Seminar

Viral pneumonia

Olli Ruuskanen, Elina Lahti, Lance C Jennings, David R Murdoch

Department of Paediatrics, Turku University Hospitals, Turku, Finland
(Prof O Ruuskanen MD, E Lahti MD)**; and Microbiology Unit, Canterbury Health Laboratories, and Department of Pathology, University of Otago, Christchurch, New Zealand**
(Prof D R Murdoch MD, L C Jennings PhD)

Correspondence to:
Prof Olli Ruuskanen, Department of Paediatrics, Turku University Hospitals, PL 52, 20521 Turku, Finland
olli.ruuskanen@tyks.fi

About 200 million cases of viral community-acquired pneumonia occur every year—100 million in children and 100 million in adults. Molecular diagnostic tests have greatly increased our uwnderstanding of the role of viruses in pneumonia, and findings indicate that the incidence of viral pneumonia has been underestimated. In children, respiratory syncytial virus, rhinovirus, human metapneumovirus, human bocavirus, and parainfluenza viruses are the agents identified most frequently in both developed and developing countries. Dual viral infections are common, and a third of children have evidence of viral-bacterial co-infection. In adults, viruses are the putative causative agents in a third of cases of community-acquired pneumonia, in particular influenza viruses, rhinoviruses, and coronaviruses. Bacteria continue to have a predominant role in adults with pneumonia. Presence of viral epidemics in the community, patient's age, speed of onset of illness, symptoms, biomarkers, radiographic changes, and response to treatment can help differentiate viral from bacterial pneumonia. However, no clinical algorithm exists that will distinguish clearly the cause of pneumonia. No clear consensus has been reached about whether patients with obvious viral community-acquired pneumonia need to be treated with antibiotics. Apart from neuraminidase inhibitors for pneumonia caused by influenza viruses, there is no clear role for use of specific antivirals to treat viral community-acquired pneumonia. Influenza vaccines are the only available specific preventive measures. Further studies are needed to better understand the cause and pathogenesis of community-acquired pneumonia. Furthermore, regional differences in cause of pneumonia should be investigated, in particular to obtain more data from developing countries.

Introduction

Pneumonia is a common illness that continues to be the major killer of young children in developing countries and elderly people in developed countries. Many microorganisms are associated with pneumonia, and now attention is turning to the importance of viruses as pathogens. Widespread introduction of *Haemophilus influenzae* type b and pneumococcal conjugate vaccines into immunisation programmes has led to speculation about the growing predominance of viruses as causes of childhood pneumonia. The emergence of severe acute respiratory syndrome (SARS), avian influenza A (H5N1) virus, and the 2009 pandemic influenza A (H1N1) virus has re-emphasised the important role of respiratory viruses as causes of severe pneumonia. New respiratory viruses—such as human metapneumovirus, coronaviruses NL63 and HKU1, and human bocavirus—have been discovered during the past decade. Importantly, the availability of molecular diagnostic assays (such as PCR) has greatly increased our ability to detect and characterise the epidemiology of respiratory virus infections. Findings of previous studies, in which conventional virological diagnostic techniques were used, have most likely underestimated the role of viruses as pneumonia pathogens.[1–5] In this Seminar, we review viral community-acquired pneumonia in immunocompetent children and adults, focusing on studies that have used modern molecular diagnostic techniques.

Epidemiology of pneumonia

According to WHO estimates, 450 million cases of pneumonia are recorded every year; about 4 million people die from this illness, accounting for 7% of total mortality of 57 million people.[6,7] The highest incidences arise in children younger than 5 years and in adults older than 75 years (figure 1).[8] In developing countries, incidence could be five times higher than in developed regions. In children, 156 million episodes of pneumonia are recorded annually, of which 151 million are present in developing countries.[6,7] In 2008, 1·6 million children younger than 5 years died from pneumonia.[9] 5 million cases of childhood community-acquired pneumonia are reported yearly in developed countries, but mortality has declined strikingly and is now very rare. In a Canadian study, 25 319 admissions for childhood pneumonia took place during the 9-year study period; 11 deaths were recorded and only one death did not have a comorbid condition.[10] Mortality of 1·2 per million previously healthy young adults has been recorded in the UK.[11] In the USA alone, the economic burden of community-acquired pneumonia has been estimated to be more than US$17 billion annually.[12]

Diagnosis of viral pneumonia

Laboratory diagnosis of viral pneumonia has relied on detection of virus or viral antigen in upper-respiratory specimens (eg, nasopharyngeal aspirates) and lower-respiratory samples (eg, induced sputum) by culture or immunofluorescence microscopy, and on measurement

of antibodies in paired serum samples. Introduction of PCR has increased the ability to detect respiratory viruses, including those that are difficult to culture. At least 26 viruses have now been associated with community-acquired pneumonia (panel).

Despite technological advances, establishing the cause of pneumonia remains challenging.[13] Specimens from the lower-respiratory tract can be hard to obtain, and distinguishing possible prolonged shedding or colonisation from infection can be difficult. For diagnosis of viral pneumonia, reliance on testing of nasopharyngeal specimens presents its own challenges; detection of a virus in the nasopharynx could represent coincidental upper-respiratory infection or a pneumonia pathogen. Measurement of background prevalence of asymptomatic nasopharyngeal viral infection in a control group might help to clarify the size of this diagnostic issue at a population level, but this approach has been used only rarely in aetiological studies. Furthermore, most research has focused on patients admitted to hospital and, therefore, findings might not be representative of mild-to-moderate disease.

Several different types of specimen from the upper and lower airway have been used in aetiological studies of community-acquired pneumonia, including: naso-pharyngeal aspirates or washes; swabs from the nasopharynx, nose, or throat; combined nasopharyngeal and throat swabs; expectorated and induced sputum; tracheal aspirates; bronchoalveolar lavage; and lung puncture.[14,15] Recovery of virus fluctuates according to specimen type, which probably accounts for some of the variability of findings between studies.

Most studies of the cause of viral pneumonia have used upper-respiratory specimens to test for viruses. In children, nasopharyngeal aspirates are generally deemed the specimen of choice because both nasal and nasopharyngeal mucus samples are gathered. Respira-tory viruses have been noted in 95% of mucus samples obtained by nasopharyngeal aspiration from children with respiratory infection.[16] Obtaining an aspirate is, however, unpleasant and requires a suction device. Nasal swabs taken with a sterile cotton swab from a depth of 2–3 cm have comparable sensitivity to nasopharyngeal aspirates for culture of all major respiratory viruses, except respiratory syncytial virus.[17] Flocked swabs with nylon fibres in a perpendicular fashion are now preferred by many clinicians because they are convenient to use and have a similar sensitivity to nasopharyngeal aspirates for detection by PCR of respiratory viruses.[15,17,18] In adults, nasopharyngeal swabs have a higher sensitivity than throat swabs, but they can be less sensitive than nasopharyngeal washes.[14] Transnasal nasopharyngeal flocked swabs also have high virus detection rates in adults.[19,20]

Lower-respiratory specimens have obvious advantages for establishing the cause of pneumonia because they come from the site of infection. However, obtaining
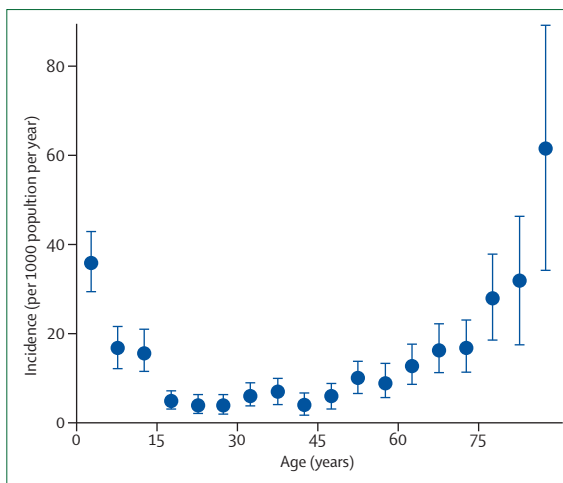

Figure 1: **Age-specific incidence of community-acquired pneumonia**
Error bars=95% CIs. Modified from reference 8 with permission of Oxford University Press.

Panel: **Viruses linked to community-acquired pneumonia in children and adults**

- Respiratory syncytial virus
- Rhinovirus
- Influenza A, B, and C viruses
- Human metapneumovirus
- Parainfluenza viruses types 1, 2, 3, and 4
- Human bocavirus*
- Coronavirus types 229E, OC43, NL63, HKU1, SARS
- Adenovirus
- Enteroviruses
- Varicella-zoster virus
- Hantavirus
- Parechoviruses
- Epstein-Barr virus
- Human herpesvirus 6 and 7
- Herpes simplex virus
- Mimivirus
- Cytomegalovirus†
- Measles†

*Mostly in children. †Mostly in developing countries.

reliable specimens that are not contaminated by flora from the upper airway is difficult. Induced sputum specimens have been used in paediatric pneumonia studies, although assuring that the specimens are representative of the lower-respiratory tract can be challenging.[21] High-quality specimens can be obtained by thoracic needle aspiration, but this technique has not been adopted widely because of safety concerns, despite a low complication rate.[22,23]

In general, PCR-based methods are between two and five times more sensitive than conventional virus diagnostic methods (culture, antigen detection, and serological assays) for detection of respiratory viruses.

	Suggests viral cause	Suggests bacterial cause
Age	Younger than 5 years	Adults
Epidemic situation	Ongoing viral epidemic	..
History of illness	Slow onset	Rapid onset
Clinical profile	Rhinitis, wheezing	High fever, tachypnoea
Biomarkers		
Total white-blood cell count	<10×10⁹ cells per L	>15×10⁹ cells per L
C-reactive protein concentration in serum	<20 mg/L	>60 mg/L
Procalcitonin concentration in serum	<0·1 μg/L	>0·5 μg/L
Chest radiograph findings	Sole interstitial infiltrates, bilaterally	Lobar alveolar infiltrates
Response to antibiotic treatment	Slow or non-responsive	Rapid

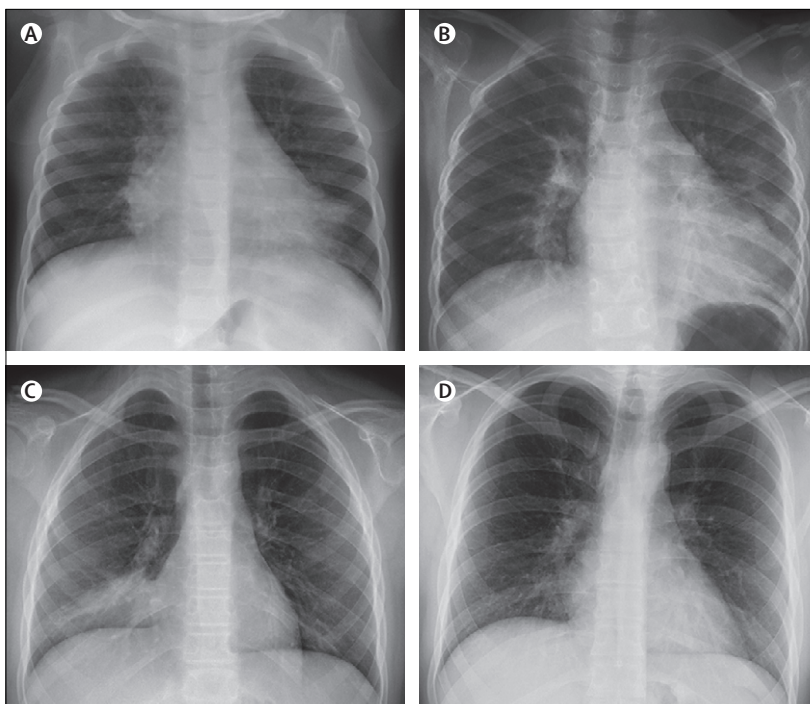*Table 1*: Variables used to distinguish viral from bacterial pneumonia

Figure 2: Chest radiographs of patients with viral pneumonia
(A) Pneumonia caused by human bocavirus in a 1-year-old girl. Chest radiograph shows alveolar infiltrates in right middle lobe and left lower lobe. (B) Pneumonia caused by metapneumovirus and *Haemophilus influenzae* in a 7-year-old girl. Chest radiograph shows alveolar infiltrate in left lower lobe. (C) Pneumonia caused by rhinovirus and *Streptococcus pneumoniae* in an 11-year-old girl. Chest radiograph shows alveolar infiltrate in right lower lobe. (D) Pneumonia caused by adenovirus in a 22-year-old man. Chest radiograph shows alveolar and interstitial infiltrates in right lower lobe.

This benefit applies particularly to adults and elderly people, who might have a smaller nasopharyngeal viral load than children.[24,25] Moreover, some respiratory viruses can only be detected readily by PCR. Development of several multiplex assays has enabled simultaneous detection of up to 15 different viruses, and use of these tests is becoming standard for identification of respiratory viruses.[26,27]

The ability to differentiate viral from bacterial pneumonia could have important management implications. Despite advances, diagnostic tests still

fail to identify causative agents in many affected individuals.[28] As a result, other variables have been used to distinguish viral from bacterial pneumonia (table 1). However, no clinical algorithm exists to discern clearly the cause of pneumonia. This absence is perhaps not surprising in view of the probable important interaction between viruses and bacteria in pathogenesis of pneumonia.

Respiratory viruses usually follow seasonal patterns of activity and are most likely to cause pneumonia during those times. Epidemics of respiratory syncytial virus typically happen every or every other year in late autumn, rhinovirus epidemics arise in autumn and spring, whereas influenza peaks are seen during late autumn and early winter. Several viruses can be co-circulating at specific times of the year, even during the highest epidemic peaks of one virus.[29]

Although viral pneumonia is being recognised increasingly in adults, it still seems to be most typical in children, especially in infants younger than 2 years.[30] According to the British Thoracic Society, fever higher than 38·5°C, a respiratory rate greater than 50 breaths per min, and chest recession are suggestive of bacterial rather than viral pneumonia; by comparison, young age, wheezing, fever less than 38·5°C, and striking chest recession are suggestive of a viral cause.[1] However, clinical signs and symptoms of viral and bacterial pneumonia are highly variable and overlap; therefore, they cannot be relied on. Importantly, typical pneumococcal pneumonia (sudden onset, high fever, chills, pleuritic chest pain, lobar infiltrates, leucocytosis) is only one part of the range of bacterial pneumonia.[31]

White-blood-cell count and concentrations in serum of C-reactive protein and procalcitonin are variables studied widely in children and adults with community-acquired pneumonia. In general, these biomarkers are raised significantly in individuals with bacterial pneumonia compared with patients with viral pneumonia (table 1),[19,32–35] although none has sufficient sensitivity or specificity to be used in isolation. Use of procalcitonin in clinical practice to identify bacterial infection and help guide antimicrobial treatment has been the focus of many studies. This substance increases within 6–12 h after onset of bacterial infection and halves daily when infection is controlled.[34] In the context of pneumonia, concentrations of procalcitonin greater than 0·5 μg/L support bacterial infection, whereas repeatedly low amounts suggest that bacterial infection is unlikely. However, the exact role of procalcitonin in management of pneumonia is still the subject of ongoing discussion and debate.[35]

Recommendations from the American Thoracic Society are that diagnosis of pneumonia should be made on the basis of chest radiography.[36] Interstitial infiltrates on chest radiographs are generally believed to suggest a viral cause of pneumonia and alveolar infiltrates to indicate a

	Rhinovirus (n=580)	Respiratory syncytial virus (n=1655)	Adenovirus (n=902)	Parainfluenza virus 1 (n=94)	Parainfluenza virus 2 (n=49)	Parainfluenza virus 3 (n=315)	Influenza A virus (n=544)	Influenza B virus (n=139)
Pneumonia	18%	16%	8%	9%	6%	14%	9%	8%
Wheezy bronchitis	22%	12%	2%	2%	4%	8%	6%	6%
Otitis media	23%	59%	24%	27%	20%	30%	26%	19%
Non-specified acute respiratory infection	14%	32%	37%	27%	22%	50%	44%	53%
Bronchiolitis	3%	34%	1%	2%	10%	5%	1%	1%
Laryngitis	2%	2%	1%	37%	53%	10%	5%	4%
Tonsillitis	2%	0	30%	1%	0	2%	5%	4%
Fever without a focus	2%	1%	5%	10%	0	2%	1%	2%
Febrile convulsion	1%	2%	7%	4%	0	5%	12%	9%
Fever ≥38°C	44%	63%	81%	77%	76%	63%	94%	89%

Rhinovirus infections are from 1987 to 2006; other respiratory virus infections are from 1980 to 1999. Modified from reference 51, with permission of John Wiley and Sons.

Table 2: Occurrence of pneumonia and other findings in 4277 children with laboratory-confirmed viral respiratory infection at Turku University Hospital, Finland

bacterial cause (figure 2). However, bacteria and viruses alone or together can induce a broad range of chest radiographic changes, and alterations are only helpful in specific cases to confirm a microbial cause of pneumonia. In one study, bacterial infection was noted in 97 (71%) of 137 children with alveolar infiltrates, whereas 97 (72%) of 134 with bacterial pneumonia had alveolar infiltrates.[33] In children with viral pneumonia, 40 (49%) had alveolar changes. Of 85 children with bacteraemic pneumococcal pneumonia, alveolar infiltrates were recorded in 77 (91%) and interstitial infiltrates alone in eight (9%).[37] Multilobe disease in various cases of viral pneumonia was reported in half of 88 adults with community-acquired pneumonia.[19] Thoracic CT indicated tree-bud opacities, multifocal consolidations, and ground-glass opacities in adults with viral pneumonia without any evidence of possible concomitant bacterial infection; however, a viral cause was never suggested by the radiologists.[38]

Intuitively, bacterial pneumonia should respond to appropriate antibacterial treatment but viral pneumonia should not. In a study of 153 children admitted with community-acquired pneumonia, median duration of fever was 14 h after onset of antibiotic treatment.[39] No difference was recorded between those diagnosed with viral and bacterial pneumonia. However, children with mixed viral and bacterial infections became afebrile over a longer period. Undetected bacterial co-infection probably accounts for the response to antibacterial treatment in patients with apparent viral pneumonia.

Community-acquired pneumonia is a dynamic situation. Biomarkers and infiltrates on chest radiographs are only snapshots of this active state. Findings of follow-up studies, after 12–24 h, might be totally different.

Causes of viral pneumonia
Paediatric studies
We identified nine studies of community-acquired pneumonia (n=4279 episodes) in which the viral cause had been searched for by PCR. In most of these

investigations, virus culture and antigen detection were also used.[21,30,40–46] Seven studies were undertaken in developed countries and two in developing countries. Evidence of viral infection was recorded in 49% (range 43–67) of cases. Prevalence of community-acquired pneumonia associated with respiratory syncytial virus (11%), influenza viruses (10%), parainfluenza viruses (8%), and adenovirus (3%) was similar to that reported in studies in which only conventional diagnostic approaches were used.[1,2] Exact numbers of different viruses are difficult to compare from one study to another because several techniques were applied. When serological assays alone were used, evidence of a viral cause was obtained in 20–43% of children with community-acquired pneumonia, and respiratory syncytial virus was dominant.[47–50] PCR has increased detection of rhinoviruses (18%) and enteroviruses (7%). Of newly described viruses, human bocavirus was recorded in 5% of cases and human metapneumovirus in 8%. Coronaviruses were seen in 22 (7%) of 338 children in one study.[41] In a 3-year prospective study in Finland, the overall probable cause of pneumonia was recorded in 85% of children, with bacterial infection in 53% and viral infection in 62%.[30] The most comprehensive study from a virological perspective searched for 14 viruses in 338 children with pneumonia over a 2-year period.[41] Prevalence of viral infection was 67%, with respiratory syncytial virus, rhinoviruses, human bocavirus, human metapneumovirus, and parainfluenza viruses being the most common agents.

Many researchers have focused on the role of single respiratory viruses as a cause of childhood community-acquired pneumonia or have studied sole virus infections and looked for pneumonia in their clinical profiles (table 2). Globally, respiratory syncytial virus continues to be the major causative viral agent of pneumonia in children and could be the predominant viral cause of severe pneumonia in this population.[52,53] With the advent of PCR techniques, rhinoviruses have been detected increasingly in childhood pneumonia.[54] The clinical profile of 643 rhinovirus

infections in children admitted to hospital has been reported in seven studies,[55–61] and 11–53% had pneumonia. However, the role of rhinoviruses in pneumonia is still questioned because of the frequent detection of rhinoviruses in asymptomatic individuals (mean prevalence 15%), strikingly more than for other respiratory viruses (prevalence 1–5%).[62] Jartti and colleagues suggested that PCR is likely to detect a true but asymptomatic infection.[62] A difficulty with rhinoviruses is the paucity of serological tests to verify acute infection. In immunocompetent individuals, rhinoviral clearance after symptomatic infection is rapid (average 1–3 weeks).[18]

Pneumonia was diagnosed in 10% of children admitted with acute human metapneumovirus respiratory infection,[63–66] with the highest prevalence (44%) in infants younger than 12 months.[66] It has also been recorded in 11–75% of children with human bocavirus infection.[67] In a study from Thailand of infants younger than 5 years admitted with pneumonia, human bocavirus was the third most prevalent agent detected, after rhinovirus and respiratory syncytial virus, accounting for 12% of all cases.[68] Although the role of human bocavirus in pneumonia is still being clarified, serological evidence suggests it is a cause of human infection. With a novel IgM and IgG enzyme immunoassay, 96% of children with a high load of human bocavirus in nasopharyngeal aspirates and 92% of wheezy children with viraemia had diagnostic seroresponses.[69] Human bocavirus was identified serologically in 12 (12%) of 101 children with community-acquired pneumonia in Italy.[70]

Although prevalence of adenovirus-associated pneumonia is fairly low (range 2–12%), this type of infection is important to recognise because it might induce severe and fatal necrotising pneumonia (especially serotypes 3, 7, and 14).[30,40–46,71] In China, adenovirus DNA was detected in 9% of post-mortem pulmonary tissue specimens from 175 children with fatal pneumonia.[72] Of note, PCR is substantially more sensitive for identification of adenovirus than is antigen detection.[73]

Human coronaviruses 229E and OC43, and newly discovered types NL63 and HKU1, have been linked to community-acquired pneumonia in children.[74,75] Infection with human coronavirus was detected in 3% of children and adolescents in a large pneumonia study in Thailand.[76]

Research in adults
We identified ten studies of adults with community-acquired pneumonia (n=2910 episodes) in which PCR was used to test for respiratory viruses. Evidence of viral infection was detected in 22% of cases.[19,20,77–85] In most of these studies, a comprehensive array of conventional virological methods were also implemented to better define the role of viruses in adults with community-acquired pneumonia. Similar to findings of paediatric studies, prevalence of infection with influenza viruses (8%), respiratory syncytial virus (3%), parainfluenza viruses (2%), and adenovirus (2%) is comparable with

values recorded with conventional diagnostic methods alone.[5,36] Serological techniques only were used in four studies; evidence of viral community-acquired pneumonia was noted in 10–23% of patients.[86–89] Use of PCR has augmented detection of viruses that are difficult to identify with conventional methods, including rhinoviruses (6%), human coronaviruses (5%), and human metapneumovirus (1%). As a result, overall prevalence of respiratory viral infection in PCR studies (15–56%) is generally higher than for studies in which PCR was not implemented. With a full set of tests, findings of three reports suggest that a third of adult cases of community-acquired pneumonia are associated with viral infection.[19,20,85]

Other researchers have focused on the role of specific respiratory viruses in adults with community-acquired pneumonia. Respiratory syncytial virus is recognised increasingly as a cause of illness in adults,[90] and roughly 2–9% of elderly patients admitted with pneumonia in the USA have infection associated with this virus.[91] Infections with respiratory syncytial virus are linked to substantial mortality.[92] Several outbreaks of severe respiratory disease (including fatal pneumonia) in elderly residents of nursing homes have been associated with rhinoviruses.[93,94] Adenoviruses have been implicated in 90% of pneumonia-related admissions in basic military trainees.[95] An outbreak of pneumonia associated with adenovirus serotype 14 has been reported.[96] When searched for systematically, coronaviruses have been detected in samples from a small proportion (2–6%) of adults with pneumonia.[76,97] These patients had clinical illnesses indistinguishable from those in individuals with community-acquired pneumonia associated with other microorganisms. 2% of asymptomatic controls also had human coronavirus infection.[76]

Infections with human metapneumovirus arise throughout adulthood. Outbreaks of this viral infection associated with fatal outcome have been reported from long-term care facilities.[98,99] Of patients admitted with human metapneumovirus infection, 27% had chest radiographic infiltrates, 12% required ventilatory support, and 7% died.[100] Human bocavirus is an uncommon cause of pneumonia in adults. As part of a surveillance project in Thailand, this virus was detected in five (1%) of 667 adults (age 20 years or older) admitted with pneumonia and in one of 126 (1%) controls without febrile or respiratory illness.[68]

Pneumonia associated with SARS, avian influenza, and 2009 pandemic influenza
During 2002 and 2003, the SARS coronavirus caused severe respiratory infection in more than 8000 people and led to 774 deaths. Up to a third of patients with SARS became critically ill. Pneumonia with lung injury arose in about 16% of all individuals infected with the virus and in 80% of critically ill patients. By contrast with other viral pneumonias, children were fairly well protected from severe illness.[101]

Since November, 2003, avian influenza A (H5N1) virus has caused more than 450 human infections, with a case-fatality proportion of about 60%. Multiorgan failure usually develops within 1 week from onset of illness, with lymphopenia, thrombocytopenia, and raised concentrations of aminotransferase and creatinine. Almost all patients with avian influenza develop pneumonia. Cause of death is most typically progressive respiratory failure.[102]

Since March, 2009, pandemic influenza A (H1N1) virus has spread in more than 200 countries over the world, causing about 18 000 deaths. In the USA alone, more than 59 million people have been infected.[103] In Australia, the rate of admission was 23 per 100 000 population. Critical illness arose most commonly in adults with a median age of 40 years and has been rare in those older than 65 years.[103–105] Half of patients with critical illness had viral pneumonitis or acute respiratory distress syndrome.[103,106] In Germany, pneumonia was diagnosed in 275 (0·7%) of 40 729 patients with pandemic H1N1 virus infection; half of these were admitted.[107] In the UK, 102 (29%) of 349 patients with chest radiographs had findings consistent with pneumonia. Median age of patients with pneumonia was 26 years.[108] Poor outcomes from H1N1 virus infection have been recorded in pregnant women, indigenous populations, and individuals with substantial obesity or serious comorbidities.

Chest radiographic infiltrates in SARS, H5N1, and H1N1 infections were most usually interstitial, patchy, and bilateral.[109]

Detection of several viruses

In 1997, Drews and colleagues[110] reviewed eight studies of a total of 1341 cases of respiratory viral infection detected mostly with conventional techniques. These researchers noted dual viral infection in 67 (5%) cases. Detection of several viruses in a fairly high proportion of cases has been a feature of pneumonia aetiological studies in which PCR was used. In particular, for childhood pneumonia, two or three viruses have been detected in 10–20% of children.[21,30,40–46] Specifically, human bocavirus is detected frequently in association with other respiratory viruses.[67–69] In a Thai pneumonia study, 40 (91%) of 44 children younger than 5 years with human bocavirus infections had co-infection with other viruses.[68] The combination of human bocavirus and rhinovirus was the most typical dual infection. In a comprehensive virological study of childhood pneumonia, two or more viruses were detected in 61 (18%) of 338 pneumonia episodes, and three viruses were recorded in nine cases.[41] Human bocavirus was associated with other viruses in 33 (69%) of 48 episodes, followed by influenza viruses (13/25; 52%) and respiratory syncytial virus (34/67; 51%). In another study, 64% of children with human bocavirus infection and co-infection with another virus had serological evidence of acute human bocavirus infection.[69]

The clinical relevance of detection of several viruses in pneumonia, and the association with severe illness, is uncertain.[111–113] Viral-viral interaction in vivo is poorly understood. Viruses might interact indirectly or directly, resulting in complementation or inhibition. Children with pneumonia caused by co-infection with human bocavirus and other viruses have more wheezing than with viral pneumonia associated with a sole pathogen.[69] In one study, viral co-infections were associated with more severe pneumonia than were single infections, when rates of admission were looked at.[41]

Viral-bacterial co-infection

Interest has grown with respect to the interaction of bacteria and viruses in the pathogenesis of pneumonia. Evidence from cell culture, ecological, post-mortem, and clinical studies support this area of interest. A favoured hypothesis is that viral infection is followed by secondary bacterial infection. Researchers who reassessed data from the influenza pandemics of 1918, 1957, and 1968 have suggested that most deaths during these periods probably resulted from secondary bacterial pneumonia.[114] This finding contrasts with avian H5N1-associated pneumonia, which seems to be a primarily viral infection.[102] In patients with 2009 pandemic H1N1 infection, secondary bacterial infection developed in 4–24% of cases.[103,106,115]

Evidence of probable mixed viral-bacterial infection has been recorded in up to 45% of cases of community-acquired pneumonia in children.[21,30,40–46] Not surprisingly, the most typical combination is *Streptococcus pneumoniae* with various respiratory viruses. In developing countries, both viruses and bacteria have been detected directly in lung aspirate samples from children with pneumonia.[22] In a study from The Gambia, 45 of 74 children had evidence of pneumococcal community-acquired pneumonia and 15 (33%) of these also had evidence of a respiratory virus infection, shown by virus culture or serological tests.[116] In a study from Nigeria,[117] virological analysis was done in 122 children with community-acquired pneumonia. 61 (50%) had evidence of viral infection and, of those, ten (16%) also had blood cultures positive for bacteria, most usually *Staphylococcus aureus*. Furthermore, ten (16%) of 62 cases with measles-associated community-acquired pneumonia had bacteraemia.[117]

Mixed viral-bacterial infections in adults with community-acquired pneumonia seem to be reported less frequently than those in children.[19,20,77–85] In one study, both viral and bacterial pathogens were noted in 35 (14%) of 242 cases.[84] In another investigation, evidence of mixed viral and bacterial infections was reported in 45 (15%) of 304 patients (median age 70 years). The most frequent combinations were rhinovirus plus *Strep pneumoniae* and influenza A plus *Strep pneumoniae*.[19] Undoubtedly, detection of several pathogens will be noted more frequently as more elaborate diagnostic tests are used as
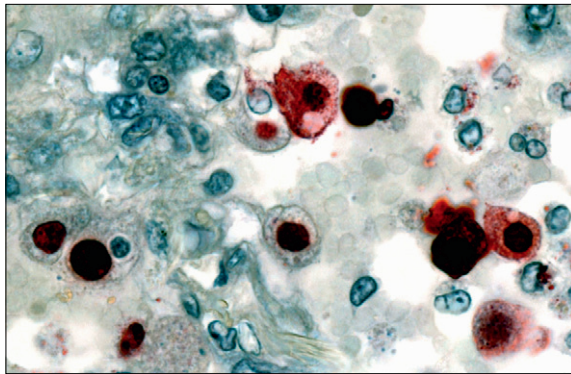
***Figure* 3: Immunolocalisation of 2009 pandemic influenza H1N1 viral antigen in lung tissue**
Viral antigens (red staining) are present in nuclei of alveolar-lining cells. Reprinted from reference 132 with permission of the American Society for Investigative Pathology.

part of pneumonia aetiological studies. Presuming that viral infection precedes bacterial infection, we are likely to continue underestimating the true incidence of viral-bacterial co-infection because of difficulties detecting the earlier infection.

Evidence, albeit sparse, suggests that mixed infections could induce a more severe inflammatory and clinical disease than individual bacterial or viral infections.[19,84,118] Concomitant influenza virus and *Staph aureus* infection can cause severe fatal pneumonia in children and adults.[119–121] Moreover, in one pneumonia study, half of children with treatment failure had evidence of mixed viral-bacterial infection.[39] Similarly, in adults, rhinovirus-pneumococcal and influenza-bacterial pneumonia co-infections are associated with severe pneumonia and raised mortality.[19,84,121] Detection of *Strep pneumoniae* in the nasopharynx of patients with 2009 pandemic H1N1 infection predicted severe disease outcome.[122]

Pathology

Post-mortem studies provide direct evidence for a viral cause of pneumonia and descriptions of characteristics of lung histopathology. Many different respiratory viruses have been detected in lung tissue in case reports or in larger series.

In 200 children who died from serious respiratory infections in Brazil, use of immunohistochemical techniques aided detection of viruses in lung tissue from 53 (34%) with bronchopneumonia and 18 (42%) with interstitial pneumonitis, predominantly respiratory syncytial virus, influenza A and B viruses, adenovirus, and parainfluenza viruses types 1, 2, and 3.[123] In another study from Mexico, PCR detected respiratory syncytial virus in lung tissue from 29 (30%) of 98 children who died from pneumonia.[124] Of archived lung tissue from 175 children who died of pneumonia in south China, 20 samples had adenovirus detected by PCR or by immunohistochemistry.[72] Rhinovirus infection of the lung has also been shown by histopathology.[125]

The nature of histopathological changes in viral pneumonia varies, possibly an indication of differences in viral infections and comorbidity. Generally, interstitial pneumonitis with lymphocytic infiltrations is seen in viral pneumonitis.[123] In fatal cases of pneumonia caused by respiratory syncytial virus infection, post-mortem evidence shows infection of both bronchial and alveolar epithelium.[126] Most cells around the bronchioles and in the alveolar interstitium were alveolar macrophages and monocytes, and CD3-positive lymphocytes were also seen frequently around bronchioles. In rhinovirus pneumonia, hyperplasia and desquamation of alveolar-lining cells and immunohistochemical localisation of rhinoviral antigen in alveolar epithelial cells and macrophages were seen.[125] In fatal cases of human metapneumovirus pneumonia, pathological analysis indicated bilateral haemorrhagic bronchopneumonia.[127]

Histopathological findings in fatal cases of SARS and avian H5N1 infection are quite similar and have been characterised by diffuse alveolar damage, desquamation of pneumocytes, oedema, and hyaline-membrane formation.[128,129] Diffuse alveolar damage has also been recorded in the lungs of people who died of 2009 pandemic H1N1 infections (figure 3). Furthermore, necrotising bronchiolitis, diffuse alveolar damage with alveolar haemorrhage, alveolar septal oedema, hyaline membranes, hyperplasia of type 2 pneumocytes, and necrosis of bronchiolar walls have been noted.[130,131] Histopathological evidence of bacterial co-infection was reported in 29 of 100 fatal H1N1 cases.[132]

Management

Do all patients with community-acquired pneumonia, including those with evidence of viral infection, need to be treated with antibiotics? To date, no clear consensus exists on this issue. Some experts recommend that all patients with pneumonia should receive antibiotic treatment, because exclusion of the presence of bacterial infection is impossible. Recommendations of the British Thoracic Society are that antibiotic treatment can be withheld in young children with mild illness in whom viral infection is likely.[1] As far as we know, only one randomised placebo-controlled study has been done to investigate the need for antibiotic treatment in childhood community-acquired pneumonia.[133] In 136 children, no clinically significant efficacy of antibiotics was recorded. Most study children had fairly mild disease and the investigation was undertaken during an epidemic of respiratory syncytial virus, so most participants probably had pneumonia caused by this virus. Further randomised placebo-controlled trials of antibiotic treatment for pneumonia are unlikely to happen because of ethical concerns.

Opportunities are currently limited in clinical practice for use of antivirals in the treatment of pneumonia (table 3).[134] Neuraminidase inhibitors, such as oseltamivir

and zanamivir, were developed during the 1990s and now have established roles in early treatment of influenza A and B infections. In children and adults, neuraminidase inhibitors reduce median time to resolution of symptoms by 0·5–2·5 days when administered within 48 h of onset of symptoms.[135] Importantly, early use of neuraminidase inhibitors can reduce development of complications such as pneumonia.[136] The Infectious Diseases Society of America extends treatment with neuraminidase inhibitors to admitted influenza patients whose onset of symptoms is more than 48 h before presentation.[137] Selection of the most appropriate antiviral to treat influenza should be made on the basis of relevant susceptibility data. Before emergence of the 2009 pandemic H1N1 virus, the seasonal H1N1 virus developed resistance to oseltamivir, and treatment with either zanamivir or amantadine or rimantidine was recommended, whereas the seasonal H3N2 virus was resistant to amantadine and rimantidine. If subtype information is unavailable, zanamivir or a combination of oseltamivir and rimantadine is recommended.[137] The 2009 pandemic H1N1 virus remains susceptible to neuraminidase inhibitors, and oseltamivir has been used widely for treatment of pneumonia caused by this virus. Although resistance to oseltamivir has been reported in people with 2009 pandemic H1N1 virus infection, it has been largely restricted to immunocompromised individuals.[103] All isolates are still susceptible to zanamivir. Intravenous use of peramivir or zanamivir could be lifesaving in critically ill patients with influenza.[138,139]

Experience with antivirals for community-acquired pneumonia caused by viruses other than influenza is scarce, with existing knowledge mainly from case reports and some treatment studies in immunosuppressed patients. Ribavirin has a broad antiviral range, including respiratory syncytial virus, human metapneumovirus, and parainfluenza and influenza viruses.[140] Efficacy of ribavirin aerosol treatment for bronchiolitis and pneumonia caused by respiratory syncytial virus infection is modest at best. Intravenous ribavirin could be considered for treatment of severe pneumonia caused by infection with respiratory syncytial virus, human metapneumovirus, or parainfluenza virus, on the basis of experience in immunosuppressed patients.[141]

New antiviral agents are in development for respiratory syncytial virus infection, including small interfering RNAs.[142] In several case studies of immunocompromised patients, clinical efficacy of cidofovir has been shown for severe adenovirus pneumonia.[143] Cidofovir should be considered for treatment of new adenovirus subtype 14 pneumonia. Researchers reported successful management of human metapneumovirus pneumonia with a combination of intravenous ribavirin and immunoglobulin.[144] Varicella pneumonia should be treated with aciclovir.[145]

Use of corticosteroids for treatment of viral community-acquired pneumonia is controversial and can vary

	Treatment	Prevention
Influenza A and B viruses	Oseltamivir (oral); zanamivir (inhalation, intravenous); peramivir (intravenous)	Vaccines (inactivated, live); oseltamivir; zanamivir
Influenza A virus	Amantadine (oral); rimantadine (oral)	..
Respiratory syncytial virus	Ribavirin (inhalation, intravenous)	Palivizumab (intramuscular)
Adenovirus	Cidofovir (intravenous)	Vaccine for types 4 and 7*
Rhinovirus	Pleconaril†	Alfa interferon (intranasal)
Enteroviruses	Pleconaril†	..
Human metapneumovirus	Ribavirin (intravenous)	..
Hantavirus	Ribavirin (intravenous)	..
Varicella-zoster virus	Aciclovir (intravenous)	Vaccine

*Long successful use in US military conscripts, no production now. †Has been used for compassionate cases.

Table 3: Possibilities for antiviral treatment and prevention of severe viral pneumonia

according to the causative virus. The ineffectiveness of these agents for treatment of respiratory syncytial virus infections is well established.[146] For management of SARS, inconclusive results were reported in 26 treatment studies, and possible harm was indicated in four trials.[147] High-dose corticosteroids were administered to a third of patients with 2009 pandemic H1N1 virus infection,[148] but use of these agents is not recommended because of prolonged viral shedding in seasonal influenza and increased mortality in avian H5N1 and, possibly, 2009 pandemic H1N1 virus infections.[103] On the other hand, some data suggest that corticosteroids can augment outcome of pneumonia caused by infection with varicella-zoster virus (in combination with aciclovir) and hantavirus.[149]

Prevention

Possibilities to prevent viral community-acquired pneumonia are limited. Influenza vaccines have been used since the mid 1940s and they now have an established role in prevention of influenza A and B virus infections. Importantly, inactivated influenza vaccine is effective in young children, including those younger than 2 years.[150] During the 2009 H1N1 pandemic, a monovalent vaccine against the virus was developed.[103] Its active use could have played a part in the course of the initial pandemic wave in some countries—eg, in Finland, only 44 fatal cases were recorded. In addition to vaccines, influenza A and B virus infections can be prevented by prophylactic use of neuraminidase inhibitors.[137] Severe respiratory syncytial virus infections in high-risk neonates have been prevented successfully with palivizumab, a humanised monoclonal antibody, which is administered during a respiratory syncytial virus epidemic.[151] This agent has been shown to prevent admissions related to respiratory syncytial virus by 50% in premature infants. Since the 1960s, several types of vaccines for respiratory syncytial virus have been developed without success. Live-attenuated vaccines produced by reverse genetics are now in clinical studies.[142] Pneumonia caused by adenovirus types 4 and 7 has been prevented in military trainees by an oral vaccine, with 95% efficacy.

Unfortunately, conflict over the manufacturing process stopped production in 1996.[95] Pneumococcal conjugate vaccine was shown to prevent a third of viral pneumonia cases in a study in South Africa, most probably by prevention of superimposed bacterial co-infections.[152]

Future research

Despite many advances, further studies are still needed to better understand the role of viruses in the cause and pathogenesis of community-acquired pneumonia. Increased availability of molecular diagnostic methods enables us to evaluate our understanding of viral pneumonia and to reassess all existing dogma. Further clarification is needed of the role of bacterial-viral interaction in the pathogenesis of pneumonia and of the importance of viruses as pneumonia pathogens in the world after widespread implementation of *H influenzae* type b and pneumococcal conjugate vaccines. Also, examination of regional differences in causes of pneumonia is needed urgently, particularly to obtain additional data from developing countries. Detailed understanding of the viral cause of community-acquired pneumonia will guide antiviral drug and vaccine developments.

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