Surveillance of viral pathogens in Australia

For many years, a sentinel laboratory system, the Laboratory Virology and Serology Reporting Scheme (LabVISE) has been collecting data on viral pathogens of public health importance in Australia. This report is one in a series of articles focussing on the epidemiology of viruses and viral groups under surveillance through LabVISE which are of current public health interest.

Respiratory syncytial virus

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Introduction

Since the identification of respiratory syncytial virus (RSV) in the late 1950s, it has been recognised as a major cause of lower respiratory tract infection in young children.[1] RSV is a member of the paramyxovirus family, an RNA virus related to other respiratory viruses such as influenza and parainfluenza. In the United States of America in 1991, disease caused by RSV was estimated to be responsible for the hospitalisation of 100,000 children at a cost of US$300 million.[2] The significance of RSV infections is the high rates of infection in very young infants, and the difficulties in diagnosis, treatment and vaccination of this high-risk group. Given this, the progress towards the development of therapies to prevent infection, or at least prevent the potentially severe consequences of infection, have been watched with great interest.

RSV infections peak annually in winter or spring in temperate climates. The annual peak of RSV infection tends to occur in the absence of other respiratory viral pathogens.[1] Annual RSV epidemics are associated with a relative decline in infections with the parainfluenza viruses and other respiratory viruses. Influenza epidemics tend to occur as the RSV epidemic declines, although RSV and influenza epidemics may coincide. The reasons for this 'interference phenomenon' in the epidemiology of RSV and other respiratory viruses remain unclear.

Viral shedding in respiratory secretions is as high as 10^7/ml in the nasal discharges of infected children. While person-to-person transmission occurs, there is evidence that transmission through contaminated fomites is also important.[3] Fomites are particularly important in hospital settings where nosocomial infection with RSV in paediatric wards is a significant problem.[4] Direct inoculation of contagious secretions from the hands into the eyes and nose of carers, leads to outbreaks of RSV in families and among hospital staff.[2]

RSV infection occurs repetitively in children as infection with RSV does not cause lasting protective immunity. A longitudinal study in a day care centre[5] showed that 98 per cent of children became infected on their first exposure to RSV, a second exposure resulted in 74 per cent of children being infected and 65 per cent of children were infected on a third exposure. There are some well-defined groups of children who are at increased risk of RSV infection. These include children of lower socioeconomic status, children who share a bedroom with more than two other children, children who attend day-care, have siblings in pre-school or school or are in a multiple birth set. Children who are born prematurely or have chronic lung disease or congenital heart disease are at a higher risk of severe RSV disease resulting in admission to hospital.[6] RSV has also been recognised as an important infection in solid organ and haemopoietic stem cell transplant patients of all ages.[7]

Although infants are recognised as the group with the largest burden of RSV disease, infections with the virus resulting in illness continue throughout life. The importance of RSV in the elderly has been recognised. Four per cent of adults with community-acquired pneumonia hospitalised during the RSV season had serological evidence of current RSV infection.[8] More recently it has been recognised that a substantial proportion (between 7 and 41 per cent) of 'influenza-like illness' reported to general practices in the United Kingdom was due to RSV infection.[9] Strains of RSV found in the community and hospital patients in the same year were similar although lineages of RSV varied year by year. These are important findings for the development and use of vaccines and anti-viral agents against respiratory viruses.

Pathogenesis

Primary infection with RSV occurs with the highest incidence in infants aged between two and eight months.[6] The infection is rarely asymptomatic with

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pneumonia, bronchiolitis and tracheobronchitis being the major clinical manifestations. Otitis media may occur in 30 to 40 per cent of infected infants. RSV is responsible for between 50 and 90 per cent of hospital admissions for bronchiolitis, 5 to 40 per cent of those for pneumonia and 10 to 30 per cent of those for tracheobronchitis in children.[2] RSV viruses invade the epithelial cells of the lower respiratory tract and spread from cell to cell by inducing cell fusion and the formation of syncytia. Ciliated epithelium is destroyed and necrosis is observed.[10] The sloughing-off of the epithelia and increased secretion of mucus obstruct small airways leads to the clinical symptoms of bronchiolitis (inflammation of the bronchioles). These symptoms include hyperinflation, atelectasis (absence of gas in part of lung due to failure of alveolar expansion) and wheezing.[2] Treatment of RSV infection in infants is largely supportive and may include administration of supplemental oxygen, mechanical ventilation and fluid replacement. Bronchodilator therapy with alpha- and beta-agonists have been used but their efficacy is uncertain.[6] Treatment with aerosolised ribavirin, a synthetic nucleoside with antiviral properties, was licensed for use in hospitalised children with RSV infection in the United States of America in 1985.[10] A recent review of randomised trials of ribavirin[11] suggests that anti-viral treatment reduces the length of ventilator support and possibly the duration of hospital stay. Larger studies are required to fully assess the efficacy of this treatment.

Various factors have been postulated to influence the clinical severity of RSV disease in infants. Infants with compromised respiratory function, such as bronchopulmonary dysplasia or congenital heart disease with increased pulmonary circulation, are at increased risk of severe RSV disease.[12] There have been suggestions that group A RSV viruses cause more severe disease than group B, but the evidence is inconclusive.[12] More recent studies have suggested the GA3 clade of group A RSV causes more severe disease than clades GA2 or GA4.[13] The viral load in infants with severe RSV disease has been shown to be 10-fold higher than that in infants with mild disease.[14] RSV viral load seems to be associated with lung consolidation and hypoxia.[15] However, other studies have shown no relation between viral titre and severity of illness,[16] possibly because of difficulties in determining when the peak in viral shedding occurs.

Investigations of the pathogenesis of RSV disease have shown a relationship between a single nucleotide polymorphism in the upstream sequence of the interleukin 8 (IL–8) gene. This polymorphism is associated with increased IL–8 production, which is a potent neutrophil chemoattractant. This allele was demonstrated to occur more frequently in infants with RSV bronchiolitis.[17] IL–8 levels in plasma are increased in infants with severe RSV disease[12] and neutrophils are predominant in RSV bronchiolitis.[18]

Further clues to the pathogenesis of RSV come from the trials of the formalin-inactivated RSV vaccine (FI–RSV) in the 1960s, which showed increased morbidity and mortality in vaccine recipients when infected with RSV. Enhanced RSV disease seen in vaccine recipients may have been mediated by the formation of immune complexes and the subsequent activation of complement resulting in haemorrhagic necrosis in the lung.[19]

Approximately 70 per cent of wheezing episodes in the first year of life are associated with respiratory viral infections. RSV, rhinovirus and influenza B are the most frequently identified viruses.[20] Following RSV infection, subsequent wheezing has been noted in 40 to 50 per cent of infants hospitalised with RSV bronchiolitis.[2] These infants have a higher risk of wheezing and abnormal pulmonary function for up to 10 years.[6] Exacerbation of existing asthma by respiratory viruses has been noted, with an asthma attack in 50 to 70 per cent of cases with culture confirmed rhinovirus, RSV or coronavirus infection.[20] A cohort study showed that children with RSV lower respiratory tract infection before age three had a threefold increased risk of infrequent wheeze and a fourfold increased risk of frequent wheeze up to the age of 6 years. The risk of wheeze declined in this group thereafter and by age 13 this group of children were no longer at increased risk.[21] These data are suggestive of an important role for RSV in the inception of childhood asthma via modulation of the local immune response or changes in the neural pathways to the lungs.[22] Control of the current 'epidemic' of asthma in Western countries may be achieved by reducing viral respiratory infections through vaccination.

Prevention of RSV: prophylaxis and vaccination

Two strategies have been employed in the prevention of RSV infection. The passive immunisation of at-risk groups using antibodies to RSV and active immunisation with vaccines. Antibodies are important in protection from RSV disease, especially neutralising antibodies directed to the RSV proteins responsible for viral attachment (G protein) and cell fusion (F protein).[18] Parenteral administration of pooled immunoglobulin with high titres of RSV neutralising antibody (RSVIG) given monthly as prophylaxis during RSV season has been shown to reduce the frequency of infections and consequent hospitalisations. RSVIG has been used in high-risk infants, but requires the administration of a large volume at monthly intervals, which is expensive and exposes infants to the risks associated with blood products. Cost effective use of RSVIG appears to be limited to children with bronchopulmonary dysplasia, where one hospitalisation is prevented by the treatment of 12 children with RSVIG.[10] More recently a RSV monoclonal antibody, ('Palivizumab', Med Immune, Gaithersburg, MD) has been licensed as a prophylactic

agent for RSV in high-risk infants. A randomised, double-blind, placebo controlled trial of ' Palivizumab' in three countries demonstrated that monthly administration during the RSV season resulted in a 55 per cent reduction in hospital admissions for RSV infection as well as a shortening of hospital stay and less need for intensive care unit admission and oxygen support.[23] In the absence of a vaccine, 'Palivizumab' is the most effective prophylaxis against RSV in at-risk children.

The development of vaccines against RSV is complicated by the need to induce an effective immune response in very young infants and in the presence of maternal antibodies. Naturally acquired immunity is neither complete nor durable, although protection from severe disease occurs after primary infection.[2] A RSV vaccine would ideally protect at-risk children who may be deficient in their immune responses. The type of protective immunity to be induced by a vaccine is uncertain, as the balance of different effector mechanisms of the immune system in pathogenesis or protection in RSV disease is unclear. Natural immunity may be limited to groups or even clades of the RSV virus and a vaccine would need to induce broad immunity. RSV vaccine development is haunted by the exacerbation of RSV disease induced by the formalin-inactivated vaccines (FI–RSV) in the 1960s. Current strategies in RSV vaccine development cover a broad range of new vaccine technologies including sub-unit, live attenuated and DNA vaccines and adenovirus and poxvirus vaccine vectors.[12] Live vaccines are more likely to be effective in infants and live attenuated cold-passaged temperature sensitive RSV vaccines have been tested in adults and seropositive and seronegative children.[24] Although there was no exacerbation of RSV disease in vaccinated children or reversion of the vaccine virus to virulence, the protective efficacy of these vaccines has yet to be demonstrated. The introduction of safe and effective vaccines against RSV into childhood vaccination schedules appears to be some years away.

Local epidemiology

In temperate regions of Australia, RSV infections occur in sharply defined annual winter epidemics. RSV infection is not a notifiable disease in Australia so local information about the disease is limited to surveillance systems such as LabVISE, hospitalisation and mortality data and published research literature.

LabVISE reports of RSV numbered between 2,555 and 4,640 annually between 1991 and 2000. The annual peak in cases occurred in July each year, with between 55 and 77 per cent of all cases identified between July and September (Figure 1).

In 2000, 87 per cent of reports were in children aged less than 5 years, 64 per cent in children less than one year, 44 per cent in infants aged less than 6 months and 35 per cent in children aged less than 3 months (Figure 2). Overall, the male to female ratio was 1.3:1.

The peak in LabVISE reports of RSV infection coincided with the peak in hospitalisations for acute bronchiolitis, of children aged less than one year (National Hospital Morbidity database, Australian Institute of Health and Welfare, Figure 3). Bronchiolitis accounted for 56 per cent of all admissions to Australian hospitals of infants aged less than one year in 2000/01. The number of LabVISE reports of RSV was of the same order as total admissions for acute bronchiolitis (Figure 3). It is likely LabVISE captures the majority of hospitalised cases of RSV through its network of tertiary hospital laboratories in major Australian cities.

Figure 1.   Laboratory reports to LabVISE of respiratory syncytial virus infection, Australia, 1991 to 2001, by month of specimen collection
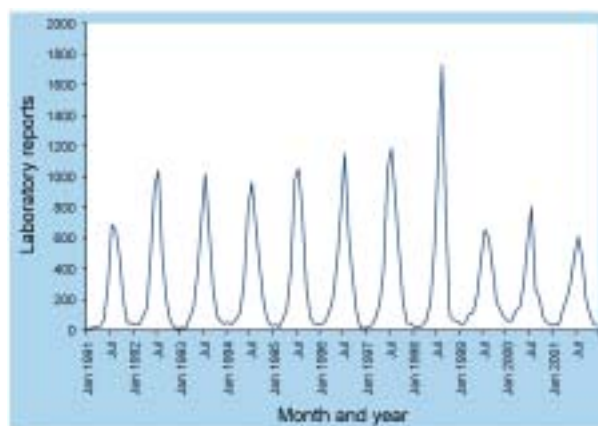

Figure 2.   Laboratory reports to LabVISE of respiratory syncytial virus infection, Australia, 2000, by age and sex
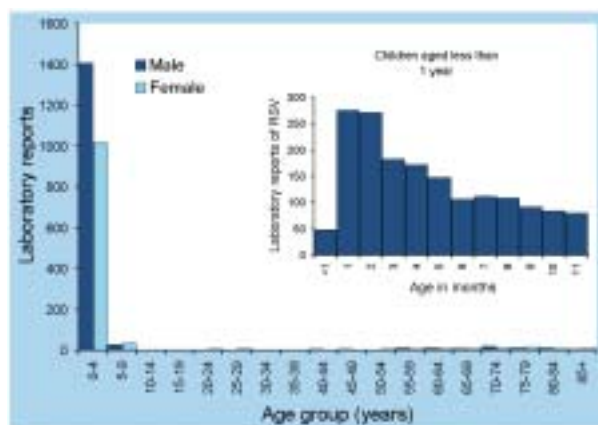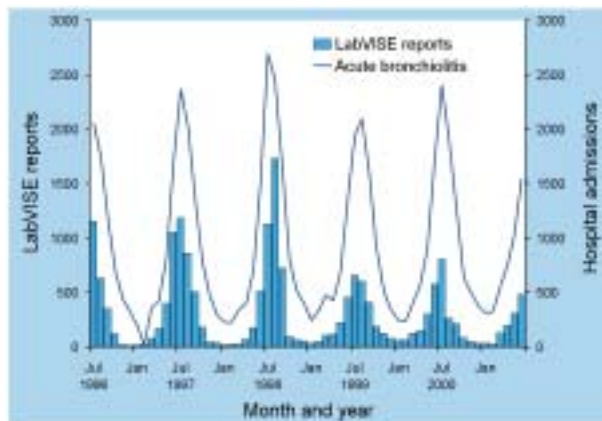
Figure 3. Laboratory reports to LabVISE of respiratory syncytial virus infection and hospitalisations with a principle diagnosis of bronchiolitis* in children aged less than one year, Australia, 1996 to 2001, by month of report or separation


*   ICD–10AM code J21

The relationship between the annual peaks in reports to LabVISE of RSV and human parainfluenza virus type 3 (HPIV–3) and influenza A and B over three seasons is shown in Figure 4. Peaks in RSV activity precede those of HPIV–3 (Panel A) and in some seasons precede, and in other seasons coincide with, peaks in activity of influenza A and B.

Given the ubiquitous nature of RSV infection in infants and young children, there are surprisingly few publications about the incidence or impact of this virus in Australia. Identification of RSV epidemics in Melbourne in 1960 and 1961 confirmed overseas findings of a distinct peak in cases in winter months, a strong link with bronchiolitis and a predilection for infecting infants and young children, causing deaths in the very young.[25,26] The severity of the RSV season in children varied from year-to-year and produced a clinical illness distinguishable from that caused by other viral respiratory pathogens, such as influenza and parainfluenza.[26] The possibility of intra-household transmission was raised with the identification of similar illnesses in the siblings of discharged children.[26] Australian papers since this time have largely consisted of case series reporting hospitalisation episodes with RSV identification, or bronchiolitis and other consistent clinical syndromes.[27,28,29,30] These papers confirm RSV as the major respiratory pathogen causing lower respiratory tract infections in infants and young children, and the seasonal nature of the annual RSV epidemics in Australia. A three year prospective study demonstrated the dominance of RSV group A infection, but suggested RSV group A and group B were similar in relation to relative clinical severity of infection.[30] Nosocomial

Figure 4. Laboratory reports to LabVISE of respiratory syncytial virus infection and human parainfluenza virus type 3 (HPIV–3), (Panel A) and influenza A and B (Panel B), Australia, 1999 to 2001, by month of report
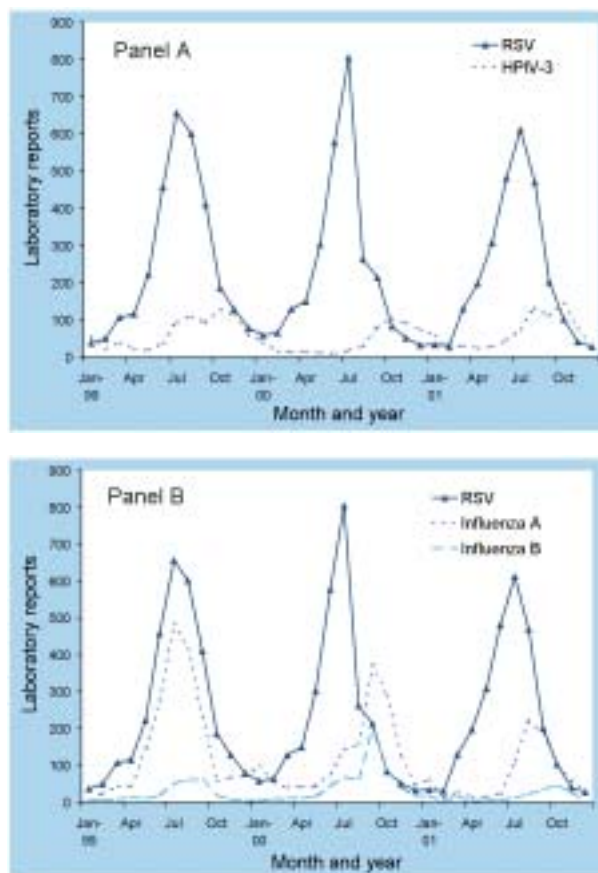
transmission of RSV in a paediatric teaching hospital in New South Wales using at-risk days for hospital-acquired RSV as the denominator, showed the rate of transmission was 2.9 cases per 1,000 at-risk days.[31]

The epidemiology of RSV in New South Wales was further examined in a review of laboratory isolations, hospital admissions for acute bronchiolitis, and deaths due to acute bronchiolitis.[32] From January 1993 to December 1997 there were between 770 and 1,131 isolations of RSV annually, with the majority of these occurring in children less than six months of age. Between 1990 and 1995 there were 22,969 admissions where the principal diagnosis was acute bronchiolitis, with approximately three-quarters occurring in infants less than 6 months of age. There were 7 deaths from acute bronchiolitis in New South Wales children between 1992 and 1996 — five in infants aged less than 3 months, and the other 2 children aged between one and 2 years of age.[32]

Other papers have examined therapeutic options in the management of patients with RSV infections. A study on the use of RSV immunoglobulin or

monoclonal antibody to prevent hospitalisation and reduce the length of stay in hospital for Australian children with RSV, came to the conclusion that its routine use was inappropriate, even in children at high risk of serious consequences of infection.[33]

The importance of bronchiolitis in Australian Indigenous children has been assessed to determine whether this group is at higher risk. Rates of hospital admission for lower respiratory tract infections were compared in Indigenous and non-Indigenous children born in Western Australia during 1986, using linked hospitalisation and birth and death datasets.[34] The cumulative incidence of hospitalisation for bronchiolitis (not RSV specific), in the first 2 years of life was 116 admissions per 1,000 live births in Indigenous children, compared with 15 admissions per 1,000 live births in non-Indigenous children. While there may be other causes of bronchiolitis in Indigenous children, a review of hospitalisation for RSV proven bronchiolitis in Townsville from January 1997 to October 1999, showed that the annual admission rate was 46 admission per 1,000 live births in Indigenous children compared with 14 admissions per 1,000 live births in non-Indigenous children.[35] There was a seasonal variation in hospitalisations in Indigenous children with March being the peak month for RSV admissions, but there was apparently no seasonality in admissions for non-Indigenous children. This peak in RSV activity is distinct from the peak seen in national hospitalisation data (Figure 3) because Townsville is in a tropical region of Australia.

Surveillance of RSV

Given the ubiquity of RSV infection in childhood, what kind of disease surveillance is appropriate in Australia? Laboratory surveillance for RSV through LabVISE appears to routinely capture data on a large proportion of hospitalised cases of RSV annually, in a timely fashion and provides important information on the interaction between the epidemiology of RSV and other respiratory viruses. The surveillance of influenza-like illness through sentinel general practice schemes such as the Australian Sentinel Practice Research Network, indirectly measures the annual impact of RSV epidemics on community respiratory disease. Since RSV infection in older children and adults may not be readily distinguished from infection with influenza and other respiratory viruses, there is a need for simpler diagnostic tools for RSV to assess the true dimensions of the RSV disease burden. For the past several seasons, Victorian influenza surveillance has provided laboratory support to sentinel sites. In 2001, samples from patients presenting with influenza-like illness were tested by multiplex polymerase chain reaction for influenza A and B, RSV, adenovirus, enterovirus and rhinovirus.[36] This project will be important in defining the relative contribution of RSV to influenza-like illness in Australia.

Conclusions

Acute respiratory infections in children accounted for an estimated 1.9 million deaths in 2000 worldwide; 70 per cent of these deaths occurred in Africa and South-East Asia.[37] Preventing RSV-associated morbidity and mortality through vaccination is a high priority. RSV is the principal cause of bronchiolitis and a major contributor to other lower respiratory tract infections, particularly in the very young. In the coming years, there may be new vaccines to prevent infection and/or the serious consequences of infection due to viral respiratory pathogens, such as RSV, parainfluenza viruses, and influenza viruses. Monitoring the relative importance of these infections and collecting more comprehensive information about their incidence and impact in our community are important prerequisites for the implementation of appropriate vaccine strategies. Use of surveillance data (from systems such as LabVISE and the Australian Institute of Health and Welfare hospitalisation and death data), expansion of sentinel influenza surveillance systems to include other respiratory viral pathogens, and targeted research studies appear to be the most efficient means of gathering these data in Australia.

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