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David M. Roth Date

Epidemiology of Opportunistic Premise Plumbing Pathogens and Associated Antibiotic Resistance

By

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Master of Science in Public Health

Environmental Health - Epidemiology

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Epidemiology of Opportunistic Premise Plumbing Pathogens and Associated Antibiotic Resistance

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Abstract

Epidemiology of Opportunistic Premise Plumbing Pathogens
and Associated Antibiotic Resistance
By David M. Roth

Purpose: Opportunistic Premise Plumbing Pathogens (OPPPs) are naturally occurring organisms that are commonly found within premise plumbing. The most commonly thought of OPPPs are the nontuberculous mycobacteria (NTM) and bacteria *Legionella* and *Pseudomonas*. Previous research has estimated that up to 30% of the U.S. population may be exposed to OPPPs. The primary objective of this analysis was to provide national and regional epidemiologic estimates for the commonly thought of OPPPs. The secondary objective was to explore predictive factors associated with antibiotic resistance in individuals hospitalized with an OPPP.

Methods: We used the 2012 Healthcare Cost and Utilization Project National Inpatient Sample for this study. Estimates of demographics, hospitalization characteristics, comorbidities, antibiotic resistance and associated costs for all three selected OPPPs were calculated using SAS survey procedures. Logistic regression techniques were used to create a parsimonious predictive model of antibiotic resistance among hospitalizations involving *Pseudomonas* pneumonia.

Results: In 2012, there were an estimated 73,565 discharges of non-institutionalized U.S. patients with an infection due to an OPPP, with 610 hospitalizations involving multiple OPPPs. *Pseudomonas* showed no variability across season or region. Legionnaires' Disease showed a distinct seasonal trend peaking in Summer/Fall. Higher relative percentage of hospitalizations were observed for NTMs in the Southeast and for Legionnaires' Disease in the Northeast/Mid-Atlantic. Antibiotic resistance was recorded in an estimated 2.2% of all hospitalizations, with the median charge of hospitalization involving an OPPP and no antibiotic resistance being $63,654. Antibiotic resistance increased the mean charge by 14%. In a backwards-eliminated predictive model of antibiotic resistance among hospitalizations involving *Pseudomonas* pneumonia, association (OR; 95%CI) was seen in age over 65 (1.20; 0.93, 1.55), female gender (1.57; 1.13, 2.17), and urinary catheterization among those aged 65+ (3.29; 1.37, 7.86). Inverse association was seen in receiving intubation (0.59; 0.41, 0.85) and being female with a chronic lung condition (0.69; 0.49, 0.97).

Conclusion: This analysis shows that individuals of all ages are at risk of an OPPP infection. In addition, the HCUP data was shown to correlate very highly with the results of the CDC Legionnaires' Disease surveillance systems confirming seasonal and regional variability in a nationally representative sample.

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Introduction

The complex network of pipes in a home or building is known as the "premise plumbing," to distinguish it from the system of pipes from the water treatment plant to the home or building (known as the distribution system). The goal of drinking water treatment is to make water safe to drink, but treatment does not make water sterile. The pipes in the distribution system and in premise plumbing can provide a welcoming ecological niche for some microorganisms.

Drinking water is regulated up until the property line by the Environmental Protection Agency (EPA). Within premise plumbing, the EPA only regulates for lead and copper, leaving the ultimate quality of the tap water up to the property owner [1]. Microorganisms that remain in the drinking water after treatment survive in the distribution system. The premise plumbing is an ideal habitat for these pathogens for multiple reasons such as the elevated water temperature, ample pipe surface area, low water flow rates, and diminishing residual chlorine, which all encourage the growth of biofilms [2].

Opportunistic Premise Plumbing Pathogens (OPPPs) are naturally occurring organisms that are commonly found within premise plumbing. Disease due to such pathogens are more commonly seen as opportunistic infections in susceptible individuals. The most commonly thought of OPPPs are the nontuberculous mycobacteria (NTM) and the gram negative bacteria *Legionella* and *Pseudomonas*. It has been estimated that up to 30% of the population may be exposed to OPPPs [3].

Economically OPPPs cost at least $1 billion annually with a significant proportion of this estimated cost coming from healthcare costs [2]. In a 2012 analysis of healthcare costs associated with waterborne diseases, Legionnaires' Disease and NTM infections were the highest cost per episode of waterborne disease with respective costs of $33,366 and $25,985. Nationally, claims for Legionnaires' Disease totaled $434 million per year [4].

It is evident that the opportunistic premise plumbing pathogens have both a significant economic and health impact, yet there is a large knowledge gap regarding their epidemiology [3]. A recent paper by Naumova and colleagues explored the burden and cost of NTMs, Legionnaires' Disease and *Pseudomonas* and associated antibiotic resistance using Medicare data [5]. Here, we explore the burden of these three OPPPs using data from all insurance sources and the uninsured. In addition, we attempt to elucidate factors associated with antibiotic resistance among patients hospitalized with *Pseudomonas* pneumonia.

Background

OPPPs flourish in premise plumbing for a variety of reasons. The hydrophobicity of NTMs [6], and *Legionella's* and *Pseudomonas'* biological functions allow these organisms to persist in environmental niches, thrive in biofilms, and resist biocides [7]. The presence of the biofilms, an assemblage of living and dead material that has attached itself to the sides of the pipe, in the drinking water distribution system can contribute to a reduction and potential loss of disinfectant residuals, thus creating an ideal environment for extended biofilm growth [8].

The concentration of organisms in biofilms in the water system has been shown to be greatly enriched in premise plumbing. NTMs have been found in showerhead biofilms at concentrations 100 fold greater than the distribution system levels. In this concentrated matrix of organisms, Mycobacterium species accounted for 28.1% of the DNA sequences present and *Pseudomonas* and *Legionella* represented 3.8% and 0.1% of the DNA sequences, respectively [9].

These three organisms result in many different clinical manifestations. *Legionella* is the most restrictive, seen as either Legionnaires' Disease or Pontiac Fever. NTMs can be seen as both an infection of the lungs or the skin, most commonly categorized as pulmonary, cutaneous, or disseminated. *Pseudomonas* infections, like those of NTM, manifest themselves in a variety of different ways ranging from swimmer's ear and hot-tub folliculitis, to serve pneumonia, urinary tract infections, and bacteremia [10].

As opportunistic infections, all three of the infections caused by these organisms tend to target individuals with some type of comorbidity. The most common

comorbidities for infections caused by an opportunistic premise plumbing pathogen are smoking, alcohol abuse, an underlying pulmonary issues (such as Chronic Obstructive Pulmonary Disease, bronchitis, or cystic fibrosis), immunosuppressive drugs or a compromised immune system, diabetes mellitus, an Intensive Care Unit stay, and mechanical ventilator application or invasive procedures [11-17].

In much of the research to date there have been calls for more detail on the epidemiology of opportunistic premise plumbing pathogens, specifically the demographic, seasonal, and geographic variability. From 2000 to 2009, the crude national incidence rate of Legionellosis increased 192% to 1.15 per 100,000 persons; while reported cases of Legionellosis increased 217% over the same period to 3,522 reported cases, of which 99.5% were Legionnaires' Disease [18]. It has been estimated that there are 17,000 to 23,000 Legionnaires' Disease cases hospitalized annually [17]. In addition, there has been a known seasonal difference and a suspected regional difference in Legionellosis cases [16, 17, 19].

Nontuberculous mycobacteria infections have also been increasing in recent decades with an 8.2% annual increase from 1997-2007 in prevalence among Medicare patients [20]. The average annual site specific prevalence of NTM infection in four health systems from 2004-2006 ranged from 1.4 to 6.6 per 100,000 persons [21]. As in Legionellosis, there are observed regional differences in incidence of nontuberculous mycobacteria infections, however the distribution of NTMs varies from that of Legionellosis [15, 20].

While a full overview of the epidemiology of *Pseudomonas* pneumonia was not found in the literature, the average annual incidence of *Pseudomonas* septicemia was 4.6 per 10,000 adult hospital discharges, decreasing from 6.5 per 10,000 in 1996 to 3.1 per 10,000 and then increasing back to 6.5 per 10,000 by 2010 [22]. As a nosocomial infection, *Pseudomonas* is the 2nd most common cause of ventilator-associated pneumonia and the 3rd/4th most common cause of multiple other hospital-acquired infections [3, 7]. CDC estimates 51,000 nosocomial pseudomonas infections per year [23]**.** Like the other OPPPs, *Pseudomonas* also shows a non-uniform geographic distribution [22].

Of particular interest in the epidemiology of *Pseudomonas* is its antibiotic resistance, especially in terms of multi-drug resistant organisms. *Pseudomonas* has been frequently shown to be multi-drug resistant, with one study showing 14% prevalence of multi drug resistance, in which all of drug resistant organisms were resistant to carbapenems and quinolones, and 91% were resistant to penicillins and cephalosporins [24]. In a study of OPPPs and antibiotic resistance among Medicare patients, 1.59% of patients hospitalized with an OPPP infection had some form of antibiotic resistance. This resistance resulted in as much as a 77% percent increase in the cost of hospitalization measured through hospital charges [5]. This has led to estimates of 13% of hospital acquired *Pseudomonas* infections are multi-drug resistant, causing an estimated 400 deaths annually [23].

Methods

Data Source

The data for this analysis were obtained from the National Inpatient Sample (NIS), one of the datasets of the Healthcare Cost and Utilization Project (HCUP) from the Agency for Healthcare Research and Quality. The NIS is the largest all-payer database of inpatient hospital stays derived from billing data, with information available from 1988-2014.

The 2012 NIS was selected for this analysis. The 2012 NIS contains over 7 million de-identified observations. The sampling frame for this dataset is estimated to cover more than 95% of the U.S population, 94% of discharges from U.S. community hospitals and 45 states [25], and uses sampling weights to make representative estimates for the entire U.S. non-institutionalized population.

Inclusion/Exclusion Criteria

The 2012 NIS includes information on up to 25 diagnoses per observation, represented through International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Infections due to any of the three selected OPPPs were selected via ICD-9 diagnostic codes. This included all patients with any diagnosis of pneumonia due to *Pseudomonas* (482.1), Legionnaires' Disease (482.84) or NTM infection (031.0-031.9). National and regional estimates were made. For cost estimates, the non-tuberculous mycobacterial infections were further classified as pulmonary (031.0), disseminated (031.2), and all other (031.1, 031.8, 031.9) NTM infections.

All cases of antibiotic resistance were captured using ICD-9-CM codes of drug resistance (V09) in any of the 25 diagnosis fields. This includes resistance to

cephalosporins and other beta-lactams, macrolides, tetracyclines, aminoglycosides, quinolones and fluoroquinolones, other specified antimycobacterial agents, and other specified drugs. We defined multi-drug resistance by the additional multi-drug resistance codes of V09.X1. All resistant cases were included for bivariate analysis. For the multivariable models, any observations with missing data among the variables of interest were excluded. The EncoderPro database (Optum 360, Salt Lake City, UT, USA) was used for the interpretation of ICD-9 codes.

Analyses

Analyses were performed in SAS Software Version 9.4 (SAS Institute Inc., Cary, NC, USA). The SAS survey procedures (PROC SURVEYFREQ and PROC SURVEYMEANS) were used to compute national and regional estimates as suggested by HCUP [26]. The proportion of hospitalizations with selected demographics (e.g. age group, gender, geographic region, income, etc.) and medical characteristics (e.g. discharge outcome, use of mechanical ventilation, presence of HIV or other immunocompromising conditions, etc.) was compared by pathogen. For each pathogen, chi-square values were calculated for categorical variables. The expected values for the chi-square tests were the percent of total discharges in the 2012 NIS, the percent of total discharges in the 2012 NIS excluding neonatal/maternal discharges, or the percent of discharges if there was no difference among categories, when appropriate. Wald p-values were used to compare the cost of hospitalization when antibiotic resistance was present vs. cost when resistance was not present.

We examined characteristics associated with antibiotic resistance using univariable and multivariable logistic regression modeling. Modeling was restricted to

hospitalizations involving *Pseudomonas* pneumonia, because antibiotic resistance was present in few hospitalizations involving NTM infection or Legionnaires' Disease. Characteristics were selected for antibiotic resistance analysis if they were meaningfully present in *Pseudomonas* patients or based on a priori knowledge. Rao-Scott Chi-Square tests were used to test homogeneity of estimates using PROC SURVEYFREQ. The SAS survey procedure for logistic regression, PROC SURVEYLOGISTIC, was used to calculate associations between antibiotic resistance and various individual and hospital factors.

From the selected risk factors analyzed for bivariate association with antibiotic resistance, estimates with a Wald p-value of <.2 or meaningful a priori association were included in the multivariable model. A full multivariable model with no interaction was initially created. Subsequently, backwards elimination was performed on models with no interaction, interaction of risk factors with gender, and interaction of risk factors with gender and age using the SAS macro for model selection in PROC SURVEYLOGISTIC developed by NORC at the University of Chicago [27]. Hierarchically well-formulated models were created from the results, followed by traditional and/or hybrid backwards elimination to generate models for each type of interaction. A final model was selected based on an analysis of the meaningfulness and usefulness of the risk factors included.

Except when noted otherwise, the alpha value of 0.05 was set a priori as the cut off for statistical significance. As stated in the HCUP NIS Data User Agreement, all estimates of 10 or less have been redacted due to the risk of individual identification. This analysis was excluded from Emory Institutional Review Board per Emory guidelines as the NIS 2012 data has been de-identified and is publically available.

Results

National Estimates

In 2012, there was an estimated total of 73,565 discharges of non-institutionalized U.S. patients hospitalized with an infection due to one or more of the three selected OPPPs. There were a total of 74,175 infections of these three OPPPs (Table 1), with an estimated 610 individuals (0.8% of all infections) infected with more than one organism. *Pseudomonas* pneumonia was the most common diagnosis, accounting for 70.6% of infections (N=52,345), followed by NTMs (N=18,150, 24.5%) and then Legionnaires' Disease (N=3,680, 5.0%). Of the 610 discharges with multiple OPPP infections, 585 discharges had both *Pseudomonas* and NTM infections. Legionnaires' Disease was most commonly diagnosed as the principal diagnosis (48.5%) among those with any diagnosis of Legionnaires' Disease; while 32.6% of *Pseudomonas* pneumonia infections and 16.4% of NTMs were a principal diagnosis.

Both *Pseudomonas* pneumonia and Legionnaires' Disease were more common in men than women (56.5% and 65.1% male, respectively) while NTMs were nearly equal across gender, with 47.1% of infections in males. Hospitalizations involving *Pseudomonas* pneumonia and Legionnaires' Disease were significantly more likely to involve a male patient, compared with all hospitalizations for any diagnosis (Table 2, p=0.0041 and p=0.0000, respectively). However, when compared to all hospitalizations except those related to the birth of a baby, only Legionnaires' Disease was significantly more likely to involve a male patient (p=0.0004). For all three OPPPs, white was the predominant race. However, race did not differ significantly from the proportions observed for all hospitalizations in the NIS. The mean and median patient age was similar

for each of the three OPPPs (ranging from 60-62 and 61-66, respectively). Hospitalizations with Legionnaires' Disease and NTM infection were more likely to involve patients over 45 when compared to all hospitalizations not involving the birth of a baby (p=0.0148 and p=0.0000, respectively).

In an analysis of region as defined by Census Division, hospitalizations involving neither *Pseudomonas* pneumonia nor NTMs were statistically different than the total discharged by region. Legionnaires' Disease had significantly higher percentages of discharges in New England, Middle Atlantic and East North Central (Figure 1) with lower than expected percentages in the western regions. These differences were statistically significant among total U.S. 2012 discharges (p=0.0046) and discharges excluding neonatal/maternal discharges (p=0.0142).

Neither hospitalizations involving *Pseudomonas* pneumonia nor NTMs had any statistically significant differences among month of admission, with a range of 7.5-8.9% of admissions occurring each month. Legionnaires' Disease exhibited a trend of seasonality (Figure 2), with peaks of 15.9% of total hospitalizations involving Legionnaires' Disease admitted in August and 12.6% in September. In a month by month comparison, Legionnaires' Disease was statistically significant compared to no seasonality at all (p=0.0375) and to compared to all the discharges in the 2012 NIS (p=0.0351).

When considering hospital and hospitalization characteristics (Table 2), all three OPPPs were similar for many characteristics. The most common characteristics seen across hospitalizations involving OPPPs were a large hospital, a private not-for profit

hospital, an urban/teaching hospital, non-elective admission, and not being transferred in to the hospital. Patient's residence was most commonly large central metro areas with declining counts as size of town/city decreased. Medicare was the dominant payer followed by private insurance and then Medicaid.

Discharge status did differ among the pathogens. Among hospitalizations with *Pseudomonas* pneumonia, 39.5% of patients were discharged to another healthcare institution, 19.1% to home healthcare, and 25.6% underwent a routine discharge. However, among hospitalizations with either Legionnaires' Disease or NTM, the majority of patients underwent a routine discharge (55.8% and 52.6%, respectively). Among hospitalizations involving Legionnaires' Disease, routine discharge was followed by discharge to another institution (20.1%) and then home health care (12.5%). The 2nd and 3rd most common discharge statuses were reversed in NTMs with discharge to home health care (20.4%) followed by discharge to another institution (18.8%). The fourth most common discharge status was in-hospital death with 11.8%, 7.5% and 5.3% of hospitalizations involving *Pseudomonas* pneumonia, Legionnaires' Disease, and NTMs, respectively, resulting in death. The length of stay varied greatly by OPPP. Patients hospitalized with *Pseudomonas* pneumonia had a mean length of stay of 17.3 days (SE: 0.29) and a median of 10.2 days (SE: 0.15). For hospitalizations involving Legionnaires' Disease and NTM, length of stay was noticeably shorter with respective means of 9.4 (SE: 0.38) and 9.4 (SE: 0.24), and medians of 5.7 (SE: 0.21) and 5.3 (SE: 0.10).

Thirty one health conditions were considered for association with discharge from a hospitalization where an OPPP infection occurred (Table 3). Across all three OPPPs, roughly one-third (Range: 33.1-38.9%) of discharges included indication of hypertension.

Fluid disorders was the most commonly listed health condition, seen in 70.2% of hospitalizations involving Legionnaires' Disease, 50.4% of hospitalizations involving *Pseudomonas* pneumonia, and 39.3% of hospitalizations involving NTM. Many other conditions showed great variability across the pathogens. Individuals with immune compromising conditions accounted for a noticeably larger percent of NTM observations (32.5%) in comparison to *Pseudomonas* and Legionnaires' Disease observations (18.8% and 14.9%, respectively). In particular, 18.7% of hospitalizations involving NTM listed HIV as a comorbidity, while only 2.2% hospitalizations with Legionnaires' Disease and 1.0% hospitalizations with *Pseudomonas* pneumonia had a code for HIV.

There were noticeably fewer hospitalizations involving Legionnaires' Disease and a chronic lung disease comorbidity (26.1%) than the other two pathogens (*Pseudomonas*: 51.6% and NTM: 45.3%). Respiratory failure was present in 48.0% of hospitalizations involving *Pseudomonas* pneumonia, 37.6% of hospitalizations involving Legionnaires' Disease discharges, and only 15.6% of hospitalizations involving NTM. The severity of the Diagnostic-Related Group (a statistical classification based on all ICD-9 codes in the record) varied across the pathogens. The majority of hospitalizations involving *Pseudomonas* pneumonia (62.3%) had the highest Diagnostic-Related Group severity (extreme loss of function). In hospitalizations involving NTM, the majority (50.6%) had the second highest severity (major loss of function), while 30.2% had extreme loss of function. Hospitalizations involving Legionnaires' Disease were primarily split between the two highest severity levels with 39.7% in the highest level and 37.2% in the second highest level.

Of the 73,565 discharges with an OPPP in 2012, 1,635 (2.2%) had known drug resistance captured by an ICD-9 code (Table 4). Of those with known drug resistance, 1,075 (65.8%) had resistance to multiple classes of antibiotics. The majority of the detected resistance cases were in patients with *Pseudomonas* pneumonia (N=1,470; 89.9% of cases with resistance; 2.8% of hospitalizations involving *Pseudomonas* pneumonia). With no exclusions of outliers to represent the true charges, the median charge of a hospitalization with an OPPP infection and no antibiotic resistance was $63,654 with a mean of $151,421. Of the individual OPPPs, hospitalizations with *Pseudomonas* pneumonia were the most costly with mean and median charges of $182,641 and $80,544, respectively. For all the OPPPs, the presence of antibiotic resistance increased the mean charges per case by $21,906 (p=<0.0001; Ratio: 1.15). Among all NTMs the charges increase $66,542 (p=<0.0001; Ratio: 1.87) and among those with Legionnaires' Disease the charges increased by $36,812 (P=<0.0001; Ratio: 1.45) while charges decreased for those with resistance among *Pseudomonas* pneumonia patients by $6,055 (P=0.0305; Ratio: 0.97).

Antibiotic Resistance Modeling

Of the estimated 52,345 hospitalizations in 2012 involving known *Pseudomonas* pneumonia, 1,470 had known antibiotic resistance (Table 4). Associations of risk factors with antibiotic resistance (AR) was measured amongst factors with a priori knowledge or that were meaningfully present in *Pseudomonas* pneumonia patients (Table 5). Of these factors, categorical age, presence of any cancer, intubation, and quartiles of length of stay were statistically significantly different than the expected values. The highest percentage

of AR cases were aged 65-84, of white race, and with a roughly equal split across genders.

Without adjustment, antibiotic resistance in patients hospitalized with *Pseudomonas* pneumonia was associated with multiple factors (Table 5). While the presence of antibiotic resistance was not associated with race, it was associated (OR; 95%CI) with being age 18-44 (2.71; 1.32, 5.58), being female (1.22; 0.96, 1.55) and being hospitalized in a larger hospital (Medium: 1.50; 0.95, 2.36 and Large: 1.28; 0.83, 1.98). Interestingly, presence of antibiotic resistance was found to be inversely associated with having a cancer diagnosis (0.64; 0.42, 0.99) and being intubated while hospitalized (0.59; 0.04, 0.85). Length of stay in the hospital, which is both a risk factor for, and result of antibiotic resistance was associated with presence of antibiotic resistance. In particular, being in the third quartile for length of stay as compared to the first was statistically significant (OR: 1.66; 95% CI: 1.14, 2.40). This association was also seen in the second quartile (1.66; 0.80, 1.69) and fourth quartile (1.35; 0.90, 2.03) but was not statistically significant.

The final model, which was selected via backwards elimination, included the predictive factors of dichotomous age, gender, intubation while hospitalized, urinary catheterization by age when hospitalized and presence of a chronic lung condition by gender (Table 6). Upon adjustment, presence of antibiotic resistance was found to be meaningfully associated (OR; 95%CI) with age over 65 (1.20; 0.93, 1.55), female gender (1.57; 1.13, 2.17), and urinary catheterization among those aged 65+ (3.29; 1.37, 7.86). Interestingly, a statistically significant inverse relationship was found between the

presence of antibiotic resistance during hospitalization and both intubation (0.59; 0.41, 0.85) and being female with a chronic lung condition (0.69; 0.49, 0.97).

Discussion

OPPPs in the United States are causing an increasing burden of disease and have been recognized as a growing public health problem. In 2012, we found there to be an estimated 3,680 hospitalizations involving Legionnaires' Disease. This estimate fits well with other CDC surveillance data for 2012 where 3,688 cases of Legionellosis were reported through passive surveillance to the National Notifiable Disease Surveillance System (NNDSS) and 3,362 cases were reported through active surveillance to the Active Bacterial Core surveillance (ABCs) system [16]. Of reported cases, 99.5% are Legionnaires' Disease and 0.5% are Pontiac Fever [18]. Legionnaires' Disease is thought to be chronically underreported for multiple reasons, including a lack of awareness and diagnosis. Previous studies have estimated 17,000 to 23,000 Legionnaires' Disease cases hospitalized annually, with a recent and well-respect population based pneumonia etiology study estimating 8,000 to 18,000 hospitalizations with Legionnaires' Disease annually [17].

Our gender and age estimates for Legionnaires' Disease where also very similar to those seen in the 2012 NNDSS summary. The HCUP data estimates that 65.1% of hospitalizations with Legionnaires' Disease were among men while NNDSS shows that 63.4% of Legionnaires' Disease cases reported were among men, both of which are consistent with the literature [17, 28]. Our estimates show that 40.1% of cases are over the age of 65 with the proportion of cases reported to NNDSS almost exactly matching at 40.0% [28].

Our estimates show distinct regional differences in the prevalence of hospitalizations with Legionnaires' Disease (Figure 1). Both our estimates and the cases

reported to NNDSS show the highest proportion of cases in the Middle Atlantic, East North Central, and South Atlantic census regions [28]. However, absolute percentage of hospitalizations is not necessarily the best measure because the U.S. census divisions cover differing percentages of the U.S. population, ranging from almost 5% in New England to almost 20% in the South Atlantic Division. Taking this into account, we looked at percentages of Legionnaires' Disease in relation to a baseline of all discharges in the HCUP 2012 NIS. The same trend was observed with the New England, Middle Atlantic and East North Central divisions have a higher percentage of hospitalizations with Legionnaires' Disease than for all causes. This increased percentage is countered with lower percentages of in the West South Central, Mountain and Pacific divisions. Both these specific regional differences and the general trend of higher incidence and case counts in the northeast are supported by the literature [16-18]. Despite this established trend, it is unknown whether the regional differences are due to actual differences in epidemiologic and ecologic factors or due to variations in awareness and reporting.

We observed a distinct seasonal trend in our estimates of hospitalizations with Legionnaires' Disease with peak diagnoses in August, September and October, accounting for 36.3% of the annual hospitalizations and June-October accounting for 58.1% (Figure 2). This increase was matched with a decrease in February, March and April, when only 9.7% of those diagnosed with Legionnaires' Disease were hospitalized. This seasonal difference is consistent with the literature estimates where rates were highest in summer and early fall, with June-October accounting for 62% of cases [17,

18]. As with the geographic variability, further research needs to be completed to elucidate reasons for the seasonality of Legionnaires' Disease.

In our analysis of the epidemiology of nontuberculous mycobacteria we found no statistically significant difference in percentage of cases by season or by region. However, we did notice an elevated number of cases in the South Atlantic region. We observed 34.1% of our NTM cases in the South Atlantic and East South Central census divisions. A recent prevalence study of the Medicare population by Adjemian et al. observed one-third of pulmonary NTM cases resided in the Southeast [20]. The Adjemian study also observed a high period prevalence in the west which was not seen in our data.

As with NTMs, we did not observe a statistically significant difference in percentage of hospitalization with *Pseudomonas* pneumonia by season or by region. In a similar trend as that seen in NTMs we observed slightly elevated counts in the South Atlantic and East South Central census divisions. While pneumonia and septicemia are not directly comparable due to different exposure routes, Werth et al. observed the highest incidence of *Pseudomonas* septicemia in the Northeast and West [22].

Our estimates of the burden of antibiotic resistance among those hospitalized with an OPPP infection mirror the burden found by Naumova et al [5]. Our estimates show roughly 2.2% of those hospitalized with any OPPP have an antibiotic resistance infection compared to the 1.59% found by Naumova. While our estimates of overall resistance are similar, Naumova found 7.59% of the antibiotic resistant cases to be multi-drug resistant while we found 65.7% to be multi-drug resistant when using the same ICD-9 codes. *Pseudomonas* accounted for the majority of our estimated antibiotic resistance. Similar to

our overall numbers, 68% of hospitalizations with *Pseudomonas* pneumonia and antibiotic resistance were multidrug resistant. A European study found 18% of isolates of *Pseudomonas* to be multi-drug resistant [7], while the crude proportion of multi-drug resistant *Pseudomonas Aeruginosa* was estimated to have increased in children from 15.4% to 26% from 1999-2012 [11]. The CDC estimates that 13% of the 51,000 hospital acquired pseudomonas infections each year are multidrug resistant [23]. Our noticeably larger percentage of multiple drug resistance organisms than what is seen in the literature may be explained through two methods. First, it may be a result of ICD-9 coding and specifically in comparison to Naumova et al, our analysis extends through 25 ICD-9 diagnosis codes while theirs only looks at the first 10. If multi drug resistance is coded later on, it would not be caught by Naumova. Second, the difference in estimates may be a result of the possibility that individuals with multiple drug resistance are those being tested and we are missing a large portion of individuals who are only resistant to one antibiotic.

The most common payer for all three pathogens was Medicare, which is to be expected as the majority of those hospitalized with an OPPP are elderly. By expanding our analysis beyond Medicare to include all payers, we were able to obtain generalizable charge estimates for hospitalizations. Regardless of the presence or absence of an antibiotic resistant infection, we found that hospitalization with *Pseudomonas* pneumonia was the most expensive of the three selected OPPPs, with Naumova et al. finding the same results. We estimated the mean hospital charges for a non-resistant OPPP to be $151,421. As with most hospital charges, this value is skewed with the typical case paying closer to the median value of $63,654. Our analysis showed the charge per case

hospitalized with Legionnaires' Disease and no antibiotic resistance to be $81,097. In comparison, Naumova et al. found the charge per case for the same criteria to be $42,810. In estimating costs, Collier et al. found the total cost per case of Legionnaires' Disease to be $38,363 with the Medicare average lower than the commercial insurance average.

While our financial burden estimates may differ from others in the literature, they may be broadly comparable taking the following caveats into account. First, we have estimated the charges the hospital has billed, while Naumova et al. and Collier et al. have estimated the costs individuals paid. Secondly, as measured by the Medical Care Consumer Price Index (Bureau of Labor Statistics, US Department of Labor), the price of healthcare has risen faster than inflation. The estimates in these papers use the dollar value of three different time periods (1991-2006 by Naumova et al. and 2007 by Collier et al.), making a one to one comparison difficult. Third, this analysis uses all insurance sources with costs shown to be higher in commercial sources than Medicare for OPPPs [4]. Finally, due to their opportunistic nature, infections from an OPPP may be present in individuals hospitalized for a variety of extremely complicated conditions and no exclusions of outliers were done in this analysis as may have been done in others.

The cost of healthcare in the presence of an antibiotic resistant infection was also noticed to change, as expected due to longer stays, more complications, etc. When antibiotic resistance was present we observed a 14% increase in hospital charges for all OPPP infections, a 45% increase for hospitalizations with Legionnaires' Disease and an 86% increase for cases of NTM. The charge of a hospitalization with pulmonary NTM doubled when antibiotic resistance was present. Naumova et al. observed similar results

with increases of 32.8% for all OPPPs, 18.1% for Legionnaires' Disease, and 48.2% for NTMs [5].

Our final model of the association between antibiotic resistance and selected hospitalization characteristics produced both expected and unexpected results. As *Pseudomonas* is the second most common cause of ventilator associated pneumonia, we expected to see antibiotic resistance correlated with those on a ventilator [23]. Our finding of increased risk among those over the age of 65 is consistent with this. However, our decreased risk when intubated is incongruous to literature results that have mechanical ventilation as a known risk factor [13]. The result of the presence of a chronic lung co-morbidity acting in a protective manner is also a non-logical result. A possible explanation for these results is that the ICD-9 codes for antibiotic resistance are not specific to *Pseudomonas* or to pneumonia infections. Thus, it is possible that these individuals had a resistant infection elsewhere in their body that is unrelated to the presence of *Pseudomonas* pneumonia. The presence of a significant association between antibiotic resistance and urinary catheterization among those over the age of 65 is expected and represents urinary tract infections, commonly caused by *Pseudomonas* [23]. Our inability to account for the known risk factor of previous antibiotic use in this model is a significant limitation.

A major limitation of this analysis is its dependency on ICD-9 codes from discharge reports. Previous estimates for the sensitivity of ICD-9 codes vary from 27% to 50% [12]. In particular, the sensitivity for coding of NTM (ICD-9: 031.0) has been estimated to be 26.9% [21]. This low sensitivity contributes to the chronic under reporting of both OPPP infections and antibiotic resistance. Patients are routinely

admitted and treated based on their symptoms with no need for a pathogen-based diagnosis.

Many of the previous studies, including that of NTMs by Adjemian et al. and OPPPs by Naumova et al. were done in populations over the age of 65. While this is the population that is traditionally at greater risk for OPPPs, our data show that individuals of all ages are susceptible to infection with an OPPP with roughly 50% of the *Pseudomonas* pneumonia and NTM population under the age of 65 and roughly 40% of those hospitalized with Legionnaires' Disease under the age of 65.

Conclusions and Recommendations

While most studies are typically done in an elderly population, this analysis of all ages shows that individuals of all ages are at risk of an OPPP infection. Hospitalizations due to these organisms result in a large financial burden, which is usually increased in the presence of antibiotic resistance. This financial burden does not take into account any additional societal costs. In addition, the HCUP data was shown to correlate very highly with the results of the CDC Legionnaires' Disease surveillance systems allowing for future research on associated conditions and trends of disease.

Future research into the epidemiology and ecology of OPPPs is necessary. It has been established that there are specific regional trends, however the reasons for such trends are still unknown. Further research on describing the demographic, seasonal and regional variability is crucial. In addition, this and many other analyses focus on the hospitalized population, capturing the severe cases. Research expanded to study the burden and cost of disease in the general population is of the utmost importance as almost everyone comes into contact with water from premise plumbing on a daily basis.

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Tables and Figures

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Table 1: National Demographic Estimates for selected OPPPs from HCUP 2012 NIS database. There were a total of 73,565 discharges with an infection of interest and 74,175 total infections.

	Pseudomonas pneumonia		Legionnaires' Disease		Nontuberculous mycobacteria		Expected Values	
Characteristic	**N**	**Percent (95% CI)**	**N**	**Percent (95% CI)**	**N**	**Percent (95% CI)**	**All 2012 NIS Discharges (%)[ac]**	**Excluding Neonatal/ Maternal Discharges (%)[bd]**
Infections (N=74175)	52345		3680		18150			
Principal Diagnosis	17050	32.6 (31.3, 33.8)	1785	48.5 (44.9, 52.1)	2975	16.4 (14.9, 17.9)		
Multiple OPPPs								
Pseudomonas	N/A		20		585			
Legionnaires'	20		N/A		~			
NTMS	585		~		N/A			
Sex								
Male	29580	56.5 (55.5, 57.5) [a]	2395	65.1 (61.7, 68.5) [ab]	8545	47.1 (45.2, 49.0)	42.3	47.3
Female	22765	43.5 (42.5, 44.5)	1285	34.9 (31.5, 38.3)	9605	52.9 (51.0, 54.8)	57.7	52.7
Race								
White	36055	72.5 (71.0, 74.1)	2570	72.5 (68.7, 76.3)	11550	65.6 (63.2, 67.9)	66.2	
Black	6755	13.6 (12.5, 14.7)	570	16.1 (13.1, 19.0)	3295	18.7 (16.7, 20.7)	14.8	
Hispanic	3755	7.6 (6.7, 8.5)	215	6.1 (4.3, 7.8)	1540	8.7 (7.0, 10.5)	11.9	
Asian, Pacific Islander	1310	2.6 (2.1, 3.1)	50	1.4 (0.5, 2.3)	635	3.6 (2.8, 4.4)	2.7	
Native American	340	0.7 (0.5, 0.9)	~	~	60	0.3 (0.1, 0.5)	0.7	
Other	1490	3.0 (2.4, 3.6)	135	3.8 (1.9, 5.7)	535	3.0 (2.1, 4.0)	3.8	
Age (Continuous)								
Mean	61.91		60.81		60.26			
Q1 (25%)	52.13		51.04		46.68			
Median	66.46		60.84		63.38			

Table 1 Continued

Characteristic	N	*Pseudomonas* pneumonia Percent (95% CI)	N	Legionnaires' Disease Percent (95% CI)	N	Nontuberculous mycobacteria Percent (95% CI)	Expected Values All 2012 NIS Discharges (%)[ac]	Expected Values Excluding Neonatal/ Maternal Discharges (%)[bd]
Q3 (75%)	76.54		71.38		76.28			
Age Categorical								
<1	510	1.0 (0.8, 1.2) [a]	~	~ [ab]	~	~	11.7	1.2
1-17	2005	3.8 (2.7, 5.0) [c]	~	~ [cd]	560	3.1 (2.3, 3.8) [d]	4.0	4.9
18-44	6700	12.8 (11.7, 13.9)	505	13.7 (11.3, 16.2)	3435	18.9 (17.3, 20.6)	24.7	17.4
45-64	14115	27.0 (25.9, 28.0)	1660	45.1 (41.7, 48.5)	5225	28.8 (27.1, 30.5)	24.7	31.7
65-84	23860	45.6 (44.1, 47.0)	1265	34.4 (30.9, 37.8)	7270	40.1 (38.0, 42.1)	26.7	34.3
85+	5150	9.8 (9.1, 10.5)	235	6.4 (4.5, 8.2)	1660	9.1 (8.1, 10.2)	8.2	10.5
Region								
New England	2255	4.3 (3.7, 5.0)	355	9.6 (7.1, 12.2) [ab]	585	3.2 (2.5, 3.9)	4.7	4.9
Middle Atlantic	5605	10.7 (9.4, 12.0)	830	22.6 (19.3, 25.9)	2690	14.8 (12.8, 16.9)	14.4	15.0
East North Central	8380	16.0 (14.4, 17.6)	855	23.2 (19.6, 26.8)	2255	12.4 (10.5, 14.3)	15.7	16.1
West North Central	3045	5.8 (5.0, 6.6)	180	4.9 (3.2, 6.6)	795	4.4 (3.1, 5.7)	6.9	6.9
South Atlantic	11810	22.6 (20.9, 24.2)	670	18.2 (15.0, 21.4)	4955	27.3 (24.8, 29.8)	20.1	20.5
East South Central	4930	9.4 (7.6, 11.2)	210	5.7 (3.3, 8.1)	1230	6.8 (5.5, 8.1)	6.9	7.2
West South Central	6465	12.4 (10.8, 13.9)	245	6.7 (4.6, 8.7)	2155	11.9 (9.9, 13.9)	11.7	11.2
Mountain	2600	5.0 (4.1, 5.8)	100	2.7 (1.4, 4.1)	965	5.3 (4.1, 6.5)	6.1	5.7
Pacific	7255	13.9 (12.6, 15.1)	235	6.4 (4.6, 8.2)	2520	13.9 (12.0, 15.8)	13.5	12.6
Admission Month								
January	4610	8.8 (8.3, 9.4)	250	6.9 (5.0, 8.8) [ab]	1575	8.9 (7.9, 9.8)	8.6	
February	4460	8.5 (8.0, 9.1)	95	2.6 (1.5, 3.8)	1535	8.6 (7.7, 9.6)	8.2	
March	4345	8.3 (7.8, 8.8)	110	3.0 (1.8, 4.3)	1515	8.5 (7.6, 9.4)	8.7	
April	4110	7.9 (7.3, 8.4)	150	4.1 (2.6, 5.6)	1510	8.5 (7.6, 9.4)	8.2	

Table 1 Continued

Characteristic	*Pseudomonas* pneumonia N	*Pseudomonas* pneumonia Percent (95% CI)	Legionnaires' Disease N	Legionnaires' Disease Percent (95% CI)	Nontuberculous mycobacteria N	Nontuberculous mycobacteria Percent (95% CI)	Expected Values: All 2012 NIS Discharges (%)[ac]	Expected Values: Excluding Neonatal/ Maternal Discharges (%)[bd]
May	4300	8.2 (7.7, 8.8)	340	9.3 (7.2, 11.4)	1720	9.7 (8.6, 10.7)	8.5	
June	4080	7.8 (7.3, 8.3)	360	9.9 (7.7, 12.1)	1350	7.6 (6.7, 8.4)	8.1	
July	3915	7.5 (7.0, 8.0)	305	8.4 (6.4, 10.4)	1405	7.9 (7.0, 8.8)	8.3	
August	4580	8.8 (8.2, 9.3)	580	15.9 (13.3, 18.6)	1415	8.0 (7.1, 8.9)	8.5	
September	4160	8.0 (7.5, 8.5)	460	12.6 (10.2, 15.1)	1475	8.3 (7.4, 9.2)	8.0	
October	4690	9.0 (8.4, 9.5)	410	11.3 (8.9, 13.6)	1480	8.3 (7.4, 9.2)	8.5	
November	4535	8.7 (8.1, 9.2)	330	9.1 (7.0, 11.1)	1465	8.2 (7.3, 9.2)	8.0	
December	4485	8.6 (8.0, 9.1)	250	6.9 (5.0, 8.7)	1340	7.5 (6.7, 8.4)	8.2	

~Values not shown for cells with counts ≤10

[a] Percentage is statistically different than expected value

[b] Percentage is statistically different than expected value of HCUP 2012 NIS discharges excluding neonatal/maternal discharges at alpha 0.05

[C] Percentage is statistically different than expected value of all HCUP 2012 NIS discharges at alpha 0.05 when cases <1 year are excluded

[d] Percentage is statistically different than expected value of HCUP 2012 NIS discharges excluding neonatal/maternal discharges at alpha 0.05 when cases <1 year are excluded

Table 2: Hospital and Hospitalization Characteristic Estimates. There were a total of 73,565 discharges with an infection of interest and 74,175 total infections.

	***Pseudomonas* pneumonia**		**Legionnaires' Disease**		**Nontuberculous mycobacteria**	
	N	**Percent (95% CI)**	**N**	**Percent (95% CI)**	**N**	**Percent (95% CI)**
Total Infections	52345		3680		18150	
Hospital Size						
Small	6660	12.7 (12.7, 12.7)	660	17.9 (14.8, 21.1)	2005	11.0 (9.6, 12.5)
Medium	12535	23.9 (23.9, 23.9)	1035	28.1 (24.4, 31.8)	4225	23.3 (21.2, 25.4)
Large	33150	63.3 (63.3, 63.3)	1985	53.9 (49.8, 58.1)	11920	65.7 (63.2, 68.1)
Hospital Ownership						
Government non-federal	7105	13.6 (13.6, 13.6)	330	9.0 (6.6, 11.3)	3185	17.5 (15.0, 20.1)
Private not-for-profit	37895	72.4 (72.4, 72.4)	2990	81.3 (78.1, 84.4)	12625	69.6 (66.8, 72.3)
Private investor-owned	7345	14.0 (14.0, 14.0)	360	9.8 (7.4, 12.1)	2340	12.9 (11.3, 14.5)
Hospital Location/Teaching Status						
Rural	6150	11.7 (11.7, 11.7)	305	8.3 (5.9, 10.7)	1045	5.8 (4.8, 6.7)
Urban, non-teaching	17685	33.8 (33.8, 33.8)	1230	33.4 (29.5, 37.3)	5605	30.9 (28.5, 33.2)
Urban, teaching	28510	54.5 (54.5, 54.5)	2145	58.3 (54.2, 62.4)	11500	63.4 (60.8, 65.9)
Admission Type						
Non-elective	46250	88.5 (88.5, 88.5)	3440	93.6 (91.7, 95.5)	15650	86.4 (84.9, 87.9)
Elective	5995	11.5 (11.5, 11.5)	235	6.4 (4.5, 8.3)	2460	13.6 (12.1, 15.1)
Transferred In						
Not a transfer	43995	84.5 (84.5, 84.5)	3400	92.5 (90.5, 94.5)	16605	92.0 (91.0, 93.0)
Acute Care Hospital	4505	8.6 (8.6, 8.6)	210	5.7 (4.0, 7.5)	895	5.0 (4.1, 5.8)
Other Health Facility	3590	6.9 (6.9, 6.9)	65	1.8 (0.8, 2.7)	555	3.1 (2.4, 3.8)
Payer						
Medicare	33670	64.4 (64.4, 64.4)	1645	44.8 (41.2, 48.5)	10265	56.8 (54.5, 59.0)
Medicaid	7935	15.2 (15.2, 15.2)	370	10.1 (8.0, 12.2)	3295	18.2 (16.6, 19.9)
Private Insurance	8315	15.9 (15.9, 15.9)	1225	33.4 (29.9, 36.8)	3325	18.4 (16.7, 20.1)

Table 2 Continued	*Pseudomonas* pneumonia		Legionnaires' Disease		Nontuberculous mycobacteria	
	N	Percent (95% CI)	N	Percent (95% CI)	N	Percent (95% CI)
Self-pay	895	1.7 (1.7, 1.7)	300	8.2 (6.2, 10.1)	725	4.0 (3.3, 4.8)
No charge	75	0.1 (0.1, 0.1)	30	0.8 (0.2, 1.4)	75	0.4 (0.2, 0.7)
Other	1355	2.6 (2.6, 2.6)	100	2.7 (1.6, 3.9)	400	2.2 (1.7, 2.8)
Median Income Quartiles						
1st ($1-38,999)	16970	33.2 (33.2, 33.2)	950	26.7 (23.2, 30.3)	5505	31.5 (29.5, 33.5)
2nd ($39,000-47,999)	13240	25.9 (25.9, 25.9)	815	22.9 (19.7, 26.1)	4000	22.9 (21.3, 24.5)
3rd ($48,000-62,999)	11395	22.3 (22.3, 22.3)	950	26.7 (23.4, 30.1)	4070	23.3 (21.7, 24.9)
4th ($63,000+)	9585	18.7 (18.7, 18.7)	840	23.6 (20.2, 27.1)	3905	22.3 (20.3, 24.4)
Discharge Status						
Routine Discharge	13380	25.6 (25.6, 25.6)	2055	55.8 (52.1, 59.6)	9535	52.6 (50.7, 54.5)
Short-term hospital	1870	3.6 (3.6, 3.6)	105	2.9 (1.6, 4.1)	315	1.7 (1.3, 2.2)
Another institution (LTCF, Rehab, etc.)	20660	39.5 (39.5, 39.5)	740	20.1 (17.2, 23.0)	3415	18.84 (17.45, 20.22)
Home Healthcare	9985	19.1 (19.1, 19.1)	460	12.5 (10.1, 14.9)	3705	20.4 (19.0, 21.9)
Against medical advice	180	0.3 (0.3, 0.3)	40	1.1 (0.3, 1.8)	195	1.1 (0.8, 1.4)
In-Hospital Death	6185	11.8 (11.8, 11.8)	275	7.5 (5.5, 9.5)	965	5.3 (4.6, 6.1)
Alive, destination unknown	75	0.1 (0.1, 0.1)	~	~	~	~
Transfer Out						
No transfer	29805	57.0 (57.0, 57.0)	2835	77.0 (74.0, 80.1)	14400	79.4 (78.0, 80.9)
Transfer to acute care hospital	1870	3.6 (3.6, 3.6)	105	2.9 (1.6, 4.1)	315	1.7 (1.3, 2.2)
Transfer to another health facility	20660	39.5 (39.5, 39.5)	740	20.1 (17.2, 23.0)	3415	18.8 (17.4, 20.2)
Patient Residence						
Large central metro	14485	27.8 (27.8, 27.8)	1140	31.5 (27.5, 35.5)	6560	37.0 (34.0, 40.0)
Suburbs "Fringe Metro"	11405	21.9 (21.9, 21.9)	1015	28.1 (24.2, 31.9)	4365	24.6 (22.0, 27.2)
Medium Metro	10160	19.5 (19.5, 19.5)	655	18.1 (14.8, 21.4)	3130	17.6 (15.2, 20.1)

Table 2 Continued	***Pseudomonas* pneumonia**		**Legionnaires' Disease**		**Nontuberculous mycobacteria**	
	N	**Percent (95% CI)**	**N**	**Percent (95% CI)**	**N**	**Percent (95% CI)**
Small Metro	5135	9.8 (9.8, 9.8)	280	7.7 (5.5, 10.0)	1465	8.3 (6.7, 9.8)
Micropolitan	6205	11.9 (11.9, 11.9)	280	7.7 (5.7, 9.8)	1420	8.0 (6.9, 9.1)
Rural	4770	9.1 (9.1, 9.1)	245	6.8 (4.5, 9.0)	805	4.5 (3.6, 5.5)
Length of Stay (Days)		**Estimate; SE**		**Estimate; SE**		**Estimate; SE**
Mean		17.3; 0.3		9.36; 0.38		9.4; 0.2
Q1 (25%)		5.7; 0.1		3.32; 0.12		2.8; 0.1
Median		10.2; 0.2		5.70; 0.21		5.3; 0.1
Q3 (75%)		18.7; 0.3		10.82; 0.44		10.3; 0.2
Total Charges						
Mean		$182,474.00; $5,552.62		$81,303.00; $5,073.52		$78,285.00; $2,888.62
Min		$948.00		$1,080.00		$308.00
Q1 (25%)		$36,669.00; $0,812.95		$19,530.00; $1,061.25		$19,986.00; $0,502.65
Median		$80,985.00; $2,118.46		$38,924.00; $2,142.63		$38,729.00; $1,006.94
Q3 (75%)		$196,276.00; $6,035.75		$89,454.00; $6,905.11		$79,033.00; $2,204.40
Max		$4,503,406.00		$1,491,606.00		$3,257,062.00

~Values not shown for cells with counts ≤10

Table 3: Health Conditions and Comorbidities of discharges with an OPPP from the HCUP 2012 NIS. There were a total of 73,565 discharges with an infection of interest and 74,175 total infections.

	***Pseudomonas* pneumonia (N=52345)**		**Legionnaires' Disease (N=3680)**		**Nontuberculous mycobacteria (N=18150)**	
Health Condition	**N**	**Percent (95% CI)**	**N**	**Percent (95% CI)**	**N**	**Percent (95% CI)**
Immunocompromised	9850	18.8 (17.7, 19.9)	550	14.9 (12.1, 17.8)	5895	32.5 (30.3, 34.6)
Smoking	5195	9.9 (9.3, 10.6)	1105	30.0 (26.5, 33.5)	2885	15.9 (14.4, 17.4)
Diabetes	12300	23.5 (22.5, 24.5)	820	22.3 (19.3, 25.2)	2155	11.9 (10.7, 13.1)
Diabetes with Chronic Complications	1430	2.7 (2.4, 3.1)	165	4.5 (2.9, 6.0)	285	1.6 (1.2, 2.0)
Staph Infection	1200	2.3 (2.0, 2.6)	25	0.7 (0.1, 1.3)	460	2.5 (2.0, 3.1)
Skin Infection	1485	2.8 (2.5, 3.2)	35	1.0 (0.3, 1.7)	570	3.1 (2.5, 3.8)
Hospital Complication	7705	14.7 (13.6, 15.8)	180	4.9 (3.2, 6.5)	1505	8.3 (7.2, 9.4)
Major OR Procedure	10620	20.3 (19.3, 21.2)	260	7.1 (5.1, 9.0)	2980	16.4 (15.0, 17.8)
Organ Transplant	1865	3.6 (2.8, 4.4)	110	3.0 (1.7, 4.3)	550	3.0 (2.2, 3.8)
Cystic Fibrosis	3220	6.2 (4.5, 7.8)	~	~	635	3.5 (2.7, 4.3)
Cancer	5945	11.4 (10.6, 12.1)	375	10.2 (7.9, 12.5)	1835	10.1 (9.0, 11.2)
Cancer with Metastasis	1910	3.6 (3.3, 4.0)	55	1.5 (0.6, 2.4)	415	2.3 (1.8, 2.8)
Cancer with or without Metastasis	6300	12.0 (11.3, 12.8)	390	10.6 (8.3, 12.9)	1910	10.5 (9.4, 11.6)
HIV	520	1.0 (0.8, 1.2)	80	2.2 (1.1, 3.3)	3395	18.7 (16.7, 20.7)
Dialysis	985	1.9 (1.6, 2.2)	45	1.2 (0.4, 2.1)	310	1.7 (1.3, 2.2)
Illicit Drug Use	810	1.5 (1.3, 1.8)	65	1.8 (0.8, 2.7)	555	3.1 (2.5, 3.6)
Pneumonia with unknown Organism	835	1.6 (1.3, 1.9)	220	6.0 (4.3, 7.7)	2950	16.3 (14.9, 17.6)
Fluid Disorders	26370	50.4 (49.0, 51.8)	2585	70.2 (67.0, 73.5)	7140	39.3 (37.6, 41.1)
Anemia	540	1.0 (0.8, 1.2)	~	~	185	1.0 (0.7, 1.3)
Hypertension	17350	33.1 (32.0, 34.3)	1430	38.9 (35.2, 42.5)	5850	32.2 (30.5, 33.9)
Acute Myocardial Infarction	2445	4.7 (4.2, 5.1)	130	3.5 (2.2, 4.8)	305	1.7 (1.3, 2.1)
Congestive Heart Failure	11680	22.3 (21.3, 23.4)	505	13.7 (11.2, 16.2)	2275	12.5 (11.3, 13.8)

Table 3 Continued

Health Condition	*Pseudomonas* pneumonia (N=52345)		Legionnaires' Disease (N=3680)		Nontuberculous mycobacteria (N=18150)	
	N	Percent (95% CI)	N	Percent (95% CI)	N	Percent (95% CI)
Acute Bronchitis	600	1.1 (0.9, 1.4)	~	~	165	0.9 (0.6, 1.2)
Acute Renal Failure	10220	19.5 (18.6, 20.4)	1250	34.0 (30.5, 37.4)	2070	11.4 (10.3, 12.5)
Acute Cystis	65	0.1 (0.1, 0.2)	~	~	~	~
Urinary Tract Infection	9030	17.3 (16.4, 18.1)	370	10.1 (7.8, 12.3)	1315	7.2 (6.4, 8.1)
Chronic Kidney Disease	8010	15.3 (14.5, 16.1)	540	14.7 (11.9, 17.4)	1480	8.2 (7.2, 9.1)
Atrial Fibrillation	11370	21.7 (20.7, 22.7)	760	20.7 (17.7, 23.6)	2545	14.0 (12.8, 15.2)
Respiratory Failure	25140	48.0 (46.7, 49.4)	1385	37.6 (33.9, 41.3)	2825	15.6 (14.4, 16.8)
Sepsis/Septic Shock	12765	24.4 (23.3, 25.5)	1065	28.9 (25.5, 32.3)	1490	8.2 (7.3, 9.2)
Chronic Lung Disease	27020	51.6 (50.2, 53.0)	960	26.1 (22.8, 29.3)	8215	45.3 (43.4, 47.1)
DRG Severity						
No Class Specified (0)	45	0.1 (0.0, 0.1)	~	~	~	~
Minor Loss of Function (1)	45	0.1 (0.0, 0.1)	140	3.8 (2.5, 5.2)	255	1.4 (0.9, 1.9)
Moderate Loss of Function (2)	5420	10.4 (9.7, 11.0)	710	19.3 (16.3, 22.2)	3220	17.7 (16.4, 19.0)
Major Loss of Function (3)	14200	27.1 (26.2, 28.1)	1370	37.2 (33.7, 40.8)	9190	50.6 (49.0, 52.3)
Extreme Loss of Function (4)	32635	62.3 (61.2, 63.5)	1460	39.7 (36.0, 43.4)	5475	30.2 (28.6, 31.8)

~Values not shown for cells with counts ≤10

Table 4: Weighted estimates and hospitalization charges of cases and cases with antibiotic resistance by ICD-9 Code for discharges with an OPPP in the HCUP 2012 NIS.

	Any OPPP Infection	Pseudomonas Pneumonia	Legionnaires' Disease	Nontuberculous mycobacterium			
				All	Pulmonary	Disseminated	Other[a]
	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Counts							
Total Cases	73565 (1394)	52345 (1153)	3680 (156)	18150 (526)	8615 (321)	6890 (272)	2660 (142)
Cases with resistance	1635 (113)	1470 (107)	20 (10)	165 (30)	85 (23)	45 (15)	35 (13)
Multiple Drug Resistance	1075 (89)	1000 (87)	~	85 (20)	45 (15)	30 (12)	~
Charges per case by Resistance Status (U.S. Dollars)							
Median							
Non-resistant	$63,654 (1440)	$80,544 (2082)	$38,924 (2106)	$38,561 (1019)	$38,548 (1208)	$37,714 (1717)	$44,031 (3244)
Resistant	$91,374 (7662)	$92,510 (7658)	$28,046 (81659)	$77,637 (18496)	$58,542 (14943)	$108,797 (31823)	$181,579 (68169)
Mean							
Non-resistant	$151,421 (4264)	$182,641 (5546)	$81,097 (5077)	$77,690 (2821)	$74,618 (3802)	$77,206 (4190)	$90,305 (7907)
Resistant	$173,327 (19550)	$176,586 (21055)	$117,909 (66461)	$144,233 (43470)	$150,328 (79300)	$109,442 (19575)	$179,149 (44910)
Difference of Mean (Resistant-Non)	$21,906*	-$6055*	$36,812*	$66,542*	$75,710*	$32,236*	$88,844*
Ratio of Mean (Resistant/Non)	1.14	0.97	1.45	1.86	2.01	1.42	1.98

*Significant P-value at alpha 0.05 calculated with t-test

[a]Specified and unspecified NTM infection

~Values not shown for cells with counts ≤10

Table 5: Bivariate Associations for selected risk factors with antibiotic resistance among cases hospitalized with *Pseudomonas* pneumonia from the HCUP 2012 NIS.

	Antibiotic Resistance (N=1470)		No Antibiotic Resistance (N=50875)			Unadjusted Associations	
Predictive/Risk Factor	**N**	**Percent (95% CI)**	**N**	**Percent (95% CI)**	**p-value[a]**	**OR (95% CI)[c]**	**p-value[b]**
Age							
0-17	45	3.1 (1.1, 5.0)	2470	4.9 (3.6, 6.1)	0.0006	Ref.	
18-44	315	21.4 (16.0, 26.8)	6385	12.6 (11.4, 13.7)		2.71 (1.32, 5.58)	<0.0001
45-64	380	25.9 (20.6, 31.1)	13735	27.0 (25.9, 28.1)		1.52 (0.74, 3.12)	0.9513
65-84	610	41.5 (35.4, 47.6)	23250	45.7 (44.2, 47.2)		1.44 (0.72, 2.88)	0.7041
85+	120	8.2 (5.0, 11.3)	5030	9.9 (9.2, 10.6)		1.31 (0.61, 2.84)	0.4359
Gender							
Male	760	51.7 (45.9, 57.5)	28820	56.6 (55.6, 57.6)	0.0967	Ref.	
Female	710	48.3 (42.5, 54.1)	22055	43.4 (42.4, 44.4)		1.22 (0.96, 1.55)	0.0002
Race							
White	1035	74.2 (68.9, 79.5)	35020	72.5 (70.9, 74.0)	0.7402	Ref.	
Black	185	13.3 (9.0, 17.5)	6570	13.6 (12.5, 14.7)		0.95 (0.65, 1.40)	0.868
Hispanic	80	5.7 (2.8, 8.7)	3675	7.6 (6.7, 8.5)		0.74 (0.43, 1.28)	0.2903
Other	95	6.8 (4.0, 9.7)	3050	6.3 (5.6, 7.1)		1.05 (0.67, 1.65)	0.4833
Smoke							
No	1360	92.5 (89.3, 95.7)	45790	90.0 (89.4, 90.7)	0.1767	Ref.	
Yes	110	7.5 (4.3, 10.7)	5085	10.0 (9.3, 10.6)		0.79 (0.49, 1.25)	0.3067
Immunocompromised							
No	1215	82.7 (77.7, 87.6)	41280	81.1 (80.1, 82.2)	0.5627	Ref.	
Yes	255	17.3 (12.4, 22.3)	9595	18.9 (17.8, 19.9)		0.90 (0.64, 1.28)	0.1907
HIV							
No	1450	98.6 (97.3, 100.0)	50375	99.0 (98.8, 99.2)	0.5218	Ref.	
Yes	20	1.4 (0.0, 2.7)	500	1.0 (0.8, 1.2)		1.39 (0.51, 3.83)	0.1747

Table 5 Continued

Predictive/Risk Factor	Antibiotic Resistance (N=1470) N	Antibiotic Resistance (N=1470) Percent (95% CI)	No Antibiotic Resistance (N=50875) N	No Antibiotic Resistance (N=50875) Percent (95% CI)	p-value[a]	Unadjusted Associations OR (95% CI)[c]	Unadjusted Associations p-value[b]
Cancer (All)							
No	1350	91.8 (88.5, 95.1)	44695	87.9 (87.1, 88.6)	0.0434	Ref.	
Yes	120	8.2 (4.9, 11.5)	6180	12.1 (11.4, 12.9)		0.64 (0.42, 0.99)	<0.0001
Diabetes							
No	1070	72.8 (67.2, 78.3)	38975	76.6 (75.6, 77.6)	0.1577	Ref.	
Yes	400	27.2 (21.7, 32.8)	11900	23.4 (22.4, 24.4)		1.22 (0.92, 1.62)	0.0019
Transplant							
No	1395	94.9 (91.5, 98.3)	49085	96.5 (95.7, 97.3)	0.243	Ref.	
Yes	75	5.1 (1.7, 8.5)	1790	3.5 (2.7, 4.3)		1.47 (0.76, 2.85)	0.0144
Chronic Lung Disease							
No	760	51.7 (45.6, 57.8)	24565	48.3 (46.9, 49.6)	0.2674	Ref.	
Yes	710	48.3 (42.2, 54.4)	26310	51.7 (50.4, 53.1)		0.87 (0.69, 1.11)	0.0132
Congestive Heart Failure							
No	1185	80.6 (76.1, 85.1)	39480	77.6 (76.5, 78.7)	0.2201	Ref.	
Yes	285	19.4 (14.9, 23.9)	11395	22.4 (21.3, 23.5)		0.83 (0.62, 1.12)	0.0053
Acute Renal Failure							
No	1215	82.7 (77.4, 87.9)	40910	80.4 (79.5, 81.3)	0.426	Ref.	
Yes	255	17.3 (12.1, 22.6)	9965	19.6 (18.7, 20.5)		0.86 (0.60, 1.24)	0.0708
Transfer In							
No	155	10.6 (7.0, 14.2)	4350	8.6 (7.7, 9.4)	0.2336	Ref.	
Yes	1305	89.4 (85.8, 93.0)	46280	91.4 (90.6, 92.3)		0.79 (0.54, 1.16)	0.2344
Elective Admission							
No	1330	90.5 (87.0, 93.9)	44920	88.5 (87.6, 89.3)	0.2998	Ref.	
Yes	140	9.5 (6.1, 13.0)	5855	11.5 (10.7, 12.4)		0.81 (0.54, 1.21)	0.3014
Hospital Size							
Small	145	9.9 (6.1, 13.6)	6515	12.8 (11.9, 13.7)	0.2229	Ref.	

Table 5 Continued

Predictive/Risk Factor	Antibiotic Resistance (N=1470) N	Antibiotic Resistance (N=1470) Percent (95% CI)	No Antibiotic Resistance (N=50875) N	No Antibiotic Resistance (N=50875) Percent (95% CI)	p-value[a]	Unadjusted Associations OR (95% CI)[c]	Unadjusted Associations p-value[b]
Medium	405	27.6 (21.7, 33.4)	12130	23.8 (22.4, 25.3)		1.50 (0.95, 2.36)	0.0819
Large	920	62.6 (56.1, 69.1)	32230	63.4 (61.6, 65.1)		1.28 (0.83, 1.98)	0.7595
Major OR Procedure							
No	1245	84.7 (79.5, 89.9)	40480	79.6 (78.6, 80.5)	0.0816	Ref.	
Yes	225	15.3 (10.1, 20.5)	10395	20.4 (19.5, 21.4)		0.70 (0.47, 1.05)	0.0823
Mechanical Ventilation							
No	870	59.2 (53.1, 65.3)	28470	56.0 (54.6, 57.3)	0.3115	Ref.	
Yes	600	40.8 (34.7, 46.9)	22405	44.0 (42.7, 45.4)		0.88 (0.68, 1.13)	0.3116
Intubation							
No	1255	85.4 (81.0, 89.7)	39485	77.6 (76.6, 78.7)	0.0036	Ref.	
Yes	215	14.6 (10.3, 19.0)	11390	22.4 (21.3, 23.4)		0.59 (0.04, 0.85)	0.0039
Central Venous Line							
No	1035	70.4 (65.2, 75.6)	36505	71.8 (70.6, 72.9)	0.6073	Ref.	
Yes	435	29.6 (24.4, 34.8)	14370	28.2 (27.1, 29.4)		1.07 (0.83, 1.37)	0.6073
Indwelling Urinary Catheter							
No	1435	97.6 (95.6, 99.6)	50155	98.6 (98.3, 98.9)	0.2264	Ref.	
Yes	35	2.4 (0.4, 4.4)	720	1.4 (1.1, 1.7)		1.70 (0.71, 4.05)	0.2317
Length of Stay (Quartiles)							
Q1	235	16.0 (11.5, 20.5)	10560	20.8 (19.8, 21.7)	0.0373	Ref.	
Q2	380	25.9 (20.6, 31.1)	14675	28.8 (27.8, 29.8)		1.16 (0.80, 1.69)	0.4035
Q3	455	31.0 (25.6, 36.4)	12345	24.3 (23.3, 25.2)		1.66 (1.14, 2.40)	0.0072
Q4	400	27.2 (21.6, 32.8)	13295	26.1 (25.0, 27.2)		1.35 (0.90, 2.03)	0.5791

[a]Rao-Scott Chi Square

[b]Wald p-value

[c]95% Cis calculated with Taylor series variance estimation and not missing completely at random

Table 6: Multivariable model associations for predictive risk factors with antibiotic resistance among cases hospitalized with *Pseudomonas* pneumonia from the HCUP 2012 NIS. Final risk factors considered interaction with age and gender and were determined via backwards elimination.

Predictive Factor	**Adjusted OR (95% CI)[b]**	**p-value[a]**
Age		
0-65	Ref.	
65+	1.20 (0.93, 1.55)	0.1542
Gender		
Male	Ref.	
Female	1.57 (1.13, 2.17)	0.0070
Intubation		
No	Ref.	
Yes	0.59 (0.41, 0.85)	0.0040
Urinary Catheter by Age		
No	Ref.	
Yes - Among 0-65	0.49 (0.07, 3.57)	0.4833
Yes - Among 65+	3.29 (1.37, 7.86)	0.0008
Chronic Lung by Gender		
No	Ref.	
Yes - Male	1.10 (0.79, 1.55)	0.5651
Yes - Female	0.69 (0.49, 0.97)	0.0320

[a]Wald p-value

[b]95% Cis calculated with Taylor series variance estimation and missing values treated as not missing completely at random

Figure 1.

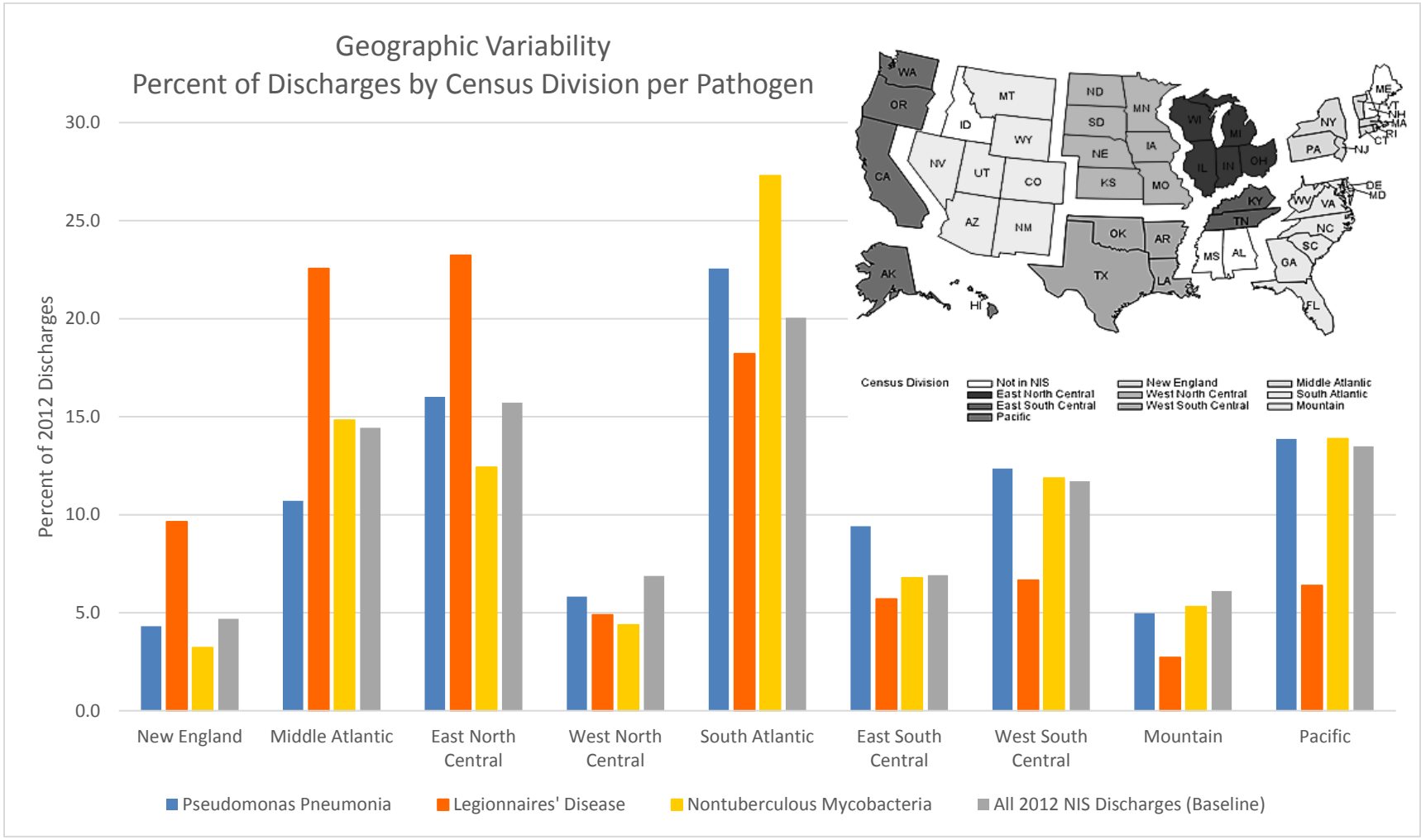
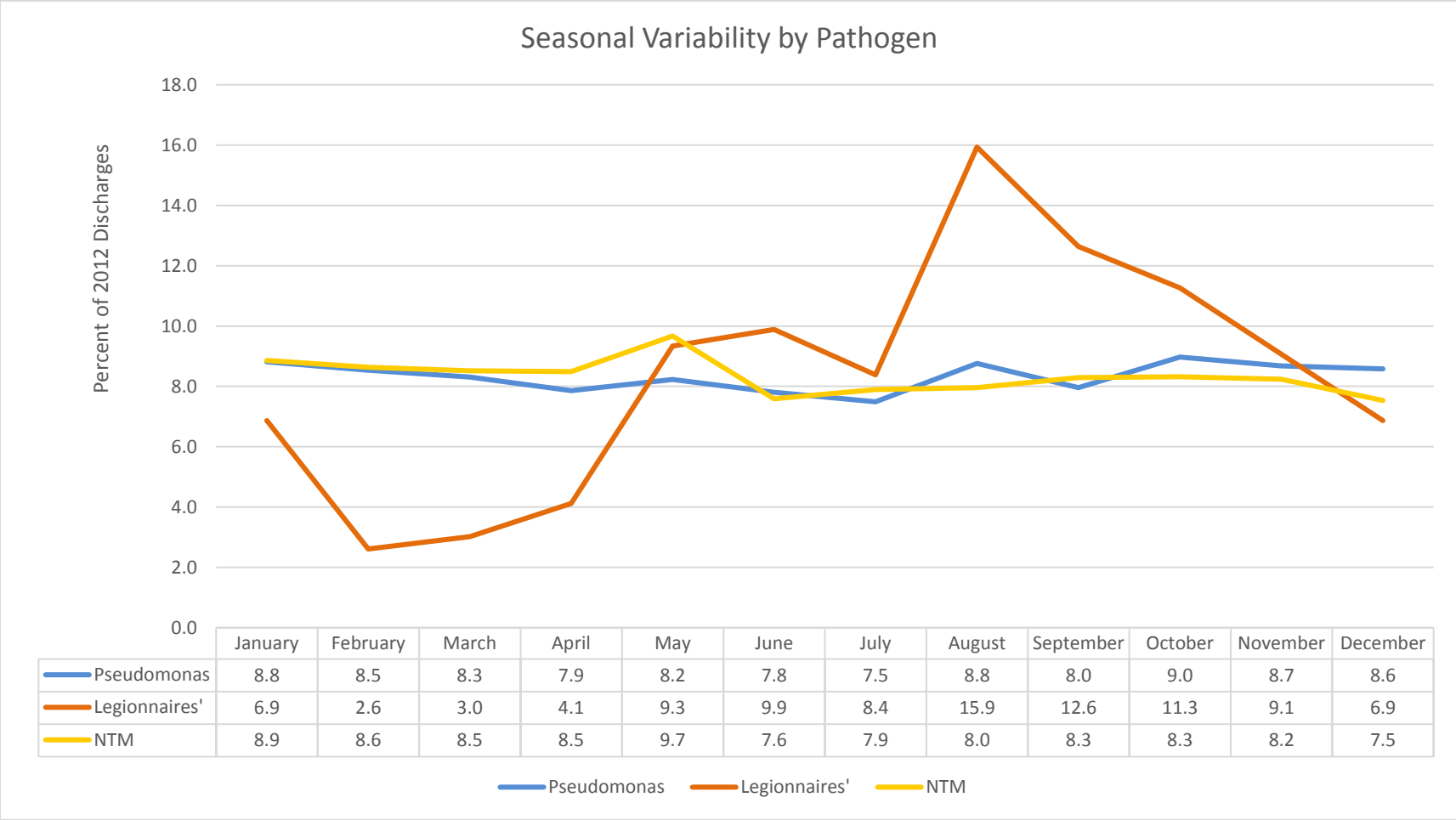

Geographic Variability
Percent of Discharges by Census Division per Pathogen
Percent of 2012 Discharges
30.0
25.0
20.0
15.0
10.0
5.0
0.0
New England
Middle Atlantic
East North Central
West North Central
South Atlantic
East South Central
West South Central
Mountain
Pacific
Pseudomonas Pneumonia
Legionnaires' Disease
Nontuberculous Mycobacteria
All 2012 NIS Discharges (Baseline)
Census Division
Not in NIS
New England
East North Central
West North Central
East South Central
West South Central
Middle Atlantic
South Atlantic
Mountain
Pacific
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
MN
IA
MO
OK
TX
AR
LA
WI
IL
MI
IN
OH
KY
TN
MS
AL
GA
FL
SC
NC
VA
WV
PA
NY
NJ
DE
MD
ME
VT
NH
MA
RI
CT
AK
HI

Figure 2.



	January	February	March	April	May	June	July	August	September	October	November	December
Pseudomonas	8.8	8.5	8.3	7.9	8.2	7.8	7.5	8.8	8.0	9.0	8.7	8.6
Legionnaires'	6.9	2.6	3.0	4.1	9.3	9.9	8.4	15.9	12.6	11.3	9.1	6.9
NTM	8.9	8.6	8.5	8.5	9.7	7.6	7.9	8.0	8.3	8.3	8.2	7.5