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Pneumococcal disease seasonality: incidence, severity, and the role of influenza activity

Short title: Influenza-pneumococcal interactions

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ABSTRACT

BACKGROUND: We tested whether the effect of influenza activity on invasive pneumococcal disease incidence and severity varies between age and co-morbidity groups.

METHODS: Weekly rates of invasive pneumococcal disease were obtained from the Danish National Laboratory Surveillance System (1977-2007). Influenza-like illness data were collected from a-sentinel surveillance system, Statens Serum Institut. We fit Poisson regression models for invasive pneumococcal disease, with predictors for seasonality, trends, and influenza activity, and allowed the influenza activity variable to vary by co-morbidity level and clinical presentation.

RESULTS: Influenza activity accounted for 8.4% (95%CI 4.8–11.9%) and 6.9% (95%CI: 5.4-10.2%) of all invasive pneumococcal disease cases among 15-39 and 40+ year olds, respectively but had no measureable impact among children under 15 years. Influenza activity was associated with significant increases in the incidence of invasive pneumococcal pneumonia in both children and adults. The association was more pronounced among younger adults without co-morbidities. Case-fatality also varied seasonally among the elderly, and this variation might be associated with influenza activity.

CONCLUSIONS: Pneumococcal incidence and the severity of disease varied seasonally and between age groups. The effect of influenza activity on pneumococcal disease varied between children and adults, and this difference was largely due to differences in disease presentation.

KEYWORDS: Pneumococcal, *Streptococcus pneumoniae*, influenza co-infection, co-morbidity

INTRODUCTION

Streptococcus pneumoniae, or pneumococcus, causes a large proportion of pneumonia cases worldwide [1] as well as meningitis, septicemia, and otitis media. While pediatric conjugate vaccines have successfully reduced disease burden in vaccinated age groups [2], pneumococcal pneumonia remains a significant cause of morbidity, particularly in adults. Understanding the etiology of pneumococcal disease in different risk groups can help to inform clinical decision making, to determine the potential impact of viral epidemics and pandemics, and to better tailor public health interventions to prevent disease.

Pneumococcal disease frequently occurs following a primary viral infection, and the importance of prior or concomitant infection with influenza virus has been particularly well documented [3-10]. Evidence from epidemiological studies and experimental animal models support a role for influenza in affecting both transmission and host susceptibility to pneumococcus [9, 11-17].

Host characteristics likely affect the synergistic relationship between influenza and pneumococcus. During the 2009 influenza A(H1N1) pandemic, the effect of influenza on pneumococcal pneumonia varied significantly between age groups, with a particularly strong effect among school-aged children [10]. Aside from age, co-morbidities could influence the relative importance of influenza. In a study of severe pandemic influenza infections in intensive care units, patients with bacterial co-infections tended to be younger and with fewer underlying conditions than patients without co-infections [18].

In the present study, we used data from Danish national registries spanning three decades to determine whether the importance of the interaction between influenza activity and pneumococcus varies with age and underlying conditions.

METHODS

Data sources

Invasive pneumococcal disease (IPD) data were obtained from the Danish National Laboratory Surveillance System at the Statens Serum Institut (SSI), which has maintained individual-level information on pneumococcal disease patients since 1977 [19, 20]. All IPD cases were used for estimation of the seasonal incidence curves, and all cases that occurred during years in which weekly influenza data were available (1982/83-1990/91 and 1994/95-2006/07) were used to fit the models. Cases of invasive pneumococcal pneumonia (IPP) were defined as the occurrence of culture confirmed pneumococcal bacteremia in a hospitalized patient who received a discharge code of pneumonia (codes 073, 471, 480-486 from the WHO International Classification of Disease (ICD)-8 and codes J12-J18 from ICD-10th)[20]. Date of hospital admission, patient age, clinical presentation (IPD, with or without a pneumonia diagnosis), and co-morbidities were compiled for each patient. A summary index for patient co-morbidity was estimated by the Charlson index as previously described [20]. Weekly time series were created for each age group (0-4, 5-14, 15-24, 25-39, 40-64, 65+ years), clinical presentation, and co-morbidity group, as indicated. For the regressions, the time series were collapsed into broader age groups to increase statistical power: (0-14, 15-39, 40+ years).

Weekly influenza-like illness (ILI), defined as acute onset of fever, myalgia and respiratory symptoms, data were used as a proxy for influenza viral activity [21, 22]. The data were collected from two sources, both managed by SSI. The Danish sentinel surveillance system, covering the period 1994/95-2006/07, is based on voluntary participation of up to 150 nationwide general practitioners. Between week 40 and week 20 of the following calendar year,

general practitioners report the weekly number of ILI consultations and the number of total consultations in their practice [23]. For 1982/83-1990/91, data were obtained from nationwide reports of general practitioners. Weekly ILI data were not available between 1991/92 and 1993/94.The ILI data from both surveillance systems were scaled by dividing by the mean winter activity for the respective surveillance system and then subtracting the mean summer value to anchor the minimum values to 0.

The study was approved by the Danish Data Protection Agency (record number 2007-41-0229).

Seasonality of IPD incidence

We determined the total number of cases of IPD in each July-June period from 1977/78-2006/07 and the percent of this total occurring in each week. We then calculated the mean percent and 95% confidence interval for each week using data from all of the years, with the average weighted by the total number of isolates in the July-June period.

Effect of ILI on pneumococcal incidence

To determine the effect of ILI on the incidence of IPD, we fit a Poisson regression model based, in part, on methods described elsewhere [3, 8, 10]. Respiratory seasons ran from July to June of each year, and for these analyses, we focused only on the seasons with available data on ILI activity (n=22 seasons, 1982/83-1990/91 and 1994/95-2006/07). As indicated, data were stratified by clinical presentation (IPD with or without a pneumonia diagnosis) and Charlson co-morbidity score.

AIC criteria were used to identify the most parsimonious model. The best model included 52-week harmonic terms that varied between strata as well as 26- week harmonic terms and dummy variables for weeks 51-52 and 1-3 that did not vary between strata. Alternative models included simpler ones that fit a single seasonal baseline for all strata or more complicated models that allowed all of the components to vary between strata. The final model was:

$$\ln(Y_{ij}/Z_j) = \alpha + \tau_j + \beta_m * \text{week}_m + \gamma_q * \sin\theta_q + \delta_k * \cos\theta_q + \varepsilon * \text{flu} + \kappa_j * \text{flu} + \upsilon_{52j} * \sin\theta_{52} + \varphi_{52j} * \cos\theta_{52}$$

Where Y_{ij} is the weekly number of pneumococcal cases in week i for comorbidity- and syndrome-strata j, and Z_j is an offset representing the mean number of cases during non-ILI summer weeks (July-November and April-June of each respiratory season). This offset effectively adjusts for changes in detection/reporting, multi-year changes in incidence, and changes in population size. **α and τ_j** are the overall and strata-specific intercepts. "**week_m**" are indicator variables for weeks of the year 51,52,1,2,3, which control for the mid-winter spike and drop in incidence; ***$\sin\theta q$ and $\cos\theta q$*** are harmonic terms representing annual and semi-annual periodicities (52 week and 26 week) to control for baseline seasonal fluctuations. "**flu**" represents weekly ILI activity, lagged by 1 week (lags of 0 and 2 weeks were also evaluated and gave similar results). For the flu and the 52-week harmonic terms, we estimated both an overall average effect and a strata-specific effect (interactions with dummy variable for stratum). The combination of ε and κ_j gives the overall effect of ILI. The model was fit separately to data from each age group, and the ILI-attributable fraction of pneumococcal disease was calculated as described elsewhere [8, 10]. Confidence intervals were calculated using seasonal block bootstraps[24] with 1000 replicates.

In sensitivity analyses, we fit the model to data from each strata separately and found the overall patterns to be the same, albeit with more variability. We also fit a simplified model where the seasonal harmonic terms did not vary between strata, and this did influence the estimates of the flu effect, as described. The simplified model was:

$$\ln(Y_{ij}/Z_j) = \alpha + \tau_j + \beta_m * week_m + \gamma_q * sin\theta_q + \delta_k * cos\theta_q + \varepsilon * flu + \kappa_j * flu$$

Seasonality of case-fatality ratio and effect of ILI activity by age group

To test whether the case fatality ratio of IPP varied seasonally and whether some of these variations could be associated with ILI activity, we used logistic regression models (binomial distribution, log link). The endpoint was death due to any cause occurring within 30 days of an IPD-related admission [20]. The model outcome was deaths/ IPP cases and predictors included ILI epidemic period (dichotomous) and month of the year, as indicated. For the model that included month of the year, there were indicator variables for each month between November and March, and the reference group was April-September. Serfling regression [25] was used to determine the seasonal baseline for ILI and to define "ILI epidemic" weeks. The risk ratios were calculated by exponentiating the relevant regression coefficients. The analysis was stratified by age group (40-64 years, 65+) and co-morbidity level (low Charlson score of 0, or medium/high Charlson score (score of 1 or more). Younger age groups had too few deaths for analysis, and due to sparser numbers in the early years, we focused on the period 1994/95-2006/07 for this analysis.

Models were fit using PROC GENMOD, SAS software, version 9.2 (SAS Institute, Cary, North Carolina, United States).

RESULTS

Population and disease characteristics

From 1977-2007, there were 18,858 cases of IPD in Denmark reported to SSI, of which 11,878 (63%) had an ICD-coded diagnosis of pneumonia. Of these, 47% (n=5633) had medium or high Charlson co-morbidity scores (>= 1) (Table 1). Most patients under 65 years old with IPP had a low level of co-morbidity as estimated by the Charlson index (score of 0) while the majority of the cases in the 65 years and older population had medium/high co-morbidity scores (score of ≥1) (Table 1).

The incidence of IPD in all age groups demonstrated winter seasonality (**Figure 1**). Among those older than 65 years, there was a broad seasonal curve with the minimum incidence occurring in August and a sharp spike in disease that occurred during the last weeks of December, corresponding to the Christmas holiday (Figure 1E). A similar pattern was observed in the 40-64 year old population, although the late-December spike in incidence was less pronounced in this group (Figure 1D). The 0-4, 5-14, 15-24, and 25-39 year old populations had broad seasonal peaks without a strong winter spike, and in all age groups, there was a modest drop in incidence during late-December/early-January (Figures 1A-C). In patients aged 65 years and older, the seasonal distributions were comparable regardless of co-morbidity (Figure S1).

The effect of ILI varies by age group and clinical manifestation

We first estimated the association between ILI and the incidence of IPD. ILI was associated with significant increases in the incidence of IPD above the seasonal baseline among 15-39, and 40+ year olds. In these age groups, 8.4% (95% CI 4.8, 11.9) and 6.9% (95% CI: 5.4,

10.2) of IPD cases were attributable to ILI, respectively. In contrast, there was no detectable increase in the incidence of IPD above the seasonal baseline among the <15 year olds (etiological percent: 0.6%; 95%CI: -3.8,5.5%).

Most IPD cases in adults presented with pneumonia, while most cases in children did not (Table 1). To evaluate whether this difference in disease presentation might explain the lack of a detectable effect in children, we next stratified the cases based on whether they had a clinical diagnosis of pneumonia. Among the <15 year olds, ILI was associated with a significant percent of IPD cases with a pneumonia diagnosis (etiological fraction: 7.7%; 95%CI: 0.9,14.0) but there was no detectable effect of ILI on the incidence of IPD without a pneumonia diagnosis (-3.1%; 95%CI: -8.9, 3.2) (Figure 2). The effect of ILI on the incidence of IPP was comparable between children and adults (**Figure 2**). Among adults, ILI had a significant impact on the incidence of IPD with or without a pneumonia diagnosis (**Figure 2**).

Co-morbidity and the effect of ILI

We next considered whether underlying conditions might affect the ILI-IPD interaction. For the age groups where we had sufficient data, we stratified the analysis by Charlson co-morbidity score. Among the 15-39 year olds, ILI was associated with a significant increase in IPD among those with low co-morbidity levels (etiologic fraction: 9.9%; 95%CI: 6.0-13.0%) but had no detectable effect among those with known co-morbidities (etiologic fraction: 0.3%; 95%CI: -8.4-9.7%) (**Table 2**). In contrast, among the 40+ year olds, the effect of ILI was of a comparable magnitude among those with or without underlying conditions (**Table 2**). This general pattern held when we further stratified the data based on clinical manifestation (**Table 2**), although the confidence intervals were broad due to small numbers in each strata.

Severity of invasive pneumococcal pneumonia is seasonal

Finally, we considered whether pneumococcal disease severity, in addition to incidence, varies seasonally and whether ILI might influence these variations. Case-fatality ratios (CFR) for IPP demonstrated significant seasonal variation in the 65+ population. Those with low co-morbidity scores had an increased risk of death in January compared with April-October (**Table 3**, Risk ratio: 1.71; 95% CI: 1.17-2.49). The risk of death in this group was elevated for the period from November-March, although only the increase in January was statistically significant. Among the 65+ year olds with medium/high co-morbidity scores, the risk of death was significantly higher in December (RR: 1.37; 95%CI: 1.14-1.65) and February (RR:1.31; 95%CI: 1.06-1.62) compared with April-October (Table 3). In contrast, among the 40-64 year olds, there were no significant increases in case-fatality rates during the winter months (**Table 3**).

In a multivariate model that included terms for month of the year and ILI activity (ILI activity above a seasonal threshold), we found that the risk of death increased by 42% during ILI epidemic periods among 65+ year olds with low co-morbidity scores (RR 1.42; 95%CI: 1.06-1.90). ILI activity was not associated with any detectable change in the population-level risk of death due to IPP among the 65+ population with medium/high co-morbidity scores or among 40-64 years old cases, regardless of co-morbidity.

DISCUSSION

Based on data spanning three decades and a dataset of almost 19,000 IPD cases, we demonstrate that the incidence and severity of IPD both vary seasonally, and these seasonal patterns differ between age groups. The relative importance of ILI in driving the incidence of

IPD varied between age groups, and some of this variation can be explained by differences in clinical manifestation (pneumonia in older age groups, non-pneumonia in younger age groups). The importance of ILI might also vary by host co-morbidity, but the numbers of cases in the stratified analyses were too small to draw firm conclusions. These findings are significant because they suggest that the characteristics of patients presenting with pneumococcal disease will differ seasonally and during influenza epidemic/pandemic periods and non-influenza periods. This information could be used to improve planning for pandemic scenarios.

Our estimates of the fraction of IPD attributable to ILI are largely in line with previous estimates from Sweden (6-7%) [3] and the United States (4.5-6%)[8]. In the US study, they found that the effect of influenza was detectable only among pneumonia cases. In contrast, we found that influenza activity was associated with significant increases in the incidence of IPD without a pneumonia diagnosis among adults not among children. It is possible that the pneumonia case definitions used in this study were different from those in the US, where an active surveillance system is in place. However, the proportion of adult IPD cases with a pneumonia diagnosis is comparable in the two populations.

It is unclear why influenza would be associated with increases in non-pneumonia IPD cases. One possibility is that the observed increases in adult IPD result from both increased susceptibility to pneumococcal invasion in viral-infected individuals and increased transmission of the bacteria in the population, which would influence IPD incidence in individuals with or without a primary viral infection. Also, since this is a register-based study, some confounding could occur when assigning pneumonia diagnosis codes to patients admitted to a hospital with IPD. However this would not be expected to be systematic throughout the dataset.

The seasonal patterns of IPD incidence among Danish adults mirrored those described in the US [26, 27], with a sharp mid-winter spike that corresponds in time to the Christmas holidays. However, we found that the seasonal pattern in younger age groups was distinct—not only was there a lack of a winter spike, but there was a significant drop in incidence in January, perhaps reflecting decreased transmission following the school holiday.

Aside from the seasonal variations in disease incidence, we also found that the risk of death from invasive pneumococcal pneumonia also varied seasonally among the elderly. These increases were especially pronounced during influenza epidemic periods, suggesting that influenza-associated cases might be more severe, but additional studies are needed to support this observation. This finding is consistent with clinical studies demonstrating that mixed influenza-bacterial infections have a higher case-fatality than viral or bacterial infections alone [28]. The reason for the different seasonal pattern in case fatality between the elderly and the middle aged adults could be related to increased susceptibility to environmental stresses among the elderly.

These analyses focus on IPD (pneumococcal bacteraemia or meningitis), which constitutes a small percentage of all pneumococcal disease [29]. Studies of all-cause pneumonia suggest that influenza also accounts for a relatively small percentage of total cases [29]. More detailed analyses could focus on the effect of influenza on the incidence of all-cause pneumonia in different risk groups.

The ecological design of this study has both strengths and weaknesses. We have tried to control for unrelated seasonal factors by using harmonic terms, but we cannot draw a strong causal link due to the design. As a strength, ecological study designs do not suffer from biases in testing between age groups and is less affected by poor sensitivity of the viral tests.

We evaluated the relationship between influenza and pneumococcal disease with a 1-week lag. The impact of influenza on the risk for bacterial disease is thought to be transient, which is supported by the observation that pneumococcal disease cases quickly returned to baseline levels following the 2009 influenza pandemic [10].

There are some limitations of the dataset that we used. The "pneumonia" category was based on clinical judgment and subsequent ICD coding, so there is a potential for misclassification to occur. Such misclassification would likely reduce any differences between the pneumonia and non-pneumonia categories. Additionally, over the course of the 30 year study period, the rates and sensitivity of blood culturing and the reporting of isolates to SSI could have changed and could potentially influence the results reported here. Moreover, our definition of co-morbidity is based on broad diagnoses covered by the Charlson index, and we might detect stronger differences if we could stratify by the type of co-morbidity (ie immune-compromising conditions vs diabetes). Finally, we did not have information on the rate of blood culturing among hospitalized cases in the different age and co-morbidity groups. If the rate of blood culturing during influenza periods differs between risk groups, this will introduce some confounding to the calculation of the estimates.

These analyses have demonstrated that the seasonal variations of pneumococcal disease incidence and severity differ between age groups, and the impact of influenza on pneumococcal disease differs by age, clinical presentation, and co-morbidity status. When comparing studies or projecting the impact of pneumococcal vaccine-associated changes, it will be necessary to take these heterogeneities into account.

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FIGURE LEGENDS

FIGURE 1: Seasonal fluctuations in the incidence of invasive pneumococcal disease, expressed as percent of disease occurring in each week out of the total cases in each July-June season, +/- 95% confidence intervals by age group.

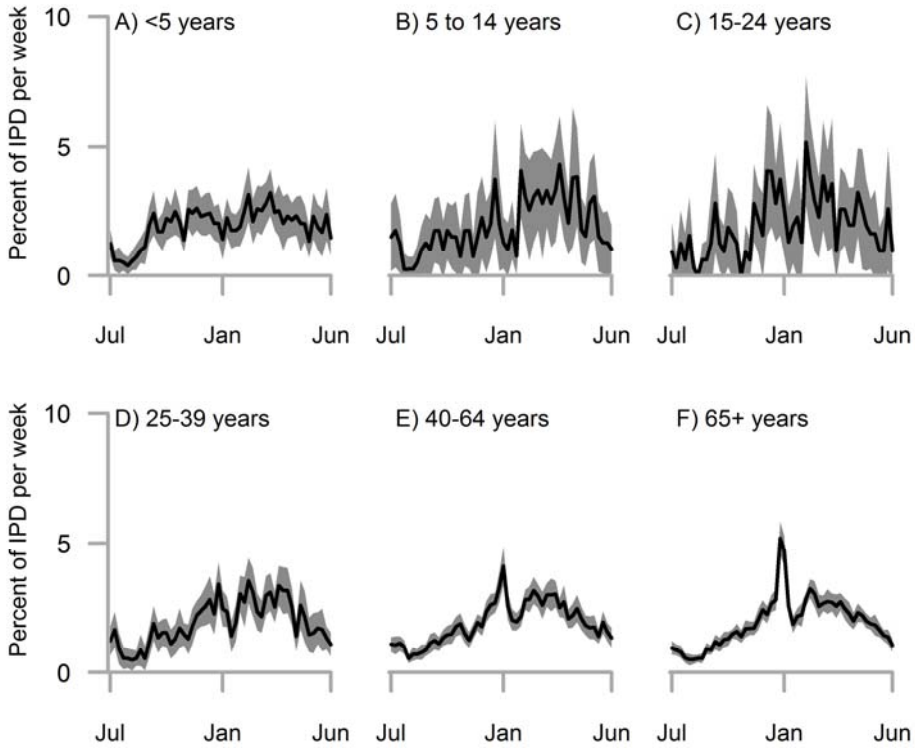

FIGURE 2: Effect of influenza-like illness on incidence of invasive pneumococcal disease by age and clinical manifestation (IPD cases with or without a diagnosis of pneumonia). +/-95% confidence intervals.

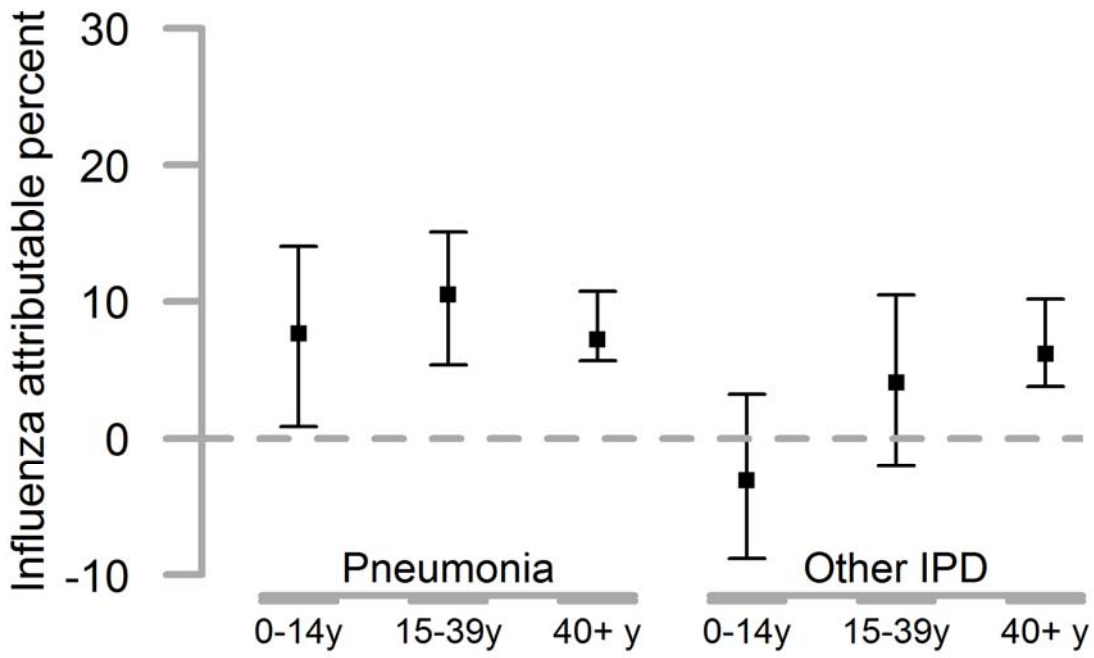

FIGURE S1. Seasonal variation in invasive pneumococcal disease incidence among the 40+ population with a diagnosis of pneumonia or non-pneumonia and stratified by Charlson co-morbidity score. Expressed as percent of disease occurring in each week out of the total cases in each July-June season, +/- 95% confidence intervals. Brown dash: pneumonia, low co-morbidity; green dash: pneumonia, medium/high co-morbidity; red dash: non-pneumonia, low co-morbidity; blue solid: non-pneumonia, medium/high co-morbidity.

FIGURE S2. Example of model fit, showing weekly IPD cases among 40+ year olds during 1994/95-2006/07. Blue is predicted from the full model, black is the predicted seasonal baseline (subtracting the estimated effect of influenza-like illness) estimated from the full model, and grey is observed, smoothed with a 6-week Hamming window. The model was fit to the unsmoothed weekly data.

Table 1. Cases of IPD by age group and Charlson co-morbidity score 1977-2007, N=18,858.

Age (years)	Invasive Pneumonia (N)	Other IPD (N)
<5 Total	394	1187
Low co-morbidity (Charlson=0)	337	1125
Medium/High co-morbidity (Charlson≥1)	57	62
5-14 Total	188	224
Low co-morbidity (Charlson=0)	166	184
Medium/High co-morbidity (Charlson≥1)	22	40
15-24 Total	215	112
Low co-morbidity (Charlson=0)	186	83
Medium/High co-morbidity (Charlson≥1)	29	29
25-39 Total	1140	532
Low co-morbidity (Charlson=0)	955	415
Medium/High co-morbidity (Charlson≥1)	185	117
40-64 Total	3507	2182
Low co-morbidity (Charlson=0)	2065	1245
Medium/High co-morbidity (Charlson≥1)	1442	937
65+ Total	6434	2743
Low co-morbidity (Charlson=0)	2536	1224
Medium/High co-morbidity (Charlson≥1)	3898	1519

Table 2. Percent of invasive pneumococcal disease attributable to influenza-like illness activity. Stratified by co-morbidity and by clinical manifestation . Denmark, 1977-2007, N= 13,882 cases of IPD.

	Age (years)	
	15-39	40+
All IPD		
Low co-morbidity (Charlson=0)	9.9 (6.0-13.0)	7.6 (5.1-11.6)
Medium/High co-morbidity (Charlson≥1)	0.3 (-8.4-9.7)	6.2 (4.3-9.3)
IPD with pneumonia diagnosis		
Low co-morbidity (Charlson=0)	11.2 (6.5-14.8)	7.8 (5.8-11.7)
Medium/High co-morbidity (Charlson≥1)	5.4 (-5.0-18.7)	6.5 (4.4-10.1)
IPD with other diagnosis		
Low co-morbidity (Charlson=0)	6.6 (-1.2-14.3)	6.9 (1.8-12.8)
Medium/High co-morbidity (Charlson≥1)	-6.6 (-25.7-7.6)	5.3 (2.5-8.9)

The <14 year olds were excluded from this analysis due to small numbers in the medium/high co-morbidity group

Table 3. Risk of death from invasive pneumococcal pneumonia in each month compared with July-September, by age group and Charlson co-morbidity score[‡], 1994-2007.

Age (y)	Co-morbidity score[‡]	Month	Die (N)	Survive (N)	Case-fatality (%)	Risk ratio
40-64	Low	November	9	84	9.7	1.0 (0.5-2.0)
		December	27	177	13.2	1.4 (0.9-2.2)
		January	16	150	9.6	1.0 (0.6-1.7)
		February	12	166	6.7	0.7 (0.4-1.3)
		March	11	196	5.3	0.6 (0.3-1.1)
		April-October	55	529	9.4	REF
	Medium/High	November	10	64	13.5	0.8 (0.4-1.4)
		December	18	112	13.9	0.8 (0.5-1.3)
		January	21	75	21.9	1.2 (0.8-1.9)
		February	22	102	17.7	1.0 (0.6-1.7)
		March	11	117	8.6	0.7 (0.4-1.3)
		April-October	81	381	17.5	REF
65+	Low	November	19	132	12.6	1.1 (0.7-1.8)
		December	42	235	15.2	1.4 (0.9-1.9)
		January	34	144	19.1	1.7 (1.2-2.5)*
		February	32	178	15.2	1.4 (0.9-2.0)
		March	30	169	15.1	1.3 (0.9-2.0)
		April-October	68	540	11.2	REF
	Medium/High	November	45	203	18.2	0.9 (0.7-1.2)
		December	129	328	28.2	1.4 (1.1-1.6)*
		January	68	225	23.2	1.1 (0.9-1.4)
		February	84	227	27.0	1.3 (1.1-1.6)*
		March	69	238	22.5	1.1 (0.9-1.4)
		April-October				REF

[‡] low co-morbidity: Charlson=0; medium/high co-morbidity: Charlson ≥1

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