Welcome to this May issue of Respiratory Research Review where we will focus on infectious lung disease; we are dividing our attention between influenza and pneumonia. Medical news has been highlighting two possible bird flu viruses: H5N1 and a novel H7N9. We start with reviewing data on the novel H7N9 virus, drawing from the Centre of Disease Control and Prevention, where the interested reader finds well-presented, up-to-date, easily digestible information (http://www.cdc.gov/flu/avianflu/). The real question in our minds is addressed in an insightful editorial by David Morens from the NIH, Allergy and Infectious Diseases (Clin Infect Dis 2013;56[9]:1213–5): 'Pandemic H5N1: receding risk or coming catastrophe?’. He is exploring the option that one of the avian flu viruses could be a new ‘founder virus’ and we are observing a pandemic of unbelievable dimensions in the making with a possible mortality of 59%. The current virus possibly won’t have this pandemic potential; however, it may mutate. In that case, it is helpful to reflect on what we have learned from the H1N1 virus epidemic: vaccinating mothers to reduce foetal death, several vaccination strategies work and school closure may help to reduce an epidemic spread.

In the second half of this issue of Respiratory Research Review, we are focussing on the effect of medication in pneumonia, which still has an in-hospital mortality of 24%. This risk may be increased in patients taking benzodiazepines or PPIs. We close with articles reviewing data on possible increased excess mortality in patients treated with macrolide antibiotics. The true answer may well be in the trial design or the question you ask.

Thank you for your comments and feedback. We are looking forward to further email discussion.

Kind regards
Associate Professor Lutz Beckert
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In this issue:

- Human infection with a novel H7N9 influenza virus
- Cost effectiveness of vaccination against pandemic influenza
- Foetal death after H1N1 infection/vaccination
- Narcolepsy and AS03 adjuvanted H1N1 vaccine
- Effect of school closures for H1N1 on acute respiratory illnesses
- Benzodiazepines increase CAP and its mortality
- PPIs and risk of mortality and rehospitalisation in the elderly
- Single vs. combination antibiotics in hospitalised CAP
- CV events after clarithromycin use
- Azithromycin and CV-related mortality

Abbreviations used in this issue

CAP = community-acquired pneumonia
COPD = chronic obstructive pulmonary disease
CV = cardiovascular
HR = hazard ratio
OR = odds ratio
PPI = proton-pump inhibitor

Human infection with a novel avian-origin influenza A (H7N9) virus

Authors: Gao R et al

Summary: These researchers analysed clinical, epidemiological and virological data from three urban residents of the Shanghai or Anhui regions in China in whom a novel influenza A (H7N9) virus was identified in respiratory specimens. All the viral genes were found to be of avian origin, with six internal genes originating from avian influenza A (H9N2) viruses. The A/Anhui/1/2013 and A/Shanghai/2/2013 viruses (but not the A/Shanghai/1/2013 virus) had substitution Q226L (H3 numbering) at the 210-loop in the haemagglutinin gene, and all three viruses had a T160A mutation at the 150-loop in the HA gene and deletion of five amino acids in the neuraminidase stalk region. All three patients presented with fever, cough and dyspnoea, and two had a recent history of exposure to poultry. Diffuse opacities and consolidation were seen on chest x-ray. Complications included acute respiratory distress syndrome and multiorgan failure, and all cases had a fatal outcome.

Comment: Mankind has probably always been affected directly or indirectly by viruses from bird sources; however, we have never ‘seen’ a pandemic virus emerging. The pandemics in 1957, 1968 and 2009 were essentially updates of the 1918 pandemic virus. It is therefore of interest that this Chinese group described a novel H5N7 avian virus causing higher fevers, respiratory symptoms, acute respiratory distress syndrome and death. Many editorials reflect on the possible clinical meaning of the emerging virus; the accompanying perspective article does just this (N Engl J Med 2013;368[20]:1862–4) – bottom line: at this stage, these avian viruses haven’t demonstrated human-to-human transmission.


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Cost effectiveness of vaccination against pandemic influenza in European countries

**Authors:** Lugnér AK et al

**Summary:** An economic and epidemic model was used to compare the cost effectiveness of different strategies in various pandemic scenarios for Germany, the Netherlands and the UK to determine if a single optimal vaccination strategy exists. The age-structured susceptible-exposed-infected-recovered transmission model that described spread of influenza A virus compared no vaccination, blanket vaccination, vaccination of individuals aged ≥65 years and vaccination of those aged 5–19 years (high transmitters). All vaccination strategies were cost effective. In scenarios where the vaccine became available at the pandemic peak and pre-existing immunity existed among the elderly, the incremental cost effectiveness ratios for vaccinating high transmitters were €7325, €10,216 and €7280 per quality-adjusted life-year gained for Germany, the Netherlands and the UK, respectively. Differences in cost effectiveness were seen among the pandemic scenarios as well as among the countries, and these differences were due mainly to the countries’ demographic characteristics.

**Comment:** Researchers from several European countries used data from the recent swine flu to explore the most cost-effective vaccination strategy. Would you: a) offer no vaccination; b) aim to vaccinate the whole population; c) vaccinate the elderly because of high mortality in this group; or d) vaccinate young people aged 5–19 years because they are the highest transmitters. The group concluded all three vaccination strategies were cost effective; vaccinating the whole population was the least cost-effective strategy. **Bottom line:** in countries with a high population (>20%) above 65 years of age, vaccinate the elderly – otherwise focus on highly transmitting young people aged 5–19 years.

Reference: BMJ 2012;345:e4445
http://www.bmj.com/content/345/bmj.e4445

Risk of fetal death after pandemic influenza virus infection or vaccination

**Authors:** Håberg SE et al

**Summary:** The safety of the influenza vaccine in pregnant women and their foetuses was studied in 117,347 eligible pregnancies in Norway; foetal mortality was 4.9 deaths per 1000 births during the study period (2009–10). During the 2009 influenza A (H1N1) pandemic, 54% of pregnant women received influenza vaccine during their second or third trimester, resulting in a significant reduction in the risk of an influenza diagnosis (adjusted HR 0.30 [95% CI 0.25, 0.34]). Moreover, the risk of foetal death was significantly increased in women diagnosed with influenza, but not in those who received influenza vaccine (respective adjusted HRs 1.91 [95% CI 1.07, 3.41] and 0.88 [0.66, 1.17]).

**Comment:** These Norwegian population data are important for forming an evidenced-based opinion beyond case reports. During influenza epidemics, pregnant women are particularly susceptible. However, case reports of miscarriage and foetal death have been reported after vaccination. Despite a general recommendation for vaccination, only about half of all pregnant women were vaccinated against influenza and so created a ‘natural experiment’ to evaluate the effectiveness and the effect of the influenza. Norway reported 117,347 births in 2009–10, including 570 foetal deaths (4.3 per 1000 births). **Bottom line:** vaccination of pregnant women during an influenza pandemic does not harm, and possibly benefits, the foetus.


Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine

**Authors:** Miller E et al

**Summary:** This retrospective analysis of clinical and sleep test data for 75 patients aged 4–18 years with narcolepsy found that 11 had received influenza vaccine before narcolepsy onset. Compared with age-matched controls, children with narcolepsy were significantly more likely to have been vaccinated at any time and within 6 months before narcolepsy (respective ORs 14.4 [95% CI 4.3, 48.5] and 16.2 [3.1, 84.5]). A self-controlled case series analysis showed that the relative incidence of narcolepsy in patients vaccinated within 6 months of onset versus those vaccinated outside that period was 9.9 (95% CI 2.1, 47.9). The estimated attributable risk was 1 in 52,000–57,500 vaccine doses.

**Comment:** The addition of an adjuvant to a pandemic vaccine boosts the potency of the body’s immune response and may even provide cover after a viral antigen drift with time. GlaxoSmithKline patented the immunological adjuvant AS03 containing vitamin E, squalene and polysorbate 80. The 2009 NZ influenza vaccines were Fluarix (GlaxoSmithKline) and Fluvax (CSL), which use phosphate-buffered saline as adjuvant. This paper explores the biological plausibility of an autoimmune link between influenza, the adjuvant and the development of narcolepsy. **Bottom line:** the influenza vaccine with the adjuvant AS03 seems to increase the risk of narcolepsy; this vaccine was not used in NZ during the pandemic vaccination campaign.

Reference: BMJ 2013;346:f794
http://www.bmj.com/content/346/bmj.f794

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Respiratory Research Review

Independent commentary by Associate Professor Lutz Beckert, Respiratory Physician at Christchurch Hospital.

For full bio CLICK HERE

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Effectiveness of a school district closure for pandemic influenza A (H1N1) on acute respiratory illnesses in the community

Authors: Copeland DL et al

Summary: Household data were gathered after pandemic influenza A (H1N1) was detected in Dallas/Fort Worth, Texas, US in this natural experiment; one school district closed all schools for 8 days, while schools mostly remained open in other school districts. The increase in self-reported acute respiratory illnesses from before to during the school closure period was lower in the district that closed its schools than in the other districts (0.6% to 1.2% vs. 0.4% to 1.5%), adjusted OR 0.49 (p<0.03), and the increase was even lower for households with school-aged children only (adjusted OR 0.28 [p<0.001]). Similarly, the increase in influenza-related emergency department visits from before to during the school closure period was lower in the district that closed its schools than in the other districts (2.8% to 4.4% vs. 2.9% to 6.2%), with the rate remaining near constant among children aged 6–18 years from schools that closed (5.1% to 5.2%), compared with doubling in districts with schools that remained open (5.2% to 10.3%).

Comment: When the H1N1 flu epidemic emerged in 2009, uncertainty existed about the best disease mitigating strategy. School-aged children were known to be disproportionately affected. Two neighbouring districts in Texas used different strategies: the Tarrant County closed all schools and kindergartens for 1 week between the 30 April and 7 May 2009; Dallas/Fort Worth did not close any educational facilities. The research explored the incidence of ‘acute respiratory illness’ in both districts before, during and after the closure. Bottom line: school closure during a pandemic leads to a reduction of respiratory illness and flu-related ED visits.

http://cid.oxfordjournals.org/content/56/4/509.full

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The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia

Authors: Obiora E et al

Summary: This UK research explored the relationships between benzodiazepine use and incidences of infections and sepsis-related mortality in 4964 cases of CAP and 29,697 controls. Cox regression revealed that benzodiazepine exposure was significantly linked to increased risks of pneumonia (HR 1.54 [95% CI 1.42, 1.67]) and death both within 30 days (HR 1.22 [95% CI 1.06, 1.39]) and long term (1.32 [1.19, 1.47]) in patients with a prior diagnosis of pneumonia. Analyses of individual benzodiazepines showed that exposure to diazepam, lorazepam and temazepam, but not chlordiazepoxide, were associated with an increased incidence of CAP, and all four agents were associated with long-term mortality in patients with a prior diagnosis of pneumonia.

Comment: In last month’s issue, we reviewed studies on the increase of fractures in elderly patients taking benzodiazepine and nonbenzodiazepine sedatives (Respiratory Research Review 87). Benzodiazepines attract negative attention again because of a possible effect on the risk of, and mortality from, pneumonia. These British researchers used the data from the Health Improvement Network and found almost 5000 cases of pneumonia. While an immunosuppressive mechanism is suspected, this observational study cannot prove causality. Bottom line: benzodiazepines and nonbenzodiazepine hypnotics (e.g. zopiclone) both increase the risk of, and mortality from, pneumonia by about 50%.

Reference: Thorax 2013;68(2):163–70
http://thorax.bmj.com/content/68/2/163.abstract

Proton pump inhibitors and risk of 1-year mortality and rehospitalization in older patients discharged from acute care hospitals

Authors: Maggio M et al

Summary: The associations between PPI use and mortality and rehospitalisation were explored in 491 patients aged ≥65 years discharged from acute care medical wards. A Cox regression analysis showed that compared with PPI nonuse, use of these agents was significantly, independently associated with mortality (HR 1.51 [95% CI 1.03, 2.77]), especially for high-dose PPI use (2.59 [1.22, 7.16]), but not the combined endpoint of mortality or rehospitalisation (1.49 [0.98, 2.17]).

Comment: PPIs decrease acid production and may thereby interfere with the nonspecific defence system. An increased risk of CAP and Clostridium difficile has been reported in the past. These Italian authors reported a general increased risk of mortality while taking a PPI. They are cautious about the mechanism and call for more randomised controlled trials; this may be particularly pertinent, because it has been estimated that between 30–80% of patients may take PPIs inappropriately. Bottom line: the use of PPIs is associated with about 50% increased mortality in the elderly. While awaiting further studies, be cautious with prescribing.


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Cardiovascular events after clarithromycin use in lower respiratory tract infections

Authors: Schembri S et al

Summary: These researchers studied the relationship between clarithromycin exposure and CV events using data from 1343 and 1631 patients hospitalised with acute COPD and CAP, respectively, from two prospective cohort studies; there were 268 and 171 CV events over a 1-year period in the respective cohorts. Multivariate analyses showed that clarithromycin exposure significantly increased the CV event risk in the acute COPD exacerbation and CAP cohorts (respective HRs 1.50 [95% CI 1.13, 1.97] and 1.68 [1.18, 2.38]), and the acute coronary syndrome risk in the acute COPD exacerbation cohort but not the CAP cohort (1.67 [1.04, 2.68] and 1.65 [0.97, 2.80]). Clarithromycin use was also found to be significantly associated with CV mortality in the acute COPD exacerbation cohort but not the CAP cohort (1.83 [1.01, 3.31] and 1.89 [1.16, 3.08]). Clarithromycin use increased the CV event risk in the acute COPD exacerbation and CAP cohorts (respective HRs 1.52 [95% CI 1.02, 2.26]), but not all-cause mortality (1.16 [0.90, 1.51]): no such associations were seen in the CAP cohort. CV events increased as duration of clarithromycin use increased. No association was evident between β-lactam antibiotic or doxycycline use and CV events in the acute COPD exacerbation cohort, suggesting that the effect is specific to clarithromycin.

Comment: In previous issues (e.g. Respiratory Research Review 83), we reflected on the excess cardiac mortality in patients with COPD. These British authors’ data are potentially unsettling, as they describe an excess cardiac mortality in patients treated with macrolides detectable up to 2 years after prescribing the antibiotic. A similar effect on CV mortality has also been described for azithromycin (N Engl J Med 2013;366:1366–73). These retrospective studies don’t allow causality links to be drawn, although the authors commented on possible QT prolongation and the effect on ‘vulnerable plaques’. Bottom line: macrolide antibiotics may be associated with an increased risk of CV events.

Reference: BMJ 2013;346:f1235
http://www.bmj.com/content/346/bmj.f1235

Use of azithromycin and death from cardiovascular causes

Authors: Svanström H et al

Summary: This nationwide historical cohort study of Danish adults aged 18–64 years included 1102,050 episodes of azithromycin use, which were compared with 1:1 matched controls without any antibiotic use and 736,292 episodes of penicillin V use for an effect on CV-related mortality. Current azithromycin use (a 5-day treatment episode) significantly increased the risk of CV-related mortality compared with no antibiotic use (rate ratio 2.85 [95% CI 1.13, 7.24]), but not compared with penicillin V use after propensity score adjustment (0.93 [0.56, 1.55]). The adjusted absolute risk difference for current azithromycin use versus penicillin V use was –1 CV death per 1 million treatment episodes.

Comment: Some reassurance may be taken from this retrospective study. These Danish authors confirmed an increase in CV mortality with azithromycin use compared with no antibiotic use. When they compared the use of azithromycin with the use of penicillin V, azithromycin was not associated with increased cardiac mortality in a general population. It is possible the infection itself and not the antibiotic causes excess cardiac mortality. Prospective studies will still be needed, and azithromycin may still be associated with increased CV mortality in a high-risk population. Bottom line: follow international guidelines when choosing empirical antibiotic therapy.


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