

Weighing up risk factors for pneumonia: the role of mental illness and benzodiazepine use

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Pneumonia causes a significant public health burden in the UK in terms of morbidity and mortality. Historically, the annual incidence of community acquired pneumonia has been reported to be between 5 and 11 per 1000 adult population,^{1–3} estimated more recently to be between 207 and 233 per 100 000 in England.⁴ In 2010, influenza and pneumonia were responsible for 4.5% of all male deaths, and 5.8% of all female deaths ranking them 5th and 4th in terms of causes of mortality in men and women respectively in England and Wales.⁵ With such a huge mortality burden, it is important to identify modifiable risk factors to help decrease the incidence of the disease. The commonest cause of community acquired pneumonia, accounting for over a third of cases, is *Streptococcus pneumoniae*.^{6–7} *S pneumoniae* is also an important cause of septicaemia, meningitis, infective exacerbations of chronic obstructive pulmonary disease and bronchiectasis. Vaccination against *S pneumoniae* is recommended in many countries for high risk groups. In the UK, these groups include all children, all those over 65 years, as well as subjects with chronic medical conditions that are associated with a higher risk of pneumococcal disease including COPD, renal impairment and cardiovascular disease.⁸

Several factors that are associated with an increased risk of pneumonia and pneumococcal disease, including being underweight, excessive alcohol intake and smoking,^{8–10} are also commoner in patients with mental illnesses such as psychosis and depression. So, is mental illness also a modifiable and important risk factor for pneumonia and pneumococcal disease? In this issue of the journal, two papers are published suggesting it is. Seminog and Goldacre¹¹ investigated the risk of pneumococcal disease in people

with severe mental illness. Using two electronic databases, the English national dataset of linked Hospital Episode Statistics and mortality statistics and the Oxford Record Linkage Study, they identified individuals with schizophrenia, bipolar disorder, depression and phobic anxiety disorders and calculated rates of pneumococcal disease and, using indirect standardisation, obtained standardised mortality ratios (age and sex adjusted). The sample size was large; however, misclassification of outcome was an issue, as lobar pneumonia was included as a pneumococcal disease outcome but in reality could have been caused by a range of pathogens, only the dominant one of which will be *S pneumoniae*. However, this would be true for the controls, thus effectively leaving the OR unaltered. The authors found an approximately twofold increase in the risk of pneumococcal disease in each of the psychiatric subgroups. There was a stronger relationship seen when the analysis was restricted to those under the age of 60, perhaps because the general risk of pneumococcal disease is reduced in this younger age group. The authors were able to assess whether routine introduction of the pneumococcal vaccine to high-risk adults in England in 1999 affected the relative risk of pneumonia and pneumococcal disease. Surprisingly, post-1999 the relative risk was stronger rather than reduced, and this change is difficult to explain. However, unmeasured confounders and temporal bias associated with changes in practice in treatment of mental illness makes the reliable comparison of pre- and post-1999 data difficult, especially as individual data on pneumococcal vaccination were not available.

Interestingly, the relative risk was strikingly similar between the four very different psychiatric diagnoses indicating the increased susceptibility to pneumococcal disease was due to general effects of mental illness rather than linked to a specific diagnosis. What these effects are remains unclear; unfortunately, data on important confounders such as deprivation and smoking were not available in this study, but it seems unlikely that patients with anxiety and with

schizophrenia will have the same range of social indicators and rates of smoking or alcohol abuse. Alternative reasons for the increased susceptibility to pneumococcal disease could be the effects of mental illness on cognitive function and healthcare behaviour resulting in relative neglect of minor infections that then become more serious. There are also data suggesting a link between mental state and immune function such as cytokine levels, and potentially mental illness could result in a relative decrease in effective immunological function.¹² Data showing an increased association of mental illness with other infective conditions would support either of these hypotheses.

One other important possibility why a wide range of mental illness increases the risk of pneumococcal disease could be that the treatments used may alter susceptibility to *S pneumoniae* (and perhaps other pathogens). For example, benzodiazepines have been shown in animal studies to increase the risk of infection perhaps by activation of white cell Gamma-Amino Butyric Acid (GABA_A) receptors.^{13–14} Obiora and colleagues¹⁵ using records from a large, longitudinal UK database The Health Improvement Network, (THIN) undertook both a matched nested case-control analysis and a survival analysis to assess the relationship between diazepam use and pneumonia. Their data support the results of Seminog and Goldacre,¹¹ as pneumonia cases were more likely to have a psychiatric diagnosis: depression (unadjusted OR 1.71) or psychosis (unadjusted OR 1.54). Their results also supported the possibility that drug therapy for mental illness could increase susceptibility to pneumonia and pneumococcal infection; benzodiazepine exposure was associated with an increased the risk of pneumonia even ORs of 1.89, 1.95 and 1.39 for current, recent and past benzodiazepine use after adjusting for several potential confounding factors such as smoking.¹⁵ Zopiclone, another GABA_A receptor agonist, but not chlorthalidoxepoxide, was also associated with an increased risk of pneumonia, perhaps suggesting that the relationship between benzodiazepines and pneumonia was related to effects on the GABA_A receptor rather than just due to sedation.

While an association was clear with an overall adjusted OR for pneumonia risk for any benzodiazepine used at any time of 1.54 95% CI (1.42 to 1.67), disentangling the effect of benzodiazepines themselves versus underlying reasons for their use as a cause for increased risk is not so clear. While the authors adjusted for multiple medical and psychiatric comorbidities in the analysis, as with all observational

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studies, there may still be residual confounding (eg, they did not include neurological disease as a potential confounder), and selection bias remains a risk in cohort studies. One of the advantages of the study of Obiora and colleagues¹⁵ was that reporting bias and temporal bias associated with benzodiazepine prescription was unlikely to be an issue; however, it is important to remember that prescription data do not always correlate to drug use, particularly with drugs prescribed pro re nata. As with all electronic database studies, there may be some misclassification, particularly as there were no chest x-rays to confirm or refute a pneumonia diagnosis; however, the authors provided a comprehensive code list used to identify pneumonia for their analyses that has been used in previous studies of respiratory infection. As there were both community and hospital treated pneumonia cases in the study, pneumonia severity cannot be taken into account, but as pneumonia risk and mortality are dependent factors this is unlikely to be important. The overall message of the study was clear, and the near 50% increase in risk of pneumonia with a similar associated mortality risk cannot be ignored. These data pave the way for future prospective cohort studies to investigate the safety of benzodiazepine prescription with pneumonia incidence and mortality. Another interesting and perhaps counterintuitive finding was that when stratified by comorbidity index score, the association between benzodiazepines and all cause mortality weakened with increasing comorbidities. The authors hypothesised that this could be due to reduction in GABA_A receptors, resulting from comorbid inflammation, but this is highly speculative.

What should be done about these data demonstrating an increased risk of pneumonia and pneumococcal disease in subjects with mental illness and/or using benzodiazepines? Although confirmatory studies are needed, the question is raised as to whether routinely vaccinating those with severe mental illness against pneumococcal disease may be a cost effective and life saving strategy in the future. The relative risk of mental illness was similar to that of diabetes, which is an indication for the *S pneumoniae* vaccine, and the risk of

pneumonia or pneumococcal disease was about 1.5% in the under 60s over a 6-year follow-up period. This would suggest patients with mental disease should be routinely vaccinated with the adult *S pneumoniae* vaccine, Pneumovax. However, the majority of the increased risk was due to pneumonia rather than *S pneumoniae* septicaemia or meningitis, and Pneumovax has no real efficacy at preventing *S pneumoniae* pneumonia.¹⁶ Health workers involved in the care of patients with mental illness and the patients themselves need to be educated so that they are aware of the increased risk of pneumonia and pneumococcal disease. However, whether vaccination is necessary will require confirmatory studies for the relative risk, clinical trials of the efficacy of Pneumovax in psychiatric patients, or the introduction of an adult vaccine that clearly reduces the incidence of pneumonia. Both studies identify potentially modifiable risk factors for pneumonia and again highlight the importance of reducing both the incidence of and mortality associated with pneumonia. These data raise questions about how current public health strategy can be improved, and pave the way for future studies.

Contributors Both authors contributed to drafting the editorial and have agreed on the final version of the editorial submitted.

Funding UCLH/UCL receive a proportion of funding from the Department of Health's NIHR Biomedical Research Centre's funding scheme. Work in Professor Brown's laboratory is supported by the Medical Research Council, Rosetrees Trust and the Wellcome Trust. Dr Quint is funded by the Medical Research Council.

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Quint JK, Brown JS. *Thorax* 2013;**68**: 121–122.

Received 26 July 2012

Revised 15 November 2012

Accepted 22 November 2012

Published Online First 18 December 2012



► <http://dx.doi.org/10.1136/thoraxjnl-2012-202374>

► <http://dx.doi.org/10.1136/thoraxjnl-2012-202480>

Thorax 2013;**68**:121–122.

doi:10.1136/thoraxjnl-2012-202818

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