ISSN 1178-6205

Respiratory Research Review™

Making Education Easy

Issue 147 – 2018

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Abbreviations used in this issue

AUC = area under the receiver operating characteristic curve
CT = computed tomography
ED = emergency department
ICU = intensive care unit
IIV4/RIV4 = quadrivalent inactivated/recombinant influenza vaccine
MI = myocardial infarction
OR = odds ratio
PCV = pneumococcal conjugate vaccine

Welcome to issue 147 of Respiratory Research Review.

Almost exactly 100 years ago, early 1918, an influenza epidemic emerged, causing 50–100 million deaths, changing the world forever. If one would ever have wanted to engineer a flu pandemic, the conditions at the end of the First World War were an 'ideal' backdrop; exhausted soldiers living in poor conditions, military camps, including a camp piggery, near the resting stop for 50 million birds migrating between Africa and the Arctic, and of course victorious troops welcomed by ecstatic homecoming parties. The virus, which had kept most of its bird flu characteristics, underwent a tiny mutation, rendering it highly contagious. The scholarly book by Laura Spinney, the Pale Rider (ISBN 9781910702376), contains powerful stories about the chaos of this era and has been reviewed by Talha Khan Burki with the title 'Spanish flu – the first horseman'.

You may have seen the Respirology review series on respiratory infections in the Asia-Pacific region. It was written by expert authors, and hopefully we only need to know where to look in case the next flu season doesn't bring back the 'Aussie flu' from the Northern Hemisphere, but instead brings a new wave of bird flu H5N1 or H7N9. We have discussed H5N1 and H7N9 before (Respiratory Research Review, issue 88); both appeared to have a case fatality rate of 50%. H5N1 has killed about 500 people in Asia, Africa and Egypt, and H7N9 caused small epidemics in China, several Asian countries and Canada; however, so far most transmissions appear to be from sick poultry/wild birds and not human-to-human (Respirology). Another great resource is on coronaviruses causing human disease, which include MERS (Middle East respiratory syndrome), SARS (severe acute respiratory syndrome) and others (Respirology).

The Northern Hemisphere is currently going through a severe bout of seasonal influenza, and Anita Simond's comments for the Royal Brompton provide very helpful insight in the light of alarming media reports: 'Influenza news from the frontlines: what is happening?'. It is a seasonal flu, 62% influenza A, not a pandemic, death rates are in the expected range and mainly in the elderly, and so far oseltamivir/zanamivir remains effective. Some of her take-home messages are: i) hand washing remains the key measure to prevent spread (but doesn't make for great newspaper headlines); ii) the quadrivalent vaccine, which NZ has purchased, is of good effectiveness; and iii) with the centennial year of the 'Spanish flu' in mind, we need to plan for a pandemic and embrace molecular biological techniques in vaccine production. A brief reminder, the 2017 paper of the year in Respirology reporting regular paracetamol (acetaminophen) has no effect on viral shedding, temperature or clinical symptoms in patients with PCR (polymerase chain reaction)-confirmed influenza; you can watch a 3-minute summary here.

Hopefully, you enjoy the selection of articles, starting with the well-documented effect on the adult population derived from infant immunisation (Thorax). The interested reader may refer to the new internationally endorsed guidelines on the management of hospital-acquired pneumonia and ventilator-associated pneumonia. Also, David Feller-Kopman and Richard Light published an authoritative review on pleural disease, and Respirology published a review also co-authored by Richard Light on 'Unexpandable lung from pleural disease'.

We appreciate feedback and comments and wish for all of us that the flu season won't hit our communities too hard.

Kind regards

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Population-level impact of infant 10-valent pneumococcal conjugate vaccination on adult pneumonia hospitalisations in Finland

Authors: Okasha O et al.

Summary: This article reports national trends in pneumococcal and all-cause pneumonia hospitalisations in adults before and after the introduction of the infant PCV10 (10-valent pneumococcal conjugate vaccine) programmes in Finland in 2010. Before PCV10, the all-cause pneumonia rate in individuals aged ≥18 years increased annually by 2.4%; this was followed by an annual decline of 4.7% during the PCV10 period. In 2014–2015, the overall all-cause pneumonia hospitalisation rate was 109.3 per 100,000, which was 15.4% lower than the expected rate. Individuals aged ≥65 years experienced a significant decline of 6.7% (131.5 per 100,000), translating to 1456 fewer pneumonia hospitalisations annually. Notably, hospitalisations for reasons other than pneumonia decreased by 3.5% annually over the entire study period.

Comment: The NZ Immunisation Handbook 2017 recommends protection with PCV13 followed by the unconjugated (23PPV) vaccination for patients with chronic (respiratory) illness at least 8 weeks later. However, this is not funded and uptake is low. Good news can be taken from this article on a Finish population, which reports a 'herd immunity' effect about 4 years after initiation of the infant vaccination programme. Because of the use of population statistics, the editorial by Carlos Grijalva is easier to read than the article itself. **Bottom line: an infant pneumococcal vaccination programme, like the one adopted in NZ, significantly reduced pneumonia hospitalisation in the elderly.**

Reference: Thorax 2018;73:262–9
Abstract

Efficacy of recombinant influenza vaccine in adults 50 years of age or older

Authors: Dunkle LM et al., for the PSC12 Study Team

Summary: Adults aged ≥50 years were randomised to receive RIV4 (quadrivalent, recombinant influenza vaccine), consisting of 45µg of recombinant haemagglutinin per strain and 180µg of protein per dose, or egg-grown IIV4 (quadrivalent, inactivated influenza vaccine), with 15µg of haemagglutinin per strain 60µg of protein per dose (standard dose), in this research; 8855 participants received a vaccine, with 8604 completing follow-up. The confirmed influenza attack rate was 2.2% among RIV4 recipients in both modified per-protocol and intent-to-treat analyses, and among IIV4 recipients, the respective attack rates for the two analysis types were 3.2% and 3.1%. There were 181 cases of influenza A/H3N2 infection, 47 of influenza B infection and six of nonsubtypeable influenza A infection. Compared with IIV4, RIV4 decreased the likelihood of infection by 30% (p=0.006); prespecified criteria for noninferiority were met. The two groups had similar safety findings.

Comment: Some of the shortcomings of the seasonal influenza vaccine are related to its production in eggs; they include so-called egg-adapted changes that reduce the effectiveness of the vaccine, the 6-month turnaround time and limited production ability. The current trivalent vaccine only has an overall effectiveness against the H3N2 strain of 33% and around 10% in the over 65-year olds. This article demonstrates in 9000 participants that a vaccine designed by molecular engineering is at least as effective as the standard vaccine produced in eggs. **Bottom line: the genetically engineered vaccine showed improved protection against influenza-like illness in adults aged 50 years and older.**

Reference: N Engl J Med 2017;376:2427–36
Abstract

Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital

Authors: Gravenstein S et al.

Summary: Long-stay residents aged ≥65 years and half the staff at US nursing homes were cluster-randomised to receive high-dose (409 facilities) or standard-dose (414 facilities) influenza vaccine for the 2013–14 season. Compared with facilities that were allocated to standard-dose vaccination, the incidence of respiratory-related hospital admissions during the influenza season (primary outcome) was significantly lower for facilities allocated to high-dose vaccination (0.185 vs. 0.211 per 1000 resident-days; adjusted relative risk 0.873 [95% CI 0.776, 0.982]).

Comment: Paradoxically, patients who are at the highest risk of dying of seasonal influenza are less well protected by the influenza vaccination. We have discussed the hope for a universal influenza vaccine before (Respiratory Research Review, issue 76) and also mentioned the increased efficacy of molecularly engineered vaccines above. A group of American researchers reports a blinded, cluster randomised trial in 50,000 patients in long-stay care residences comparing a standard-dose versus a high-dose vaccine. The higher dose was well tolerated, and participants had fewer respiratory illness-associated hospital admissions. **Bottom line: high-dose influenza vaccination has greater effectiveness against H1N1 in an elderly population.**

Reference: Lancet Respir Med 2017;5:738–46
Abstract

For more information, please go to www.medsafe.govt.nz

The use of benzodiazepine receptor agonists and the risk of hospitalization for pneumonia

Authors: Chen T-Y et al.

Summary: The relationship between use of benzodiazepine receptor agonists and hospitalisation for pneumonia was explored in this nested case-control study of the Taiwanese population; 12,002 patients hospitalised for pneumonia were compared with the same number of matched controls. Current use of benzodiazepine receptor agonists was associated with an increased likelihood of hospitalisation for pneumonia (adjusted OR 1.86 [95% CI 1.75, 1.97]), with midazolam conferring the greatest risk (5.77 [4.31, 7.73]). The risk of hospitalisation for pneumonia was higher for benzodiazepine hypnotic agent use (adjusted OR 2.42 [95% CI 2.16, 2.71]) than it was for benzodiazepine anxiolytic agent use (1.53 [1.44, 1.63]) and nonbenzodiazepine hypnotic agent use (1.60 [1.46, 1.76]), and the risk was also increased for ultrashort-acting and short- to intermediate-acting agents, higher daily doses and the number of benzodiazepine receptor agonists used.

Comment: Vaccination strategies are most promising against pneumonia. This group of researchers utilising data from the Taiwan National Health Insurance Database demonstrate a correlation between benzodiazepine receptor agonists and pneumonia, possibly as a result of increased sedation. Apparently, about 5% of adults in the US and 22% of people in Taiwan are using these preparations. The authors corrected carefully for comorbid factors and point out they can't prove causation. **Bottom line: benzodiazepine receptor agonists, in particular zopiclone, lorazepam, alprazolam, triazolam and especially midazolam, were associated with a risk of pneumonia.**

Reference: Chest 2018;153:161–71
Abstract

Prehospital antibiotics in the ambulance for sepsis

Authors: Alam N et al., on behalf of the PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands

Summary: In this study, emergency medical service personnel from ten ambulance services serving 34 hospitals in the Netherlands received training on how to recognise and treat sepsis. A total of 2698 patients were randomised to receive fluid resuscitation and supplementary oxygen (usual care) with (n=1535) or without (n=1137) open-label intravenous ceftriaxone 2000mg administered in the ambulance. There was no significant difference between the prehospital antibiotic and usual care groups for median time to receiving antibiotics after arriving at the ED (70 vs. 93 minutes [p=0.142]), or for the 28-day mortality rate ([primary outcome; 8% vs. 8%; relative risk 0.95 [95% CI 0.74, 1.24]), but the 28-day readmission rate was significantly lower in the prehospital antibiotic group (7% vs 10% [p=0.0004]).

Comment: If prompt antibiotic administration is more important than the correct antibiotic, this trial should have been positive. Despite the enormous efforts and amazing enthusiasm of the PHANTASi team in the Netherlands, this trial was negative. Jean-Louis Vincent from Belgium argues that the team may have been overenthusiastic, had a low threshold to enrol and a short median travel time of 26 minutes. He favours telemedicine assessment instead of early antibiotics before full evaluation (Lancet Respir Med Comment). Vincent Quinten and colleagues argue that the long-term outcome of these patients was better and the approach needs fine tuning (Lancet Respir Med Correspondence). **Bottom line: antibiotic treatment of septic patients in the ambulance did not improve survival.**

Reference: Lancet Respir Med 2018;6:40–50
Abstract

Three-hour bundle compliance and outcomes in patients with undiagnosed severe sepsis

Authors: Deis AS et al.

Summary: This retrospective analysis of a cohort of 5631 adults with severe sepsis admitted to an ED measured and compared the Surviving Sepsis Campaign 3-hour treatment recommendations along with patient-centred outcomes for those who received an ICD-9 code of 995.92 ('severe sepsis'; 32.8% of the cohort) versus those who did not. Only 8.72% of patients underwent completion of all four bundle components within 3 hours of ED admission; 31.3% completed the therapeutic components (a broad-spectrum antibiotic and intravenous fluids). Patients who received a severe sepsis diagnosis code had higher rates of completing all four bundle components (10.2% vs. 7.9% [p<0.005]) and the therapeutic components (36.0% vs. 29.0% [p<0.001]), but also had a higher mortality rate (6.3% vs. 2.3% [p<0.001]), a higher ICU admission rate (44.7% vs. 22.5% [p<0.001]) and longer hospital stays (9.2 vs. 6.9 days [p<0.001]), compared with patients with no diagnosis code.

Comment: This idea is similar to the concept of giving antibiotics early, even in ambulances. Based on retrospective audit data the authors postulated that making an early diagnosis of sepsis, i.e. coding an illness as sepsis, will reduce hospital stay and complications, and improve survival. Based on 10 years of hospital admission data, the researchers discovered that only a small number of patients were coded with sepsis within 3 hours of admission. Patients with a sepsis code were at least three times more likely to receive broad-spectrum antibiotics and intravenous fluids. **Bottom line: patients who were diagnosed earlier had higher treatment rates, but not improved outcomes.**

Reference: Chest 2018;153:39–45
Abstract

Efficacy of clarithromycin-naproxen-oseltamivir combination in the treatment of patients hospitalized for influenza A(H3N2) infection

Authors: Hung IFN et al.

Summary: Adult patients hospitalised for influenza A (H3N2) infection were randomised to receive combination clarithromycin 50mg, naproxen 200mg and oseltamivir 75mg twice daily for 2 days followed by 3 days of oseltamivir (n=107) or oseltamivir 75mg twice daily for 5 days (n=110) in this open-label phase 2b/3 trial. There were ten deaths over 30 days, with a significantly lower rate in the combination group (primary endpoint; adjusted OR 0.06 [95% CI 0.004, 0.94]). Combination therapy was also associated with fewer high-dependency unit admissions (p=0.009), shorter hospital stays (p<0.0001), lower Pneumonia Severity Index scores during days 1–3 (p<0.01) and fewer serial nasopharyngeal aspirate specimens with ≥5% neuraminidase-inhibitor-resistant A(H3N2) virus quasispecies during days 1–2 (p<0.01).

Comment: This study was performed in Hong Kong during a seasonal influenza epidemic with the H3N2 (Switzerland) influenza virus, which had antigenically drifted. Within 3 months, the authors had identified more than 300 H3N2 swab-positive subjects with an average age of 80 years. All had chest x-ray infiltrates, and all received amoxicillin/clavulanic acid and esomeprazole. The active treatment group also received the following combination of three medications, which have at least some theoretical antiviral activity: clarithromycin, naproxen and oseltamivir. The control group only received oseltamivir. **Bottom line: the clarithromycin-naproxen-oseltamivir treatment group had reduced mortality, hospital stays, ICU admissions, lower severity scores and lower viral titres.**

Reference: Chest 2017;151:1069–80
Abstract

Estimates of global seasonal influenza-associated respiratory mortality

Authors: Iuliano AD et al., for the Global Seasonal Influenza-associated Mortality Collaborator Network

Summary: Using time series log-linear regression modelling of vital death records and influenza surveillance data, these researchers estimated country-specific influenza-associated respiratory excess mortality rates for 33 countries, divided into three age groups (<65, 65–74 and ≥75 years). Countries contributing excess mortality rate data represented 57% of the global population. Estimated mean annual influenza-associated respiratory excess mortality rate ranges were 0.1–6.4 per 100,000 for the <65-year age group, 2.9–44.0 per 100,000 for the 65- to 74-year age group and 17.9–223.5 per 100,000 for the >75-year age group; the overall estimated seasonal influenza-associated respiratory death rate was 4.0–8.8 per 100,000 per year. Sub-Saharan Africa, Southeast Asia and individuals aged >75 years had the highest estimated mortality rate ranges (2.8–16.5, 3.5–9.2 and 51.3–99.4 per 100,000, respectively). Across 92 countries, it was estimated that 9243–105,690 annual influenza-associated respiratory deaths occur each year among children aged <5 years.

Comment: The WHO estimates that the annual global burden of influenza deaths is 250,000–500,000. This group of researchers from the Global Seasonal Influenza-associated Mortality Collaborator Network recalculated the estimates paying particular attention, as difficult as it is, to the countries with the highest influenza burden, i.e. Western Pacific, Southeast Asia and sub-Saharan Africa. These regions don't normally have population-wide vaccination programmes and the death rate can be up to 110–225 per 100,000 in individuals above the age of 75 years; also, it was estimated that each year about 100,000 children aged less than 5 years die of influenza. **Bottom line: probably closer to 600,000 people die each year of influenza, with the greatest burden in lower income countries.**

Reference: Lancet 2018;391:1285–300
Abstract

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Respiratory Research Review

Laboratory-confirmed respiratory infections as triggers for acute myocardial infarction and stroke

Authors: Warren-Gash C et al.

Summary: These authors identified adults with a laboratory-confirmed respiratory infection and either a first MI (myocardial infarction) or stroke using 10 years of Scottish surveillance and morbidity data. A self-controlled case series analysis was used to generated age- and season-adjusted incidence rates for MI (n=1227) and stroke (n=762) following infections versus baseline. MI rates 1–3 days after *Streptococcus pneumoniae* and influenza virus infection were increased (respective adjusted incidence rates 5.98 [95% CI 2.47, 14.4] and 9.80 [2.37, 40.5]), as were stroke rates 1–3 days postinfection (12.3 [5.48, 27.7] and 7.82 [1.07, 56.9]); the stroke rates remained elevated out to 28 days. Other respiratory viruses were associated with raised point estimates for both MI and stroke, but only the day 4–7 estimate for stroke rate was statistically significant.

Comment: The previous article, from the Lancet, reported an increased burden of influenza-associated mortality compared with previous estimates; however, it only counted death. In this article, the researchers used the Scottish Morbidity Record, which has been available since 1968, and applied the statistical method of a self-controlled case series using conditional Poisson regression comparing laboratory-confirmed respiratory infections with the incidence of MI and stroke. **Bottom line: within the first 3 days of an influenza infection, the risk of an MI was about 10-fold and of a stroke 8-fold, and within 3 days of an *S. pneumoniae* infection, the risk of an MI was 6-fold and of a stroke 12-fold.**

Reference: Eur Respir J 2018;51:1701794
Abstract

Computed tomography scoring system for discriminating between parapneumonic effusions eventually drained and those cured only with antibiotics

Authors: Porcel JM et al.

Summary: An 8-year retrospective review was conducted of patients with parapneumonic effusions who underwent thoracentesis and a chest CT scan prior to attempted tube thoracostomy placement if applicable. The data were used to compare eleven chest CT characteristics between 90 patients with complicated parapneumonic effusions (eventually requiring chest drainage) and 60 with noncomplicated effusions. A logistic regression analysis identified the following independent predictors of complicated parapneumonic effusion, which were incorporated into a CT scoring system: pleural contrast enhancement, which contributed 3 points to the scoring system, and pleural microbubbles, increased extrapleural fat attenuation and fluid volume ≥400 mL, each contributing 1 point. In this derivation population, a total score of ≥4 yielded sensitivity and specificity values of 84% and 75%, respectively, diagnostic accuracy of 81%, positive and negative likelihood ratios of 3.4 and 0.22, respectively, and an AUC value of 0.829 for identifying complicated parapneumonic effusions. These findings were reproduced in an independent validation sample of 59 patients with parapneumonic effusions. The CT scoring system also showed fair ability for identifying patients who required surgery or would die from their pleural infection (AUC 0.76).

Comment: Depending on how hard one looks, between 20% and 50% of patients with bacterial pneumonia have an accompanying pleural effusion. Deirdre Fitzgerald and Gary Lee point out in their accompanying editorial that many of us still work on the principle 'the sun should never set on a parapneumonic effusion', yet some effusions will resolve with antibiotic therapy alone. These Spanish authors looked at their data retrospectively and derived an algorithm to predict which effusions are more likely to be complicated and need urgent drainage. **Bottom line: pleural contrast enhancement, pleural microbubbles, increased attenuation of pleural fat and a pleural fluid volume of more than 400mL predicted a complicated effusion.**

Reference: Respirology 2017;22:1199–204
Abstract

Independent commentary by Professor Lutz Beckert.

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