community-based respiratory illness in children, particularly those costs borne by the patient and family, are required to guide future vaccine use and other control measures. Given the circulation patterns of these viruses, particularly respiratory syncytial virus and influenza virus, we collected information about respiratory illness in winter and spring.

We report here burden information for community-based respiratory illnesses in urban Australian children, and use these to calculate an average cost for these episodes.

Method

We conducted a prospective cohort study of healthy children in metropolitan Melbourne, Victoria, between 1 July and 1 December 2001. The Royal Children’s Hospital Ethics in Human Research Committee approved the study and written informed consent was obtained from parents/guardians. Methods for this study have been described elsewhere. Eligible children were between 12 and 71 months of age at enrolment without pre-existing chronic respiratory or other medical problems. Children aged between 12 and 23 months were recruited largely via maternal and child health nurses (MCHNs) and immunisation providers in 23 local council areas across greater Melbourne. We invited participation from families with older children who had previously participated in a (non-respiratory pathogen) vaccine study conducted by our group, and also distributed flyers and posters through childcare centres. More than one child per family could be enrolled. We collected household demographic features at enrolment. Gross household income was collected in four brackets: bracket 1, ≤ $21,000; bracket 2, $21,101 to $33,000; bracket 3, $33,001 to $56,000; and bracket 4, > $56,000.

Parents/guardians completed a symptom diary card for each day the child was on the study. We designated an important respiratory illness to be an influenza-like illness (ILI) using the criteria described by Belshe et al in the CAIV-T efficacy study conducted in the USA during 1996 and 1997. An ILI was defined as having occurred if a child had at least one category A symptom or at least two category B symptoms (Table 1). All information about symptoms was from parental report only. Individual episodes began on the first day on which there were sufficient symptoms to meet the definition of an ILI, and finished on the final day there were any documented symptoms associated with the ILI. A new episode was deemed to have commenced if there were three or more symptom-free days since the last day with any symptoms of the previous episode. Number and duration of ILIs was ascertained;
incidence rates were calculated using child-months (person-time) as the denominator, and 95 per cent confidence intervals (CI) were produced using the standard method for incidence rate data.\textsuperscript{10}

We used incident-based costing to derive an average cost of community-managed episodes (not including illnesses in which there was a hospitalisation). Once a child developed an ILI we asked parents to complete a burden diary on healthcare use, travel costs seeking healthcare (including car used and kilometres travelled), medication usage, investigations performed, time spent seeking healthcare during the episode, and excess time spent caring for a sick child—that is, time over and above that normally required for the care of the child when well.

Cost data were calculated from a societal perspective using 2001–2002 financial year Australian dollar values (Table 2). Discounting is not relevant as costs were collected in a single year. Direct and indirect costs were included, and we allocated costs as being borne either by the patient and family, the healthcare sector, or by another sector.\textsuperscript{11} Details of sources for all costs are provided (Tables 2 and 3). An average cost per episode was calculated using the total number of illnesses, not just those where burden information was available, as the denominator.

Carer time spent seeking healthcare and excess time spent caring for an ill child were collected in three categories: time away from work with pay lost; time away from work with no pay lost; and time away from usual activities. We applied a sex-weighted hourly rate derived from the Australian Bureau of Statistics average weekly earnings (females: $19.69 per hour; males: $22.44 per hour) for reported times.\textsuperscript{12} For time away from work with pay lost and time away from usual activities we allocated the cost to the patient and family sector; and for time away from work with no pay lost, we allocated the cost to the employer (other sector), who was paying for working hours not performed.

We identified the key cost drivers for illness, and calculated an average resource unit used per episode and 95 per cent confidence intervals (95% CI) using standard methods.\textsuperscript{13} Where information was not available for an illness, we applied a zero value for missing data when calculating means and CIs. One-way sensitivity analyses were undertaken by using the 95 per cent confidence limits for these key cost drivers, and we calculated an average cost for all episodes, by including those illnesses where there was a hospitalisation. We also used the confidence limits to perform multi-way sensitivity analyses, with a least expensive and most expensive scenario for community-managed episodes.

Calculations were performed using Microsoft Excel.

Results

One hundred and twenty-one children from 80 households were enrolled; complete individual and household demographic data about 118 children (98%)—52 females and 66 males—from 78 households (97.5%) were available and these are included in this analysis. These 118 children provided 14,430 child-days (477.3 child-months) of follow-up between 1 July and 1 December 2001. Most study households came from the highest annual income bracket: 73 per cent from bracket 4 (income > $56,000); 15 per cent from bracket 3; 6 per cent from bracket 2; and 5 per cent from bracket 1. There were 15 households with a couple and one child, 41 with a couple and two children, 17 with a couple and three children, three with a couple and four children, one household with a single parent and two children, and one household with a single parent and three children. Eight children (7%) were one year of age at enrolment, 62 (53%) were two years of age, 19 (16%) were three years of age, 18 (15%) were four years of age, and 11 (9%) were five years of age.

Table 1. Defining symptoms of an influenza-like illness

<table>
<thead>
<tr>
<th>Category A symptoms</th>
<th>Category B symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>fever (either identified without measurement or a measured temperature of 37.6°C or higher by auxiliary thermometer)</td>
<td>runny nose/nasal congestion</td>
</tr>
<tr>
<td>wheezing</td>
<td>sore throat</td>
</tr>
<tr>
<td>shortness of breath</td>
<td>cough</td>
</tr>
<tr>
<td>pulmonary congestion (moist cough)</td>
<td>muscle aches</td>
</tr>
<tr>
<td>pneumonia (diagnosed by a healthcare provider)</td>
<td>chills</td>
</tr>
<tr>
<td>ear infection (suspected by parent/guardian or diagnosed by healthcare provider)</td>
<td>headache</td>
</tr>
<tr>
<td></td>
<td>irritability</td>
</tr>
<tr>
<td></td>
<td>decreased activity (lethargy/weakness)</td>
</tr>
<tr>
<td></td>
<td>vomiting</td>
</tr>
</tbody>
</table>

\textsuperscript{10} Incidence rate is defined as the number of new cases of a disease occurring in a defined population during a specified time interval divided by the average population size during the same interval, multiplied by a constant to express the rate as a per person-time unit.\textsuperscript{11} Direct costs are associated with the delivery of health care, whereas indirect costs refer to the loss of productivity due to illness and the effects of the illness on productivity.\textsuperscript{12} Hourly rates were sex-weighted using average weekly earnings for the year 2001–2002.\textsuperscript{13} Sensitivity analysis is a method of assessing the robustness of results by varying the values of assumed parameters.
Table 2. Summary of resources consumed during 202 influenza-like illnesses in 118 Melbourne children during winter and spring 2001

<table>
<thead>
<tr>
<th>Resource</th>
<th>Units consumed</th>
<th>Patient and family sector</th>
<th>Healthcare sector</th>
<th>Other sectors</th>
<th>% ILI cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>General practice visits*</td>
<td>89</td>
<td>$255.43</td>
<td>$2,174.94</td>
<td>–</td>
<td>5.0%</td>
</tr>
<tr>
<td>Other healthcare provider visits†</td>
<td>10</td>
<td>$156.42</td>
<td>$115.00</td>
<td>–</td>
<td>0.2%</td>
</tr>
<tr>
<td>Hospital emergency department visit (no admission)‡</td>
<td>4</td>
<td>–</td>
<td>$160.00</td>
<td>–</td>
<td>0.3%</td>
</tr>
<tr>
<td>Diagnostic tests§</td>
<td>1</td>
<td>$5.00</td>
<td>$28.31</td>
<td>–</td>
<td>0.1%</td>
</tr>
<tr>
<td>Antibiotics ‡</td>
<td>42</td>
<td>$579.47</td>
<td>–</td>
<td>–</td>
<td>1.2%</td>
</tr>
<tr>
<td>Other prescription medication‖</td>
<td>24</td>
<td>$336.92</td>
<td>–</td>
<td>–</td>
<td>0.7%</td>
</tr>
<tr>
<td>Over-the-counter and other medication§</td>
<td>244</td>
<td>$2,617.40</td>
<td>–</td>
<td>–</td>
<td>5.4%</td>
</tr>
<tr>
<td>Paid childcare for other children**</td>
<td>11 episodes</td>
<td>$133.00</td>
<td>–</td>
<td>–</td>
<td>0.3%</td>
</tr>
<tr>
<td>Travel costs seeking healthcare†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Car</td>
<td>460.6 kms</td>
<td>$209.96</td>
<td>–</td>
<td>–</td>
<td>0.4%</td>
</tr>
<tr>
<td>Parking</td>
<td>3 episodes</td>
<td>$13.00</td>
<td>–</td>
<td>–</td>
<td>0.0%</td>
</tr>
<tr>
<td>Time seeking healthcare†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time away from work, pay lost</td>
<td>34.5 hours</td>
<td>$679.31</td>
<td>–</td>
<td>–</td>
<td>1.4%</td>
</tr>
<tr>
<td>Time away from work, no pay lost</td>
<td>22.25 hours</td>
<td>–</td>
<td>–</td>
<td>$438.10</td>
<td>0.9%</td>
</tr>
<tr>
<td>Time away from usual activities</td>
<td>67.04 hours</td>
<td>$1,329.18</td>
<td>–</td>
<td>–</td>
<td>2.7%</td>
</tr>
<tr>
<td>Excess time caring for ill child††</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time away from work, pay lost</td>
<td>81.50 hours</td>
<td>$1,604.74</td>
<td>–</td>
<td>–</td>
<td>3.3%</td>
</tr>
<tr>
<td>Time away from work, no pay lost</td>
<td>178.60 hours</td>
<td>–</td>
<td>–</td>
<td>$3,609.03</td>
<td>7.4%</td>
</tr>
<tr>
<td>Time away from usual activities</td>
<td>1682.54 hours</td>
<td>$34,212.06</td>
<td>–</td>
<td>–</td>
<td>70.3%</td>
</tr>
<tr>
<td>Sector total‡</td>
<td></td>
<td>$42,131.87</td>
<td>$2,478.24</td>
<td>$4,047.14</td>
<td>100%</td>
</tr>
<tr>
<td>Sector cost per ILI</td>
<td></td>
<td>$208.57</td>
<td>$12.27</td>
<td>$20.04</td>
<td></td>
</tr>
<tr>
<td>Sector per cent</td>
<td></td>
<td>86.6%</td>
<td>5.1%</td>
<td>8.3%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>$48,657.25</td>
<td>Total cost per ILI</td>
<td>$240.88</td>
<td></td>
</tr>
</tbody>
</table>

* Based on 2001 Medicare Benefits Schedule rates for healthcare sector costs (85% of code 23—$28.75) and mean patient cost per GP/vocational registered GP visit for 2001 ($2.87) for patient and family cost.†
† Based on parent-reported costs for visits to naturopaths (2 visits) and chiropractors (6 visits), and 2001 Medicare Benefits Schedule fee rates for 2 specialist visits (85% of MBS code 104—$57.50) and mean patient cost per specialist visit for 2001 ($15.71) for patient and family cost.‡
‡ Hospital emergency department (ED) visits based on the cost for emergency department presentation for the Australian Ambulatory Classes group 23: Other respiratory diseases without procedure ($40). §
§ Actual cost paid by parent charged not uniformly available. Government cost based on 85% of 2001 Medicare Benefits Schedule fees for one chest x-ray (MBS code 58500—$33.30). The cost allocated to patient and family was the difference between the Medicare rebate and the schedule fee (15% of the Medicare Benefits Schedule Fee).‖
‖ Given the high proportion of households in the study from the highest income bracket, we have costed all prescription medication for general PBS beneficiaries (no concessional beneficiaries); we have also assumed they were purchased without a Safety Net Entitlement Card. Prescription medication costs were the maximum recordable value for the Safety Net from the Schedule of Pharmaceutical Benefits for Approved Pharmacists and Medical Practitioners. ‡ None of these individual costs exceed the maximum cost for a pharmaceutical benefit item ($21.90), so all costs were allocated to the patient and family sector.
¶ Over-the-counter medication from pharmacies is the MIMS Australia cited cost, and other medication (for example, natural therapies) based on parent-report.
‖‖ Parent-reported childcare costs for other children whilst seeking care for ill child.
†† Car running costs per kilometre (business cost) from the Royal Automobile Club of Victoria (RACV) based on type, age, and engine size of car used. ‡‡ Parking costs as reported by parents in seeking healthcare.
‡‡ All time based on parent-reported hours. Cost applied from sex-weighted Australian Bureau of Statistics (ABS) average weekly earnings, November 2001; male ($852.70 per 38 hour week) and female ($748.20 per 38 hour week). Cost allocated to the employer (other sector) for time away from work, no pay lost, and to patient and family sector for time away from work, pay lost and time away from usual activities.
§§ Columns do not add exactly to total due to rounding.
There were 202 ILI community-managed episodes identified, giving an incidence rate of 0.42 ILIs per child-month (95% CI 0.36 to 0.48). There were three episodes that resulted in hospitalisation, and these were not included in general calculations. During the period, 21 children had no episodes of ILI, 35 children had one episode, 30 children had two episodes, 24 children had three episodes, five children had four episodes, and three children had five episodes. We received costing information for 180 (89%) of these illnesses (Table 2). The illnesses where we did not receive burden data were shorter (median duration: 2.5 days versus 5 days) and less likely to have parent-reported fever or ear infection (proportion with uncomplicated illness: 77% versus 48%), compared to those illnesses where burden data were available. Parents may have been less likely to report burden information for illnesses they felt were trivial, or resulted in no excess resource consumption.

Using the costs from these 180 for all 202 illnesses gave an average cost per ILI episode of $241 (95% CI $191 to $291). The average cost using only those illnesses we had information on was $270. The key cost driver for ILI in children was carer time spent caring for the ill child away from usual activities, making up 70 per cent of total costs. Females spent an average of 6.38 hours per episode (95% CI 4.61 to 8.15) caring for the ill child away from their usual activities, and males an average of 1.95 hours per episode (95% CI 1.05 to 2.84). The next most important non-carer time related drivers were use of non-prescription medication (5.4% of total costs, 244 episodes of use, 95% CI 215 to 273), and general practitioner visits (5.0% of total costs, 89 visits, 95% CI 68 to 110 visits).

The average cost per episode was lowest for those illnesses occurring in households from the highest income bracket: bracket 4, $208; bracket 2, $290; bracket 1, $377; and bracket 3, $449. These rankings remained the same when illnesses where there was no information available were removed from average calculations (bracket 4, $235; bracket 2, $327; bracket 1, $431; and bracket 3, $474).

Funding the resource use during illness was predominantly the responsibility of the patient and family, with this sector being responsible for meeting 87 per cent of total costs. The healthcare sector met five per cent of costs, and other sectors met eight per cent of costs.

As key costs drivers, carer time away from usual activities, non-prescription medication, and general practice visits were individually varied in one-way sensitivity analyses, according to the upper and lower 95 per cent confidence limits. The average cost per episode varied little for the sensitivity analyses involving non-prescription medication and general practice visits (Table 3), but ranged from $186 to $296 when carer time away from usual activities was varied. The one-way sensitivity analysis which included the three illnesses with hospitalisations increased average cost per episode to $287 (Table 3). Two scenarios were tested producing a least expensive average cost per episode of $177, and a most expensive average cost per episode of $304 (Table 3). Unsurprisingly, these values varied little from those generated in the one-way analyses of carer time away from usual activities.

**Discussion**

As demonstrated by our findings, acute respiratory illness in healthy, urban children during winter and spring is common, with the costs borne largely by the patient and family. These findings have implications for preventive strategies in Australian children, particularly vaccine use. The impact carer time away from usual activities has on the average cost per episode can be seen in a number of ways: the proportion of total costs made up by this single variable (70%); and in the multi-way sensitivity analyses producing least and most expensive cost per episode scenarios varying little from the one-way sensitivity analysis of this variable alone. Not including carer time away from usual activities, as recommended for submissions to have drugs listed on the Pharmaceutical Benefits Scheme, would substantially under-estimate the true impact of community-managed disease of this nature. In this regard, these illnesses may be similar to chickenpox, being common and usually community-managed, with the direct costs of a proposed infant vaccination program in Australia outweighing the direct costs associated with not implementing such a program.

A significant proportion of the illnesses identified in this study are likely to have been caused by respiratory viral infections, including respiratory syncytial virus, influenza virus, parainfluenza viruses, human metapneumovirus, coronaviruses, adenoviruses, and rhinoviruses. The Victorian Infectious Diseases Reference Laboratory identifies 2001 as a year of normal seasonal activity for influenza from the collaborative sentinel influenza surveillance scheme. Injectable influenza vaccine is licensed in Australia for children down to six months of age. The recent licensing in the USA of the intranasal CAIV-T vaccine provides the possibility of better access, acceptability, and delivery of public influenza vaccination programs, especially if the license for use extends to a lower age-group. The current price of the vaccine, though set to fall to US$23.50 for the 2004/2005 influenza season in the United States of America, will remain an impediment to its wider use. Vaccines against other respiratory viruses are
<table>
<thead>
<tr>
<th>Sensitivity analyses</th>
<th>Modification</th>
<th>Values used</th>
<th>Average cost per episode</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One-way analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General practice visits</td>
<td>Number of general practice visits and dependent variables*</td>
<td>Lower value: 68 visits</td>
<td>$233.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper value: 110 visits</td>
<td>$247.94</td>
</tr>
<tr>
<td>Over-the-counter and other medication</td>
<td>Number of episodes of over-the-counter and other medication use</td>
<td>Lower value: 215 episodes</td>
<td>$239.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper value: 273 episodes</td>
<td>$242.42</td>
</tr>
<tr>
<td>Carer time away from usual activities</td>
<td>Time spent caring from ill child away from usual activities</td>
<td>Lower value: 5.67 hours</td>
<td>$186.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4.61 female, 1.05 male)</td>
<td>$295.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper value: 10.99 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(8.15 female, 2.84 male)</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>Addition of three ILIs with a hospitalisation</td>
<td>All costs for these ILIs added to total</td>
<td>$287.03</td>
</tr>
<tr>
<td><strong>Multi-way analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Least expensive scenario</td>
<td>General practice visits*</td>
<td>68 visits</td>
<td>$177.17</td>
</tr>
<tr>
<td></td>
<td>Over-the-counter and other medication</td>
<td>215 episodes of use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carer time from usual activities</td>
<td>Female carers: 4.61 hours per episode</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male carers: 1.05 hours per episode</td>
<td></td>
</tr>
<tr>
<td>Most expensive scenario</td>
<td>General practice visits*</td>
<td>110 visits</td>
<td>$304.33</td>
</tr>
<tr>
<td></td>
<td>Over-the-counter and other medication</td>
<td>273 episodes of use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carer time from usual activities</td>
<td>Female carers: 8.15 hours per episode</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male carers: 2.84 hours per episode</td>
<td></td>
</tr>
</tbody>
</table>

- Changes in the number of general practice visits included proportionate changes in the cost of other variables that rely on a general practice visit: diagnostic tests, antibiotics and other prescription medication, travel seeking healthcare, parking, and time seeking healthcare.
- † Costing for non-hospital related costs in three additional ILIs as per Table 1. Extra diagnostic tests performed outside of hospital: urine microscopy, culture, and sensitivity (MBS code 69312—$33.00—with 2 performed), full blood evaluation (MBS code 65070—$16.70—with 2 performed), and serum biochemistry (MBS code 66515—$19.20—with 2 performed). Healthcare sector cost based on 85% of 2001 Medicare Benefits Schedule, the cost allocated to patient and family for diagnostic tests was the difference between the Medicare rebate and the schedule fee (15% of the Medicare Benefits Schedule Fee). Ambulance cost from Victorian Ambulance Service for emergency transport to hospital less than 10kms away (one transfer). Public hospital admission National Hospital Cost Data Collection code E62C ($2,395). Private hospital admission costs as reported by the two private hospitals: overnight admission for respiratory infection $228 paid by patient and family to private hospital; overnight admission for febrile convulsion $400 paid by health insurance company (other sector cost), and $222 paid by patient and family to private hospital. Private health insurance fees not included.

under development, but still likely to be some way off; the possibility for preventing such illnesses at present is limited to influenza. Beginning in 2004 the Advisory Committee on Immunisation Practices (ACIP) in the USA have made injectable influenza vaccine part of the routine childhood immunisation schedule—for children from six months up to two years of age. This recommendation extends to household contacts (including older children) and out-of-home caregivers of all children less than two years of age. Interest in this recommendation was driven by the USA Centers for Disease Control and Prevention initiating national surveillance for paediatric influenza-associated deaths. It is also possible that use of vaccine in this age group may lead to reduced incidence of disease in other age-groups due to herd protection, similar to effects seen from vaccinating school-aged children against influenza, and more recently, seen in vaccinating USA infants with conjugate pneumococcal vaccine.

Vaccination programs against illnesses that are largely managed in the community may not appear cost-effective if the impact of lost productivity is ignored. Vaccines against influenza and other viral respiratory pathogens may be recommended for young children in the near future, but may not pass the cost-effectiveness hurdle for public funding. There are few published studies looking at the cost-effectiveness of influenza vaccine specifically in children. Given the findings of our study, it will not be surprising that a childhood influenza vaccine program could be potentially cost-saving if indirect costs are included. The reduction in indirect costs is central to the economic benefits of vaccina-
tion,23–25 with previous studies showing that these benefits are greatest when parents are prevented from missing work to care for an ill child.24

The majority of households (73%) in our study came from the highest income bracket. This compares with approximately 40 per cent of Victorian family households being in this income range, according to 2001 Census data.26 This may have had a number of impacts: members of lower income households have been shown to have a higher incidence of respiratory viral infections, thought to be due to the impact of crowding;27 but in this study we did not find a lower rate of illness in children from high income families.8 It could be argued that parents from relatively higher income households might be more likely to expend more resources in caring for a sick child, as compared with those from a lower income household; but we found that the average cost per episode was lowest in households from the highest income bracket. In our study, high-income households were more likely to have both parents spending some time working outside the home. Parents in these households might have different thresholds for seeking medical attention or using medication for illnesses that are perceived to be mild or of minor significance. If anything, due to the lower average cost per episode in higher income households, the over-representation of such households in our study may have made our cost estimate conservative.

Costing studies such as this, together with studies that measure the relative role of specific pathogens, will not only inform local cost-effectiveness studies, but failing public funding of programs, will provide important information for vaccine providers and parents about the likely benefits of paying for available vaccines themselves.

Acknowledgements

We would like to thank the research staff who assisted with this study—Jacinta O’Sullivan, Samantha Colquhoun, Ethna Macken, and Sally Mizrahi. Recruitment of younger children for this study was only possible through the kind assistance of local government Maternal and Child Health Nurses in the greater Melbourne area. We extend our appreciation to the children and families who participated in the study. Stephen Lambert is a National Health and Medical Research Council Public Health Postgraduate Scholar. Support for this study was provided in part by a grant to the Murdoch Childrens Research Institute from CSL Ltd.

References


A.2

Respiratory illness during winter: A cohort study of urban children from temperate Australia

SB Lambert,1,2 KF O’Grady,1 SH Gabriel1 and TM Nolan1,2

1Murdoch Childrens Research Institute, Royal Children’s Hospital, and 2School of Population Health, University of Melbourne, Melbourne, Victoria, Australia

Objective: To examine the epidemiology and burden of respiratory illness during winter in urban children from temperate Australia.

Methods: We conducted a cohort study of healthy Melbourne children, aged from 12 to 71 months. Parents kept a daily respiratory symptom diary and recorded resource use when an influenza-like illness (ILI) occurred.

Results: One-hundred and eighteen children had 137 ILI episodes over 12 weeks for a rate of 0.53 ILI episodes per child-month (95% CI 0.44–0.61). Risk factors for ILI included younger age, fewer people residing in the household, structured exposure to other children outside the home, and a higher household income. Episodes had a mean duration of 10.4 days with 64 visits to a general practitioner (46.7 GP visits per 100 episodes), 27 antibiotic courses prescribed (19.7 antibiotic courses per 100 episodes), and three overnight hospitalizations (2.2 admissions per 100 episodes). Parents reported an average of 11.7 h excess time spent caring for a child per episode.

Conclusions: Respiratory illnesses are a common and largely neglected cause of illness in Australian children. Pathogen-specific data are required to better assess the likely impact of available and developing vaccines and other treatment options.

Key words: child; epidemiology; influenza; respiratory tract infections; viruses.

In Australia there are no reliable population-based data on the burden of disease caused by viral ARI in the community, with information largely limited to secondary surveillance data. Influenza is the exception with surveillance for influenza-like illness (ILI) through sentinel general practice sites existing in a number of states and territories,1 and laboratory-confirmed infection becoming nationally notifiable from January 2001.2 However, the sentinel surveillance schemes across Australia are not coordinated, and lack standard methods for identifying cases, collating information and reporting findings.3 Information about respiratory syncytial virus (RSV) and other important viral pathogens is only available through monitoring laboratory diagnoses,4 hospital discharge codes5 and targeted research projects.6

Where local data are available they suggest that, as is the case globally,7,8 children suffer disproportionately from the serious consequences of ARI. Since becoming notifiable, rates of laboratory-confirmed influenza have been highest in children under the age of 5 years, even outstripping rates in the elderly,9 a finding matched by hospitalization data.10

A new live, cold-adapted, intranasal, trivalent influenza vaccine (CAIT-V) has been licensed in the United States for healthy children down to the age of 5 years,11 with the likelihood of a wider age indication in the future. Vaccines to protect against respiratory syncytial virus12,13 and paramyxovirus viruses14 are under development. Some of these new vaccines could contain antigens that protect against a number of infections, including the recently identified human metapneumovirus.15 Baseline data about the epidemiology and burden of viral respiratory illnesses in Australian children are required to assist with vaccine and treatment policy development, cost effectiveness estimates and impact assessments. To be meaningful, these data need to incorporate not only serious infections that result in laboratory-confirmation or hospitalization, but the vast majority of infections that are managed in the community.

In an effort to begin to capture this information, we conducted a cohort study over the 2001 winter respiratory illness season to determine the frequency of ILI in children aged one to less than 6 years in metropolitan Melbourne. We also sought to estimate the burden associated with these illnesses by collecting information about resource use due to the illness.

MATERIALS AND METHODS

We conducted a prospective cohort study of healthy children in metropolitan Melbourne, Victoria, between July 2001 and December 2001. The Royal Children’s Hospital Ethics in Human Research Committee approved the study and written informed consent was obtained from parents/guardians.

Children were eligible to participate if they were generally healthy and between 12 and 71 months of age at the time of enrolment. Children between 12 and 23 months of age were recruited via maternal and child health (MCH) nurses and immunization providers in local council areas across the greater Melbourne area. We invited participation from families with older children who had previously participated in a (non-respiratory pathogen) vaccine study conducted by our group, and also distributed flyers and posters through childcare centres. More than one child per family could be recruited. Children at increased risk of
respiratory infection or increased risk of severe disease following infection, such as those with chronic pulmonary or cardiovascular disorders, immune system disorders or other chronic illnesses, were excluded. Demographic information on the child and the household was collected at enrolment.

Parents/guardians completed a symptom diary card for each day the child was on the study. Regular telephone contact from a research assistant during the influenza season assisted parents/guardians to identify illnesses and complete documentation. Once a child developed an ILI an extra diary (burden diary) collected information on healthcare use, medication usage, investigations performed and time spent on healthcare visits for the episode. With this diary parents also estimated any excess time spent caring for a sick child – time over and above that normally required for the care of the child when well.

We defined an ILI according to the criteria used by Belshe et al. in an intranasal influenza-virus vaccine efficacy study conducted in the United States during 1996 and 1997. All information about symptoms was from parental report. An illness episode was based on symptoms in two categories (Table 1) and then classified as follows: (i) ILI: at least one category A symptom OR at least two category B symptoms; (ii) Febrile ILI: ILI with a parental report of fever (with or without a recorded temperature) during the episode; (iii) ILI with otitis media: ILI with parental suspicion of, or healthcare provider diagnosed, otitis media during the episode; and (iv) Febrile ILI with otitis media: ILI with a parental report of both fever (with or without a recorded temperature) and parental suspicion of, or healthcare provider diagnosed, otitis media during the episode.

We used this definition and classification of illness as the Belshe study provides efficacy estimates for the prevention of not only laboratory-confirmed influenza infection (up to 95%) in ILI identified using this method, but also febrile illness (21%) and febrile otitis media (30%).

The number and duration of ILI episodes were ascertained. Individual episodes began on the first day on which there were sufficient symptoms to meet the definition of an ILI, and finished on the final day there were any documented symptoms associated with the ILI. A new episode was deemed to have commenced if there were three or more symptom-free days since the last day with symptoms of the previous episode. Incident rates were calculated using child-months (person-time) as the denominator.

Of particular interest were the ILI episodes occurring within the local influenza season, as these were more likely to represent currently preventable illnesses using available efficacy estimates for laboratory-confirmed influenza infection, febrile illness and febrile otitis media. The timing of the local influenza season was identified using the Victorian influenza surveillance system, managed by the Victorian Infectious Diseases Reference Laboratory and the Department of Human Services.

Prior to study commencement, based on figures from previous years, we defined the start of the local influenza season as the beginning of the first fortnight in which there were five or more laboratory isolates of influenza viruses (type A or B), in the presence of an increasing proportion of ILI being notified by the Victorian General Practice Surveillance Scheme.

The end of the local influenza season was defined as the end of the fortnight preceding the first fortnight in which there were less than 15 laboratory isolates of influenza viruses (type A or B), in the presence of a decreasing proportion of ILI being notified by the Victorian General Practice Surveillance Scheme.

This was a pilot study undertaken to examine the feasibility and practicality of instituting a larger, longer term community cohort study. As such, we did not perform a sample size calculation in preparing for this study. Univariate incidence rate ratios were calculated for specific exposures, and the corresponding 95% confidence intervals were produced using the standard method for incidence rate ratios.

RESULTS

One hundred and twenty-one children from 80 households in 23 local council areas in greater Melbourne were enrolled; complete data about 118 children (98%) from 78 households (97.5%) were available and these are included in this analysis.

Of the 118 children, 52 were female and 66 were male. On enrolment eight (6.8%) children were 1 years of age, 62 (52.5%) were 2 years old, 19 (16.1%) were 3 years old, 18 (15.3%) were 4 years old, and 11 (9.3%) were 5 years old. Sixty-seven children (56.8%) attended childcare, 23 (19.5%) preschool and five (4.2%) school, leaving 22 (18.6%) children with no structured exposure of this type to other children outside the home. No child had previously received an influenza vaccine.

A majority of households had four people living in them: 14 households (18%) with three people, 44 households (56%) with four people, 17 households (22%) with five people, two households (3%) with six people, and one household (1%) with seven people. Almost three-quarters of study households were in the highest total household annual income band: >$56 000 band, 57 households (73%); $33 001 to $56 000 band, 12 households (15%); $21 001 to $33 000 band, five households (6%); and ≤ $21 000 band, four households (5%). In keeping with this, over three-quarters of study households had private health insurance, with 36 households (46%) having hospital and ancillary cover, 24 households (31%) having hospital only cover and 18 households (23%) reporting no private health insurance.

We identified 205 ILI episodes in 477.3 child-months between 1 July and 1 December 2001. The local influenza season commenced on 15 July and ended on 6 October 2001. The season encompassed 260.4 child-months (7926 child-days) of

| Table 1 Respiratory symptoms used to define influenza-like illness

<table>
<thead>
<tr>
<th>Category A symptoms</th>
<th>Category B symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• fever (either identified without measurement or a measured temperature of 37.6°C or higher by axillary thermometer)</td>
<td>• runny nose/nasal congestion</td>
</tr>
<tr>
<td>• wheezing</td>
<td>• sore throat</td>
</tr>
<tr>
<td>• shortness of breath</td>
<td>• cough</td>
</tr>
<tr>
<td>• pulmonary congestion (moist cough)</td>
<td>• muscle aches</td>
</tr>
<tr>
<td>• pneumonia (diagnosed by a healthcare provider)</td>
<td>• chills</td>
</tr>
<tr>
<td>• ear infection (suspected by parent/guardian or diagnosed by healthcare provider)</td>
<td>• headache</td>
</tr>
<tr>
<td></td>
<td>• irritability</td>
</tr>
<tr>
<td></td>
<td>• decreased activity (lethargy/weakness)</td>
</tr>
<tr>
<td></td>
<td>• vomiting</td>
</tr>
</tbody>
</table>
observation, with 137 ILI episodes documented (Fig. 1), giving an incidence rate of 0.53 ILI episodes per child-month (95% CI 0.44–0.61). The incidence rate ratio for ILI episodes in the influenza season versus the non-influenza season was 1.68 (95% CI 1.25–2.24). The remainder of this report describes episodes during the influenza season only.

The 137 episodes occurred in 89 (75.4%) children from 65 (83.3%) households. For all 118 children, this equates to a mean of 1.16 ILI events per child during the season (median one event, range 0–4). Of the 137 events, 69 (50.4%) were ILI only, 54 (39.4%) were ILI with fever, seven (5.1%) were ILI with otitis media, and seven (5.1%) were ILI with febrile otitis media. These events resulted in a total of 1427 illness days (18% of observed days) with an average duration of 10.4 days per episode (median 8 days, range 1–66). Thirty-six ILI (26.3%) continued for more that 2 weeks. There were 140 (9.8%) days on which a fever was reported and 236 (16.5%) days with decreased activity (mean: 1.72 days of decreased activity per episode).

In an attempt to identify risk factors for ILI episodes in the influenza season, we calculated rate ratios for various exposures (Table 2). Rates of ILI fell with increasing age at time of enrolment and increasing number of children per household. Children were also more likely to have an ILI if they had structured exposure to other children outside the home (childcare, preschool or school) and came from a household that had private health insurance coverage or a higher annual income level.

Burden diary cards were available for 122 (89.1%) of the 137 ILI that occurred during the influenza season. These 122 episodes resulted in 77 visits to a healthcare provider: 64 general practitioner (GP) visits, five hospital visits and eight visits to other providers (chiropractors, naturopaths). Twenty-seven courses of an antibiotic were prescribed in 24 (17.5%) ILI episodes: 22 events with a single course, one event with two courses, and one event with three courses. There were 20 prescriptions for other medications in 13 episodes (9.4%). Over-the-counter medicines were used 182 times in 119 episodes. Four episodes resulted in diagnostic tests being performed: two chest radiographs, two haematological and biochemical blood examinations, and two urine microscopy, culture and sensitivity.

### Table 2

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Rate (ILI episodes per child-month)</th>
<th>Rate ratios (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at enrolment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.72</td>
<td>1.92 (0.82–4.52)</td>
</tr>
<tr>
<td>2</td>
<td>0.55</td>
<td>1.49 (0.77–2.88)</td>
</tr>
<tr>
<td>3</td>
<td>0.49</td>
<td>1.33 (0.63–2.82)</td>
</tr>
<tr>
<td>4</td>
<td>0.50</td>
<td>1.34 (0.63–2.85)</td>
</tr>
<tr>
<td>5</td>
<td>0.37</td>
<td>referent group</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.49</td>
<td>referent group</td>
</tr>
<tr>
<td>Male</td>
<td>0.55</td>
<td>1.12 (0.79–1.57)</td>
</tr>
<tr>
<td>Number of children in the household</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.62</td>
<td>1.91 (0.56–6.45)</td>
</tr>
<tr>
<td>2</td>
<td>0.53</td>
<td>1.62 (0.51–5.15)</td>
</tr>
<tr>
<td>3</td>
<td>0.50</td>
<td>1.54 (0.48–4.96)</td>
</tr>
<tr>
<td>4</td>
<td>0.33</td>
<td>referent group</td>
</tr>
<tr>
<td>Structured exposure to other children outside the home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.43</td>
<td>referent group</td>
</tr>
<tr>
<td>Childcare</td>
<td>0.58</td>
<td>1.35 (0.82–2.21)</td>
</tr>
<tr>
<td>Preschool</td>
<td>0.47</td>
<td>1.09 (0.60–1.97)</td>
</tr>
<tr>
<td>School</td>
<td>0.48</td>
<td>1.12 (0.45–2.81)</td>
</tr>
<tr>
<td>Any</td>
<td>0.55</td>
<td>1.27 (0.78–2.06)</td>
</tr>
<tr>
<td>Family private health insurance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.56</td>
<td>1.42 (0.91–2.20)</td>
</tr>
<tr>
<td>No</td>
<td>0.40</td>
<td>referent group</td>
</tr>
<tr>
<td>Household income per annum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤$56 000</td>
<td>0.36</td>
<td>referent group</td>
</tr>
<tr>
<td>≥$56 000</td>
<td>0.57</td>
<td>1.57 (0.98–2.53)</td>
</tr>
</tbody>
</table>

ILI, influenza-like illness.
Of the five hospital visits, two were managed as emergency department outpatients and three resulted in overnight admissions: a 4-year-old male admitted for rehydration following an ILI with cough and vomiting; a 5-year-old female with a history of febrile seizures who was taken to hospital by ambulance following a prolonged febrile seizure at home during an ILI; and a 2-year-old male admitted for intravenous antibiotics to treat pneumonia.

The most common mode of travel whilst seeking health-care was the family’s private car with 58 visits requiring 644 kilometres of travel. Time spent seeking healthcare was reported for 41 (53.2%) of the 77 provider visits, giving a total of 125 h. For all 77 visits to a healthcare provider, this gives mean values of 8.4 kilometres travelled and 1.6 h per visit. Excess time spent caring for a sick child was reported in 76 (62.3%) of the 122 ILI episodes where information was available. The total time spent providing this care was 1597 h (263 h away from work, 1334 h away from usual activities), and included 1261 h of care by the primary care giver and 336 h by another care giver. For all 137 episodes this gives a mean excess time spent caring for a child with ILI of 11.7 h.

DISCUSSION

The findings from this cohort study identify respiratory illnesses during winter as an important cause of morbidity in healthy children in our community. The urban children on this study experienced, on average, at least one ILI episode during the 2001 respiratory virus season, a year of normal seasonal activity for influenza in Victoria.20 These events consumed considerable resources, both in societal and family terms.

As has been documented in other studies, we found the rate of respiratory illness highest in younger children and in those that had structured exposure to other children outside of the home through day care, preschool or school attendance. In previous studies in developed settings, the rate of infection with a household has decreased with increasing household income, though to be a reflection of greater household crowding.20 but in this study we found the opposite. Also in contrast to previous studies, having fewer people in the household increased the rate of infection. These findings may be related to the changing nature of home life in Australia. In the past, children from relatively higher income households may have not only avoided overcrowding in the home but may have also had a caregiver remain at home with them, thereby avoiding childcare. With the increasing expense of raising a family and the need for both parents to work outside of the home, these children may have lost their previously held advantage due to an increasing likelihood of attending childcare.

More than 50% of the identified ILI had duration greater than 1 week, with more than a quarter lasting beyond 2 weeks. A United Kingdom study showed that 56% of children with upper respiratory tract infections had not recovered 1 week from onset, and 26% had not recovered by day 10.21 A Melbourne community-based study that used a more sensitive case definition for a respiratory episode (1 day of runny nose, sore throat or cough) found children under the age of two shared the longest mean duration of illness (6.8 days) with those aged 31–40 years, with the duration for all illnesses ranging from 1 to 70 days.22 Respiratory problems are the most common reasons for a GP visit in Australia, accounting for 14.2% of problems managed, and antibiotics are the most commonly administered group of medications with 13.8 prescriptions written for every 100 consultations.23 Our findings on illness duration may have an impact on the likelihood parents will present their child to a GP when they have a self-limiting respiratory illness, whether they leave with an antibiotic, or be asked to re-present if a child has not fully recovered after a limited period of time.

There was substantial resource use associated with these ILI, with the major impact on families likely to be the excess time spent caring for a sick child. These indirect costs were major findings in other ILI costing studies,24 potentially surpassing direct costs.25 For this reason, cost effectiveness evaluations of any intervention to prevent these illnesses should be from a societal perspective and include family and patient costs in the model.

There are some issues which need to be considered when interpreting the findings of this study. The study was conducted over one winter season only and respiratory specimens were not obtained to confirm the aetiology of the illness. The number and cause of respiratory infections change year to year. Only a proportion of all illness identified would be preventable, or modifiable, through the use of influenza vaccine. Even in years when influenza virus is circulating in the community, RSV is responsible for more hospitalizations in young children.20 RSV was more common than influenza in a community study of Sydney infants, being detected by polymerase chain reaction testing in 16 of 101 specimens collected, compared with only one specimen positive for influenza A, but both were less common than rhinovirus, found in 35 specimens.27 Convenience sampling was employed in this study as it is not feasible to randomly select a representative sample of children for a study of this nature. This may mean point estimates of rates are biased, however, the rates of ILI we identified were comparable to those seen in the placebo-controlled arm of the CAIT-V study.16 There was a relative over-representation of higher income households in our study population, which might be expected to increase the resource use during an ILI episode. The inclusion of more than one child from each household may have been expected to have a clustering effect on the identification of ILI, although this would not seem to be the case as rates of infection fell with increasing numbers of children in the household.

Timely community-level information about respiratory tract infections in Australia is scarce, and previously gathered data may not be meaningful in today’s context. The nature of family life in Australia and other countries has changed substantially since community respiratory illness studies conducted in the United States from the 1950s to 1980s, and these changes may have impacted on respiratory infection epidemiology. The proportion of Australian children under 12 years of age using formal and/or informal child care has increased in the last two decades, from 38% in 1984 to 51% in 1999,28 and 49% in 2002,29 with the increase most marked in children aged less than 2 years. ARI are common in children who attend child care, particularly those less than 2 years of age,30 and increased child care utilization may have led to previously undocumented increases in individual and household incidence of ARI.

There is a need for pathogen-specific baseline data to quantify the epidemiology and impact of respiratory viruses in children so that cost-effective decisions about interventions can be made. Using information from this study to assist in the planning, our group is currently conducting another community-based study of children with the addition of multiplex polymerase chain reaction (PCR) testing for common respiratory viruses – influenza, respiratory syncytial virus, parainfluenza viruses, adenovirus and picornaviruses – at the time of an ILI episode. Data from this study should provide the basis on which to assess the benefits of introducing vaccines or therapy for respiratory virus infections in Australian children.
ACKNOWLEDGEMENTS

Support for this study was provided in part by a grant to the Murdoch Childrens Research Institute from CSL Ltd. We thank the research staff who assisted with this study – Jacinta O’Sullivan, Samantha Colquhoun, Ethna Macken and Sally Mizrahi. Recruitment of younger children for this study was only possible through the kind assistance of local government Maternal and Child Health Nurses in the greater Melbourne area. We extend our appreciation to the children and families who participated in the study.

REFERENCES

A.3

ARTICLE

Community Epidemiology of Human Metapneumovirus, Human Coronavirus NL63, and Other Respiratory Viruses in Healthy Preschool-Aged Children Using Parent-Collected Specimens

Stephen B. Lambert, MBBSa,b, Kelly M. Allen, MPHa,b, Julian D. Druce, PhD, Chris J. Birch, PhD, Ian M. Mackay, PhD, John B. Carlin, PhD, Jonathan R. Carapetis, PhD, Theo P. Sloots, PhD, Michael D. Nissen, MBBS, Terence M. Nolan, PhD

aSchool of Population Health and Department of Paediatrics, University of Melbourne, Victoria, Australia; bMurdoch Children’s Research Institute, Melbourne, Victoria, Australia; cVictorian Infectious Diseases Reference Laboratory, Victoria, Australia; dClinical Medical Virology Centre, University of Queensland, Brisbane, Australia; eQueensland Paediatric Infectious Diseases Laboratory, Sir Albert Sakzewski Virus Research Centre, Royal Children’s Hospital, Queensland, Australia; fMenzies School of Health Research, Charles Darwin University, Northern Territory, Australia

The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVES. The purpose of this work was to assess the impact of recently described human metapneumovirus and human coronavirus NL63 compared with other respiratory viruses by using sensitive molecular techniques in a cohort of healthy preschool-aged children. We also aimed to assess the use of parent collection to obtain an adequate respiratory specimen from acutely unwell children in the community.

PATIENTS AND METHODS. The community epidemiology and burden of human metapneumovirus and other respiratory viruses (influenza A, influenza B, respiratory syncytial virus, parainfluenza viruses, adenoviruses, and picornaviruses) were examined in a cohort of 234 preschool-aged children from Melbourne, Australia, over a 12-month period by using polymerase chain reaction testing. Parents collected a daily symptom diary for the duration of the study and were taught to collect a combined nose-throat swab and complete an impact diary when the study child had an acute respiratory illness.

RESULTS. The average incidence of acute respiratory illness was 0.48 per child-month for the duration of the study, with a winter peak. Of 543 illnesses with ≥1 specimen returned, 33 were positive for human metapneumovirus (6.1%) and 18 for human coronavirus NL63 (3.3%). Of all of the viruses for which we tested, human metapneumovirus and human coronavirus NL63 were most strongly linked to child care attendance, occurring in 82% and 78% of infected children, respectively. Picornaviruses were the most commonly identified virus group (269 [49.5%]). Influenza virus and adenovirus illnesses had the greatest impact, with fever in more than three quarters and requiring, on average, 1 local doctor visit per illness.

CONCLUSIONS. Recently identified human metapneumovirus and human coronavirus NL63 are important pathogens in community-based illness in children, particularly in those who attend child care. Picornaviruses were detected in half of the nose-throat swabs collected during acute respiratory illness in children but resulted in milder illnesses; influenza and adenovirus caused the highest-impact illnesses. The use of parent-collected specimens should be considered for additional community-based epidemiologic studies and vaccine trials.

www.pediatrics.org/cgi/doi/10.1542/peds.2006-3703
doi:10.1542/peds.2006-3703
Part of the material in this article was presented at the International Symposium on Respiratory Viral Infections; March 3–6, 2005; Curacao, Dutch Antilles; and the Communicable Diseases Control Conference; May 2–3, 2005, Sydney, Australia.

Dr Lambert’s current affiliation is Queensland Paediatric Infectious Diseases Laboratory, Sir Albert Sakzewski Virus Research Centre, Royal Children’s Hospital, Queensland, Australia.

Ms Allen’s current affiliation is Monash Institute of Health Services Research, Monash University and Southern Health, Melbourne, Victoria, Australia.

Key Words
respiratory viruses, human metapneumovirus, human coronavirus NL63, epidemiology, childhood

Abbreviations
ARI—acute respiratory illness
hMPV—human metapneumovirus
hCoV—human coronavirus
VIDRL—Victorian Infectious Diseases Reference Laboratory
PCR—polymerase chain reaction
RSV—respiratory syncytial virus
PIV—parainfluenza virus
CI—confidence interval
GP—general practitioner

Accepted for publication Mar 14, 2007
Address correspondence to Stephen B. Lambert, MBBS, Queensland Paediatric Infectious Diseases Laboratory, Sir Albert Sakzewski Virus Research Centre, Royal Children’s Hospital, Herston 4029, Queensland, Australia. E-mail: slambert@uq.edu.au

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2007 by the American Academy of Pediatrics
Acute respiratory illnesses (ARIs) in children are common, often caused by viruses, and can be serious or life threatening. Available information for viral ARIs in children is largely based on findings from those with illnesses severe enough to warrant hospitalization or on community-based studies performed previously without the use of sensitive molecular techniques. This means our current understanding not only lacks detail of the community epidemiology of recently identified pathogens, such as human metapneumovirus (hMPV) and human coronavirus (hCoV)-NL63, but also of other viruses for which traditional, nonmolecular techniques are less sensitive.

Since their initial discovery, hMPV and hCoV-NL63 have been identified with varying prevalence in specimens from healthy and compromised children and adults presenting to the hospital with mild or severe respiratory illnesses. However, information about community incidence and severity using molecular techniques for these and other respiratory viruses is lacking.

New respiratory virus vaccines are now in clinical trials with human subjects, and there is promise of other novel therapeutic options. Large-scale public health interventions to limit the impact of a significant proportion of respiratory viral infections, particularly in childhood, are now a real possibility. With this study we sought to describe the population epidemiology and impact of common respiratory viruses in children. This information is required to inform public health prevention strategies and to fill the gap in the literature around community-based data derived using molecular techniques. We also sought to compare the relative importance of the recently discovered hMPV and hCoV-NL63 to other viruses.

**PATIENTS AND METHODS**

**Study Cohort**

This study was conducted in the greater Melbourne area. Data and specimen collection commenced on January 17, 2003, and concluded on January 31, 2004. Recruitment and enrollment of children were progressive, with the last child enrolled on November 5, 2003. Recruitment took place through maternal and child health nurses from 26 local councils; by placing advertising material at child care and playgroup centers; and through bulletin boards and staff e-mail lists at the Royal Children’s and the Royal Women’s Hospitals in Melbourne. This was a dynamic cohort with subjects able to temporarily leave the study (such as during family holidays) and rejoin at a later date.

We enrolled 1 child <5 years of age as the primary study subject from each participating family. Where >1 child per household was eligible, we enrolled the child whose birthday fell next. Screening and enrollment home visits were conducted by a research assistant, where study procedures were explained. Risk-factor and household demographic data were collected at the enrollment visit and updated during the study. Children were eligible for enrollment and continuing participation if they were generally healthy and did not have any specific condition that predisposed them to acquiring ARIs or more severe illness with ARIs, such as being born at <36 weeks’ gestation; a chronic heart or respiratory disorder, including a diagnosis of asthma; or another chronic health problem, such as diabetes, kidney disease, or an immune disorder. The study was approved by the Royal Children’s Hospital Ethics in Human Research Committee, and written informed consent was obtained from parents or guardians before participation.

**Illness Identification and Evaluation**

Parents kept a daily symptom diary for the study child based on that used in the study by Belshe et al to assess the efficacy of the live, cold-adapted, intranasal, trivalent influenza vaccine in children. Symptoms were classified as category A (fever, wheezing, shortness of breath, pulmonary congestion or moist cough, pneumonia, or ear infection) and category B (runny nose or nasal congestion, sore throat, cough, muscle aches, chills, headache, irritability, decreased activity or lethargy or weakness, or vomiting). An ARI of interest required ≥1 category A or 2 category B symptoms on a single day. Other than pneumonia, which we asked parents to record only if supported by a health care professional’s diagnosis, no illness or symptom details were validated by study staff or health care professionals. A new ARI could not commence unless there were ≥3 symptom-free days since the end of the previous ARI. This meant an ARI could contain no more than 2 consecutive symptom-free days.

When a new ARI occurred, parents were asked to collect a combined nose and throat swab and to complete an impact diary detailing resources used in illness management. Parents were taught specimen collection at the enrollment visit, and simple instructions were left for reference. Parents could seek telephone guidance, and research staff were available to visit the home to assist with or perform specimen collection, where required. Separate swabs for the nose and throat were pooled into viral transport media and transported via courier in a small polystyrene transport container with an ice brick to the Victorian Infectious Diseases Reference Laboratory (VIDRL). If collected overnight or on a weekend, specimens were stored in a biohazard bag in the household refrigerator and collected the next working day.

Study families were contacted by telephone or e-mail regularly, every 2 to 3 weeks, to encourage compliance with study procedures, diary return, and to assess continuing eligibility. Subsequent respiratory illnesses in household contacts were recorded where onset was
within 7 days of ARI symptoms in the study child. Families were informed of virus testing results by mail when they became available.

Laboratory Studies
Specimens were tested for respiratory viruses by polymerase chain reaction (PCR) testing at VIDRL the same day or the next working day after arrival, and original specimens and nucleic acid extracts were then stored at –70°C. The testing and validation of a diagnostic multiplex PCR for detecting respiratory viruses by VIDRL has been published elsewhere. These assays were used to test specimens for influenza A virus (H1 and H3 subtypes), influenza B virus, adenoviruses, respiratory syncytial virus (RSV), picornaviruses (enteroviruses and rhinoviruses), and parainfluenza virus (PIV) types 1, 2, and 3, corresponding with tubes 1, 2, and 3, as described previously.

All of the specimens were transferred on dry ice at study completion to the Queensland Pediatric Infectious Diseases Laboratory at the Royal Children’s Hospital, Brisbane, for hMPV PCR testing using a real-time assay and hCoV-NL63 PCR testing using 2 nested assays, all as described previously.

Statistical Analysis
The total number of ARIs and incidence rates with 95% confidence intervals (CIs) are presented. In calculating incidence rates, only at-risk child-days were included in the denominator, with the removal of those days contained within an ARI and the 3 days subsequent. Stratum-specific rates and univariate incident rate ratios by age, child care attendance as categorized by the Australian Bureau of Statistics, month, and other risk factors were also calculated. All of the calculations were performed using Stata 9.2 for Windows (Stata Corp, College Station, TX).

RESULTS
Study Cohort
A total of 234 under 5 years of age were enrolled progressively on the study. We received 56 397 child-days of data (82.5%) from a maximum possible 68 400 days from 229 children. No daily data were received from 5 children (2.1%).

The greatest representation (28%) of child-days came from children aged between 1 and 2 years (Table 1). Using the child’s age on each day of data submission, the mean age of contributing child time was 29.0 months. Similar numbers of child-days were contributed by boys and girls. Children not in any child care accounted for approximately one third of enrolled subjects and person time (Table 1).

Acute Respiratory Infections
A total of 730 ARIs were identified. Of the 56 397 child-days of data available, 8926 (15.8%) were contained within an ARI (mean duration: 12.2 days), and 2138 days were subsequent not-at-risk days, leaving 46 063 at-risk child-days (including the first day of each ARI), or 1513 child-months, for rate calculations. This gives an incidence rate of 0.48 ARIs per child-month (95% CI: 0.45–0.52) or 5.8 ARIs per child year (95% CI: 5.4–6.2).

The peak rate of ARIs was in June at 0.87 ARIs per child-month (Fig 1). The proportion of specimens positive for any virus was highest in October (84%) and lowest in August (62%; Fig 1). Children aged between 1 and 2 years had the highest rate of ARIs at 0.56 per child-month, with those >5 years having the lowest ARI rate at 0.21 per

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Children (of Total Enrolled)</th>
<th>Person Time Contribution in Child-Days (% of Total Possible Child-Days From Stratum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>65 (28)</td>
<td>8661 (90)</td>
</tr>
<tr>
<td>1</td>
<td>56 (24)</td>
<td>16 003 (80)</td>
</tr>
<tr>
<td>2</td>
<td>45 (19)</td>
<td>11 835 (81)</td>
</tr>
<tr>
<td>3</td>
<td>46 (20)</td>
<td>10 343 (81)</td>
</tr>
<tr>
<td>4</td>
<td>22 (9)</td>
<td>8112 (86)</td>
</tr>
<tr>
<td>5a</td>
<td>0 (0)</td>
<td>1443 (79)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>119 (51)</td>
<td>28 811 (84)</td>
</tr>
<tr>
<td>Male</td>
<td>115 (49)</td>
<td>27 586 (81)</td>
</tr>
<tr>
<td>Child care usage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No child care</td>
<td>75 (32)</td>
<td>18 490 (86)</td>
</tr>
<tr>
<td>Informal child care only</td>
<td>23 (10)</td>
<td>6386 (85)</td>
</tr>
<tr>
<td>Formal child care only</td>
<td>114 (49)</td>
<td>26 552 (81)</td>
</tr>
<tr>
<td>Informal and formal child care</td>
<td>22 (9)</td>
<td>4969 (75)</td>
</tr>
</tbody>
</table>

a Data are number and percentage of children this age at time of enrollment.
b No child was >5 years of age at enrollment, per eligibility criteria. Children were able to stay on the study when they turned 5 years of age, thus contributing person time to this age stratum.
child-month (Table 2). Child care attendance significantly increased the rate of ARI by 40% (Table 2).

**Specimen Return and Viral Diagnosis**

Of the 730 ARIs identified, 543 (74%) had ≥1 specimen returned. There was no virus identified in 142 ARIs (26%), 1 virus in 347 ARIs (64%), 2 in 49 ARIs (9%), and 3 in 5 ARIs (1%). The median duration of symptoms for virus-positive ARIs was 12.0 days, with a mean of 14.2 days. Details of illnesses, including duration and health care usage, by availability of specimen and virus identification, are provided (Table 3).

Human metapneumovirus was identified in 33 illnesses (Fig 2) in 7 of the 13 months of the study, with the peak month being June 2003 (Table 3). Thirteen of the ARIs (39%) involved another virus: 5 hMPV/picornavirus coinfections, 3 hMPV/adenovirus coinfections, and 1 each of hMPV/RSV, hMPV/hCoV-NL63, hMPV/picornavirus/PIV, hMPV/picornavirus/hCoV-NL63, and hMPV/picornavirus/adenovirus coinfection. Twenty seven (82%) of the 33 hMPV-positive children were in child care. In those ARIs where hMPV was the only virus identified, there was a general practitioner (GP) visit rate of 8.7 visits per 10 illnesses.

hCoV-NL63 was identified in 18 ARIs and, like hMPV, peaked in June (Fig 2). Ten (56%) of the ARIs involved another virus: 6 hCoV-NL63/picornavirus coinfections, and 1 each of hCoV-NL63/RSV, hCoV-NL63/influenza A virus, hCoV-NL63/hMPV, and hCoV-NL63/hMPV/picornavirus coinfection. Fourteen (78%) of the 18 children positive for hCoV-NL63 were in child care. In ARIs where hCoV-NL63 was identified alone, the GP visit rate was 5 visits per 10 illnesses, and 33% were followed by a subsequent illness in ≥1 household contact.

---

**TABLE 2**  
**ARIs Incidence Rates and Rate Ratios According to Age, Gender, and Child Care Status:**  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute Respiratory Illness Rate, Per Child-Month (95% CI)</th>
<th>Incidence Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.50 (0.42–0.60)</td>
<td>2.39 (1.21–5.35)</td>
</tr>
<tr>
<td>1</td>
<td>0.56 (0.50–0.64)</td>
<td>2.70 (1.40–5.98)</td>
</tr>
<tr>
<td>2</td>
<td>0.51 (0.44–0.59)</td>
<td>2.44 (1.25–5.42)</td>
</tr>
<tr>
<td>3</td>
<td>0.44 (0.37–0.52)</td>
<td>2.05 (1.07–4.68)</td>
</tr>
<tr>
<td>4</td>
<td>0.39 (0.32–0.48)</td>
<td>1.88 (0.95–4.26)</td>
</tr>
<tr>
<td>5</td>
<td>0.21 (0.11–0.40)</td>
<td>Reference rate</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.49 (0.44–0.54)</td>
<td>1.03 (0.89–1.19)</td>
</tr>
<tr>
<td>Male</td>
<td>0.48 (0.43–0.53)</td>
<td>Reference rate</td>
</tr>
<tr>
<td><strong>Child care usage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No child care</td>
<td>0.38 (0.33–0.44)</td>
<td>Reference rate</td>
</tr>
<tr>
<td>Any child care</td>
<td>0.54 (0.49–0.58)</td>
<td>1.99 (1.19–1.65)</td>
</tr>
<tr>
<td>Informal child care</td>
<td>0.46 (0.37–0.58)</td>
<td>1.21 (0.92–1.58)</td>
</tr>
<tr>
<td>Formal child care only</td>
<td>0.55 (0.49–0.60)</td>
<td>1.43 (1.20–1.70)</td>
</tr>
<tr>
<td>Informal and formal child care</td>
<td>0.57 (0.45–0.72)</td>
<td>1.49 (1.12–1.96)</td>
</tr>
</tbody>
</table>
Picornaviruses were the most commonly identified virus group, being present in half (269) of the ARIs where a specimen was returned, followed by adenoviruses (43 [8%]), RSV (40 [7%]), PIVs (33 [6%]), hMPV (33 [6%]), influenza A virus (24 [4%], and hCoV-NL63 (18 [3%]). There were no identifications of influenza B virus despite its presence at Victorian sentinel influenza surveillance sites during the season.23 Picornavirus-related illness tended to be relatively mild, appearing least likely to be associated with fever, and having the lowest rate of primary care presentation (Table 3). Influenza A virus and adenoviruses were associated with more severe illness. Influenza A illnesses were almost universally associated with fever (95%), resulted in a similar illness in ≥1 household contact in 61% of infections, and were associated with >1 primary care attendance, on average, per illness (Table 3). Adenoviruses were identified in every month of the study, and illnesses where adenovirus was the only virus identified had a mean duration of 18.6 days. Three quarters were associated with fever and were associated with the highest rate of GP presentation, at ~13 for every 10 illnesses (Table 3). Adenovirus infections had the highest percentage of identifications with another virus present (60%). Codetections resulted in a longer median duration of illness but did not seem to impact the likelihood of fever or the rate of primary care attendances (Table 3).

Health Care Attendances

In the 528 ARIs with an impact diary returned, no general practice visit was recorded for 55% (292 of 528). There were 29 hospital presentations during ARIs (incidence rate: 23 presentations per 100 child years), with 5 resulting in admission (Table 3). All of the admissions resulted from a febrile respiratory illness, including 2 episodes of pneumonia; 4 had specimens collected (Table 3) with 1 RSV infection (4-year-old boy: pneumonia, admission duration 3 days), 1 influenza A virus infection (6-month-old girl: fever, dehydration, 2 days), 1 picornavirus infection (1-year-old girl: fever, wheeze, rash illness, 2 days), and 1 adenovirus/picornavirus coinfection (1-year-old girl: pneumonia, 3 days). The admission without a specimen collected (1-year-old boy) was for fever, wheeze, cough, and shortness of breath and had an admission duration of 2 days.

**DISCUSSION**

Our study adds to existing knowledge about respiratory viral infections in childhood in the following ways: it is the first to quantify the relative roles of hMPV and...
hCoV-NL63 in a community sample of healthy children; it provides community-based data on common respiratory viral pathogens in children under the age of 5 years using molecular techniques; it provides initial comparative impact data for the range of respiratory viruses tested for; and it demonstrates a safe, effective, sensitive, and efficient method for the conduct of community-based studies using nucleic acid testing methods.

The frequency of ARIs, using our sensitive definition, approached 1 per child-month during the winter peak, and overall a virus could be detected by PCR testing in 74% of illnesses with a specimen available. During 2003 in Melbourne, hMPV and hCoV-NL63 circulated in the community among preschool children with other respiratory viruses. The association between child care attendance and childhood ARI has been well documented and was confirmed by this study, with the 2 viruses most strongly linked being hMPV and hCoV-NL63. Infections with hMPV resulted in relatively high rate of GP attendance at 8.7 visits per 10 illnesses, supporting findings from an Italian study, which suggested that hMPV illness had a similar impact on resource use as influenza. Comparative data for other respiratory viruses reinforce the predominant role of picornaviruses in community-managed ARIs, most likely to be rhinoviruses. Although individual illnesses caused by picornaviruses resulted in relatively milder illness, as a group they were responsible for the highest absolute number of general practice and emergency department presentations of any virus group. Although conducted during a season with higher-than-normal influenza activity, influenza A was associated with fewer but more severe illnesses (24 [4.4%]) than RSV, having 95% of infections associated with fever, the highest figure for subsequent illness in ≥1 household contact (61%), and, on average, ≥1 primary physician visit per illness.
As with all observational studies, there are some limitations that must be considered with these data. For some viruses, the data in the impact table are generated from small numbers of infections, and point estimates should be interpreted with caution. It is reassuring that, for individual viruses, the variety of impact data, such as the presence of fever, GP visits, and likelihood of subsequent illness in a household contact, are all in agreement. Parents received details of PCR testing, including negative results, by mail as they became available, and receipt of this information may have introduced an information bias. Knowledge of the viral cause of an illness may have altered the way parents reported resource use, particularly for influenza, which is more prominent in the media. One factor would suggest that the impact of such a bias, if it occurred, is likely to be minimal: ARIs where no virus was identified seemed no less severe than other illnesses where viruses were identified.

Other recent studies have used molecular methods for virus identification in specimens from community-based infants. An English home-visit study, which followed 88 infants with ≥1 atopic, asthma parent during their first winter, tested for respiratory viruses, some bacterial pathogens, hCoV-OC43, and hCoV-229E, but not hMPV or hCoV-NL63, and identified a respiratory pathogen in 103 (83%) of 123 episodes.27 A similarly designed Western Australian study followed ARIs in 263 infants (with ≥1 parent having a diagnosis of asthma, hay fever, or eczema) during their first year (including testing for hMPV, hCoV-OC43, and hCoV-229E) and identified a virus in 69% of illnesses.28 This study had an unexplained very low rate of hMPV detection, being present in only 1.8% of specimens collected during illnesses. Different overall detection rates in our study and the English and Western Australian studies may be because of a number of factors, including seasonality, the relative presence of the different pathogens, the different ages and inclusion criteria for the studies, different methods for virus identification, and the nature of specimen collection (nose-throat swab versus nasal lavage or nasopharyngeal aspirate). It is likely that the proportion of all specimens from such studies with a virus identified will increase with the addition of coronavirus HKU129 and a newly identified parvovirus, human bocavirus,10 to testing panels.

Coronaviruses hCoV-OC43 and hCoV-229E were not tested for in our study and may account for some of the virus-negative specimens we received. In the English and Western Australian studies, these viruses were identified in 9.0%27 and 5.5% (including from 4.4% of control subjects)28 of specimens, respectively. In Victorian hospital and influenza sentinel surveillance specimens, these 2 coronaviruses (largely hCoV-OC43) were a reasonably common cause of influenza-like illness in children. They were found in 6% of influenza surveillance specimens and 12% of hospital specimens overall and peaked in August 2003, possibly accounting for the increase in virus-negative specimens that we found in August and September (Fig 1).

Our reliance on data from previous decades is most likely because of the cost of undertaking a large, community-based study: it has been suggested that this approach of studying individuals for the presence of specific viruses, as opposed to hospital-based retrospective studies, is now prohibitively expensive,31 presumably because of the time commitment by trained staff and travel time and costs. From a pilot study, we knew parents could recognize and document ARIs of interest,12,31 and reports in the literature suggested that parents could be trained to collect an adequate respiratory specimen.34–37 Previous community-based work on respiratory viral infections has most commonly required research staff to collect a specimen.1 Direct contact between subject and study staff requires additional expense but allows for the collection of clinical information. The future benefit of these data, over and above virus identification and resource consumption, is not clear. Home visits may alter health-seeking behavior and medication use, invalidating impact data.

CONCLUSIONS
There is a clear and unmet need for accurate and timely information about the community-based epidemiology of previously known and recently identified respiratory viruses in all age groups. Hospital-based studies and even community studies based around primary care18 have the potential to miss most illnesses: primary care physicians were consulted in only 45% of ARIs in this study. Options are currently available for the prevention and treatment of influenza with possibilities for other viruses, including vaccines and intranasal short interfering RNAs.18 We have shown that it is feasible to conduct large, community-based studies with personal or parent specimen collection using sensitive molecular techniques for diagnosis. Future studies should preferably be conducted in all ages at centers with concurrent hospital-based surveillance of respiratory viruses for comparison. Specimens should be tested for known viruses and stored for retesting when new pathogens are recognized. This approach also provides an efficient way of conducting vaccine or treatment efficacy studies requiring hundreds or thousands of participants.

ACKNOWLEDGMENTS
This study was funded by the Public Health Branch of the Victorian Department of Human Services, the Murdoch Children’s Research Institute, and the Melbourne Research Grants Scheme of the University of Melbourne. Dr Lambert was the recipient of a National Health and Medical Research Council Public Health Postgraduate Scholarship.
We thank the research staff who assisted with the conduct of this study: Janet Briggs, Clare Brophy, Jim Buttery, Samantha Colquhoun, Dale Cooper, Susan Gabriel, Genevieve Hamilton, Tara Harris, Marita Keeford, Betty Lim, Ethna Macken, Bernadette McCudden, Liz McGrath, Sally Mizrahi, Jane Nelson, Kerry-An O’Grady, Jacinta O’Sullivan, Jan Renehan, Jane Ryrie, Pam Sinclair, Amanda Tehran, and Helen Wlord. We also thank laboratory staff Seweryn Biłasiewicz and Katherine Arden (Queensland), who tested specimens, and Kris Jansen and Suzanna Vidmar, who assisted with the Stata programming. This study would not have been possible without the generous support of the Maternal and Child Health Nurses from the greater Melbourne area and the children and families who volunteered, kept study documents, and collected specimens diligently.

REFERENCES


34. Buchta RM. Use of a rapid strep test (First Response) by parents


A.4

The cost of community-managed viral respiratory illnesses in a cohort of healthy preschool-aged children

Stephen B Lambert*1,2, Kelly M Allen1,3, Robert C Carter4,5 and Terence M Nolan1

Address: 1Vaccine and Immunisation Research Group, Murdoch Children’s Research Institute, Royal Children’s Hospital, and School of Population Health, University of Melbourne, Melbourne, Victoria, Australia, 2Queensland Paediatric Infectious Diseases Laboratory, Sir Albert Sakzewski Virus Research Centre, Royal Children’s Hospital, and Clinical Medical Virology Centre, University of Queensland, Brisbane, Queensland, Australia, 3Centre for Clinical Effectiveness Southern Health and Monash Institute of Health Services Research, Monash University, Melbourne, Victoria, Australia, 4Centre for Health Policy, Programs and Economics, School of Population Health, University of Melbourne, Melbourne, Victoria, Australia and 5Health Economics Unit, School of Health & Social Development, Deakin University, Burwood, Victoria, Australia

Email: Stephen B Lambert* - sblambert@uq.edu.au; Kelly M Allen - kelly.allen@med.monash.edu.au; Robert C Carter - rob.carter@deakin.edu.au; Terence M Nolan - t.nolan@unimelb.edu.au

* Corresponding author

Abstract

Background: Acute respiratory illnesses (ARIs) during childhood are often caused by respiratory viruses, result in significant morbidity, and have associated costs for families and society. Despite their ubiquity, there is a lack of interdisciplinary epidemiologic and economic research that has collected primary impact data, particularly associated with indirect costs, from families during ARIs in children.

Methods: We conducted a 12-month cohort study in 234 preschool children with impact diary recording and PCR testing of nose-throat swabs for viruses during an ARI. We used applied values to estimate a virus-specific mean cost of ARIs.

Results: Impact diaries were available for 72% (523/725) of community-managed illnesses between January 2003 and January 2004. The mean cost of ARIs was AU$309 (95% confidence interval $263 to $354). Influenza illnesses had a mean cost of $904, compared with RSV, $304, the next most expensive single-virus illness, although confidence intervals overlapped. Mean carer time away from usual activity per day was two hours for influenza ARIs and between 30 and 45 minutes for all other ARI categories.

Conclusion: From a societal perspective, community-managed ARIs are a significant cost burden on families and society. The point estimate of the mean cost of community-managed influenza illnesses in healthy preschool aged children is three times greater than those illnesses caused by RSV and other respiratory viruses. Indirect costs, particularly carer time away from usual activity, are the key cost drivers for ARIs in children. The use of parent-collected specimens may enhance ARI surveillance and reduce any potential Hawthorne effect caused by compliance with study procedures. These findings reinforce the need for further integrated epidemiologic and economic research of ARIs in children to allow for comprehensive cost-effectiveness assessments of preventive and therapeutic options.
Background
Respiratory virus infections are a major cause of morbidity and healthcare usage in children, resulting in substantial costs for families and society [1-5]. Given their ubiquity, there has been surprisingly little research examining the costs associated with childhood respiratory infections that have involved collecting primary data from families. Even for influenza, the most studied of all respiratory viruses, cost-of-illness and vaccine cost-effectiveness evaluations in children have tended to rely on assumptions or use retrospectively collected estimates, often from surveys, for resource utilisation, such as carer time away from work in seeking healthcare or caring for an ill child [6-9].

There are three pieces of evidence required by those developing health policy in assessing whether to recommend or implement a publicly-funded vaccination program, or any intervention, against respiratory viruses: epidemiology of the targeted illness, the efficacy of the intervention, and the cost-effectiveness of the intervention [10]. All interventions to prevent or treat infections will be associated with a cost of implementation, but cost-effectiveness is determined not only by the cost of the intervention, but also by costs arising from the illness. Getting these data for respiratory viruses, particularly information on indirect costs incurred by families, requires a conjunction of epidemiologic and economic research [11].

The prospect of new and improved influenza vaccines [12], the hope of new vaccines against other respiratory viruses [13], development of novel therapeutic possibilities [14], and the possible use of nonpharmaceutical interventions to contain virus transmission [15-18] all underline the need to more critically weigh the costs and benefits of prevention and treatment for common respiratory tract viruses.

We present here findings from a community-based cohort study using parent-collected specimens for etiologic assignment and diary recording of impact data. These data have been used to calculate virus-specific costs of illness from a societal perspective, including often neglected indirect costs.

Methods
The study cohort and acute respiratory illness surveillance
Details of recruitment, composition, and maintenance of the dynamic study cohort have been published elsewhere [19]. Ethics approval for the study was given by the Royal Children’s Hospital Ethics in Human Research Committee, Melbourne, and written informed consent was obtained from parents before participation.

This dynamic cohort consisted of one healthy child less than five years of age at time of recruitment from each study family. Children involved in this study were recruited from a number of sources. In Victoria, Australia, maternal and child health nurses (MCHNs) provide support to families during the early childhood years, particularly on issues to do with general health and vaccination. Based on a model used by our group for community vaccine studies [20], MCHNs from 26 local councils assisted with recruitment by providing study information to parents of eligible children. Advertising material for the study was placed in child care and playgroup centers and, because of proximity, we also used bulletin boards and staff e-mail lists at the Royal Children’s and the Royal Women’s Hospitals in Melbourne. Details about the study child and household demographics were collected at an enrolment home visit, including annual gross household income collected in 2003/2004 Australian dollar values (AUD$). Income was separated into four bands, roughly dividing the study households into quartiles: band 1, less than $52,000 (24% of study households); band 2, $52,000 to $77,999 (28%); band 3, $78,000 to $103,999 (23%); and band 4, $104,000 or greater (25%). The approximate proportions for Australian households during the same period were: band 1, 54%, band 2, 20%, band 3, 13%, and band 4, 13% [21].

Parents undertook daily respiratory symptom surveillance of the study child using a diary card and collected a combined nose-throat swab (NTS) and completed a summary impact diary when the child had an acute respiratory illness (ARI). For this study we used a sensitive ARI definition that had previously been used in an influenza vaccine efficacy study [22] and our pilot study [23,24]. Symptoms were classified as category A (fever, wheezing, shortness of breath, pulmonary congestion or moist cough, pneumonia, or ear infection) and category B (runny nose or nasal congestion, sore throat, cough, muscle aches, chills, headache, irritability, decreased activity or lethargy or weakness, or vomiting). An ARI of interest required one category A or two category B symptoms on a single day [22]. Other than pneumonia, which we asked parents to record only if supported by a health care professional’s diagnosis, no illness or symptom details, including a report of otitis media, were validated by study staff or health care professionals. A new ARI could not commence unless there were three symptom free days since the end of the previous ARI. This meant an ARI could contain no more than two consecutive symptom-free days. Study families were asked to continue normal healthcare seeking behaviour and treatments, and were not alerted about the start of the influenza season or asked to alter surveillance during the winter season. Pre-stamped envelopes were provided and families were asked to return all completed study documents (daily symptom diary, impact diaries) at the end of each month. ARI duration was calculated using symptom diary data and ARIs were classified
by study staff as being simple (no fever or otitis media recorded), or occurring with fever, otitis media, or with both fever and otitis media [22-24].

The NTS was couriered to the Victorian Infectious Diseases Reference Laboratory (VIDRL) where it was tested for a number of common respiratory viruses using a polymerase chain reaction (PCR) method for adenoviruses and reverse transcription (RT) PCR for RNA viruses: influenza A virus, influenza B virus, respiratory syncytial virus (RSV), parainfluenza viruses I, II, and III (PIVs), and picornaviruses [19]. A letter outlining these test results was sent to parents when these details became available. At completion of the study all specimens were transported to the Queensland Paediatric Infectious Diseases (Qpid) Laboratory where they were tested for human metapneumovirus (hMPV) and human coronavirus NL63 (hCoV-NL63) using RT-PCR [19].

**Impact diary completion**

A summary impact diary was used to collect details of resources used during the study child’s ARI and was based on an impact diary used in a pilot study [23,24], with some simplification. The units of resource use requested were:

- health care visits: number and timing of primary care (general practice) visits, hospital presentations and admissions, and visits to other providers (such as naturopaths, homeopaths);
- use of prescribed antibiotics;
- laboratory tests performed to investigate the illness;
- carer time consumed during the illness seeking health care; and
- excess carer time during the illness spent caring for the ill child.

We did not collect information about some items that were shown not to be major cost drivers in the pilot study: non-antibiotic prescription medication, over-the-counter and other medication, paid childcare for other children whilst normal carers were spending time caring for the ill study subject, and travel costs seeking health care. The average total cost for these items in the pilot study [23] was AUD$16 per ARI.

Time values were captured in hours and minutes. Parents were not given instructions about when or how frequently they should capture time data during an ARI. For both carer time spent seeking healthcare and excess time spent caring for an ill child, time was recorded as a total value for the ARI in two categories: time away from work and time away from usual, non-work activities.

**Costing methods**

All costs were incurred over a 380 day period between 17 January 2003 and 31 January 2004. Costs are reported in this manuscript using Australian dollar values, with 2003 taken as the reference year for reporting unit prices. The mean exchange rates for major currencies during the study were: United Kingdom (UK) pound £1 = AUD$2.49, Euro €1 = AUD$1.73, and United States (US) $1 = AUD$1.50 [25]. Discounting costs for time preference is not routinely considered for periods of time less than 12 months, and as this study period barely exceeds this time frame, no costs have been discounted.

Details of the source and value for all costs are provided (Table 1). Applied costs were retrieved, where possible, from published sources, and where no standard published cost was available we used costs derived from the pilot study. Resource costs were allocated as being borne by either the ‘patient and family’ sector, the ‘healthcare’ sector, or the ‘employer’ of absent staff. The proportions of time away from work seeking healthcare or time away from work caring for an ill child that were incurred by either the patient and family sector or met by an employer were not collected, and these values have been derived from the same proportions in the pilot study, based on 202 illnesses (Table 1) [23].

We applied a sex-weighted hourly wage rate derived from the Australian Bureau of Statistics average weekly full-time adult total earnings for all reported times [26]. We calculated mean costs (total and by categories) with 95% confidence intervals (95% CI) and median costs with interquartile ranges for ARIs in study children. Data were analysed using Stata 9.2 for Windows (StataCorp, Texas, USA).

**Results**

There were 234 children, one from each study family, progressively enrolled in the study and we identified 730 ARIs in 56,397 child-days of follow-up [19]. Of these, 487 ARIs (67%) had at least one specimen and an impact diary available, 41 (6%) had an impact diary returned but no specimen, 56 (8%) had at least one specimen returned but no impact diary available, and 146 (20%) had neither a specimen nor impact diary returned. Children aged between one and two-years of age contributed the most person-time to the study (28% of all child-days) and had the highest acute respiratory illness (ARI) incidence rate (0.56 ARIs per child-month). Contribution by males and females was equivalent, and children who attended some form of out-of-home care were responsible for 67% of all person-time [19].
Table 1: Source, sector distribution, and value of applied costs used in costing calculations for acute respiratory illnesses

<table>
<thead>
<tr>
<th>Resource item</th>
<th>Sector</th>
<th>Source of applied cost</th>
<th>Applied cost</th>
<th>Value</th>
</tr>
</thead>
</table>
| Primary care visits                  | Patient and family            | Medicare Australia [60,61]           | Mean patient contribution per service by quarter, patient and bulk billed services from general practitioners and vocationally registered general practitioners | January to March 2003: $4.03  
April to June 2003: $4.08  
July to September 2003: $4.34  
October to December 2003: $4.61  
January 2004: $4.64  
January to October 2003: $25.05  
November 2003 to January 2004: $25.70 |
| Health                               | Medicare Australia [62,63]    | 85% (reimbursable amount) of code 23, Medicare Benefits Schedule |                                                                              |                                            |
| Specialist visits                    | Patient and family            | Medicare Australia [60,61]           | Mean patient contribution per specialist visit by quarter                     | January to March 2003: $19.30  
April to June 2003: $19.56  
July to September 2003: $19.74  
October to December 2003: $20.36  
January 2004: $21.65  
January to October 2003: $58.95  
November 2003 to January 2004: $60.45 |
| Health                               | Medicare Australia [62,63]    | 85% (reimbursable amount) of code 104, Medicare Benefits Schedule |                                                                              |                                            |
| Other health care provider visits    | Patient and family            | Pilot study [23]                     | Mean other health care provider visit cost from pilot study, derived from 10 visits | $15.63 per visit to allied and alternative health professionals |
| Hospital emergency department visits without admission | Health | The Australian Government Department of Health and Ageing [64] | Australian Ambulatory Classes group 23 (other respiratory diseases without procedure) | $40 per visit |
| Diagnostic tests                     | 15% Patient and family        | Medicare Australia [62,63]           | Medicare Benefits Scheduled fee for diagnostic tests                           | January 2003 to January 2004  
$28.35 Chest x-ray (code 58500)  
January to October 2003  
$14.20 Full blood examination (code 65070)  
$16.35 Urea, electrolytes, creatinine, liver function tests (code 66515)  
$17.10 Urine microscopy, culture, identification, and sensitivity (code 69333)  
November 2003 to January 2004  
$14.65 Full blood examination (code 65070)  
$16.85 Urea, electrolytes, creatinine, liver function tests (code 66515)  
$17.60 Urine microscopy, culture, identification, and sensitivity (code 69333) |
| 85% Health                           |                               |                                     |                                                                              |                                            |
| Antibiotics                          | Patient and family            | Pilot study [23]                     | Mean antibiotic course cost from pilot study, derived from 42 courses          | $13.80 per course |

296
There were five illnesses which involved a hospital admission, all with an impact diary available. The mean cost of these five ARIs, including the cost of admission, was $3,409 (95% CI $2,798 to $4,020). Of the remaining 725 ARIs, the 202 illnesses without an impact diary had a mean duration of 8.8 days compared with 13.5 days for ARIs with impact data available; median 6 days versus 11 days. Simple ARIs made up 57% (116/202) of no impact diary ARIs and 47% (248/523) of ARIs with an impact diary.

The 523 illnesses with a diary returned that did not involve a hospital admission had a total cost of $161,454 (Table 2), and mean cost of $309 (95% CI $263 to $354). As our particular interest is in the cost of community-managed ARIs, that is, those illnesses that do not require hospitalization.

### Table 1: Source, sector distribution, and value of applied costs used in costing calculations for acute respiratory illnesses (Continued)

<table>
<thead>
<tr>
<th>Time seeking health care away from usual activity</th>
<th>Patient and family</th>
<th>Excess time caring for ill child away from work</th>
<th>31% Patient and family</th>
<th>69% Employer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>Health</td>
<td>Public hospital admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Victorian values for code</td>
<td>$2,331</td>
<td>$2,441</td>
<td>$2.331</td>
<td>$2.441</td>
</tr>
<tr>
<td>Round 7 (2002/2003)</td>
<td>$1,508</td>
<td>$2,441</td>
<td>$2.331</td>
<td>$2.441</td>
</tr>
<tr>
<td>Round 8 (2003/2004)</td>
<td>$2,441</td>
<td>$2,441</td>
<td>$2.331</td>
<td>$2.441</td>
</tr>
</tbody>
</table>

There were five illnesses which involved a hospital admission, all with an impact diary available. The mean cost of these five ARIs, including the cost of admission, was $3,409 (95% CI $2,798 to $4,020). Of the remaining 725 ARIs, the 202 illnesses without an impact diary had a mean duration of 8.8 days compared with 13.5 days for ARIs with impact data available; median 6 days versus 11 days. Simple ARIs made up 57% (116/202) of no impact diary ARIs and 47% (248/523) of ARIs with an impact diary.

The 523 illnesses with a diary returned that did not involve a hospital admission had a total cost of $161,454 (Table 2), and mean cost of $309 (95% CI $263 to $354). As our particular interest is in the cost of community-managed ARIs, that is, those illnesses that do not require hospitalization.

### Table 2: Total cost, mean cost (95% confidence interval), and median cost (interquartile range) of acute respiratory illnesses by virus identification

<table>
<thead>
<tr>
<th>Virus</th>
<th>Number (%)</th>
<th>Total cost</th>
<th>Mean cost</th>
<th>95% confidence interval</th>
<th>Median cost</th>
<th>Interquartile range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A virus</td>
<td>17 (3.3%)</td>
<td>$15,366</td>
<td>$904</td>
<td>$89 to $1719</td>
<td>$571</td>
<td>$162, $1023</td>
</tr>
<tr>
<td>RSVk</td>
<td>33 (6.3%)</td>
<td>$10,047</td>
<td>$304</td>
<td>$194 to $415</td>
<td>$198</td>
<td>$60, $398</td>
</tr>
<tr>
<td>Picornaviruses</td>
<td>197 (37.7%)</td>
<td>$52,597</td>
<td>$267</td>
<td>$211 to $323</td>
<td>$124</td>
<td>$32, $337</td>
</tr>
<tr>
<td>hCoV-NL63b</td>
<td>6 (1.1%)</td>
<td>$1,508</td>
<td>$251</td>
<td>-$77 to $580</td>
<td>$83</td>
<td>$30, $625</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>17 (3.3%)</td>
<td>$4,212</td>
<td>$248</td>
<td>$140 to $356</td>
<td>$185</td>
<td>$90, $341</td>
</tr>
<tr>
<td>PIVs*</td>
<td>21 (4.0%)</td>
<td>$4,804</td>
<td>$229</td>
<td>$104 to $354</td>
<td>$112</td>
<td>$84, $291</td>
</tr>
<tr>
<td>hMPV*</td>
<td>15 (2.9%)</td>
<td>$3,284</td>
<td>$219</td>
<td>$109 to $328</td>
<td>$204</td>
<td>$57, $324</td>
</tr>
<tr>
<td>Co-identifications</td>
<td>51 (9.8%)</td>
<td>$17,503</td>
<td>$343</td>
<td>$212 to $475</td>
<td>$185</td>
<td>$72, $431</td>
</tr>
<tr>
<td>No virus identified</td>
<td>126 (24.1%)</td>
<td>$39,853</td>
<td>$316</td>
<td>$208 to $425</td>
<td>$151</td>
<td>$44, $364</td>
</tr>
<tr>
<td>No specimen</td>
<td>40 (7.6%)</td>
<td>$12,281</td>
<td>$307</td>
<td>$212 to $402</td>
<td>$216</td>
<td>$88, $434</td>
</tr>
<tr>
<td>All ARIs*</td>
<td>523 (100.0%)</td>
<td>$161,454</td>
<td>$309</td>
<td>$263 to $354</td>
<td>$156</td>
<td>$45, $378</td>
</tr>
</tbody>
</table>

* Respiratory syncytial virus.
* Human coronavirus NL63.
* Para-influenza viruses.
* Human metapneumovirus.
* Acute respiratory illnesses.
* Column total does not equal column sum due to rounding.
an admission to hospital, further analyses will include only these 523 illnesses.

There were 248 simple ARIs (ARIs without fever or otitis media), with a mean cost of $180 (95% CI $131 to $230). The 207 ARIs with fever had a mean cost $406 (95% CI $318 to $494), the 26 ARIs with otitis media had a mean cost $362 (95% CI $203 to $520), and the 42 ARIs with fever and otitis media had a mean cost of $553 (95% CI $395 to $711). By household income band, there were 121 ARIs from the lowest band (ARI incidence rate: 0.35 per child-month) with a mean cost of $222 (95% CI $174 to $270), 144 ARIs from band 2 (0.37 ARIs per child-month) had a mean cost $375 (95% CI $244 to $506), 110 ARIs from band 3 (0.44 ARIs per child-month) with mean cost $366 (95% CI $282 to $451), and 148 ARIs from band 4 (0.43 ARIs per child-month) with mean cost $272 (95% CI $208 to $337). The mean cost of an ARI in a female subject was $67 greater than their male counterparts: female mean cost $341 (95% CI $265 to $418), male mean cost $274 (95% CI $228 to $319).

The mean and median costs by virus identification, including co-identification and specimen availability, are provided (Table 2). The differences between the mean values and the median values demonstrate the right-skewed nature of these data, similar to other health-related costs [27]. Whilst confidence intervals overlap, the point estimate of the mean cost of an influenza A ARI, $904, is three times higher than the next most expensive single virus ARI: RSV $304. Of the 51 ARIs where more than one virus was identified, influenza A virus was present in four: two illnesses with co-identification with a picornavirus alone, one illness with hCoV-NL63 alone, and one illness with a picornavirus and PIV. These four illnesses had a mean cost of $499. There were no illnesses where influenza B virus was identified. Three children had received influenza vaccine in the year prior to the study and none had an influenza-positive ARI.

As the difference in mean cost between the most expensive (RSV: $304) and least expensive (hMPV: $219) non-influenza single virus ARI falls within a comparatively narrow band ($85) we collapsed these data into a single category for further comparisons (Table 3). The mean cost for non-influenza single virus ARIs was $265 (95% CI $223 to $306). The cost of excess carer time away from a usual activity averaged $706 per ARI for influenza A, making up 78% of the total mean cost of illness, compared with $164 and 62% for other single virus illnesses.

Of the mean cost for all illnesses, $19 (6%) was met by the healthcare sector, $245 (79%) by the patient and family sector, and $45 (15%) was met by employers paying for an employee who was seeking healthcare for or caring for an ill child. The equivalent values for influenza A infections are: $36 (4%), $780 (86%), and $87 (10%), respectively. In influenza A ARIs the key cost driver, carer time away from usual activity, resulted in a mean loss of two hours per day per illness. For all other illness categories, this value ranged from one half to three quarters of an hour per day per ARI.

There was little difference in the mean duration of influenza A illnesses and other single virus illnesses, but co-identifications were 2.2 and 3.6 days longer than each of these respectively (Table 4). The mean delay between illness onset and a result letter being sent was shortest in influenza illnesses at 6.3 days (Table 4).

Discussion
In this study we present the costs associated with community-managed respiratory viral infections in healthy preschool aged children. These costs are based on the direct recording of impact information captured by parents when the study child was unwell. The study has a unique combination of features including a sensitive definition for ARI, parent-collected specimens, laboratory testing for respiratory viruses using sensitive molecular methods, and, based on findings from our pilot study, comprehen-

Table 3: Mean values and mean cost of components of resource use during ARIs

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of ARIs</th>
<th>Primary care visits</th>
<th>All other healthcare costs</th>
<th>Seeking healthcare time off work</th>
<th>Excess care time away from usual activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean number</td>
<td>Mean cost</td>
<td>Mean cost</td>
<td>Mean time</td>
<td>Mean cost</td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>17</td>
<td>$32.85</td>
<td>$12.84</td>
<td>0.00</td>
<td>0.12</td>
</tr>
<tr>
<td>Other single virus</td>
<td>289</td>
<td>$16.73</td>
<td>$7.19</td>
<td>0.02</td>
<td>0.55</td>
</tr>
<tr>
<td>Co-identifications</td>
<td>51</td>
<td>$22.46</td>
<td>$3.79</td>
<td>0.00</td>
<td>0.38</td>
</tr>
<tr>
<td>No virus identified</td>
<td>126</td>
<td>$18.65</td>
<td>$7.07</td>
<td>0.02</td>
<td>0.22</td>
</tr>
<tr>
<td>No specimen returned</td>
<td>40</td>
<td>$23.72</td>
<td>$12.70</td>
<td>0.00</td>
<td>0.48</td>
</tr>
<tr>
<td>All ARIs</td>
<td>523</td>
<td>$18.81</td>
<td>$8.43</td>
<td>0.02</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*All other healthcare costs is the sum of hospital emergency department presentations, other provider costs (specialists, other therapists), laboratory tests, and prescribed antibiotics.

**All time recorded in hours.

Acute respiratory illnesses.
and intervention studies show children have comparitively higher rates of influenza infection and are the most important transmitters of infection within households and communities. Whilst dollar amounts may not directly translate, impact data from this study may be transferable to other countries with developed economies, and similar disease epidemiology and healthcare systems. Ideally further studies in other countries should be conducted to allow for an examination of how impact and cost data vary with the nature of the healthcare system, local virus epidemiology, and other societal factors, including household structure.

Despite lower mean costs than influenza illnesses and the lack of population-based prevention options, the importance of working towards the prevention of other respiratory viral infections is obvious. Picornavirus ARIs, though typically milder and more difficult to be certain of a causal association with illness [37,38], were associated with the highest overall costs of any viral group totalling over $50,000 or one-third of all costs, for the 12-month study period. In the absence of specific vaccines and therapies for other viruses, the application of nonpharmaceutical interventions at a population level, such as improved hand and respiratory hygiene, may have an important place in reducing illness due to respiratory viruses [16].

Our findings reinforce the importance of virus testing in such studies to accurately estimate epidemiology and costs [11]. These data add to accumulating evidence that laboratory confirmation of influenza, in particular, is required, rather than less specific influenza-like illness (ILI) definitions or hospital coding. Other recent studies have found laboratory-confirmed influenza hospitalizations were two to four times more costly [39-41] than shown in previous studies using coding-based estimates [6,42-44]. When ILI definitions or coding are used, rather than laboratory confirmation, a lack of specificity results in influenza illnesses being mixed with other agents, thereby considerably diluting cost differences [45,46]. A direct comparison of parent-collected NTS specimens with collection of a more invasive specimen, such as a nasopharyngeal aspirate, by a healthcare worker at the time of an ARI was beyond the scope of this study. Any reduction in sensitivity caused by the type of specimen used is likely to minor: our finding that 74% of all specimens collected from children in this study were positive for at least one virus is within the range of values from recent home visit studies which also used PCR for diagnosis and nasopharyngeal aspirates (69%) [47] or nasal lavages (83%) [48].

There are clearly some issues about the cost of illnesses caused by respiratory viruses in children unresolved by our study, and some issues that need to be considered before interpretation. Despite being a relatively large

<table>
<thead>
<tr>
<th>Table 4: Mean duration of ARI and mean delay for result letter</th>
<th>Mean duration (days)</th>
<th>Mean delay from ARIsn onset to results letter being sent (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza A virus</td>
<td>15.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Other single virus</td>
<td>13.8</td>
<td>8.9</td>
</tr>
<tr>
<td>Co-identifications</td>
<td>17.4</td>
<td>8.8</td>
</tr>
<tr>
<td>No virus identified</td>
<td>12.2</td>
<td>8.4</td>
</tr>
<tr>
<td>No specimen returned</td>
<td>10.5</td>
<td>--</td>
</tr>
<tr>
<td>All ARIsa,b</td>
<td>13.5</td>
<td>8.7</td>
</tr>
</tbody>
</table>

a Acute respiratory illnesses.
b Includes all ARIs with a specimen returned.

The availability of preventive vaccines and specific therapeutic options makes influenza the most studied of respiratory viruses in all age groups; no other virus is more predictably disruptive year-on-year than annual interpandemic influenza [2-5]. Studies conducted in the second half of last century [28-31] and recent observation [32,33] and intervention [34-36] studies show children have comp
cohort the number of illnesses on which to make costing estimates for some virus types is quite small. Further community-based estimates are required to not only confirm our findings but to improve precision around point estimates.

Compared with the Australian population, households with lower incomes were under-represented in our study sample, and, despite overlapping confidence intervals around income band point estimates of mean costs, this may have lead to an overestimation of total costs. However, this may be balanced somewhat by the over-representation of households from the top income band which had a relatively lower mean ARI cost ($272). This pattern of household income distribution was similar to that found in the pilot study [23]. For this study we sought to make our study sample more representative of the general community by focusing our recruitment efforts in local council areas with a higher proportion of lower income households. We have no empiric data available that would allow us to quantify the effect of any potential bias resulting from this skewed sample. Other recent burden studies do not report similar household level income data to allow for comparison [49-51]. It may be the case that lower income households are under-represented as they do not have the spare capacity required, in time or other resources, to allow for study involvement.

We received impact diaries for just over 70% of all ARIs identified by daily symptom surveillance. ARIs without a diary were more likely to be shorter and without fever or otitis media; any information bias resulting from this would likely be in the direction of inflating mean illness costs. Our study only captured information from a single season with higher than normal influenza activity with H3N2 influenza A (drifted strain subtype A/Fujian/411/2002-like) being the predominant circulating type [52]. Variations in incidence and severity year-by-year for all respiratory viruses make it difficult to directly translate our findings to other years.

We believe documenting all time spent on caring for an ill child is important, even when taken away from a usual activity. We appreciate that applying standard wage rates to leisure time is not a straightforward issue in economics. This approach values carer leisure time and non-paid working time in a similar way to a worker’s time consistent with neoclassical theories of labour economics [53]. In attaching value to leisure time and using sex-weighted wage rates, we have made our assumptions explicit, and provided sufficient detail (Table 3) so that others can adjust unit prices using different approaches. Previous burden data [49] have been used to assess the cost-effectiveness (C/E) of using influenza vaccine in children [54]. If our cost values, incorporating these indirect costs, were used in the numerator of C/E calculations, there is a distinct possibility of double counting [55]. Double counting is likely where the denominator is a utility measure that incorporates a quality assessment (such as the quality adjusted life year or QALY), and most economists would see leisure time as a logical component of the QALY. There is also debate [53] about the inclusion, measurement, and valuation of lost working time in economic evaluations, with the debate centring on whether in practice QALY instruments capture income effects related to absenteeism.

For all illnesses where a specimen was tested, parents received a result letter by mail. The delay between illness onset and posting the letter was shortest for influenza illnesses, but for most illnesses parents would have been aware of the result before illness end. Pandemic influenza was not being widely discussed in Australia during 2003, but interpandemic influenza does receive media coverage annually encouraging vaccine uptake, and this may have caused parents to overestimate key parameters associated with their child’s influenza-positive illness. However, if such a bias was in operation it might also be expected that time values for illnesses where no virus was identified may be relatively understated when compared to ARIs with one or more viruses present. We did not find such a phenomenon; ARIs with no virus identified had a higher mean cost than those with a single virus present, and for the key cost driver of excess carer time away from a usual activity, no cause illnesses had higher values than both single and multiple virus ARIs.

Despite the impact of respiratory viral infections in children there are relatively few burden comparisons available that collect primary data from ill children. An Italian study examining the impact of hMPV, RSV, and influenza in children less than 15-years of age presenting to an emergency department found hMPV illnesses to be significantly more burdensome than RSV, having a similar impact to influenza [50]. In our study hMPV was the least expensive single-virus illness. This finding may be due to the different nature of illnesses that result in hospital presentation or hospital admission, compared with community managed illness. Of the 730 ARIs in this study only 4.0% (n = 29) prompted hospital presentation, with less than 1% (n = 5) requiring admission. An excellent community-based Finnish study describing the burden of influenza in children 13-years of age or younger over two seasons, with 2231 child-seasons of data, also contrasts this imbalance between community-managed and hospitalized cases of influenza, with only three emergency department referrals and one hospital admission in 131 children less than three years of age with influenza [49]. This study differed from ours in that whilst it used laboratory confirmation, it did not employ more sensitive
molecular diagnostics [56], families were required to visit the study clinic when the study child had fever or signs of respiratory infection, indirect costs did not include non-work time away from a usual activity, and the study did not provide a comparison with other viral acute respiratory illnesses [49]. The findings from the Finnish study reinforce the need to follow children for ARIs over more than one season, with different rates of influenza infection from year-to-year in each age group. These differences extended to changes in likelihood of infection between age groups: for example, the rate of laboratory-confirmed influenza increased by one-third from season one (2000–2001) to season two (2001–2002) for children less than three years of age, but the rates for three to six year olds and seven to 13 year olds fell 47% and 86%, respectively. A German study, recruiting children less than three years of age with lower respiratory tract infection (LRTI) through office and hospital-based paediatricians, collected cost of illness from a societal perspective, including loss of work days by caregivers [51]. This study showed that non-hospitalized cases of influenza LRTI had twice the cost of PIV LRTI and were one-third more costly than RSV LRTI, with this difference made up entirely by indirect costs [51].

Whilst methods vary, previous cost effectiveness studies of influenza vaccine in children are characterised by two findings: first, that cost-effectiveness is unsurprisingly enhanced by taking a societal perspective through the inclusion of indirect costs [5,6,8,43,54,57]. Our findings reinforce the importance of indirect costs [51], and highlight a previously inadequately measured layer of burden – carer time away from a usual, non-work activity. Second, the potential cost-effectiveness of implementing a vaccination program is improved by flexible or non-individual based delivery programs [6,43]. Vaccine delivered through pharmacies for a small service fee – improving access and negating the time and costs associated with a primary care visit – or large school-based programs, are likely to be acceptable to parents and providers. It is likely that the cost benefits of preventing influenza in children would extend beyond the targeted age-group [58], similar to the indirect effects in older age groups seen following the introduction of childhood conjugate pneumococcal vaccination in the US [59].

Conclusion
Our study reinforces the costly impact of all respiratory viruses, but particularly interpandemic influenza, on children, their families, and society. Efforts to further explore the costs associated with community-managed illness over a number of seasons for all respiratory infections are needed. Similar to recent hospital-based findings, using laboratory-confirmation to specifically identify influenza appears to increase the cost of illness many fold; a finding that may make population-based vaccination programs a more cost-effective proposition.

We believe the use of parent-collected specimens may have important effects in reducing bias in both the epidemiologic and impact data collected. Not requiring parents to either present with their ill child to a health clinic or host a home visit by study staff may result in enhanced ARI surveillance, but more importantly, allows for the reporting of impact data uncontaminated by compliance with study procedures, thereby reducing any impact a Hawthorne effect may have. Further studies that collect primary, integrated epidemiologic and economic data, particularly indirect costs, directly from families about community-managed ARIs in children, are required. Such data would allow for a more informed exploration of the cost-effectiveness of vaccine programs and other interventions designed to reduce the morbidity associated with ARIs in children.

Abbreviations
ARI: Acute respiratory illness; AUD: Australian dollars; C/E: Cost effectiveness ratio; CI: Confidence interval; hCoV: Human coronavirus; hMPV: Human metapneumovirus; ILI: Influenza-like illness; LRTI: Lower respiratory tract infection; MCHN: Maternal and child health nurse; NTS: Nose-throat swab; PCR: Polymerase chain reaction; PIV: Parainfluenza virus; QALY: Quality adjusted life year; Qpid: Queensland Paediatric Infectious Diseases; RNA: Ribonucleic acid; RSV: Respiratory syncytial virus; RT: Reverse transcription; UK: United Kingdom; US: United States; VIDRL: Victorian Infectious Diseases Reference Laboratory.

Competing interests
Terence Nolan and Stephen Lambert have, in the past five years, received research grants for epidemiological and vaccine related research from CSL Limited, Medimmune, GSK Biologicals, Wyeth, and Merck. Kelly Allen and Robert Carter have no competing interests to declare.

Authors’ contributions
All authors were involved in the study design and approach and SBL and TMN developed the original protocol. KMA and SBL were responsible for the day-to-day conduct of the study. SBL performed the analysis and drafted the article. All authors contributed to and approved the final manuscript.

Acknowledgements
The work was supported by project grants from the Victorian Department of Human Services, the Murdoch Children’s Research Institute, and the University of Melbourne. Stephen Lambert was the recipient of a National Health and Medical Research Council Public Health Postgraduate Scholarship. We thank all children and families who volunteered to participate in the study. This study would not have been possible without the generous
support of the Maternal and Child Health Nursing Research Group who assisted with the conduct of this study: Janet Briggs, Clare Brophy, Jim Butt,ery, Samantha Colquhoun, Dale Cooper, Susan Gabriel, Genevieve Hamilton, Tara Harris, Marita Keeford, Betty Lim, Ethna Macken, Bernadette McCudden, Liz McGrath, Sally Mizrahi, Jane Nelson, Kerry-Ann O'Grady, Jacinta O'Sullivan, Jan Renehan, Jane Ryrie, Pam Sinclair, Amanda Tehan, and Helen Worland. The Victorian Infectious Diseases Reference Laboratory and the Queensland Paediatric Infectious Diseases Laboratory performed the laboratory testing of specimens. Kris Jansen and Suzanna Vidmar from the Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, assisted with Stata programming. Jonathan Carapetis and John Carlin assisted with useful discussions about the study.

References


A.5

Parent-collected respiratory specimens—A novel method for respiratory virus and vaccine efficacy research

Stephen B. Lambert *, Kelly M. Allen, Terence M. Nolan

Vaccine and Immunisation Research Group, Murdoch Children’s Research Institute, Royal Children’s Hospital, Melbourne, and School of Population Health, University of Melbourne, Australia

Received 20 September 2007; received in revised form 28 January 2008; accepted 30 January 2008
Available online 22 February 2008

KEYWORDS
Vaccine efficacy research; Respiratory viruses; Respiratory specimen collection

Summary Population-based respiratory research and vaccine efficacy studies have previously required clinic or home visits when a subject had an acute respiratory illness. This method may mean parents are unwilling to enrol their child or report an illness of interest. We conducted a community-based cohort study into respiratory illnesses in 234 pre-school aged children using parent-collected specimens. Between January 2003 and January 2004 there were 563 specimens collected from 730 identified illnesses and these were tested using a panel of respiratory virus polymerase chain reaction (PCR) assays; 409 (73%) were positive for any virus. Specimens were not more likely to be positive when collected by a healthcare worker parent, when they included a throat swab, or when a very good collection technique was reported. A delay from illness onset to specimen collection of up to 5 days did not appear to impact on sensitivity of virus identification, but a delay of six or more days with minor delays in testing saw positivity fall. Combined with daily symptom diary completion and PCR testing, parent-collected specimens are an efficient and acceptable method for the conduct of future vaccine efficacy studies and other community-based respiratory virus research.

© 2008 Elsevier Ltd. All rights reserved.

Introduction

The advent of sophisticated molecular techniques for the routine identification of known respiratory viruses and the discovery of new pathogens has changed our understanding of these organisms and their role in human disease. Increased understanding of the burden caused by these infections has been mirrored by a parallel interest in preventative strategies that might be applied at a population level. This particularly applies to candidate vaccines and therapeutic interventions that may limit duration of symptoms and transmission.

Recent efficacy studies of influenza vaccines have relied on the traditional model of clinic or home visits, for clinical examination and data and specimen collection, when a child had an illness of interest [1–3]. Such an approach is
cumbersome and expensive and, with an increasing number of households in developed economies having two parents working, may prove excessively onerous on families with young children. This could result in either an unrepresentative study population, incomplete reporting of significant illness, or, at the very least, logistical challenges for the recruitment and retention of study cohorts.

We suggest here a novel method that may be useful in the future conduct of respiratory virus vaccine or therapeutic efficacy studies based on daily symptom surveillance in a study child and parent-collected specimens for polymerase chain reaction (PCR) testing for the pathogen of interest. We focus particular attention on features of this method that might impact on successful specimen collection and a positive test result.

**Methods**

**The respiratory virus study**

We conducted a community-based cohort study — the respiratory virus study (ReVS) — over a 12-month period from January 2003 and concluding data collection at the end of January 2004 [4,5]. The Human Research and Ethics Committee at the Royal Children’s Hospital, Melbourne, approved the study, and written informed consent for involvement was obtained at a home visit conducted by a research assistant.

Details of the methods used in the study have been provided in other papers [4,5]. We were assisted by Maternal and Child Health Nurses at 26 local councils around Melbourne to recruit subjects for the study. We also approached day care centres and used bulletin boards and staff email lists at the Royal Children’s and Royal Women’s Hospitals in Melbourne. Given this use of hospitals, we classified parents as healthcare workers, who may have been expected to have a better specimen collection technique, or as non-healthcare workers. Healthcare workers included doctors, nurses, ambulance paramedics, scientists in medical research or health-related service delivery, or allied health professionals (such as occupational, speech, or physical therapists).

**Daily symptom diary**

Parents completed a daily tick-box symptom diary. Symptoms were classified as being Category A: fever, wheezing, shortness of breath, pulmonary congestion (moist cough), pneumonia, ear infection; or Category B: runny nose (nasal congestion), sore throat, cough, muscle aches, chills, headache, irritability, decreased activity (lethargy/weakness), vomiting. A double-sided monthly A4 diary card was provided containing a daily symptom grid. Parents were provided with pre-stamped envelopes, and encouraged to return this diary, with any other study paperwork, at the end of each month.

We based acute respiratory illness (ARI) identification on a sensitive definition used for influenza-like illness (ILI) in a vaccine efficacy study [6] and that we used in a pilot study [7,8]. An ARI of interest, warranting burden diary completion and nose–throat swab (NTS) collection, had to have at least one Category A symptom or at least two Category B symptoms present on the same day. A new ARI could not commence without there being at least three preceding symptom-free days.

**Specimen collection**

A research assistant provided training in the process of collecting an NTS at the enrolment visit. All research assistants enrolling subjects were given standardised instructions and training in this process. Parents were given a practical demonstration in the collection of an NTS specimen, and were left with simple written instructions, including a diagram, as a guide. The offer of graduated support at the time of NTS collection was also made: beginning initially with further instruction and support over the telephone, stepping up to a research assistant visiting the home to supervise parent collection, and failing that, having the research assistant visit to collect the specimen. During the course of the study, telephone support was only occasionally provided, usually when a parent was collecting the first specimen after an extended period since the enrolment visit. No parent required a home visit to assist with specimen collection.

Households were left with two wooden-shaft sterile cotton-tipped swabs for specimen collection (Copan red capped swab in labelled tube, 150C), a polystyrene cooler box (esky), an ice-brick, and a tube of viral transport media (VTM) — produced in-house using a standard recipe at the Victorian Infectious Diseases Reference Laboratory (VIDRL). Both the VTM and ice-brick were stored in the household freezer. Collecting the nasal swab involved rubbing a single swab against the internal anterior walls of both nostrils. We anticipated that there may be situations where parents might be reluctant to collect a throat swab or have difficulty doing so. At the enrolment visit we asked that parents make a reasonable attempt to collect a throat swab for every ARI. We asked the throat swab be collected after the nasal swab as we perceived this to be the more difficult specimen to collect and that failure to secure an adequate throat swab specimen as the first specimen might result in the subject becoming distressed and refusing further intervention. We acknowledged that it would not always be possible to collect an NTS and let parents know we would accept a nose-only swab, and provided a check box on the request slip to inform us of specimen type, consisting of a combined nose—throat swab or a nose-only swab. Also on the request slip we asked parents to subjectively rate their collection technique as very good, good, or poor. Both the nose and throat swab were pooled in the single VTM tube. The VTM and request form were put in a sealed plastic biohazard bag and placed with an ice-brick in the esky for collection. The esky was couriered initially to VIDRL for virus testing and then transported at study end to the Queensland Paediatric Infectious Diseases (Qpid) Laboratory where they were further tested for a number of respiratory viruses (Table 3) as described previously [4]. Some parents provided more than one specimen for an ARI. All specimens tested and reported in this manuscript were collected during an illness that met the ARI definition; there were no asymptomatic control specimens collected from study subjects.
Table 1  Frequency of symptoms in study children during the respiratory virus study

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Symptom category</th>
<th>Days present</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptom</td>
<td></td>
<td>43,677</td>
<td>(77.4)</td>
</tr>
<tr>
<td>Any symptom</td>
<td></td>
<td>12,720</td>
<td>(22.6)</td>
</tr>
<tr>
<td>Fever</td>
<td>A</td>
<td>849</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Wheeze</td>
<td>A</td>
<td>248</td>
<td>(0.4)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>A</td>
<td>132</td>
<td>(0.2)</td>
</tr>
<tr>
<td>Pulmonary congestion (moist cough)</td>
<td>A</td>
<td>905</td>
<td>(1.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>A</td>
<td>20</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Ear infection</td>
<td>A</td>
<td>428</td>
<td>(0.8)</td>
</tr>
<tr>
<td>Runny nose (nasal congestion)</td>
<td>B</td>
<td>9,024</td>
<td>(16.0)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>B</td>
<td>568</td>
<td>(1.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>B</td>
<td>5,027</td>
<td>(8.9)</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>B</td>
<td>46</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Chills</td>
<td>B</td>
<td>119</td>
<td>(0.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>B</td>
<td>72</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Irritability</td>
<td>B</td>
<td>1,671</td>
<td>(3.0)</td>
</tr>
<tr>
<td>Decreased activity (lethargy, weakness)</td>
<td>B</td>
<td>918</td>
<td>(1.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>B</td>
<td>354</td>
<td>(0.6)</td>
</tr>
</tbody>
</table>

Household contacts

With the onset of illness in a study child we asked for surveillance to commence to identify similar illnesses in household contacts occurring within 7 days of symptoms in the study child. When such an illness occurred, we asked for completion of a symptom diary, burden diary, and collection of an NTS from the contact. These contact NTS specimens have not yet been tested for viruses.

Study conclusion questionnaire

At completion of ReVS we asked families their opinion about aspects of the study using a short, mailed questionnaire. ReVS followed children for a single year; we asked parents what their likely response would have been if we had asked them to continue in the study for another year, as might be the case in larger, prolonged community-based study. We asked parents to nominate the single most difficult study related task from a list, including tasks involving household contacts. Our research group conducts community-based vaccine studies, and we were also interested in the likelihood parents would include their child in a hypothetical experimental respiratory virus vaccine study, conducted for 5 months over the winter season. We described this study as including daily symptom diary completion and collecting an NTS when the child had an ARI.

Statistical analysis

Two-sided, two-sample tests of proportion were performed to compare virus positivity and a \( \chi^2 \)-test for trend was performed when comparing proportions of specimens positive for any virus with reported quality of collection. We used a level of \( p < 0.05 \) for significance and analyses were performed using Intercooled Stata 9.2 for Windows (StataCorp., TX, USA).

Results

Subjects were enrolled between 17 January 2003 and 05 November 2003. The last day of data collection for all subjects was 31 January 2004. Two hundred and thirty-four children were enrolled with 229 returning at least one of the monthly symptom diaries, providing 56,397 child-days of data. This represented 82.5% of 68,400 possible child-days of data had all diaries been returned. There was at least one symptom present on 12,720 (22.6%) study days, with Category B more common than Category A symptoms (Table 1). The most frequent symptom was runny nose/nasal congestion, present on 9024 days (16.0%). Symptoms were most commonly present in June and August 2003 being found on 32% of child-days both months, and least common during January 2004, present only on 8% of child-days.

Of all study households, 229 were dual parent families and 5 were single parent families. At the enrolment interview, 26% (60/234) of study mothers and 9% (20/229) of study fathers were classified as healthcare workers. There was at least one healthcare worker in 68 (29%) households.

Of the 730 ARIs identified, no specimen was returned for 187 (25.6%) and at least one specimen was returned for 543 (74.4%): 524 ARIs with one specimen, 18 with two specimens, and one with three specimens, bringing the total number of evaluable specimens to 563. There were 409 (73%) specimens that were positive for at least one virus: 154 (27%) had no virus detected; 354 (63%) had one virus detected; 50 (9%) had two viruses detected; and 5 (1%) had three viruses detected.

We explored whether specimens were positive for any virus by a number of categories: if the collecting parent was a healthcare worker, inclusion of a throat swab, and collector reported quality of the collection method (Table 2). There was no apparent difference in the likelihood of identifying any virus by healthcare worker parent or by the collector’s impression of collection quality. A throat swab was included in 70% of specimens (394/563), but its presence did not improve the likelihood of a positive result (Table 2).
We examined whether a throat swab made any difference to positivity for individual virus types (Table 3). For all RNA viruses the likelihood of positivity was very similar for both specimen types, other than parainfluenza viruses which were more commonly identified in a nose-only swab ($p = 0.046$). A higher proportion of specimens that included a throat swab identified an adenovirus, 9% versus 5%.

We calculated the delay between ARI onset and specimen collection, and specimen collection and testing, to see if they had any impact on swab positivity (Table 4). A short delay between onset and collection appeared to have little impact on positivity, with all specimens collected within 5 days of onset having a minimum positivity rate of 71% regardless of the delay in testing, and an overall positivity rate of 74%. The rate of positivity appeared to fall for specimens collected following a delay from onset to collection of six or more days when combined with a delay in testing of two (63% positive) or more days (61%).

There were 205 household contact illnesses identified following 175 ARIs in a study child: 148 with a single subsequent illness, 24 with two illnesses, and three with three illnesses. This resulted in the collection of 184 specimens from household contacts, with 74 (40%) of these being self-collected. These specimens are currently stored in a minus 70°C freezer waiting complete respiratory virus PCR testing.

We received completed study conclusion questionnaires from 183 (78%) families. Most of these families (87%) reported that they would have been willing to continue with the study for another year. The most difficult study procedure was reported to be collecting a throat swab from the study child (58%), followed by completing the burden diary for the study child (21%), keeping the daily symptom diary (11%), collecting a nose swab (3%), taking swabs from household contacts (2%), and completing a burden diary for the household contacts (1%). Four percent of participants found no task difficult. When parents were asked whether they would enrol their child into a hypothetical vaccine study using similar methods to ReVS (daily symptom diary and NTS collection): 35% said yes without qualification; 45% said they would consider it, but would need to hear more about the study before deciding; the remaining 20% said no, either because they were not happy for their child to receive an experimental vaccine (13%), were not happy to collect daily symptoms and specimens (3%), or were not happy to have an experimental vaccine, nor collect daily symptoms and specimens (4%).

### Discussion

Findings from our study reinforce the high prevalence and burden of respiratory symptoms, particularly during winter months, in healthy pre-school aged children, and the benefits there might be for improved prevention and control of these [4,5]. The most common symptoms were present on approximately one-third of child-days in peak months. The positivity rate of parent-collected swabs was not affected by whether the collector worked in a health-related field or the collector’s perception of collection quality. Interestingly, including a throat swab did not increase the overall virus positivity. Ours was not a simultaneous, head-to-head comparison of nose-only versus nose—throat swabs, but in this setting, nose-only specimens had a higher rate of positivity (78% vs. 71%), although this difference was not significant. This finding may have been confounded by illness severity and virus shedding. A child with more severe illness may have been shedding more virus at the time of specimen collection, and in these children parents may have been less likely to attempt collection of the additionally invasive throat specimen. The only viral

---

**Table 2** Swab positivity for any virus by collector status, specimen type, and quality

<table>
<thead>
<tr>
<th>Collector status</th>
<th>Swab positivity</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare worker</td>
<td>138/185 (75%)</td>
<td>0.468</td>
</tr>
<tr>
<td>Non-healthcare worker</td>
<td>271/378 (72%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Swab positivity</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose-only swab</td>
<td>131/169 (78%)</td>
<td></td>
</tr>
<tr>
<td>Nose—throat swab</td>
<td>278/394 (71%)</td>
<td>0.090</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality</th>
<th>Swab positivity</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>153/202 (76%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Good</td>
<td>216/305 (71%)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>40/56 (71%)</td>
<td>0.511</td>
</tr>
</tbody>
</table>

$^a$ $\chi^2$-test for trend, $p = 0.29$.

$^b$ Compared to very good stratum.

---

**Table 3** Individual virus positivity by specimen type

<table>
<thead>
<tr>
<th>Virus identified</th>
<th>Specimen type</th>
<th>$p$-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picornaviruses</td>
<td>Nose-only swab</td>
<td>83/169 (49%)</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>Nose-only swab</td>
<td>9/169 (5%)</td>
</tr>
<tr>
<td>PIVs</td>
<td>Nose-only swab</td>
<td>15/169 (9%)</td>
</tr>
<tr>
<td>RSV</td>
<td>Nose-only swab</td>
<td>15/196 (9%)</td>
</tr>
<tr>
<td>Influenza A</td>
<td>Nose-only swab</td>
<td>8/169 (5%)</td>
</tr>
<tr>
<td>hMPV</td>
<td>Nose-only swab</td>
<td>9/169 (5%)</td>
</tr>
<tr>
<td>hCoV-NL63</td>
<td>Nose-only swab</td>
<td>5/169 (3%)</td>
</tr>
<tr>
<td>Any virus$^a$</td>
<td>Nose-only swab</td>
<td>131/169 (78%)</td>
</tr>
</tbody>
</table>

PIVs: parainfluenza viruses; RSV: respiratory syncytial virus; hMPV: human metapneumovirus; hCoV-NL63: human coronavirus NL63.

$^a$ Total numerator does not equal sum of row numerators due to the co-identification of viruses in swabs.
group where throat swabs appeared to improve detection was the adenoviruses, where a throat swab may have been more likely to capture adenoviral persistence in the oropharynx rather than acute infection, particularly in the age group under study [9]. A recent study showed that detecting adenoviral persistence 1–12 weeks after initial positivity was not possible using nose swabs alone in children 6 months to 4 years of age [10].

In our study, a delay from illness onset to specimen collection of up to 5 days did not appear to lower positivity using our method of couriersing specimens from a subject’s home to a central laboratory for PCR testing. The delay from collection to testing is more difficult to interpret, but it appears that six or more days delay from onset to collection combined with even minor delays in testing are not optimal for virus identification.

In the past, using antigen-based techniques for respiratory syncytial virus diagnosis, nasal, throat, and nasopharyngeal swabs have not performed as well as nasopharyngeal aspirates (NPAs) or nasal washes, with a reduction in sensitivity of up to one-third [11]. In our study, the use of PCR and collection of specimens in the early stages of illness may have minimised differences caused by site of collection, with nose-only swabs performing as well as throat swabs for virus positivity. Our rate for detection of any virus in all specimens compares favourably with other recent community-based studies using molecular methods [12,13], and these values are similar to hospital-based findings using mainly NPAs and a comprehensive panel of respiratory virus PCR assays [14]. Ideally, future research should attempt a direct comparison of NPAs to parent-collected specimens to quantify any loss of sensitivity using this method. A recent report has shown increased return of cells using flocked swabs to collect a specimen from either the nasopharynx or the nose; but subjects reported a non-statistically significant higher pain score for use of a flocked nasopharyngeal swab compared with a rayon swab (100 mm visual analog scale for pain: 61.5 vs. 43.8 mm, p = 0.06) [15]. Flocked swabs were not available when we commenced this study, however, we do not believe parents would be comfortable in the collection of the more invasive and potentially more uncomfortable nasopharyngeal specimen either using a flocked swab or a standard swab at home in a study subject. The use of molecular methods for virus detection may also make any improvement in sensitivity for virus detection, using a flocked swab over an NTS, from the nasopharynx over an NTS or a nose-only swab, marginal.

This is the first large-scale implementation of a community-based study reliant on parents collecting respiratory specimens. Parents were generally positively disposed to the study, and it is of interest that a high proportion of all study families reported they would have been happy to continue for another year. The most difficult part of the study was reported as being the collection of a throat specimen from an ill study child, but, based on the swab positivity results for all but adenoviruses, it may not be required—a well collected nose swab may suffice. Use of this method for experimental studies should be considered, and it is of interest that 80% of questionnaire respondents would have been happy to consider involvement in a hypothetical respiratory virus vaccine study using the same procedures as ReVS. Modifications to the protocol could make the current method simpler and more efficient, depending on study requirements. These could include using dry swabs for specimen collection to avoid the need for viral transport media to be stored in a subject’s home, transporting dry swabs through the mail to reduce the reliance on more expensive couriers, and a heightened focus on diary completion, return, and specimen collection to minimise information bias. The high proportion of self-collected specimens from household contacts also demonstrates that the method could be expanded to include all ages, which would allow for contemporary household transmission studies to be performed using modern molecular testing methods.

Based on previous streptococcal research we were confident parents could be trained to collect an adequate respiratory specimen from an ill child without ongoing supervision [16–19]. We believe parent-collected specimens are a simple and efficient means of conducting future community-based epidemiological, costing, and vaccine and therapeutics efficacy studies. Parents involved in future studies can be reassured that any concern they might have about not being a healthcare worker or having a poor collection technique is unlikely to have any impact on results. Making the effort to collect a specimen in the first instance appears to be the most important step in identifying a causative virus.

Acknowledgements

We extend our warm thanks to all children and families who volunteered to participate in the study and to the Maternal and Child Health Nurses from local councils who assisted with recruitment. Thanks to Professors Jonathan Carapetis, John Carlin, and Rob Carter for helpful advice and comments. We also acknowledge the excellent work done by the research staff of the Vaccine and Immuni-

---

### Table 4 Swab positivity for any virus by delay from onset to collection, and collection to testing

<table>
<thead>
<tr>
<th>Delay from onset of ARI to specimen collection (days)</th>
<th>Delay from specimen collection to test (days)</th>
<th>≤1</th>
<th>2</th>
<th>≥3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td></td>
<td>41/58 (71%)</td>
<td>40/53 (75%)</td>
<td>48/61 (79%)</td>
<td>129/172 (75%)</td>
</tr>
<tr>
<td>2–3</td>
<td></td>
<td>45/60 (75%)</td>
<td>47/63 (75%)</td>
<td>39/57 (68%)</td>
<td>131/180 (73%)</td>
</tr>
<tr>
<td>4–5</td>
<td></td>
<td>25/34 (74%)</td>
<td>15/22 (68%)</td>
<td>31/40 (78%)</td>
<td>71/96 (74%)</td>
</tr>
<tr>
<td>≥6</td>
<td></td>
<td>35/45 (78%)</td>
<td>20/32 (63%)</td>
<td>23/38 (61%)</td>
<td>78/115 (68%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>146/197 (74%)</td>
<td>122/170 (72%)</td>
<td>141/196 (72%)</td>
<td>409/563 (73%)</td>
</tr>
</tbody>
</table>

---

Appendix A.5
sation Research Group during the conduct of the study. The Victorian Infectious Diseases Reference Laboratory, the Queensland Paediatric Infectious Diseases Laboratory, and the Clinical Epidemiology and Biostatistics Unit, Royal Children's Hospital, assisted with specimen testing and data analysis aspects of the study.

References


Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Lambert, Stephen Bernard

Title:
The epidemiology and impact of viral respiratory infections in pre-school aged children

Date:
2009

Citation:

Publication Status:
Unpublished

Persistent Link:
http://hdl.handle.net/11343/35486

File Description:
The epidemiology and impact of viral respiratory infections in pre-school aged children

Terms and Conditions:
Terms and Conditions: Copyright in works deposited in Minerva Access is retained by the copyright owner. The work may not be altered without permission from the copyright owner. Readers may only download, print and save electronic copies of whole works for their own personal non-commercial use. Any use that exceeds these limits requires permission from the copyright owner. Attribution is essential when quoting or paraphrasing from these works.