Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease

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ABSTRACT

Pneumococcal disease (including community-acquired pneumonia and invasive pneumococcal disease) poses a burden to the community all year round, especially in those with chronic underlying conditions. Individuals with COPD, asthma or who smoke, and those with chronic heart disease or diabetes mellitus have been shown to be at increased risk of pneumococcal disease compared with those without these risk factors. These conditions, and smoking, can also adversely affect patient outcomes, including short-term and long-term mortality rates, following pneumonia. Community-acquired pneumonia, and in particular pneumococcal pneumonia, is associated with a significant economic burden, especially in those who are hospitalised, and also has an impact on a patient's quality of life. Therefore, physicians should target individuals with COPD, asthma, heart disease or diabetes mellitus, and those who smoke, for pneumococcal vaccination at the earliest opportunity at any time of the year.

INTRODUCTION

Pneumococcal disease in adults, including community-acquired pneumonia (CAP) and invasive pneumococcal disease (IPD), is a global problem,[1–4] especially in individuals with chronic diseases such as COPD, diabetes mellitus and chronic heart disease (CHD). Due to the chronic nature of these conditions, affected individuals are at risk of CAP and IPD all year round, not only during the winter, unlike seasonal influenza.[5]

This review addresses two key questions concerning the burden of pneumococcal disease to help physicians target vaccination to appropriate individuals: who is at increased risk of CAP and IPD; and what are the effects of risk factors on the severity and prognosis of pneumococcal disease? It also highlights the economic burden of pneumococcal disease, the impact of pneumococcal disease on underlying comorbidities, and the importance of timely vaccination. We have focused primarily on COPD, asthma, smoking, diabetes and/or CHD as these are common risk factors for pneumococcal disease in primary practice. There are, however, many other risk factors.[6–8] As *Streptococcus pneumoniae* is the most frequent cause of CAP irrespective of age and comorbidity,[1 9] information has been provided on all-cause pneumonia (ie, CAP) and pneumococcal pneumonia.

SEARCH METHODOLOGY

A broad search strategy was used to find English language publications in human adults indexed on PubMed (2004–November 2014). Relevant publications were manually selected from the following searches: pneumonia AND risk factor, CHD AND pneumonia, diabetes AND pneumonia, lung disease AND pneumonia, asthma AND pneumonia, COPD AND pneumonia, tobacco OR smoking AND pneumonia, and economic data AND pneumonia. Data comparing the risk of pneumococcal disease in adults with the above risk factors versus those without risk factors were tabulated (excluding publications prior to 2008 or with data prior to 2000), and these data used to discuss the risk of pneumococcal disease in individuals with these risk factors.

POPULATIONS AT RISK OF PNEUMOCOCCAL DISEASE

Individuals with COPD, asthma or who smoke, and those with CHD or diabetes mellitus, are at increased risk of pneumococcal disease (CAP and IPD) compared with those without these risk factors.[7 10–15] Similar rate ratios for all-cause pneumonia (CAP), pneumococcal pneumonia and IPD have been reported in individuals with comorbidities (versus those without comorbidities).[7]

Chronic respiratory diseases

Patients with chronic respiratory disease (COPD, chronic bronchitis and/or asthma) are at a higher risk of CAP and IPD than individuals without these comorbidities with fold increases of between 1.3 and 13.5 for CAP and 1.3 and 16.8 for IPD (OR; table 1; see online supplementary table S1).[7 8 12 13 15–26]

Risk of CAP varies with condition and age, with older individuals (≥65 years of age) with COPD being at especially high risk.[19–21] Among individuals with COPD, those aged 65–79 or ≥80 years have been shown to have an increasingly higher risk of CAP than those aged 45–65 years.[21] Having COPD, and greater age, lack of pneumococcal vaccination, and corticosteroid therapy have been identified as independent factors for recurrent CAP in adults.[17]

The severity of the underlying respiratory condition affects the risk of CAP.[15 19 21] Individuals aged ≥65 years who have mild lung disease (not requiring medication or oxygen) have been shown to be twice as likely to have CAP as those without lung

Table 1 Overview of risk factors associated with community-acquired pneumonia and pneumococcal disease

Risk factor	Cohort studies		Case-control studies	
	Number of cohorts*	Risk range†	Number of cohorts*	Risk range†
Community-acquired pneumonia				
Chronic respiratory diseases	8‡	OR: 1.5 HR: 2.9 Rate ratio: 3.8–8.6	15§	OR: 1.3–13.5 RR: 1.6–2.8 HR: 1.2
Current smoking status	4	HR: 1.1 Rate ratio: 3.3–4.0	6	OR: 1.0–2.3 HR: 2.0 RR: 1.5
Diabetes mellitus	7	HR: 1.0–1.9 Rate ratio: 1.6–3.1	9	OR: 1.0–1.4 HR: 1.1 RR: 1.2–1.3
Chronic heart disease	6	HR: 1.5–3.1 Rate ratio: 3.8–4.9	17	OR: 1.0–3.3 HR: 1.3 RR: 1.3–2.6
Pneumococcal pneumonia				
Chronic respiratory diseases	6¶	Rate ratio: 3.7–9.8	0	–
Current smoking status	3	Rate ratio: 3.0–4.4	0	–
Diabetes mellitus	6	RR: 2.3 Rate ratio: 1.5–3.1	0	–
Chronic heart disease	3	Rate ratio: 3.8–5.1	0	–
Invasive pneumococcal disease				
Chronic respiratory diseases	9**	OR: 2.1–16.8 Rate ratio: 2.5–7.7	4††	OR: 1.3–4.7
Current smoking status	5	OR: 2.2 RR: 2.7 Rate ratio: 3.6–4.3	1	OR: 1.1
Diabetes mellitus	10	OR: 1.4–4.6 Rate ratio: 1.5–3.9	2	OR: 1.5–1.7
Chronic heart disease	5	OR: 3.0–6.9 Rate ratio: 2.9–3.9	4	OR: 1.7–9.9

*For studies that only reported data separately for each cohort, all cohorts were included; for studies that reported data for the overall study population, the summary data were used.
†Risk in individuals with factor versus risk in those without risk factor; ranges are based on the lowest and highest values from the publications evaluated using the risk terminology (eg, relative risk or risk ratio) as stated in the original publications.
‡Comprising the following diseases (number of cohorts): asthma (3), bronchitis (0), COPD (1), lung disease (not specified; 4).
§Comprising the following diseases (number of cohorts): asthma (3), bronchitis (1), COPD (5), lung disease (not specified; 6).
¶Comprising the following diseases (number of cohorts): asthma (3), lung disease (not specified; 3).
**Comprising the following diseases (number of cohorts): asthma (4), lung disease (not specified; 5).
††Comprising the following diseases (number of cohorts): asthma (2), COPD (2).
HR, hazard ratio; OR, odds ratio; RR, relative risk.

disease, whereas those with severe lung disease (requiring oxygen) are eight times more likely to have CAP.[19] Similarly, moderate and severe lung disease (percentage predicted FEV_1: 50–80% and <50%, respectively) have been identified as significant risk factors for CAP in individuals aged ≥65 years compared with normal or mild lung disease (HR: 1.78 and 2.90, respectively).[15] Moderate COPD exacerbation and hospitalisation due to severe COPD exacerbation have also been identified as independent risk factors for CAP in patients with COPD aged ≥45 years.[21]

Use of inhaled corticosteroids, a frequent medication in COPD, has been associated with an increased risk of CAP.[16 18] In a case–control study conducted in hospitalised patients aged ≥65 years, use of inhaled corticosteroids was found to be an independent risk factor for CAP (adjusted OR: 2.89).[18] Inhaled corticosteroids were also associated with CAP in another case–control study involving individuals over 14 years of age (OR: 3.09).[16] In both these studies, the risk of CAP was higher in those receiving inhaled corticosteroids than in those receiving β_2-adrenergic agonists.[16 18] Furthermore, the use of inhalers, especially with a chamber spacer, was identified as an independent risk factor for CAP (multivariate OR: 1.57),[16] which may be due to contamination of the inhaler or deep inhalation of pressurised aerosols aiding penetration of microorganisms into the bronchial tree.

Another study found that inhaled corticosteroids increased the risk of CAP in patients with COPD, whereas inhaled anticholinergics increased the risk of CAP in patients with asthma.[27] Inhaled β_2-adrenergic agonists, however, did not appear to affect the risk of CAP.[27] The authors of this study concluded that these associations may not be causal but reflect the severity of the underlying conditions. A recent Cochrane review concluded that the inhaled corticosteroids budesonide and fluticasone, administered alone or in combination with a long-acting β_2 agonist, increase the risk of pneumonia requiring hospitalisation in patients with COPD, although they do not significantly affect mortality compared with controls.[28]

Within a patient population with underlying lung diseases, patients with COPD have been found to have a higher risk of IPD than those with asthma, regardless of age (fourfold vs twofold increased risk of IPD).[13] The increased risk of IPD in individuals with COPD may be due to reduced innate defence mechanisms in the airways, smoking and/or use of corticosteroids.[13]

Smoking status

Smoking has also been identified as a risk factor for CAP (ORs for current smoking: 1.0–2.3) with the risk varying according to smoking history (table 1; see online supplementary table S2).[7 15 16 18 19 21 22 24 29] The effect of smoking on the risk of CAP has been explored in a case–control study.[16] Compared with individuals who had never smoked, current smokers and ex-smokers were found to have a higher risk of CAP (OR: 1.34 and 1.37, respectively), with smoking confirmed as an independent risk factor in a multivariate analysis. This risk increased with the number of pack-years (OR vs 0 pack-years: 1.46 for >150 pack-years and 1.01 for ≤150 pack-years). Among the ex-smokers, those who had stopped smoking >4 years ago had a significantly reduced risk of CAP than those who had stopped smoking <1 year ago (OR: 0.39). Individuals aged >65 years who had never smoked but were exposed to passive smoking were also at significantly increased risk of CAP (OR adjusted for age and sex: 1.56).[16] Similarly, in a separate study, individuals aged ≥65 years who were exposed to passive smoke at home had an increased risk of CAP (relative risk (RR): 1.48 vs those not exposed to passive smoke).[29]

In another study in individuals aged ≥65 years, current smokers had a higher risk of CAP than ex-smokers irrespective of age (OR for all ages: 1.8 vs 1.3).[19] Based on the population attributable fraction, which is a measure of the proportion of cases attributed to a particular risk factor, Jackson *et al*[19] calculated that 2.4% of CAP cases are due to current smoking, increasing to 5.5% of cases in those with no cardiopulmonary disease. In contrast, in a study involving individuals with COPD, current smoking was not found to affect CAP incidence, which the authors attributed to inaccurate recording of current smoking status (20% of individuals were reported to have never smoked), other causes of COPD such as occupational exposures, or individuals with severe COPD ceasing to smoke.[21]

The effect of smoking status on IPD incidence is variable,[7 25 26 30] which may reflect the variable prevalence of smoking within different populations.[26] In US adults with chronic medical conditions, Shea *et al*[7] calculated rate ratios of 3.6 in smokers aged 18–49 years to 4.3 in those aged 50–64 years.

In another US study, the risk of bacteraemic pneumococcal pneumonia in adults was significantly higher in current smokers than in those who have never smoked or are not currently smoking (multivariate adjusted OR: 2.2).[25] Smokers were also shown to be 3.7 times more likely to develop pneumococcal bacteraemic pneumonia than non-smokers in an Australian study.[30] In contrast, former or current smoking was not associated with IPD in Navajo adults in whom the prevalence of smoking was low.[26]

Diabetes mellitus

Patients with diabetes have an increased risk of up to 1.4 for CAP and ranging from 1.4 to 4.6 for IPD (ORs; table 1; see online supplementary table S3).[7 8 12–16 19 21 23–26 30–34] Analysis of long-term UK data suggests that the risk of lobar pneumonia, pneumococcal pneumonia, septicaemia and meningitis in patients hospitalised with diabetes declined little between 1963 and 2011. However, a decreased risk of pneumococcal disease was observed in individuals aged <60 years in recent years (2007–11), which coincided with the introduction of pneumococcal conjugate vaccines (PCVs) in childhood vaccination programmes in 2006.[14]

Diabetes has the greatest impact on the risk of IPD and CAP in individuals aged <64 years and especially in those aged ≤40 years or without other comorbidities.[12 32] In a Danish case–control study, individuals <40 years of age with diabetes were found to have a threefold higher risk of hospitalisation due to pneumonia than individuals without diabetes of a similar age, with the RR decreasing in older age groups. The risk of pneumonia-related hospitalisation associated with diabetes was also greater in those with no other comorbidities, and in those with a longer duration of diabetes and/or poor glycaemic control (based on A1C levels).[32] Similarly, in a US study, increasing levels of A1C were associated with an increasing risk of CAP in patients with diabetes.[31] It has been suggested that the increased risk of pneumococcal infection in patients with diabetes results from the harmful effects of hyperglycaemia on immune and/or pulmonary function.[35 36]

Chronic heart disease

Patients with CHD (including congestive heart failure (CHF) and cardiovascular and valve diseases) have up to a 3.3-fold increased risk (OR) of CAP and up to a 9.9-fold increased risk (OR) of IPD compared with those without CHD, with risk varying according to the condition and age of the individual (table 1; see online supplementary table S4).[7 8 10–13 15 16 18 19 21 22 24 26] In individuals living in the US and aged ≥65 years, heart disease was identified as an independent risk factor for CAP with 16% of cases attributed to heart disease. The risk of CAP was greater in those with heart disease of a greater severity: individuals with non-CHF heart disease had only a modest increase in the risk of CAP (OR: 1.2 vs those with no heart disease), whereas those with mild or severe CHF had a twofold and threefold increased risk, respectively.[19]

These findings are supported by data from a large population-based study of 67 000 patients with pneumonia, in which patients with CHF had an almost twofold increased risk of hospitalisation as a result of pneumonia relative to those without CHF.[10] The risk of pneumonia was affected by the underlying condition associated with the heart failure and the medical treatment administered. Patients with cardiomyopathy, as well as those treated with loop diuretics, were found to be especially at risk of hospitalised CAP. Similarly, in a separate study, treatment of heart failure with amiodarone was found to be an independent risk factor for CAP.[16]

The incidence of CAP and IPD in US individuals has also been found to increase with increasing age, although the rate ratios between patients with CHD and healthy individuals was higher in the 18–49-year age group than in the older age groups due to the low background incidence in the younger age group.[7] This reflects the fact that increasing age is itself a risk factor for pneumococcal disease and as such has a diluting effect on the increased risk associated with comorbidities in the older age groups.

Multiple risk factors

Multiple risk factors for pneumococcal disease are frequently observed in individuals >65 years of age, with more than 60% having two or more underlying medical conditions.[37–39] Multiple conditions have been shown to have a cumulative effect on the risk of CAP/IPD, as well as on the mortality associated with these diseases.[7 9 40] The risk of pneumococcal disease (all-cause pneumonia, pneumococcal pneumonia and IPD) increases as the number of risk factors increases in different age groups (18–49, 50–64 and ≥65 years).[7] Rates are particularly high in those with three or more conditions (eg, RR for pneumococcal pneumonia relative to healthy individuals: 16.5, 12.8 and 9.2, respectively).

CONSEQUENCES OF CHRONIC DISEASES ON PNEUMOCOCCAL DISEASE OUTCOMES

The presence of chronic diseases not only increases the risk of an individual acquiring a pneumococcal disease, but can also adversely affect the severity and outcome of that disease. Both COPD and diabetes have been shown to be significant predictors of hospitalisation in patients with CAP.[41] Furthermore, the risk of respiratory and cardiac complications—both of which are associated with increased mortality—is greater in individuals with chronic lung and/or heart diseases than in other individuals.[42 43]

In adults hospitalised due to IPD, the following independent risk factors for respiratory failure were identified: age >50 years (OR 1.63), chronic lung disease (OR 1.54), CHD (OR 1.49), and infection caused by serotype 3 (OR 1.97), serotype 19A (OR 2.34) and serotype 19F (OR 3.55).[42]

Cardiac complications have also been found to affect more than one-quarter of individuals hospitalised as a result of CAP and were associated with a 60% increased risk of 30-day mortality.[43] An increased risk of cardiac complications was observed in individuals with increased cardiovascular risk, such as those with preexisting heart failure (OR: 4.3), cardiac arrhythmias (OR: 1.8), coronary artery disease (OR: 1.5) or arterial hypertension (OR: 1.5).

Patients with chronic comorbidities are at increased risk of death from CAP or IPD over both the short term (eg, 30 days) and long term (1 year).[44–48] Adamuz *et al* investigated the incidence, causes and risk factors associated with 1-year mortality in patients with CAP after hospital discharge. They reported a 7% 1-year mortality rate following discharge from hospital, with most patients dying as a result of infectious diseases (mostly pneumonia) or acute cardiovascular events.[45] Independent risk factors for 1-year mortality in these patients were comorbidity (including COPD and diabetes mellitus), rehospitalisation within 30 days of hospital discharge, and nursing home residence.[45]

The risk of mortality from CAP or IPD in patients with COPD varies according to the study.[49] COPD (defined using spirometry) was found to be an independent risk factor for 30-day mortality in Spanish patients with CAP,[48] whereas other studies in patients with CAP or pneumococcal bacteraemic pneumonia have not demonstrated increased 30-day mortality in patients with COPD compared with those without COPD.[44 46 50]

This variability may reflect differences in the definitions used for COPD, as not all of these studies used spirometric measurements to diagnose COPD.[44 46] However, Liapikou *et al*[50] observed a similar mortality rate in patients with spirometry-confirmed COPD to that in patients without COPD. Although patients with COPD presented with more severe respiratory failure (arterial oxygen tension/inspiratory oxygen fraction) and more severe pneumonia (pneumonia severity index), they had less multilobar infiltration and fewer pulmonary complications compared with those without COPD.[50] This reduction in pulmonary complications has been attributed to the use of inhaled corticosteroids, possibly reducing the inflammatory response in the lung in these patients. This is supported by findings that prior treatment with inhaled corticosteroids in patients with chronic respiratory disorders who develop pneumonia is associated with a lower incidence of parapneumonic effusion.[51]

Mortality risk appears to increase in those with COPD and prior cardiovascular disease; older patients with COPD and prior cardiovascular disease have been reported to have a significantly increased 12-month mortality risk (adjusted OR: 1.34) compared with those without cardiovascular disease.[52]

Smoking has been identified as an independent risk factor for mortality associated with pneumococcal bacteraemic pneumonia and CAP. In patients with pneumococcal bacteraemic pneumonia, smoking was attributed to 14.9% of the 30-day mortality, based on the population attributable proportion.[44] In a separate study of patients hospitalised with CAP, current smokers had a fivefold increased risk of 30-day mortality from pneumococcal CAP compared with non-smokers and ex-smokers, and current smoking status remained an independent risk factor for pneumococcal CAP compared with non-smoking status alone and ex-smoking status alone (OR: 4.0 and 3.9, respectively).[53]

Diabetes is an independent risk factor (OR: 1.67) for the development of bacteraemia in patients with pneumococcal pneumonia, which in turn is associated with significantly increased mortality versus non-bacteraemic pneumonia (OR: 2.57).[54]

Patients with CHF are at increased risk of a complicated episode of CAP (based on a combined endpoint of 30-day home-treated complications, hospitalisation or all-cause mortality; OR: 3.13),[55] and at increased risk of 30-day mortality.[46 47]

Analysis of data from the German Competence Network for Community-Acquired Pneumonia (CAPNETZ) study found that CHF and CHD were risk factors for 30-day mortality in patients with CAP in a univariate analysis (ORs: 4.91 and 2.76, respectively) but not in a multivariate analysis.[46] In a separate study involving Danish patients hospitalised for pneumonia, those with CHF had an increased 30-day mortality rate versus other patients (adjusted mortality rate ratio (MRR): 1.40).[47] Mortality increased with increasing severity of CHF before admission, based on medication regimen. Patients receiving loop-diuretics and spironolactone (drugs used for CHF New York Heart Association Functional Classification III–IV) were at a particularly high risk for death due to pneumonia (MRR: 1.72), whereas those using a thiazide as the sole diuretic had a mortality rate similar to that of other patients with pneumonia (MRR: 1.09).[47]

A hospital-based epidemiological study of IPD in adults in Belgium also demonstrated a significantly higher case fatality rate during hospitalisation in those with heart failure compared with those without heart failure (OR: 1.70).[56]

CAP may also worsen a patient's underlying condition, as reported in a US survey of adults aged ≥50 years with CAP, in which ≥20% of individuals experienced a worsening of COPD, asthma or hypertension.[57] This deterioration in the patient's underlying condition may in turn adversely affect the patient's prognosis. For example, previously diagnosed pneumonia in patients hospitalised for COPD exacerbation has been shown to increase inpatient mortality.[58] In another study, patients with COPD exacerbations and pneumonia had poorer outcomes, including inpatient and 90-day mortality, compared with those with non-pneumonic COPD exacerbations.[59]

Patients have been reported to have ongoing subclinical inflammation following recovery from pneumonia, and this has been associated with an increased risk of death due to cardiovascular disease in these individuals.[60] Worsening prior cardiovascular disease in patients with COPD has also been attributed as a cause of increased long-term mortality following pneumonia.[52] Similarly, deterioration of underlying cardiovascular disease has been associated with increased 1-year mortality following pneumonia in patients with diabetes mellitus versus those without diabetes.[61]

The mechanisms linking pneumonia to cardiac events such as myocardial infarction, arrhythmias and CHD are multifactorial. They include thrombogenesis/rupture of vulnerable plaques, and myocardial stress and suppression resulting from increased myocardial oxygen demand, lowered blood oxygen levels, depressed ventricular function and elevated levels of cytokines.[60 62 63]

ECONOMIC BURDEN OF PNEUMOCOCCAL DISEASE

Pneumococcal pneumonia results in a more severe disease course requiring more medical resources than non-pneumococcal pneumonia.[64] Data from the CAPNETZ study suggest that patients with pneumococcal pneumonia are more likely to be hospitalised, to have higher pneumonia severity (Confusion, Urea, Respiratory Rate and Blood Pressure (CURB)) score values on admission and pleural effusion, and to require oxygen insufflation than those with non-pneumococcal pneumonia.[64] CAP, and specifically pneumococcal pneumonia, therefore imposes a significant economic burden.[65]

Economic studies conducted in the US and in Eastern Europe suggest that healthcare costs for CAP requiring hospitalisation are high and increase with increasing risk level of CAP.[66–68] Major determinants of total healthcare costs are admission to an intensive care unit[69 70] and length of hospital stay,[69 71] which is in turn dependent on the presence of specific comorbidities, the development of complications and the severity of the pneumonia.

Bacteraemia and CHF have been found to be positive predictors of length of hospital stay in adults with pneumococcal pneumonia.[70] Independent predictors of longer length of hospital stay in patients with CAP also include chronic respiratory disease, diabetes, multilobar CAP, as well as older age (≥70 years), pneumonia severity index class on admission, and development of CAP-associated complications.[72]

In addition to inpatient care, long duration of antibiotic therapy and a large number of visits at different healthcare levels (primary care, hospital outpatient and emergency departments) have been shown to contribute to the high cost of treating CAP.[73]

It has been suggested that the higher costs of treating those with comorbidities and CAP than those without comorbidities are due to exacerbation of the underlying conditions, leading to additional costs.[74] In line with this, the proportion of CAP-related costs has been found to decrease with increasing risk for CAP, suggesting that a greater proportion of healthcare costs are associated with treating underlying conditions in high-risk versus low-risk patients.[66] Furthermore, a 20% increase in hospitalisation for pneumonia observed among US individuals aged ≥65 years from 1988–1990 to 2000–2002 has, in part, been attributed to an increase in comorbidities in these individuals.[75] Complications (especially infectious diseases), hypoalbuminaemia and previous hospital admission have also been linked with the high costs associated with hospitalised patients with CAP.[71]

Pneumococcal disease (CAP/IPD) significantly affects patients' quality of life, causing extra days off work, more frequent visits to primary care providers, and requiring additional medication and assistance from caregivers.[1 57 74] Patients with a serious chronic condition who are hospitalised for CAP are also more likely to leave their job.[74] The US survey (mentioned above) suggested that cough and weakness associated with CAP adversely affects an individual's capacity to carry out daily activities, such as housework and visiting places/other individuals.[57]

CONCLUSIONS

Adults with chronic conditions and other risk factors such as COPD, asthma, smoking, diabetes mellitus and CHD are not only at increased risk of pneumococcal infections, but also at increased risk of complications/mortality if they have pneumococcal disease. This highlights the need for timely pneumococcal vaccination in these patients.

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REFERENCES

1 Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 2012;67:71–9.
2 Ludwig E, Unal S, Bogdan M, *et al*. Opportunity for healthy ageing: lessening the burden of adult pneumococcal disease in Central and Eastern Europe, and Israel. *Cent Eur J Public Health* 2012;20:121–5.
3 Torne AN, Dias JG, Quinten C, *et al*. European enhanced surveillance of invasive pneumococcal disease in 2010: data from 26 European countries in the post-heptavalent conjugate vaccine era. *Vaccine* 2014;32:3644–50.
4 File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. *Postgrad Med* 2010;122:130–41.
5 Nicoli EJ, Trotter CL, Turner KM, *et al*. Influenza and RSV make a modest contribution to invasive pneumococcal disease incidence in the UK. *J Infect* 2013;66:512–20.
6 Torres A, Peetermans WE, Viegi G, *et al*. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax* 2013;68:1057–65.
7 Shea KM, Edelsberg J, Weycker D, *et al*. Rates of pneumococcal disease in adults with chronic medical conditions. *Open Forum Infect Dis* 2014;1:ofu024.
8 Vinogradova Y, Hippisley-Cox J, Coupland C. Identification of new risk factors for pneumonia: population-based case-control study. *Br J Gen Pract* 2009;59:e329–38.
9 Cilloniz C, Polverino E, Ewig S, *et al*. Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. *Chest* 2013;144:999–1007.
10 Mor A, Thomsen RW, Ulrichsen SP, *et al*. Chronic heart failure and risk of hospitalization with pneumonia: a population-based study. *Eur J Intern Med* 2013;24:349–53.
11 Nyboe C, Olsen MS, Nielsen-Kudsk JE, *et al*. Risk of pneumonia in adults with closed versus unclosed atrial septal defect (from a nationwide cohort study). *Am J Cardiol* 2014;114:105–10.
12 van Hoek AJ, Andrews N, Waight PA, *et al*. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. *J Infect* 2012;65:17–24.
13 Inghammar M, Engstrom G, Kahlmeter G, *et al*. Invasive pneumococcal disease in patients with an underlying pulmonary disorder. *Clin Microbiol Infect* 2013;19:1148–54.
14 Seminog OO, Goldacre MJ. Risk of pneumonia and pneumococcal disease in people hospitalized with diabetes mellitus: English record-linkage studies. *Diabet Med* 2013;30:1412–19.
15 Juthani-Mehta M, De RN, Allore H, *et al*. Modifiable risk factors for pneumonia requiring hospitalization of community-dwelling older adults: the Health, Aging, and Body Composition Study. *J Am Geriatr Soc* 2013;61:1111–18.
16 Almirall J, Bolibar I, Serra-Prat M, *et al*. New evidence of risk factors for community-acquired pneumonia: a population-based study. *Eur Respir J* 2008;31:1274–84.
17 Garcia-Vidal C, Carratala J, Fernandez-Sabe N, *et al*. Aetiology of, and risk factors for, recurrent community-acquired pneumonia. *Clin Microbiol Infect* 2009;15:1033–8.
18 Gau JT, Acharya U, Khan S, *et al*. Pharmacotherapy and the risk for community-acquired pneumonia. *BMC Geriatr* 2010;10:45.
19 Jackson ML, Nelson JC, Jackson LA. Risk factors for community-acquired pneumonia in immunocompetent seniors. *J Am Geriatr Soc* 2009;57:882–8.

20 Loeb M, Neupane B, Walter SD, *et al*. Environmental risk factors for community-acquired pneumonia hospitalization in older adults. *J Am Geriatr Soc* 2009;57:1036–40.
21 Mullerova H, Chigbo C, Hagan GW, *et al*. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. *Respir Med* 2012;106:1124–33.
22 Obiora E, Hubbard R, Sanders RD, *et al*. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax* 2013;68:163–70.
23 Rodriguez LA, Ruigomez A, Wallander MA, *et al*. Acid-suppressive drugs and community-acquired pneumonia. *Epidemiology* 2009;20:800–6.
24 Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, *et al*. Epidemiology of community-acquired pneumonia in older adults: a population-based study. *Respir Med* 2009;103:309–16.
25 Flory JH, Joffe M, Fishman NO, *et al*. Socioeconomic risk factors for bacteraemic pneumococcal pneumonia in adults. *Epidemiol Infect* 2009;137:717–26.
26 Watt JP, O'Brien KL, Benin AL, *et al*. Risk factors for invasive pneumococcal disease among Navajo adults. *Am J Epidemiol* 2007;166:1080–7.
27 Almirall J, Bolibar I, Serra-Prat M, *et al*. Inhaled drugs as risk factors for community-acquired pneumonia. *Eur Respir J* 2010;36:1080–7.
28 Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014;3:CD010115.
29 Almirall J, Serra-Prat M, Bolibar I, *et al*. Passive smoking at home is a risk factor for community-acquired pneumonia in older adults: a population-based case-control study. *BMJ Open* 2014;4:e005133.
30 Jacups SP, Cheng A. The epidemiology of community acquired bacteremic pneumonia, due to Streptococcus pneumoniae, in the top end of the Northern Territory, Australia—over 22 years. *Vaccine* 2011;29:5386–92.
31 Ehrlich SF, Quesenberry CPJ, Van Den Eeden SK, *et al*. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. *Diabetes Care* 2010;33:55–60.
32 Kornum JB, Thomsen RW, Riis A, *et al*. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. *Diabetes Care* 2008;31:1541–5.
33 Skull SA, Andrews RM, Byrnes GB, *et al*. Hospitalized community-acquired pneumonia in the elderly: an Australian case-cohort study. *Epidemiol Infect* 2009;137:194–202.
34 Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analyses. *J Epidemiol Community Health* 2012;66:1177–81.
35 Peleg AY, Weerarathna T, McCarthy JS, *et al*. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. *Diabetes Metab Res Rev* 2007;23:3–13.
36 van den Borst B, Gosker HR, Zeegers MP, *et al*. Pulmonary function in diabetes: a metaanalysis. *Chest* 2010;138:393–406.
37 Agborsangaya CB, Ngwakongnwi E, Lahtinen M, *et al*. Multimorbidity prevalence in the general population: the role of obesity in chronic disease clustering. *BMC Public Health* 2013;13:1161.
38 Ornstein SM, Nietert PJ, Jenkins RG, *et al*. The prevalence of chronic diseases and multimorbidity in primary care practice: a PPRNet report. *J Am Board Fam Med* 2013;26:518–24.
39 Violan C, Foguet-Boreu Q, Hermosilla-Perez E, *et al*. Comparison of the information provided by electronic health records data and a population health survey to estimate prevalence of selected health conditions and multimorbidity. *BMC Public Health* 2013;13:251.
40 Ricketson LJ, Nettel-Aguirre A, Vanderkooi OG, *et al*. Factors influencing early and late mortality in adults with invasive pneumococcal disease in Calgary, Canada: a prospective surveillance study. *PLoS ONE* 2013;8:e71924.
41 Sicras-Mainar A, Ibanez-Nolla J, Cifuentes I, *et al*. Retrospective epidemiological study for the characterization of community-acquired pneumonia and pneumococcal pneumonia in adults in a well-defined area of Badalona (Barcelona, Spain). *BMC Infect Dis* 2012;12:283.
42 Burgos J, Lujan M, Larrosa MN, *et al*. Risk factors for respiratory failure in pneumococcal pneumonia: the importance of pneumococcal serotypes. *Eur Respir J* 2014;43:545–53.
43 Corrales-Medina VF, Musher DM, Wells GA, *et al*. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. *Circulation* 2012;125:773–81.
44 Naucler P, Darenberg J, Morfeldt E, *et al*. Contribution of host, bacterial factors and antibiotic treatment to mortality in adult patients with bacteraemic pneumococcal pneumonia. *Thorax* 2013;68:571–9.
45 Adamuz J, Viasus D, Jimenez-Martinez E, *et al*. Incidence, timing and risk factors associated with 1-year mortality after hospitalization for community-acquired pneumonia. *J Infect* 2014;68:534–41.
46 Kothe H, Bauer T, Marre R, *et al*. Outcome of community-acquired pneumonia: influence of age, residence status and antimicrobial treatment. *Eur Respir J* 2008;32:139–46.
47 Thomsen RW, Kasatpibal N, Riis A, *et al*. The impact of pre-existing heart failure on pneumonia prognosis: population-based cohort study. *J Gen Intern Med* 2008;23:1407–13.
48 Molinos L, Clemente MG, Miranda B, *et al*. Community-acquired pneumonia in patients with and without chronic obstructive pulmonary disease. *J Infect* 2009;58:417–24.
49 Loke YK, Kwok CS, Wong JM, *et al*. Chronic obstructive pulmonary disease and mortality from pneumonia: meta-analysis. *Int J Clin Pract* 2013;67:477–87.
50 Liapikou A, Polverino E, Ewig S, *et al*. Severity and outcomes of hospitalised community-acquired pneumonia in COPD patients. *Eur Respir J* 2012;39:855–61.
51 Sellares J, Lopez-Giraldo A, Lucena C, *et al*. Influence of previous use of inhaled corticoids on the development of pleural effusion in community-acquired pneumonia. *Am J Respir Crit Care Med* 2013;187:1241–8.
52 Sibila O, Mortensen EM, Anzueto A, *et al*. Prior cardiovascular disease increases long-term mortality in COPD patients with pneumonia. *Eur Respir J* 2014;43:36–42.
53 Bello S, Menendez R, Torres A, *et al*. Tobacco smoking increases the risk for death from pneumococcal pneumonia. *Chest* 2014;146:1029–37.
54 Kang CI, Song JH, Kim SH, *et al*. Risk factors and pathogenic significance of bacteremic pneumonia in adult patients with community-acquired pneumococcal pneumonia. *J Infect* 2013;66:34–40.
55 Hak E, Bont J, Hoes AW, *et al*. Prognostic factors for serious morbidity and mortality from community-acquired lower respiratory tract infections among the elderly in primary care. *Fam Pract* 2005;22:375–80.
56 Verhaegen J, Flamaing J, De BW, *et al*. Epidemiology and outcome of invasive pneumococcal disease among adults in Belgium, 2009–2011. *Euro Surveill* 2014;19:14–22.
57 Wyrwich KW, Yu H, Sato R, *et al*. Community-acquired pneumonia: symptoms and burden of illness at diagnosis among US adults aged 50 years and older. *Patient* 2013;6:125–34.
58 Roca B, Almagro P, Lopez F, *et al*. Factors associated with mortality in patients with exacerbation of chronic obstructive pulmonary disease hospitalized in general medicine departments. *Intern Emerg Med* 2011;6:47–54.
59 Myint PK, Lowe D, Stone RA, *et al*. UK National COPD Resources and Outcomes Project 2008: patients with chronic obstructive pulmonary disease exacerbations who present with radiological pneumonia have worse outcome compared to those with non-pneumonic chronic obstructive pulmonary disease exacerbations. *Respiration* 2011;82:320–7.
60 Yende S, D'Angelo G, Kellum JA, *et al*. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008;177:1242–7.
61 Yende S, van der Poll T, Lee M, *et al*. The influence of pre-existing diabetes mellitus on the host immune response and outcome of pneumonia: analysis of two multicentre cohort studies. *Thorax* 2010;65:870–7.
62 Musher DM, Rueda AM, Kaka AS, *et al*. The association between pneumococcal pneumonia and acute cardiac events. *Clin Infect Dis* 2007;45:158–65.
63 Mortensen EM, Metersky ML. Long-term mortality after pneumonia. *Semin Respir Crit Care Med* 2012;33:319–24.
64 Pletz MW, von BH, van der Linden M, *et al*. The burden of pneumococcal pneumonia—experience of the German competence network CAPNETZ. *Pneumologie* 2012;66:470–5.
65 De Graeve D, Beutels P. Economic aspects of pneumococcal pneumonia: a review of the literature. *Pharmacoeconomics* 2004;22:719–40.
66 Sato R, Gomez RG, Nelson S, *et al*. Community-acquired pneumonia episode costs by age and risk in commercially insured US adults aged >/=50 years. *Appl Health Econ Health Policy* 2013;11:251–8.
67 Yu H, Rubin J, Dunning S, *et al*. Clinical and economic burden of community-acquired pneumonia in the Medicare fee-for-service population. *J Am Geriatr Soc* 2012;60:2137–43.
68 Tichopad A, Roberts C, Gembula I, *et al*. Clinical and economic burden of community-acquired pneumonia among adults in the Czech Republic, Hungary, Poland and Slovakia. *PLoS ONE* 2013;8:e71375.
69 Bauer TT, Welte T, Ernen C, *et al*. Cost analyses of community-acquired pneumonia from the hospital perspective. *Chest* 2005;128:2238–46.
70 Sun HK, Nicolau DP, Kuti JL. Resource utilization of adults admitted to a large urban hospital with community-acquired pneumonia caused by Streptococcus pneumoniae. *Chest* 2006;130:807–14.
71 Reyes S, Martinez R, Valles JM, *et al*. Determinants of hospital costs in community-acquired pneumonia. *Eur Respir J* 2008;31:1061–7.
72 Suter-Widmer I, Christ-Crain M, Zimmerli W, *et al*. Predictors for length of hospital stay in patients with community-acquired pneumonia: results from a Swiss multicenter study. *BMC Pulm Med* 2012;12:21.
73 Bartolome M, Almirall J, Morera J, *et al*. A population-based study of the costs of care for community-acquired pneumonia. *Eur Respir J* 2004;23:610–16.
74 Kleinman NL, Yu H, Beren IA, *et al*. Work-related and health care cost burden of community-acquired pneumonia in an employed population. *J Occup Environ Med* 2013;55:1149–56.
75 Fry AM, Shay DK, Holman RC, *et al*. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988–2002. *JAMA* 2005;294:2712–19.

Supplemental table S1 Risk of community-acquired pneumonia or pneumococcal disease in patients with chronic respiratory diseases (CRD)

Reference (country)	Methodology (N)	Disease definition	Underlying definition	No. of exposed cases with CRD	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Community-acquired pneumonia (all cause)						
Almirall 2008 [16] (Spain)	Population-based, case-control study, Nov 1999–Nov 2000 (1,336 cases)	Antibiotics, clinical and X-ray	Chronic bronchitis	216	>14	Multivariate: 1.81 (1.19–2.75)
			Asthma	375	>14	Multivariate: 1.67 (1.28–2.19)
Garcia-Vidal 2009 [17] (Spain)	Prospective, observational study, Jan 1995–Dec 2005 (146 cases, 224 episodes) Recurrent community-acquired pneumonia: new episode of community-acquired pneumonia requiring hospitalization <1 month or >3 years after first episode	Clinical, X-ray, blood culture, urinary tests	COPD	56	Adults	Multivariate: 1.53 (1.02–2.30)
Gau 2010 [18] (USA)	Retrospective case-control study, 2004–2006 (194 cases)	X-ray	COPD	91	≥65	Adjusted: 1.82 (1.17–2.82)
Jackson 2009 [19] (USA)	Population-based, nested case-control study, influenza seasons and pre-influenza periods of 2000/01 and 2002/03 (1,173 cases)	Clinical and X-ray	Lung disease, no medication or oxygen	6	≥65 65–74 75–84 85	Multivariate: 2.0 (1.5–2.7) 3.1 (1.7–5.7) 2.3 (1.5–3.5) 1.1 (0.5–2.3)
			Lung disease with medication but not oxygen	36	≥65 65–74 75–84 85	2.5 (2.2–3.0) 2.9 (2.3–3.7) 2.8 (2.2–3.6) 1.9 (1.3–2.8)
			Lung disease, using oxygen	9	≥65 65–74 75–84 85	8.3 (5.5–12.7) 8.3 (4.4–15.7) 5.2 (2.7–9.9) 16.1 (3.7–69.9)
Juthani-Mehta 2013 [15] (USA)	Case-control study using a subset of a prospective cohort, 1997–2008 (193 cases)	Hospitalized pneumonia: ICD-9 criteria, clinical and chest X-ray	Chronic lung disease	49	70–79	Bivariate HR: 1.20 (0.87–1.66)

Reference (country)	Methodology (N)	Disease definition	Underlying definition	No. of exposed cases with CRD	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Loeb 2009 [20] (Canada)	Population-based, case-control study with collection of personal interview data, Sep 2002–Apr 2005 (717 cases)	Clinical and X-ray				Adjusted:
			COPD	343	≥65	13.53 (7.80–23.48)
			Asthma	168	≥65	3.04 (2.28–4.05)
Mullerova 2012 [21] (UK)	Nested case-control population-based on retrospective COPD cohort, 1996–2005 (1,469 cases)	Diagnosis code				Multivariate:
			COPD hospitalization (severe exacerbation)		≥45 (COPD)	2.73 (2.32-3.20)
			Moderate COPD exacerbation		≥45 (COPD)	1.28 (1.13-1.46)
Obiora 2013 [22] (UK)	Nested case-control study using primary care patient database, 2001–2002 (4,964 cases)	Medical records	Lung disease	1,201	Adults	2.74 (2.54–2.96)
Rodriguez 2009 [23] (Sweden)	Nested case-control study using the Health Improvement Network database, 2000–2005 (7,297 cases)	Pneumonia diagnosis code, validated by manual review of medical records	COPD	1,144	20–79	RR: 2.82 (2.45–3.24)
			Asthma	1,807	20–79	RR: 1.58 (1.44–1.74)
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Chronic lung disease		18–49 50–64 ≥65	Rate ratio: 8.6 (8.4–8.7) Rate ratio: 8.6 (8.5–8.7) Rate ratio: 6.6 (6.6–6.7)
			Asthma		18–49 50–64 ≥65	Rate ratio: 3.8 (3.8–3.9) Rate ratio: 4.7 (4.6–4.7) Rate ratio: 4.6 (4.5–4.6)
Vila-Corcoles 2009 [24] (Spain)	Population-based cohort study in community-dwelling individuals, 2002–2005 (473 cases)	Clinical, X-ray, microbiological and diagnosis code in hospital discharge database	Chronic lung disease	171	≥65	Multivariate HR: 2.91 (2.35–3.61)
Vinogradova 2009 [8] (UK)	Nested case-control study in 443 general practices in the UK 1996–2005 (17,172 cases)	Incident diagnosis code	Chronic respiratory disease	4,468 1,493	All ages 5–64	Adjusted: 2.42 (2.31–2.53) Adjusted: 2.31 (2.15–2.48)

Reference (country)	Methodology (N)	Disease definition	Underlying definition	No. of exposed cases with CRD	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Pneumococcal pneumonia						
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Chronic lung disease		18–49 50–64 ≥65	Rate ratio: 8.9 (8.1–9.7) Rate ratio: 9.8 (9.3–10.3) Rate ratio: 7.7 (7.3–8.0)
			Asthma		18–49 50–64 ≥65	Rate ratio: 3.7 (3.4–4.0) Rate ratio: 4.9 (4.6–5.2) Rate ratio: 5.9 (5.6–6.3)
Invasive pneumococcal disease						
Flory 2009 [25] (USA)	Population-based surveillance study, 2002–2004 (609 cases)	Bacteremia pneumococcal pneumonia: microbiological	Asthma	71	≥18	Adjusted: 2.1 (1.5–2.9)
Inghammar 2013 [13] (Sweden)	Nested case-control study, 1987–2008 (4,084 cases)	Positive culture from a normally sterile fluid	COPD	248 25 147 76	≥18 18–59 60–79 ≥80	Adjusted: 4.7 (4.0–5.6) 10.3 (5.8–18.0) 6.3 (5.1–7.8) 4.0 (3.0–4.8)
			Asthma	71 26 31 14	≥18 18–59 60–79 ≥80	Adjusted: 2.0 (1.5–2.6) 4.9 (3.0–7.8) 1.9 (1.3–2.9) 1.5 (0.9–2.7)
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Chronic lung disease		18–49 50–64 ≥65	Rate ratio: 6.3 (4.7–8.5) Rate ratio: 7.7 (6.8–8.8) Rate ratio: 6.2 (5.4–7.0)
			Asthma		18–49 50–64 ≥65	Rate ratio: 2.5 (1.9–3.2) Rate ratio: 3.8 (3.2–4.5) Rate ratio: 4.1 (3.4–5.0)
van Hoek 2012 [12] (UK)	Comparison of prevalence of clinical risk factors in the general population with that in hospitalized patients with invasive pneumococcal disease, 2002–2009 (22,298 cases)	ICD diagnosis code; microbiological	Chronic respiratory disease	938 2,364	16–64 ≥65	16.8 (15.7–18.0) 5.1 (4.8–5.4)
Watt 2007 [26] (USA)	Case-control prospective study, population-based active laboratory surveillance, 1999–2002 (118 cases)	Positive culture from a normally sterile fluid	COPD Asthma	7 8	≥18 ≥18	Univariate: 4.6 (1.3–15.9) Univariate: 1.3 (0.6–2.9)

Grey rows represent cohort studies; white rows represent case-control studies. *Unless otherwise specified.

CI, confidence interval; CRD, chronic respiratory disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICD, International Classification of Diseases; OR, odds ratio, RR: relative risk.

Supplemental table S2 Risk of community-acquired pneumonia or pneumococcal disease in individuals who smoke

Reference (country)	Methodology (N)	Disease definition	Underlying definition	Number of smokers	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Community-acquired pneumonia						
Almirall 2014 [29] (Spain)	Population-based case-control study (471 cases)	Clinical, X-ray, antibiotics	Passive smoker			Adjusted:
					>14	1.18 (0.90–1.57)
					<65	0.98 (0.68–1.41)
					≥65	1.56 (1.00–2.45)
Almirall 2008 [16] (Spain)	Population-based, case-control study, Nov 1999–Nov 2000 (1,336 cases)	Antibiotics, clinical and X-ray				Univariate:
			Ex-smoker	423	>14	1.37 (1.14–1.64)
			Current smoker	365	>14	1.34 (1.11–1.62)
			Passive smoker	143	>14	1.22 (0.93–1.61)
						Multivariate:
			Pack-yrs: ≤150	354	>14	1.01 (0.81–1.26)
			Pack-yrs: >150	362	>14	1.46 (1.14–1.86)
Gau 2010 [18] (USA)	Retrospective case-control study, 2004–2006 (194 cases)	X-ray				Adjusted:
			Ex-smoker	60	≥65	1.88 (1.15–3.06)
			Current smoker	28	≥65	2.34 (1.22–4.50)
Jackson 2009 [19] (USA)	Population-based, nested case-control study, influenza seasons and pre-influenza periods of 2000/01 and 2002/03 (1,173 cases)	Clinical and X-ray	Former smoker	57		Multivariate:
					≥65	1.3 (1.1–1.5)
					65–74	1.3 (1.0–1.6)
					75–84	1.4 (1.1–1.7)
					85	1.6 (1.1–2.3)
			Current smoker	9		Multivariate:
					≥65	1.8 (1.4–2.3)
					65–74	1.6 (1.1–2.5)
					75–84	2.3 (1.5–3.7)
					85	2.4 (1.1–5.1)

Reference (country)	Methodology (N)	Disease definition	Underlying definition	Number of smokers	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Juthani-Mehta 2013 [15] (USA)	Case-control study using a subset of a prospective cohort, 1997-2008 (193 cases)	Hospitalized pneumonia: ICD-9 criteria, clinical and chest X-ray	Current smoker Former smoker Pack-yrs smoking	18 103	70–79 70–79 70–79	Bivariate HR: 1.95 (1.16–3.26) Bivariate HR: 1.68 (1.24–2.27) Multivariate HR: 1.01 (1.00–1.01)
Mullerova 2012 [21] (UK)	Nested case-control population-based on retrospective COPD cohort, 1996–2005 (1,469 cases)	Diagnosis code	Former smoker Current smoker		≥45 (COPD) ≥45 (COPD)	Multivariate: 1.04 (0.90–1.2) 0.99 (0.86–1.14)
Obiora 2013 [22] (UK)	Nested case-control study using primary care patient database, 2001–2002 (4964 cases)	Medical records	Current smoker	1,219	Adults	1.69 (1.57–1.83)
Rodriguez 2009 [23] (Sweden)	Nested case-control study using the Health Improvement Network database, 2000–2005 (7,297 cases)	Pneumonia diagnosis code, validated by manual review of medical records	Smoker Ex-smoker	3,161 1,839	20–79 20–79	RR: 1.52 (1.40–1.65) RR: 1.14 (1.04–1.25)
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Smoker		18–49 50–64 ≥65	Rate ratio: 3.3 (3.2–3.3) Rate ratio: 4.0 (3.9–4.0) Rate ratio: 3.6 (3.5–3.6)
Vila-Corcoles 2009 [24] (Spain)	Population-based cohort study in community-dwelling individuals, 2002–2005 (473 cases)	Clinical, X-ray, microbiological and diagnosis code in hospital discharge database	Smoking	58	≥65	Multivariate HR: 1.12 (0.83–1.49)
Pneumococcal pneumonia						
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Smoker		18–49 50–64 ≥65	Rate ratio: 3.0 (2.7–3.3) Rate ratio: 4.4 (4.1–4.6) Rate ratio: 3.9 (3.6–4.3)

Reference (country)	Methodology (N)	Disease definition	Underlying definition	Number of smokers	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Invasive pneumococcal disease						
Flory 2009 [25] (USA)	Population-based surveillance study, 2002–2004 (609 cases)	Bacteremia pneumococcal pneumonia: microbiological	Current smoker	207	≥18	Adjusted: 2.2 (1.7–3.0)
Jacups 2011 [30] (Australia)	Prospective surveillance cohort study, 1987–1998 (cohort 1); retrospective chart review cohort study, 1999–2008 (cohort 2) (205 cases for cohorts 1+2)	Bacteremic pneumococcal pneumonia: X-ray, microbiological	Smoker	146	≥14	Multivariate adjusted RR: 2.7 (1.9–3.7)
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Smoker		18–49 50–64 ≥65	Rate ratio: 3.6 (2.8–4.5) Rate ratio: 4.3 (3.7–5.0) Rate ratio: 4.2 (3.2–5.5)
Watt 2007 [26] (USA)	Case-control prospective study, population-based active laboratory surveillance, 1999–2002 (118 cases)	Positive culture from a normally sterile fluid	Self-reported: Former smoker Current smoker Passive smoker	 21 11 29	 ≥18 ≥18 ≥18	 Univariate: 1.5 (0.8–2.8) Univariate: 1.1 (0.5–2.3) Univariate: 0.7 (0.4–1.1)

Grey rows represent cohort studies; white rows represent case-control studies. *Unless otherwise specified.
CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; OR, odds ratio, RR: relative risk.

Supplemental table S3 Risk of community-acquired pneumonia or pneumococcal disease in patients with diabetes mellitus

Reference (country)	Methodology (N)	Disease definition	Underlying definition	Number of cases with comorbidity	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Community-acquired pneumonia						
Almirall 2008 [16] (Spain)	Population-based, case-control study, Nov 1999–Nov 2000 (1,336 cases)	Antibiotics, clinical and X-ray	Treated diabetes mellitus	135	>14	Univariate: 1.43 (1.11–1.92)
Ehrlich 2010 [31] (USA)	Retrospective, longitudinal cohort study using Kaiser Permanente Medical Care Program database, including subcohort of survey responders (70,645 patients with diabetes)	ICD-9 diagnosis code	Diabetes		≥18	Multivariate HR: 1.92 (1.84–1.99)
Jackson 2009 [19] (USA)	Population-based, nested case-control study, influenza seasons and pre-influenza periods of 2000/01 and 2002/03 (1,173 cases)	Clinical and X-ray				Univariate, adjusted:
			Diabetes without insulin	6	≥65	1.0 (0.8–1.3)
			Diabetes with insulin	11	≥65	1.3 (1.0–1.5)
Juthani-Mehta 2013 [15] (USA)	Case-control study using a subset of a prospective cohort, 1997–2008 (193 cases)	Hospitalized pneumonia: ICD-9 criteria, clinical and chest X-ray	Diabetes mellitus	56	70–79	Bivariate HR: 1.05 (0.77–1.43)
Kornum 2008 [32] (Denmark)	Population-based, case-control study, 1997–2005 (34,239 cases)	Hospitalized pneumonia: ICD discharge codes				Adjusted:
			Diabetes (overall)	4,489	≥15	RR: 1.26 (1.21–1.31)
					15–39	RR: 3.21 (2.51–4.12)
					40–64	RR: 1.65 (1.51–1.81)
					65–79	RR: 1.22 (1.15–1.29)
					≥80	RR: 1.11 (1.05–1.18)
			Type 1 diabetes	101	≥15	RR: 4.43 (3.40–5.77)
					15–39	RR: 5.15 (3.61–7.36)
					40–64	RR: 3.43 (2.14–5.50)

Reference (country)	Methodology (N)	Disease definition	Underlying definition	Number of cases with comorbidity	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Kornum 2008 (cont'd)			Type 2 diabetes	4,388	≥15 15–39 40–64 65–79 ≥80	RR: 1.23 (1.19–1.28) RR: 2.15 (1.51–3.06) RR: 1.62 (1.47–1.77) RR: 1.22 (1.15–1.29) RR: 1.11 (1.05–1.18)
			Diabetes (types 1 & 2)			
			A1C level <7%	1,149	≥15	RR: 1.22 (1.14–1.30)
			A1C level ≥9%	568	≥15	RR: 1.60 (1.44–1.76)
			Duration ≥10 years	1,224	≥15	RR: 1.37 (1.28–1.47)
Mullerova 2012 [21] (UK)	Nested case-control population-based on retrospective COPD cohort, 1996–2005 (1,469 cases)	Diagnosis code	Diabetes		≥45 (COPD)	Multivariate: 1.07 (0.89–1.28)
Rodriguez 2009 [23] (Sweden)	Nested case-control study using the Health Improvement Network database, 2000–2005 (7,297 cases)	Pneumonia diagnosis code, validated by manual review of medical records	Diabetes	792	20–79	RR: 1.28 (1.13–1.44)
Seminog 2013 [14] (UK)	Retrospective cohort study of individuals hospitalized with diabetes mellitus, using two data sets of linked hospital admission and death records (Oxford Record Linkage Study [1963–1998] and all-England linked hospital episode statistics [1999–2011])	Lobar pneumonia: ICD diagnosis codes	Diabetes mellitus	2007–2011 (England): 2,287 15,648	 <60 ≥60	 Rate ratio: 2.34 (2.23–2.47) Rate ratio: 1.61 (1.58–1.65)
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Diabetes		18–49 50–64 ≥65	Rate ratio: 3.1 (3.1–3.2) Rate ratio: 3.0 (3.0–3.0) Rate ratio: 2.8 (2.8–2.8)
Skull 2009 [33] (Australia)	Case-cohort study (1,952 cases)	Hospitalized community-acquired pneumonia: diagnosis code, X-ray	Diabetes		≥65	Multivariate: RR: 1.22 (1.05–1.42)

Reference (country)	Methodology (N)	Disease definition	Underlying definition	Number of cases with comorbidity	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Vila-Corcoles 2009 [24] (Spain)	Population-based cohort study in community-dwelling individuals, 2002–2005 (473 cases)	Clinical, X-ray, microbiological and diagnosis code in hospital discharge database	Diabetes mellitus	120	≥65	Multivariate HR: 1.04 (0.85–1.29)
Vinogradova 2009 [8] (UK)	Nested case-control study in 443 general practices in the UK 1996–2005 (17,172 cases)	Incident diagnosis code	Diabetes	1,344 264	All ages 5–64	Adjusted: 1.36 (1.27–1.47) Adjusted: 1.74 (1.49–2.02)
Pneumococcal pneumonia						
Jacups 2011 [30] (Australia)	Prospective surveillance cohort study, 1987–1998 (cohort 1); retrospective chart review cohort study, 1999–2008 (cohort 2) (205 cases for cohorts 1+2)	Bacteremic pneumococcal pneumonia: X-ray, microbiological	Diabetes	44	≥14	Multivariate, adjusted: RR: 2.3 (1.6–3.3)
Seminog 2013 [14] (UK)	Retrospective cohort study of individuals hospitalized with diabetes mellitus, using two data sets of linked hospital admission and death records (Oxford Record Linkage Study [1963–2011] and all-England linked hospital episode statistics [1999–2011])	ICD diagnosis codes	Diabetes mellitus	2007–2011 (England): 82 327	 <60 ≥60	 Rate ratio: 2.03 (1.55–2.65) Rate ratio: 1.54 (1.32–1.79)
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Diabetes		18–49 50–64 ≥65	Rate ratio: 3.1 (2.9–3.3) Rate ratio: 3.0 (2.8–3.1) Rate ratio: 2.8 (2.7–2.9)
Invasive pneumococcal disease						
Flory 2009 [25] (USA)	Population-based surveillance study, 2002–2004 (609 cases)	Bacteremia pneumococcal pneumonia: microbiological	Diabetes mellitus	65	≥18	Adjusted: 1.4 (1.0–2.0)

Reference (country)	Methodology (N)	Disease definition	Underlying definition	Number of cases with comorbidity	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Inghammar 2013 [13] (Sweden)	Nested case-control study, 1987–2008 (4084 cases)	Positive culture from a normally sterile fluid	Diabetes mellitus	298	≥18	Multivariate: 1.7 (1.5–1.9)
Seminog 2013 [14] (UK)	Retrospective cohort study of individuals hospitalized with diabetes mellitus, using two data sets of linked hospital admission and death records (Oxford Record Linkage Study [1963–1998] and all-England linked hospital episode statistics [1999–2011])	Pneumococcal septicemia and meningitis: ICD diagnosis codes	Diabetes mellitus	2007–2011 (England): 33 93	 <60 ≥60	 Rate ratio: 2.06 (1.33–3.14) Rate ratio: 1.50 (1.12–2.01)
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Diabetes		18–49 50–64 ≥65	Rate ratio: 3.0 (2.4–3.7) Rate ratio: 2.6 (2.3–2.9) Rate ratio: 2.5 (2.2–2.9)
van Hoek 2012 [12] (UK)	Comparison of prevalence of clinical risk factors in the general population with that in hospitalized patients with invasive pneumococcal disease, 2002–2009 (22,298 cases)	ICD diagnosis code; microbiological	Diabetes	703 1,495	16–64 ≥65	4.6 (4.2–5.0) 2.3 (2.2–2.5)
Watt 2007 (USA) [26]	Case-control prospective study, population-based active laboratory surveillance, 1999–2002 (118 cases)	Positive culture from a normally sterile fluid	Diabetes mellitus	37	≥18 ≥18 ≥18 (chronic renal failure)	Univariate: 1.7 (1.0–2.9) Multivariate: 1.5 (0.8–2.6) Multivariate: 5.8 (2.3–14.8)
Wotton 2012 [34] (UK)	Retrospective cohort study of individuals hospitalized with immune-mediated diseases, using two data sets of linked hospital admission and death records (Oxford Record Linkage Study [ORLS1: 1963–1998; ORLS2: 1999–2008] and all-England linked hospital episode statistics [1999–2008])	ICD diagnostic codes	Diabetes mellitus (since <30 years of age)		All ages (ORLS2) All ages (England)	Rate ratio: 3.30 (2.07–5.07) Rate ratio: 3.90 (3.55–4.28)

Grey rows represent cohort studies; white rows represent case-control studies. *Unless otherwise specified.

A1C, glycated hemoglobin; CI, confidence interval; ChI, Charlson index; HR, hazard ratio; ICD, International Classification of Diseases; OR, odds ratio, RR: relative risk.

Supplemental table S4 Risk of community-acquired pneumonia or pneumococcal disease in patients with chronic heart disease

Reference (country)	Methodology	Disease definition	Underlying definition	Number of exposed cases	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Community-acquired pneumonia						
Almirall 2008 [16] (Spain)	Population-based, case-control study, Nov 1999–Nov 2000 (1,336 cases)	Antibiotics, clinical and X-ray	CHF	114	>14	Univariate: 1.81 (1.33–2.49)
			Heart valve disease	59	>14	Univariate: 1.70 (1.11–2.61)
			Coronary artery disease	80	>14	Univariate: 1.05 (0.76–1.45)
Gau 2010 [18] (USA)	Retrospective case-control study, 2004–2006 (194 cases)	X-ray	CHF	63	≥65	Adjusted: 1.60 (1.04–2.46)
			Coronary artery disease	77	≥65	Adjusted: 1.40 (0.94–2.08)
Jackson 2009 [19] (USA)	Population-based, nested case-control study, influenza seasons and pre-influenza periods of 2000/01 and 2002/03 (1,173 cases)	Clinical and X-ray				Multivariate:
			Non-CHF heart disease	32	≥65 65–74 75–84 85	1.2 (1.1–1.4) 1.2 (1.0–1.6) 1.1 (0.9–1.4) 1.5 (1.0–2.3)
			Mild CHF	10	≥65 65–74 75–84 85	1.9 (1.5–2.5) 2.3 (1.4–4.0) 3.2 (2.2–4.8) 1.1 (0.6–1.8)
			Severe CHF	8	≥65 65–74 75–84 85	3.3 (2.3–4.7) 2.8 (1.5–5.4) 3.5 (2.1–5.8) 2.7 (1.1–6.6)
Juthani-Mehta 2013 [15] (USA)	Case-control study using a subset of a prospective cohort, 1997–2008 (193 cases)	Hospitalized pneumonia: ICD-9 criteria, clinical and chest X-ray	Coronary heart disease	70	70–79	Bivariate HR: 1.25 (0.93–1.68)

Reference (country)	Methodology	Disease definition	Underlying definition	Number of exposed cases	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Mor 2013 [10] (Denmark)	Population-based case-control study using healthcare databases in northern Denmark, 1994–2008 (67,162 cases)	Hospitalized pneumonia (including hospital-acquired pneumonia): ICD diagnosis code				Adjusted:
			Overall CHF	12,339	≥15	1.81 (1.76–1.86)
			Cardio-myopathy	371	≥15	2.05 (1.80–2.33)
			Heart valve disease	703	≥15	2.19 (2.00–2.40)
			Acute myocardial infarction	2,704	≥15	1.69 (1.59–1.80)
			Atrial fibrillation	5,713	≥15	1.72 (1.66–1.78)
			Others	2,848	≥15	1.99 (1.89–2.09)
Mullerova 2012 [21] (UK)	Nested case-control population-based on retrospective COPD cohort, 1996–2005 (1,469 cases)	Diagnosis code				Multivariate:
			Myocardial infarction		≥45 (COPD)	1.0 (0.85–1.19)
			CHF		≥45 (COPD)	1.37 (1.20–1.57)
Nyboe 2014 [11] (Denmark)	Nationwide cohort study in adults with closed versus unclosed atrial septal defect using Danish National Patient Registry, 1997–2009 (240 cases)	Diagnosis code	Atrial septal defect:			Adjusted HR:
			Closed	161	≥18	2.8 (2.3–3.5)
			Unclosed	79	≥18	3.1 (2.4–4.0)
Obiora 2013 [22] (UK)	Nested case-control study using primary care patient database, 2001–2002 (4,964 cases)	Medical records	Myocardial infarction	630	Adults	1.36 (1.23–1.50)
Rodriguez 2009 [23] (Sweden)	Nested case-control study using the Health Improvement Network database, 2000–2005 (7,297 cases)	Pneumonia diagnosis code, validated by manual review of medical records	Ischemic heart disease	1,244	20–79	RR: 1.28 (1.16–1.42)
			Myocardial infarction	512	20–79	RR: 1.42 (1.22–1.65)
			CHF	533	20–79	RR: 2.63 (2.21–3.14)
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Chronic heart disease		18–49	Rate ratio: 4.9 (4.9–5.0)
					50–64	Rate ratio: 4.3 (4.2–4.3)
					≥65	Rate ratio: 3.8 (3.8–3.8)

Reference (country)	Methodology	Disease definition	Underlying definition	Number of exposed cases	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Vila-Corcoles 2009 [24] (Spain)	Population-based cohort study in community-dwelling individuals, 2002–2005 (473 cases)	Clinical, X-ray, microbiological and diagnosis code in hospital discharge database	Chronic heart disease	99	≥65	Multivariate HR: 1.46 (1.16–1.84)
Vinogradova 2009 [8] (UK)	Nested case-control study in 443 general practices in the UK 1996–2005 (17,172 cases)	Incident diagnostic code	Chronic heart disease	3,239 321	All ages 5–64	Adjusted: 1.63 (1.54–1.72) Adjusted: 2.05 (1.78–2.37)
Pneumococcal pneumonia						
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Chronic heart disease		18–49 50–64 ≥65	Rate ratio: 5.1 (4.6–5.5) Rate ratio: 4.2 (4.0–4.4) Rate ratio: 3.8 (3.6–3.9)
Invasive pneumococcal disease						
Inghammar 2013 [13] (Sweden)	Nested case-control study, 1987–2008 (4,084 cases)	Positive culture from a normally sterile fluid	CHF	333	≥18	Multivariate: 1.7 (1.4–1.9)
Shea 2014 [7] (USA)	Retrospective cohort study using three healthcare claims repositories, 2006–2010	Diagnosis/drug codes	Chronic heart disease		18–49 50–64 ≥65	Rate ratio: 3.9 (3.0–5.1) Rate ratio: 2.9 (2.6–3.3) Rate ratio: 3.2 (2.8–3.6)
van Hoek 2012 [12] (UK)	Comparison of prevalence of clinical risk factors in the general population with that in hospitalized patients with invasive pneumococcal disease, 2002–2009 (22,298 cases)	ICD diagnosis code; microbiological	Chronic heart disease	1,213 4,841	16–64 ≥65	6.9 (6.5–7.4) 3.0 (2.9–3.1)

Reference (country)	Methodology	Disease definition	Underlying definition	Number of exposed cases	Population age (years) (other predisposing condition)	Fold risk elevation OR (95% CI)*
Watt 2007 [26] (USA)	Case-control prospective study, population-based active laboratory surveillance, 1999–2002 (118 cases)	Positive culture from a normally sterile fluid	CHF	26	≥18	Univariate: 9.9 (4.3–23.0)
			History of myocardial infarction	7	≥18	Univariate: 2.6 (0.9–7.5)
			Coronary artery disease	15	≥18	Univariate: 2.9 (1.3–6.2)

Grey rows represent cohort studies; white rows represent case-control studies. *Unless otherwise specified.
CI, confidence interval; HR, hazard ratio; CHF, congestive heart failure; ICD, International Classification of Diseases; OR, odds ratio, RR: relative risk.