Welcome to issue 135 of Respiratory Research Review.

By now most of us will have had our yearly influenza vaccination and had discussions with patients about the recommendation of yearly flu injections. Discussions include the seasonal nature linked to low humidity and low temperatures, the symptoms, including fever, myalgias, cough and malaise, and finally, the risk of staphylococcus superinfection, which is possibly responsible for much of the disease burden at the severe end. John Treanor provides an easily readable practice review based on the case of a 75-year-old man with hypertension and mild chronic obstructive pulmonary disease, who has a ‘few questions’ about the influenza vaccination. An audio version of this article is available and gives a state-of-the-art overview covering areas of future development, like the hope for the development of a vaccine against the invariant region of the haemagglutinin protein or the concern that repeat vaccination may diminish vaccine efficacy in older adults because existing antibodies decrease antigen presentation to the immune system. It is estimated that seasonal influenza is responsible for almost 500,000 hospital admissions and up to 50,000 deaths in the USA.

A great facet of my work is that reading (and writing) is encouraged, an aspect I greatly enjoy. It was a particular pleasure to read the review of laboratory diagnosis in pneumonia in Eur Respir J. Antoni Torres and colleagues start with the observation that in 1930, pneumonia was the third most common cause of death in the USA; now almost a century later it is still the fourth most common cause of death. They reflect on the virtual standstill of antibiotic discovery, recall President Obama’s call for greater research funding, and the new US FDA regulation of Generating Antibiotic Incentives Now (GAIN). The authors always retain briefness, clarity and structure; however, they also challenge our thinking when exploring weaknesses of PCR testing; that it can’t discriminate between viable and dead organisms, or comment on resistance patterns. A possible answer may be the implementation of ‘loop-mediated isothermal amplification’ (LAMP), a low-cost alternative, single-tube technique for the amplification of DNA at a fixed temperature with primers for β-lactam, macrolides and quinolone resistance genes. Or will the future hold a method with higher sensitivity, specificity and faster turnaround time, the respiratory ‘fluorescence in situ hybridisation’ (respiFISH)?

This selection of articles features NZ authors twice; in a meta-analysis of the possible preventative role of vitamin D supplementation in respiratory tract infections, and in a report on our endemic of *Legionella longbeachae*. Some UK audits reflect on the effect of miscoding pneumonia and the reduced mortality, with a further insightful editorial by Antoni Torres, wondering if the achieved reduction in CAP (community-acquired pneumonia) in the UK is enough. We review articles on the effectiveness of the PCV13 (13-valent conjugated pneumococcal vaccine) and the changing picture of pneumococcal agents in a well vaccinated population, in patients with traditional risk factors and neutropenic cancer patients.

Thank you for your comments and questions; they are motivating me to continue reading and reflecting.

Kind regards

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Abbreviations used in this issue

ARD S = acute respiratory distress syndrome

CAP = community-acquired pneumonia

ICU = intensive care unit

OR = odds ratio

PCV = pneumococcal conjugate vaccine

PPI = proton-pump inhibitor
Vitamin D supplementation to prevent acute respiratory tract infections

Authors: Martineau AR et al.

Summary: This systematic review and meta-analysis of data from 25 randomised controlled trials of vitamin D, or vitamin D supplementation (n=10,933) showed that vitamin D supplementation reduced the risk of acute respiratory tract infections among all participants (adj. OR 0.88 [95% CI 0.81, 0.96]). Among those on daily or weekly vitamin D supplementation without additional bolus doses, vitamin D supplementation was protective (adj. OR 0.81 [95% CI 0.72, 0.91]), whereas no protective benefit was seen in those receiving ≥1 bolus dose (0.97 [0.86, 1.10]). In the daily or weekly vitamin D supplementation cohort, those with low (<25 nmol/L) 25-hydroxyvitamin D levels at baseline had the strongest protection (adj. OR 0.30 [0.17, 0.53]) compared with those with baseline levels ≥25 nmol/L (0.75 [0.60, 0.95]). Vitamin D supplementation did not affect the proportion of participants experiencing ≥1 serious adverse event (adj. OR 0.98 [0.80, 1.20]).

Comment: Finally, some good news for vitamin supplementation in decreasing the risk of respiratory tract infections. Epidemiological and retrospective data have long pointed towards a causal relationship, most clearly seen with lower vitamin D levels. In vitro data have also shown that activated 25-hydroxyvitamin D induces antimicrobial peptides and other innate antimicrobial mechanisms. The debate in editorials, medical podcasts and the lay press is rather fierce, and time will tell if this analysis will change our clinical practice. Bottom line: this individual participant data meta-analysis from more than 10,000 participants supports an overall protective effect of vitamin D supplementation in reducing respiratory tract infections.

Reference: BMJ 2017;356:i6583

Abstract

Community acquired pneumonia incidence before and after proton pump inhibitor prescription

Authors: Othman F et al.

Summary: This population-based research analysed UK records over the period 1990–2013. A cohort study was undertaken to examine the risk of CAP before and after PPI prescription, as well as a self-controlled case series that explored whether unmeasured confounding explains this association. The cohort study included 160,000 new PPI users. In an adjusted Cox regression analysis, the adjusted risk for CAP was 67% higher in PPI-exposed participants than in unexposed age- and sex-matched controls. However, in the self-controlled analysis (which included 48,000 users), the risk of pneumonia was higher 30 days prior to being prescribed PPIs. The authors suggest that the association between PPIs and pneumonia was due to protopathic bias or reverse causality, or as Kristian Filion puts it in his editorial, ‘What is the cause?’

Comment: These researchers used UK clinical practice data to perform three statistical analyses exploring the possible effect of PPIs on pneumonia. The traditional Cox regression analysis was performed matching PPI-exposed patients to non-PPI-exposed patients which showed an increased risk of 1.6. However, when they used a self-control case series or a prior event rate ratio analysis, the risk of pneumonia was higher 30 days prior to being prescribed PPIs. The authors suggest that the association between PPIs and pneumonia was due to protopathic bias or reverse causality, or as Kristian Filion puts it in his editorial, ‘What is the cause?’

Reference: BMJ 2016;356:i5813

Abstract
Adults misdiagnosed and misdiagnosed as having pneumonia

Authors: Daniel P et al., for the British Thoracic Society

Summary: The results were reported for the British Thoracic Society pneumonia audit, which sought to determine the clinical characteristics and outcomes of hospitalised adults given a primary discharge code of pneumonia but who did not meet accepted diagnostic criteria for pneumonia. Compared with patients with CAP (n=6660), those miscoded as having pneumonia (n=1251) were more advanced median age (80 vs. 78 years [p<0.001]), had more comorbidities, had significantly fewer respiratory symptoms (fever, cough, dyspnoea, pleuritic pain), had more constitutional symptoms (general deterioration, falls) and were significantly less likely to die in hospital within 30 days of admission (14.3% vs. 17.0%; adjusted OR 0.75 [p=0.003]).

Comment: Statistical analysis of health outcomes is often based on data from clinical coding. The investigators reviewed the clinical notes of all 8997 participants put forward by the 158 participating hospitals. After correcting for missing and hospital-acquired pneumonia, the authors identified 1251 patients (14%) misdiagnosed as having pneumonia. Were they clinically different? Patients miscoded as pneumonia were significantly older, had more comorbidities and had significantly fewer respiratory symptoms like fever, cough, dyspnoea or pleuritic chest pain. Bottom line: patients misdiagnosed as pneumonia were older, had fewer pneumonia symptoms and a better prognosis, and yet still received the same antibiotic treatment.


Effectiveness of 13-valent pneumococcal conjugate vaccine for prevention of invasive pneumococcal disease in children in the USA

Authors: Moore MR et al.

Summary: This postlicensure matched case-control study assessed PCV13 effectiveness in 722 children aged 2–59 months with invasive pneumococcal disease and 2991 matched controls; PCV13 serotype cases (n=217) included most commonly serotypes 19A (18%), 7F (4%) and 3 (6%). Vaccination was 86.0% effective against PCV13 serotypes, mostly due to being 85.6% and 96.5% effective for serotypes 19A and 7F, respectively. Effectiveness was 79.5% against serotype 3, 65.6% against antibiotic nonsusceptible invasive pneumococcal disease and 60.2% against all-cause invasive pneumococcal disease. Vaccine effectiveness was similar between children with and without underlying conditions (81.4% and 85.8%, respectively).

Comment: The recently developed PCV13 is now used in 138 countries. These authors present important postlicensing population data in a case-control study on the effectiveness of the PCV13 vaccination in preventing pneumococcal disease. The overall effectiveness of the vaccine was about 86%; this is particularly important as it is effective against antibiotic resistant strains, in particular strain 19A. Katherine O’Brien outlines the importance of these case-control studies to ensure that the promise of this new vaccine can be realised. Bottom line: the PCV13 vaccine is highly effective at preventing invasive pneumococcal disease for the strains covered by the vaccine.


Aetiology of childhood pneumonia in a well vaccinated South African birth cohort

Authors: Zar HJ et al.

Summary: This nested case-control study investigated the incidence and causes of childhood pneumonia using data from a birth cohort (Drakenstein Child Health Study) of 967 children followed for 1145 child-years, in whom 314 pneumonia cases occurred (incidence 0.27 episodes per child-year), including 60 severe cases (0.05 per child-year); three deaths occurred for a case fatality ratio of 1%. A median of five organisms were identified in nasopharyngeal swabs from cases and controls, and a median of six organisms were detected in induced sputum. The organisms most strongly associated with pneumonia were Bordetella pertussis (OR 11.08 [95% CI 1.33, 92.54]), respiratory syncytial virus (8.05 [4.21, 15.38]) and influenza virus (4.13 [2.06, 8.26]); bocavirus, adenovirus, parainfluenza virus, Haemophilus influenzae and cytomegalovirus were also associated. Testing of both induced sputum and nasopharyngeal swabs provided incremental yield for detecting B. pertussis and several viruses in the case patients.

Comment: Despite conjugated pneumococcal and H. influenzae type b vaccinations, the burden of pneumonia as a cause of death in children remains high, accounting for about 17% of or 1 million childhood deaths. The load is heavily skewed to low-income countries. The authors, sponsored by the Bellinda and Bill Gates Foundation, investigated causes of pneumonia in a well-vaccinated population. Based on regular fortnightly nasopharyngeal swabs and swabs, blood and induced sputum specimens when sick, they detected on average six organisms in the sputum. Bottom line: respiratory syncytial virus, influenza virus and B. pertussis were strongly associated with childhood pneumonia.


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Legionnaires’ disease caused by *Legionella longbeachae*

**Authors:** Isenman HL et al.

**Summary:** The clinical features and outcomes of 107 patients with confirmed *L. longbeachae* infection were reported. The median age of the patients was 65 years, with a range of 25–90 years, 63% were male and most became unwell during spring or summer. Headache, myalgia and diarrhoea (similar to CAP) were common presenting clinical features. The patients also commonly had elevated C-reactive protein levels, hyponatraemia and liver function test abnormalities. A history of productive cough, bilateral lung involvement and high bacterial load were independently associated with Legionella cultures in lower respiratory samples. ICU admission was required by one quarter of the patients, and was less likely for those who received agents with anti-Legionella activity prior to admission. The mortality rate was 5%.

**Comment:** In this study performed by my colleagues in Christchurch, the authors review the clinical characteristics of *L. longbeachae* pneumonia. While *L. pneumophila* is the most common organism in Legionnaires disease and acquired from water sources, *L. longbeachae* is most common in NZ and associated with compost or soil exposure. Illness with *L. longbeachae* causes headache, myalgia and abnormal liver function tests, and is severe enough to require ICU admission in 25%. Interestingly, chest radiographs showed a multilobar consolidation in 60%; however, 40% had unilobar involvement. Bottom line: pneumonia caused by *L. longbeachae* is similar to other causes of pneumonia, with the exception of the spring/summer seasonality.

**Reference:** Respirology 2016;21(7):1292–9

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**Safety of reduced antibiotic prescribing for self limiting respiratory tract infections in primary care**

**Authors:** Gulliford MC et al.

**Summary:** This UK cohort study examined the safety of reduced antibiotic prescribing for self-limiting respiratory tract infections in primary care. Data for 610 UK general practices were retrieved (45.5 million person-years of follow-up). From 2005 to 2014, the proportion of respiratory tract infection consultations with antibiotics prescribed decreased from 53.9% to 50.5% in men and from 54.5% to 51.5% in women. During the same period, new episodes of meningitis, mastoiditis and peritonsillar abscesses decreased annually by 5.3%, 4.8% and 1.0%, respectively, whereas new episodes of pneumonia increased by 0.4%. Incidences for pneumonia and peritonsillar abscess were higher for practices in the lowest quartile of antibiotic prescribing compared with the highest quartile. The adjusted relative risk increases for a 10% reduction in antibiotic prescribing were 12.8% for pneumonia and 9.9% for peritonsillar abscesses. If a general practice with an average of 7000 patients reduces the proportion of respiratory tract infection consultations with antibiotics prescribed by 10%, then it might observe 1.1 more cases of pneumonia each year and 0.9 more cases of peritonsillar abscess each decade.

**Comment:** In light of growing concerns about antibiotic resistance, these researchers used data from 610 general practices and 4.5 million patients to explore if reduced antibiotic prescribing is safe. After promoting a programme of reduced antibiotic prescribing, use decreased from 54% to 51% in men. Despite this, the incidence of meningitis, mastoiditis and intracranial abscesses also decreased and no increase in empyema or Lemierre’s syndrome was noted; however, there were small increases in pneumonia and peritonsillar abscess rates. Bottom line: if we were to prescribe 10% less antibiotics, we could expect one more pneumonia case per year and one more peritonsillar abscess case per decade.

**Reference:** BMJ 2016;354:i34140

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**Independent commentary by Professor Lutz Beckert.**

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or considering future collaborations.

**Reference:** BMJ 2016;354:i3410

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**Reference:** BMJ 2016;354;i34140

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Clinical features, aetiology and outcome of bacteraemic pneumonia in neutropenic cancer patients

Authors: Gudiol C et al.

Summary: This research explored the features, aetiology and outcomes of bacteraemic pneumonia in patients with neutropenic cancer in the era of increasing antimicrobial resistance. There were 1723 episodes of bacteraemia identified, of which 795 occurred in neutropenic patients with cancer, and among these, 55 episodes of bacteraemic pneumonia were identified. Bacteraemic pneumonia was most frequently caused by *Pseudomonas aeruginosa* (39.6%), *Streptococcus pneumoniae* (20.6%) and *Escherichia coli* (6.8%). Among Gram-negative organisms detected, 12.8% were multidrug resistant. ICU admission was required by 20% of the patients with bacteraemic pneumonia, 14.8% required invasive mechanical ventilation, and 16.3% received inadequate empirical antibiotic therapy with a resultant mortality rate of 66.6%. Resistant micro-organisms were the cause of the pneumonia in eight of nine patients who died. The respective 2- and 30-day case-fatality rates were 24% and 46.2%.

Comment: Up to 30% of patients with leukaemia and 80% of patients with a bone marrow transplant will experience pneumonia. Recent research suggests that patients with solid tumours, and in particular patients with lung cancer, are also at risk of pneumonia. This Spanish group reports on 1723 bacteraemic episodes in neutropenic patients over a decade. Pneumonia was the third leading cause of bacteraemia and was associated with an early mortality of about 25% and a 30-day case mortality of nearly 50%. Bottom line: almost half of bacteraemic pneumonia occurred in patients with solid organ tumours. The most common organisms are *P. aeruginosa* and *S. pneumoniae*.

Reference: Respirology 2016;21(8):1411–8

Abstract

Epidemiological characteristics, practice of ventilation, and clinical outcome in patients at risk of acute respiratory distress syndrome in intensive care units from 16 countries (PROVENT)

Authors: Neto AS et al., for the PROVENT and the PROVE Network investigators

Summary: This international prospective study enrolled 935 ICU-admitted adults receiving mechanical ventilation and stratified them according to ARDS (acute respiratory distress syndrome) risk according to LIPS (Lung Injury Prediction Score); 282 (30%) were at risk of ARDS (LIPS score ≥4), representing 0.14 cases per ICU bed over a 1-week period. Patients at risk of ARDS had a similar median tidal volume to the median tidal volume of ARDS patients, but ARDS patients did not risk at 7.6 vs. 7.9 mL/kg predicted bodyweight (p=0.346), as did those who did versus did not develop ARDS. Compared with patients not at risk of ARDS, at-risk patients had higher median positive end-expiratory pressure (6.0 vs. 5.0 cm H₂O [p<0.0001]), a higher in-hospital mortality rate (32% vs. 16% [p<0.0001]), a higher ICU mortality rate (29% vs. 12% [p<0.0001]) and a higher 90-day mortality rate (31% vs. 17% [p<0.0001]). Their prevalence of developing ARDS was also greater (7% vs. 3% [p=0.004]).

Comment: Patients are rarely admitted with ARDS to intensive care; however, they may develop ARDS during their stay. Ventilator strategies, although lifesaving in their own right, may contribute to lung injury, possibly by overstretching of the lung parenchyma. These authors report an international, multicentre, prospective study to document risk of developing ARDS and associated ventilation modes like low tidal volume ventilation or low positive expiratory pressure ventilation. Patients with ARDS had frequent pulmonary complications and worse clinical outcomes. Positive end-expiratory pressure was higher in patients at risk of ARDS. Bottom line: about a third of patients receiving mechanical ventilation were at risk of developing ARDS.


Abstract