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Population-level Characterization of Nocardiosis in the United States

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by

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Abstract

Nocardiosis is caused by opportunistic, soil-borne bacteria in the genus *Nocardia*. The disease is characterized by severe pulmonary and systemic infections, and mild to severe skin infections. People thought to be at risk are older adults and those with underlying comorbidities, particularly immunosuppressive conditions. Treatment duration can be long and may require antimicrobial and surgical interventions. Considered a rare disease, the existing literature and knowledge base regarding the clinical presentation, persons at risk, incidence, and mortality estimates are primarily from case series or limited hospital-based retrospective analyses. Evaluating the disease characteristics from more generalizable data can aid in our understanding of the disease and may aid in identifying persons who may be at greater risk of death.

The purpose of this dissertation is to use population-level administrative data to develop generalizable estimates of the incidence and mortality, and to evaluate risk factors, including identifying a predictive comorbidity measure. The 100% Medicare Fee-For-Service data, and the Healthcare Utilization Project's State Inpatient Databases and State Ambulatory and Surgery and Services Databases were used to evaluate nocardiosis among Medicare beneficiaries as well as all payer hospitalization and visit discharges. The demographics, costs, visits, and risk factors are described from each data source, and incidence and hospitalization rates are calculated. Comorbidity measures are evaluated for prediction of mortality. Time to death and covariates associated with mortality are calculated from the person-based longitudinal Medicare data and the HCUP hospital visit-based data, respectively.

The findings of this dissertation describe nocardiosis that can be generalized to all Fee-for-Service Medicare beneficiaries and almost half the US population. Nocardiosis cases and nocardiosis-associated visits were more often male, older, and sicker than the general Medicare and US populations. Mortality was associated with disseminated nocardiosis, cerebrovascular disease, and the presence of additional comorbid conditions, when controlling for other factors. Additional findings will be discussed.

These findings can provide additional insight into persons who may be at greater risk of developing nocardiosis and can provide clinicians with factors that are associated with mortality. These findings provide a baseline from which future population-level analyses can be compared.

Preface and Acknowledgements

After more than a decade of experience in public health, it felt time to seek out additional training in the form of PhD to improve my analytic and research design skills. Continuing to work full time during this process seemed challenging but not insurmountable. The topic I choose was not exactly by choice, but by process of elimination to align with my employer's needs for time and financial support. This is both a blessing and a curse, and this process has not exactly been a labor of love.

Despite challenges with the topic, I would like to acknowledge those at CDC for their support and assistance in receiving the Long-term education award, especially Dr. William Bower. Also, I would like to thank those in my program at Georgia State for your support and encouragement, particularly the accountability calls to just finish already. Juggling a career, a personal life, and life as a student did not always work well, and I experienced many changes and disruptions during this process. Deepest of thanks to those friends, family, and colleagues who continued to support me through this process, even for the light harassment to finish.

This dissertation was a learning experience, particularly in what not to do, and I feel I have come out the other side a bit more wizened but also wiser. There are many changes I wish I could make to the analyses and results herein, but there were limitations from losing data access before recognizing mistakes. Commentary about suggested improvements to models, etc., are welcome, although may not be possible to achieve. As a learning experience, this process has shown me that limited duration of access to data should be avoided at all costs, hopefully to avoid the disheartening realization that mistakes cannot be fixed nor can additional research questions be answered.

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Abbreviations

Abbreviation	Term
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
CLABSI	Central line-associated blood stream infections
CNS	Central nervous system
CVC	Central venous catheters
CCW	Chronic Conditions Warehouse
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
ESDA	Exploratory spatial data analysis
FFS	Fee-for-Service
HCUP	Healthcare Cost and Utilization Project
HSCT	Hematopoietic stem cell transplant
HIV	Human Immunodeficiency Virus
ICD-9-CM	International Classification of Diseases 9th revision-clinical modification
ICD-10-CM	International Classification of Diseases 10th revision-clinical modification
MRI	Magnetic resonance imaging
MBSF	Master Beneficiary Summary File
OPTN	Organ Procurement and Transplant Network
RIF	Research Identifiable Files
SBRL	Special Bacteriology Reference Laboratory
SD	Standard Deviation
SASD	State Ambulatory Surgery and Services Databases
SID	State Inpatient Databases
TMP-SMX	Trimethoprim sulfamethoxazole

Chapter 1: Literature Review and Statement of Purpose

I. Overview

Population-based descriptions of the disease nocardiosis and its etiologic agent, the bacterial genus *Nocardia*, in the United States are scarce despite a substantial body of research (1-3). Nocardiosis is a medically important disease that more frequently affects immunocompromised patients (4, 5). There are varied clinical presentations that can make clinical recognition challenging (6), and as a soil-borne pathogen, prevention methods are limited (4). The disease is difficult to treat, requiring months or years of antimicrobial therapy (7), and contributes to mortality in patients with underlying conditions (8).

There are several reasons for the lack of population-level and generalizable data. First, nocardiosis is challenging to study because it is relatively rare (6), thus selecting a generalizable and nationally representative sample has been difficult. Medical discharge data could not be used because nocardiosis was combined with other bacterial and fungal agents in medical coding versions prior to 2015 (9). Meanwhile, facility-based studies lack generalizability due to social and geographic variations (3), and reports from facilities that target patient populations with known nocardiosis risk factors, such as transplant (10-12) or cancer hospitals (13, 14), are not generalizable to a wider population.

Additionally, available diagnostic methods can limit the ability to diagnose the disease accurately and rapidly (15). Many disparate laboratories in the United States perform reference testing of *Nocardia* spp., which produce non-representative reports of isolate identifications (2, 16, 17). Analysis of *Nocardia* by species is also limited, and due to major taxonomic changes over time (15), retrospective analyses of *Nocardia* species may need to be retested using modern molecular methods because of historical misidentification and misclassification (15, 18).

Due to the ageing United States population (19) and increasing prevalence of immunocompromising conditions among American adults (20), it is important to describe nocardiosis using generalizable population–level data. These descriptions may further improve

clinical recognition of nocardiosis, push clinicians to request species-level identification for improved treatment, rapid provision of appropriate antimicrobials, and provide a nationally representative description of nocardiosis for the United States.

II. Literature review

A. Microbiology

Nocardia is a genus in the class Actinobacteria and order Actinomycetales (6). The genus is composed of gram-positive, partly acid-fast bacilli with filamentous and branching growth; they tend to be slow growers and produce aerial mycelia (6, 14, 21). The taxonomy has evolved since the organism was first identified by Nocard in 1888 and first named by Trevisan a year later (22). Historically, morphologic and phenotypic characteristics were used to define species (15); however, these methods do not have the granularity to adequately differentiate species within the genus (15, 18). These limitations and other conflicts have to led to the incorrect identification of bacteria from other genera as *Nocardia*, and inaccurate classification within *Nocardia* species (15).

Nocardia asteroides was noted to have heterogeneity within the species (23). It was later termed a "complex" (15) that was separated into seven groups of species (1-6, and miscellaneous) based on antimicrobial susceptibility patterns to various classes of antimicrobials (24). These susceptibility patterns were used to determine the antimicrobial treatment regimen to maximize outcomes, because of varied antimicrobial resistance by group (24, 25).

Molecular diagnostic methods have since distinguished the *Nocardia asteroides* complex into several separate species, including the pathogenic species *N. abscessus* (previously group 1), *N. nova* (within a complex of species, group 3), *N. cyriacigeorgica* (group 4), and *N. farcinica* (group 5) (25). As a result, *N. asteroides* complex is no longer an approved name (26), and more than 80 species are now identified, of which 49 have been isolated as human pathogens (15, 25). Improved methodologies shorten diagnosis delays (15), increase the recognition of the etiologic agent (14), and enable accurate antimicrobial susceptibility testing (17).

B. Geographic distribution and ecology

A few studies have attempted to evaluate the geographic distribution of *Nocardia* species, primarily using clinical isolates (3, 27, 28). The genus *Nocardia* appears to be ubiquitous in many locations around the world (2, 27, 29-37). Yet, understanding the distribution in the United States is limited by reporting and submission bias. In a review of 765 specimens submitted to CDC over 10 years, 44 states submitted specimens, of which 18% were submitted by Alabama and 10% from Florida (2). A study from Utah over five years reported 2,198 specimens submitted from 40 states with no further geographic specification (17).

There may be geographic variation by infecting species. The previously named *N. asteroides*, which has been separated into multiple diverse species (26), and *N. farcinica* have been reported to have an even distribution across the United States (6, 38). One report claims that *N. nova* is less frequently identified in the southwest (38). Of *N. brasiliensis* case reports in the United States up to 1984, 63% were published in five states (Texas, California, Florida, North Carolina, and Oklahoma) (3), although these results are perhaps limited by publication bias. Another author based in the southwestern U.S. has stated that *N. brasiliensis* is most common in the southeast (based on the previously mentioned study) and the southwest, based on receipt of 40 *N. brasiliensis* isolates out of 455 *Nocardia* isolates in five years (38). Uhde *et al* report that 59 of 106 (56%) of *N. brasiliensis* isolates originated from Tennessee and Florida over a 10 year period (2), which supports the claim of a higher prevalence in the southeast.

Ecological characteristics likely influence the presence of *Nocardia* spp. organisms and geographic variation of *Nocardia* spp. in the soil. It is generally accepted that nocardiosis is endemic in tropical and subtropical climates, while infections are less frequent in temperate climates (6). Warmth and humidity have been associated with nocardial keratitis (39) and actinomycetoma (40). This association may be intensified by greater soil exposure due to the types of clothing and shoes worn (or not worn) in hot and humid environments (35, 39, 40). These results contradict a statement of a regionally-based author that most U.S. cases occur in the hot, dry, and windy climate of the American southwest (38).

Nocardia species diversity, but not the presence of *Nocardia* spp., may be influenced by soil characteristics. A soil study from Iran found that 60% of "*N. asteroides* complex" were

found in soil with pH 7.1-8.0, and 63.6% of *N. brasiliensis* isolates were from soil pH 8.01-9 (41). The greatest frequency of "*N. asteroides* complex" were recovered from a desert climate (41), contrary to associations of nocardiosis with humidity (39, 40). Despite the findings that soil characteristic preferences may differ by *Nocardia* species, this was not borne out in a study of human infections at a local level (28). The evaluation did not find evidence of an association of soil characteristics at case residences or geospatial clustering of case residences regardless of infecting species (28). Host susceptibility and marginal ecological variation at the local level may affect the influence of species soil preference.

In summary, a study evaluating *Nocardia* spp. in the soil in the United States would be beneficial to understand the distribution and species diversity. A population-based analysis of disease prevalence may guide such a study.

C. Clinical manifestations

There are three main forms of disease due to *Nocardia*: primary cutaneous, pulmonary, and disseminated infections (6). Less frequent sources or presentations of disease include bacteremia, ocular, and other extra-pulmonary infections (6); other authors describe additional forms of disease: extrapulmonary, central nervous system (CNS), and mycetoma (42). The most common forms will be described below, as well as a few forms of extrapulmonary disease.

Cutaneous

Primary cutaneous nocardiosis is caused by the direct inoculation with soil contaminated with *Nocardia* spp. (3, 4, 43). Some cases report no trauma, such as innocuous events including direct contact of open cuts with soil when gardening (3, 43) or a thorn prick (44). Traumatic inoculation has been reported, such as injuries from a car accident (45) and through nosocomial exposure (46). *Nocardia brasiliensis* may account for up to 80% of cutaneous infections (6, 42). Interestingly, one study in Houston found *N. farcinica* to most commonly cause skin infections, although this was in a severely immunocompromised population (14).

Primary cutaneous infection can disseminate hematogenously to cause systemic, or disseminated, nocardiosis (47). Primary cutaneous infections can present as superficial, lymphocutaneous, subcutaneous/ actinomycetoma (48). Meanwhile, it is estimated that 8-10% of cutaneous infections are secondary to a primary pulmonary infection that disseminated to the skin (42, 48).

The least severe form, patients with superficial skin infections may have ulcers (49), cellulitis (50), abscesses (51), granulomas (52), as well as pustules, plaques, or papules (53). The superficial form was found to be the most common form of cutaneous nocardiosis in the United States in one literature review of 75 cases (53). The authors also found an average time to diagnosis of 12.7 weeks (range:0.5-52) from 43 patients with superficial cutaneous nocardiosis, and only 32.6% were immunocompromised (53). Only infrequently do superficial infections progress into disseminated infections (54). Differential diagnoses include other pyogenic bacterial infections, including *Staphylococci* and group A streptococci (3, 43), sporotrichosis (6, 47), tularemia (7, 47), or *Erysipelothrix* spp. infections (7).

An estimated 1/3 of cutaneous infections progress to the lymphocutaneous form (55), which involves the lymphatic system; it is also called sporotrichoid nocardiosis because of its similarity to sporotrichosis (16). In one series, patients frequently presented with a nodule, as well as local pain, edema, erythema, warmth, and induration (43). Some patients presented with lymphangitis and lymphadenopathy (43), as well as cellulitis; the lesions may progress to subcutaneous abscesses (47, 53). Average time to diagnosis of 26 patients was 20.6 weeks (range 0.5-208) (53), slightly longer than that for superficial infections; 46.2% were immunocompromised (53). Differential diagnoses include sporotrichosis (16) and *Mycobacterium marinum* infection (7, 56).

Both forms often present on the extremities (14, 43, 47, 53), which may point to the ability for trauma to occur on uncovered skin. Specimens for diagnosis include fluid drained from abscesses or lesions for culture, or biopsies of the lesions to identify histopathologic evidence of *Nocardia* spp. bacilli (43, 47, 53). Co-infections may confuse the diagnosis (3, 56), and contamination of the wound with multiple organisms can outcompete or conflate the

causative agent of the infection (3). Finally, a full examination must be done to rule out secondary cutaneous infection due to dissemination (4).

Actinomycetoma

Bacterial subcutaneous infections are called actinomycetomas, although they are often referred to collectively as mycetoma due to variable bacterial and fungal etiologies; the fungal form is known as eumycetoma (57). The World Health Assembly agreed to add mycetoma as a neglected tropical disease in 2016 (WHA69.21). *Nocardia brasiliensis* is reportedly the most frequent nocardial etiology of bacterial mycetoma (3, 4). Actinomycetoma occurs predominately in tropical areas and is associated with humid and hot climates (35, 40), although the global distribution of actinomycetoma and eumycetoma appears to vary. Mexico reports a majority of mycetoma due to actinomycetes (58), while a majority of mycetomas in Sudan are fungal infections (59). Rarely reported in the United States, cases have primarily occurred in states bordering Mexico (53). Mycetomas are likely due to small traumatic inoculations on the feet or lower legs from walking barefoot or in open-toed shoes (35, 40).

Actinomycetomas are often chronic infections that progress to cause severe morbidity, particularly through deep tissue necrosis, bone damage, and subsequent disability (35, 40, 53). The disease most often appears as tumor-like growths, abscesses, and indolent nodules with draining sinuses predominately affecting the lower legs or feet (35, 40). Differential diagnoses include fungal infections (e.g., eumycetoma) and actinomycosis (7). Specimens for diagnosis include grains exuded from the mycetoma, either superficially collected from the draining sinuses for microscopy, or by deep biopsy for histopathology or culture (60). The color and other morphological characteristics of the grain are used to help differentiate the etiologic agent, which may allow for appropriate antimicrobial or antifungal treatment (60). Grain examination does not provide a definitive diagnosis (61);however, diagnosis is likely made at field clinics in rural areas, which relies upon clinical diagnosis in the absence of culture, PCR, pathology, or access to a referral center (62). Clinical diagnosis may not differentiate between fungal and bacterial infection, and the inappropriate treatment only delays treatment further and exacerbates morbidity (62).

Pulmonary

Primary pulmonary nocardiosis is thought to be caused from inhalation of aerosolized spores or mycelia (4). Pulmonary infection is the most common form of disease in the United States (6, 48), and more often affects patients with structural lung disease (28, 63), immunocompromising conditions (6), or those taking corticosteroids for more than six months (28, 63).

Respiratory-tract colonization is reported in many reviews of pulmonary infections (64-67). Some lung diseases, such as cystic fibrosis, may predispose patients to respiratory tract colonization (67). Georghiou *et al* found 20% of *Nocardia* spp. isolates were not associated with clinical symptoms and the patients were assumed to be colonized (55), while Fujita *et al* found 40% of immunocompetent patients were colonized (64). If a patient has symptoms or signs of lung infection and a positive *Nocardia* spp. culture from a respiratory specimen, the result should be assumed to be clinically important (64, 66).

The disease is characterized by an acute onset with inflammatory response, which progresses to granulomatous inflammation and necrotic abscess development (38, 68). Symptoms are usually nonspecific, including cough, dyspnea, and fever (14, 64, 65, 68, 69); pleuritic chest pain has also been reported (69). One study found that symptoms did not differ significantly by immune status (64).

Clinical signs include presence of leukocytosis and elevated C-reactive protein (14, 64, 68). Frequent radiographic findings include the presence of one or more lung nodules, lobar consolidation, and pleural effusion (14, 64, 65, 68); pulmonary infiltrates and necrotizing granulomas may be present (14) and lung findings are frequently bilateral (8). Cavitation is reported more frequently among immunocompromised patients (5, 64).

Time from onset to diagnosis varies widely. An older literature review found the average time to diagnosis was 11.7 weeks (SD: 16.5, range 2 days-29 months) while a more recent study found an average of 42 days (SD: 40) (33). Although reasons for the delays were not explained, more rapid diagnostic results and improved clinical recognition may be factors in the differences between periods. When differentiated by immune status, mean delay was 45.8 days

(SD: 45) for immunocompetent patients who presented with subacute infections, and 7.4 days (SD: 12) for immunosuppressed patients with acute infections (64). Delays in diagnosis (70) and acute disease (68) are associated with poor outcomes and higher mortality.

The proportion of patients that progress to disseminated infection also varies and is associated with immune status. Dissemination to an extrapulmonary site has been reported in 0-4% of immunocompetent patients and 22-28% of immunosuppressed (28, 64). When immune status is not differentiated, the proportion ranges from 8.5%-38% (14, 69, 71).

Symptoms, signs, and radiographic findings are not sufficient for diagnosis of nocardiosis due to their lack of specificity. Differential diagnoses for pulmonary nocardiosis include tuberculosis and non-tuberculosis *Mycobacterium* infections, various fungal (e.g., *Aspergillus* spp.) and bacterial infections (e.g., *Rhodococcus equi* in HIV-positive patients), and malignancy (4, 7, 72).

Early specimen collection, particularly prior to antimicrobial therapy, will improve the ability to recover organism for microbiological or histopathological diagnosis (63). Non-invasive collection methods for respiratory specimens produces good recovery of organism (14, 33); sputum and bronchoalveolar lavage are the most common specimens reported (14, 33, 63-65).

Disseminated

Disseminated, or systemic, infection is due to the hematogenous spread of the infection to a non-contiguous organ or system (6, 42). It can result from primary cutaneous or pulmonary infection; it can cause infection anywhere in the body, but predominately affects the skin, lungs, and central nervous system (CNS) (5, 42). Other relatively common locations of disseminated infection include the kidney (73), joints (74), retina (75), and heart (76).

Dissemination appears to occur more commonly in those with immunosuppression (5, 64). A study of four medical centers in Taiwan found only 6% of nocardiosis cases had dissemination (77), and a surveillance study in Spain found 13.5% had disseminated disease (34). When separated by immune status, dissemination was 0-9% among immunocompetent and 22-27% among immunocompromised patients (5, 64). Transplant recipients are at greatest risk of dissemination (5); 42.7% of patients experienced disseminated disease in a large multi-

site study (8). Radiological imaging is important to locate abscesses using computed tomography (CT) or magnetic resonance imaging (MRI) (31).

CNS

In a study of 1,050 cases, 22.7% of cases (n=238) had CNS infections, of which 42% were immunocompetent (42). Meanwhile, 44% of disseminated infections had CNS involvement (42). Similarly, 25.6% of transplant recipients had CNS involvement (8). An estimated 38% of all CNS nocardiosis infections are primary infections rather than disseminated infections (42).

Symptoms and signs of CNS infection may include fever, headaches, meningismus (78), seizures (5, 78), and neurologic deficits (5, 8). However, the absence of signs does not exclude CNS involvement; 43.3% of transplant recipients had no neurological signs or symptoms despite presence of CNS infection on imaging (8). Thus, radiological imaging (e.g., CT, MRI) and collection of cerebrospinal fluid is important for any patient with suspect nocardiosis, particularly immunocompromised patients (14, 78). In this population, disease progression may be rapid (42); the abscesses can spread by extending *Nocardia* spp. filaments (42). However, progression and onset of neurologic signs can take years in immunocompetent patients (79). Differential diagnoses may include malignancies (7, 78), vascular infarction, or other bacterial or fungal infections (7).

Extrapulmonary disease

Other extrapulmonary forms are reported in the literature, which occur either via dissemination from primary cutaneous or pulmonary infection, or direct inoculation (71).

Ocular

The eye can be affected with either a primary or disseminated infection (42). Corneal lesions or keratitis can result from traumatic inoculation of the eye, eye surgery, steroid use (80), or contamination of contact lenses (80, 81). Retinal involvement is more often associated with disseminated disease (42). Corticosteroids are frequently used as a treatment for bacterial keratitis and corneal ulcers, but may actually produce worse outcomes for nocardial infections (36).

Osteomyelitis and septic arthritis

Nocardial osteomyelitis has been recognized as an unusual presentation since 1963, with the first culture-proven infection of the vertebral column (82). Osteomyelitis has since been described in the vertebra and appendicular skeleton, and are predominately disseminated from a primary infection site (82-84). Most primary osteomyelitis cases are described in immunocompetent individuals following traumatic inoculation (51, 85-87), although two cases have been reported in patients with HIV (88, 89).

Septic arthritis infected with *Nocardia* sp. has been reported infrequently, although the first case was reported in the English literature in 1954 (90). Infections predominately affect the knee, and are described shortly following total knee replacement (91, 92) or periprosthetic infection of the knee (93, 94). Two reports have described nocardial septic arthritis of the knee joint following surgical repair of the anterior cruciate ligament in immunocompetent patients (95, 96).

D. Treatment

There are no standard recommendations for nocardiosis treatment. Treatment selection and duration must be customized to the patient based on the form and severity of disease underlying conditions, and antimicrobial sensitivity testing (6, 7).

a) Antimicrobials

Antimicrobial susceptibility varies by *Nocardia* species, which were historically divided into groups based on their susceptibility patterns to various antimicrobial classes (25, 26, 97). *In vitro* and *in vivo* antimicrobial susceptibilities can be inconsistent (6, 7), and the organism can be fastidious and outgrown by the presence of co-infecting bacteria (48). These factors can make treatment selection challenging. Additionally, there has been some dispute regarding resistance of trimethoprim sulfamethoxazole (TMP-SMX) (2, 16, 98), which is a first line and widely used treatment for nocardiosis (7, 99). A large multi-center study from six laboratories in the U.S. did not find evidence of substantial resistance to TMP-SMX (16).

Often only reference laboratories will perform susceptibility testing, which can further delay appropriate treatment (98). However, if susceptibility testing is not available, the group antimicrobial susceptibility profiles could be used as a rough gauge to determine treatment regimens (15, 25), although some of the groups have inconsistent patterns for some drug classes (6, 25). Combination therapy is recommended while awaiting susceptibility results, usually consisting of TMP-SMX and another antimicrobial agent (25). If CNS involvement is suspected, an agent that is effective for CNS infections is preferred, such as ceftriaxone or TMP-SMX (7, 25). Once the susceptibility results are known, monotherapy may be sufficient depending on the disease severity; however, patients should be monitored for drug intolerance (25).

Extended duration of treatment is recommended to prevent relapse from this intracellular bacterium (7). Immunocompetent patients with uncomplicated infections are recommended to receive at least six months of antimicrobial treatment (7, 99), although one study found an average treatment duration among patients with superficial cutaneous infections of four months (range 1-12 months) (53). Immunocompromised patients or those with complicated or disseminated disease should receive 12 months or more of antimicrobial treatment (7, 99). A suggestion for patients with CNS involvement is to treat with intravenous antimicrobials for six weeks or more, with an additional year or more of oral antimicrobial treatment (100).

Adjunctive care

Antimicrobials alone may be insufficient for many patients. Surgical excision, incision and drainage, or debridement may be required for cutaneous lesions (3, 43, 47, 101), which may be performed serially (43, 101). Skin grafts may also be needed for wound closure, particularly for necrotic lesions (3, 101). Additionally, amputation may be performed to remove appendages severely affected with actinomycetoma (3, 102). When a prosthetic joint is involved, revision or one-stage replacement of the joint have been performed to remove infected tissue and repair the prosthetic (93, 94).

E. Diagnostics and antimicrobial susceptibility testing

Nocardia spp. can have fastidious growth (4), may be overgrown by other infecting organisms (48), and clinicians may not consider an infectious etiology given similarity to some malignancies (5, 103). Culture-based diagnostic methods are slow and phenotypic tests lack specificity to differentiate species (15), both delay diagnosis and proper treatment. Correct identification to the species level enables a more accurate antimicrobial treatment regimen (25); susceptibility breakpoints have been established by the Clinical and Laboratory Standards Institute (104).

Advanced methods can be applied to isolates to more rapidly and accurately identify the species, and include gene sequencing (i.e., 16S) and matrix-assisted laser desorption ionization–time of flight mass spectrometry (15). Unfortunately, more advanced identification and susceptibility-testing methods are not frequently available at clinical laboratories (15, 98, 105). Submission to reference laboratories delays diagnosis (15).Molecular diagnostic advancements have improved the ability and timeliness to properly identify organisms (106-108), which can ensure that patients receive appropriate treatment more quickly (17). Such advancements have also most likely increased the quantity of recognized infections (98, 99), which may factor into reports of increasing incidence (14).

F. Epidemiology

i. Demographics

Many studies report that males outnumber females at a ratio of 2-3:1 (3, 65, 109-111), but other studies show a more equitable distribution with slightly fewer females (5, 13, 21, 112). The differences in distribution may be associated with an underlying association of sex with the risk factor of interest in the study. Two studies among solid organ transplant recipients reported a ratio of 1.7:1 (8) and 2:1 (109) males to females, but the latter study reported a ratio of 3:2 among all transplant patients at their facility (109). Other transplant (10, 11, 113) and older HIV studies (32, 111, 114) report a disparate ratio by sex. Malignancy studies reported ratios of 1:1 (13, 112) and 1.6:1 (14), non-specialty facilities reported ratios of 1.1:1 (66) - 1.3:1 (5), while national reference laboratory reports vary widely (1.4:1 (21)– 2.4:1 (115)).

All this is to say, there is a wide distribution by sex. Of 1,959 isolates submitted to the Centers for Disease Control and Prevention's (CDC) Special Bacteriology Reference Laboratory (SBRL) between 2008 and 2018, that were positive for *Nocardia* spp., and had information about patient sex, 1,119 (57.1%) were from males and 840 (42.9%) were from females for a ratio of 1.3:1 (unpublished CDC data).

McNeil *et al*, in the seminal summary of medically important actinomycetes, stated that cases typically are in their "third to fourth decade" (4), although some recent studies have average ages in the 50's (5, 34) and 60's (21). Reports range widely in average age reported, which also may have an association with risk factors. The average age among patients for whom isolates were sent to CDC between 2008 and 2018 with age information (n=1,894) was 58.0 (Standard deviation [SD]: 21.5, range 7 weeks-104) (unpublished CDC data).

Sources of disease

As saprophytic bacteria, *Nocardia* spp. decompose organic matter in the soil (116) and have been found widely in soil and water (117). Generally, pulmonary exposure occurs when aerosolized spores or mycelia are inhaled (4); the bacteria are frequently found in dust and bioaerosols (37, 117-119). Primary pulmonary infection more often occurs in immunocompromised individuals (6) or those with structural lung disease (28, 63).

The second exposure route is direct inoculation into the body, which is the source of most primary cutaneous infections (3, 43, 53). Inoculation can be traumatic, such as an injury sustained during a car accident (45) or mildly traumatic as a prick from a bush (44), through a nosocomial exposure (46, 95, 96, 118, 120), or through dust or dirt entering into open wounds (3, 43). In an extreme case, a patient developed nocardial meningitis following a traumatic skull fracture (121).

Nosocomial

As previously stated, nosocomial exposures are infrequently reported in the literature; source confirmation varies (118, 122). Exmelin *et al* reported an outbreak among three immunocompromised heart transplant patients in the same ward with highly similar strains; no

potential source was identified (46). Two instances of disseminated disease occurred in immunocompetent cases following insertion of prostheses (120, 123), but again, the source was not identified.

Houang *et al* reported the source of a nocardiosis outbreak in a renal unit was contaminated air ducts, as they were able to recover a small number of *Nocardia* spp. colonies from air, dust, and settle plates placed in the ward (118). Because molecular typing was not yet available to confirm the relationship of the isolates, there is not confirmatory evidence of the source of the infections. A more recent investigation used molecular typing methods to determine that the source of an outbreak among five open heart surgery patients was an anesthesiologist present at each surgery (124).

One study suggested that exposure to medical equipment was a possible source of infection (125). There was extensive *Nocardia* spp. biofilm formation found on central venous catheters used at a cancer facility where 10 patients had central line-associated blood stream *Nocardia* spp. infections and another seven were bacteremic (125). The authors did not assert that the infections were definitively from the catheters, although they recommended antimicrobial treatment of central venous catheters to reduce biofilm growth. Beyond such prophylaxis, no specific precautions are recommended to prevent *Nocardia* spp. nosocomial transmission due to its rarity and limited evidence for communicability. However, the clinical implications of environmental contamination with *Nocardia* spp. in healthcare settings may need to be reconsidered. For example, Rahdar *et al* found evidence of 25 *Nocardia* spp. isolates from 63% of Iranian hospitals that were sampled (37).

Incidence

Current knowledge of nocardiosis incidence in the United States is based on an historical survey of 171 infectious disease physicians from 1974 and isolates received at the CDC reference lab (1). This extrapolated estimate was 500-1,000 new cases annually, which has been referenced frequently and recently (67, 126) despite changing demographics of the population (19), increasing numbers of immunocompromised adults (20), longer survival (127)

and greater occurrence of higher risk conditions (based on Organ Procurement and Transplant Network data as of January 17, 2019), and improved laboratory methods (18).

Although there are no current national-level estimates of nocardiosis incidence or prevalence for the United States, there are many prevalence estimates among special patients at specific facilities. A retrospective study from a transplant facility calculated an overall prevalence rate of 0.6% among their transplant patients; by organ type, rates ranged from 0.1% among liver transplant patients to 3.5% among lung transplant patients (11).

Globally, reports are in conflict whether nocardiosis incidence is increasing or remains stable (28). In Japan, a population-based analysis of isolates from 1992-2001 found the raw count to be trending upward (128), but they did not account for population growth. A study from Quebec reported increasing incidence (98), while two studies from Spain reported a stable incidence (115) and a non-significant positive change (34).

Risk factors among the Immunocompetent

An estimated 60% of infections occur in immunocompromised individuals, and 40% are reportedly immunocompetent (79, 129). However, it is estimated that 10% or fewer infections occur in immunocompetent individuals without any risk factors (38, 68), such as chronic lung disease, on long-term corticosteroids, or have other underlying conditions that may predispose them to a lung infection (28, 65, 67). More specifically, these include chronic obstructive pulmonary disease (63), bronchiectasis (28), and cystic fibrosis (67, 130).

In one review of 59 cases of pulmonary disease, 88% had some sort of underlying pulmonary condition, including structural changes to the lung, but most were considered immunocompetent (65). Structural changes to the lungs (28, 63) may impact the respiratory immune response (131), as can ageing (131), which may increase the risk of pulmonary nocardiosis among adults 65 and older. A recent study has found an association between disseminated nocardiosis among immunocompetent individuals with granulocyte macrophage colony-stimulating factor autoantibodies (132). This association requires additional research but may help explain the ability of nocardiae to overtake an apparently healthy immune system. The remainder of immunocompetent nocardiosis cases are likely exposed to the

bacteria by inoculation (44) leading to cutaneous infection, or nosocomial exposure leading to arthritis (93, 95, 96) or eye infections (36).

Corticosteroids

Nocardiosis has been associated with the use of oral and inhaled corticosteroids (5, 28, 34). This association is not restricted to *Nocardia* spp.; a similar correlation has been found with non-tuberculosis *Mycobacterium* pulmonary infections (133). It is not clear the extent of the impact of lung structural changes compared to prolonged corticosteroid use, since many patients with structural changes are on extended corticosteroid use (63). One study of 31 pulmonary nocardiosis cases found seven (23%) cases had COPD, 4 of whom were on prolonged steroids, and 20 cases overall (64.5%) had prolonged steroid use (33). In another study, immunocompromised patients with prolonged corticosteroid use had a much higher mortality compared to both immunocompetent and immunocompromised patients not taking corticosteroids (85%, 15%, and 20% respectively) (71). Improvements in targeted immunosuppressive medications for transplant patients and others have reduced the use of broad corticosteroids (11), which may be a factor in reports of decreasing infections among transplant recipients (10, 109).

Risk factors among the Immunocompromised

Conditions that affect cell-mediated immunity dominate the risk factors for nocardiosis among the immunocompromised (48). The immune response to nocardiae begins with innate immunity; first, monophils and neutrophils phagocytize most nocardiae and inhibit their growth, although the nocardiae are not destroyed (134, 135). Adequately functioning T-lymphocytes are then required to directly contact the nocardiae, causing subsequent lysis and killing of the bacterium (136), which prevents pulmonary or systemic nocardial infection. However, adequately functioning cell-mediated immunity may aid in the development of mycetoma granulomatous inflammation (42).

Transplant

Solid organ and hematopoietic stem cell transplant (HSCT) recipients are at greater risk of bacterial infection due to induced immunosuppression required to prevent rejection (5, 137, 138). Transplant recipients remain at risk despite more precise effects of anti-rejection drugs on the cell-mediated immune system compared to older medications, such as azathioprine (10, 126, 138).

The prevalence among heart transplant patients ranges from 0.65% (129, 139) – 2.5% (11), although historical reports show rates of 13% when patients received azathioprine for immune suppression (10, 113). Peleg *et al* also calculated nocardiosis rates by organ transplant types: kidney (0.2%), liver (0.1%), small bowel/multi-visceral (1.3%), and lung (3.5%) (11). Rates reported in Spain are similar, although lower among lung transplant patients (renal [0.26%], hepatic [0.18%], and lung [1.78%]) (129). Yet, multiple reports support higher rates of infections among lung transplant patients compared to other organ transplants (129, 140, 141).

Nocardia spp. infections have occurred months to years after receipt of the transplant (129, 137, 142). Although Peleg *et al* found that 63% of transplant recipients developed nocardiosis within one year of transplant (11), a multisite study found that only 41% of recipients had onset during the same time (8). The median time from transplant to nocardiosis onset was 17.5 months (range 2-244 months), although this varied significantly by organ transplanted (8). Onset more than three years after transplant occurred in 31.6% of patients (8), and 14% had onset more than five years post-transplant (11).

Most infections are pulmonary and nodules are a common finding (8, 11, 141). Extrapulmonary dissemination ranged widely but was more common in transplant patients than others (5). Dissemination ranged from 20% – 47% (8, 11, 12, 141). Mortality also varied widely, from 14% (11) to almost 40% (28).

A number of risk factors have been identified beyond immunosuppression. Risk factors found from two studies include high dose steroid use and high calcineurin inhibitor level in previous month (11, 142). Additional risk factors include recipient age, use of the immunosuppressive drug tacrolimus, intensive care unit length of stay following the transplant (142), and cytomegalovirus infection (11).

Malignancy

Patients with solid tumors and hematologic cancers are at elevated risk of nocardiosis, likely due to cell-mediated immunosuppression (13). A surveillance study in southern France found 22% of cases had a history of malignancy (143). The majority of infections occur in patients with hematologic cancers (54.5-64%) (13, 14) followed by solid tumors (36-43.9%) (13, 14). Patients have frequently received either stem cell transplants (35.6%) (14) or bone marrow transplants (31%) (13). In a cancer population, nocardiosis frequency appears to be increasing over time—infections averaged 3.3/year from 1988-2001 (13), 4.6/year from 2002-2005, and 16.4/year from 2006-2012 at a cancer facility (14). Incidence during the first period was 60/100,000 patients with the highest incidence among bone marrow transplant recipients (701/100,000 patients) (13); incidence was not published for the latter time periods (14). The increasing frequency has been ascribed to improved testing, recognition, and survival among cancer patients (14).

Cancer patients may also be at risk because nocardiae can compose biofilms on central venous catheters (CVC) (125). Such growth can lead to central line-associated blood stream infections (CLABSI) (125), and may be related to disseminated bacteremia in patients with CVCs (110, 125). Although these infections appear to be rare, those with CLABSI had better outcomes than those with disseminated infection, including shorter hospital stay and lower mortality (125).

Nocardiosis symptoms, such as fever, may not be present due to immunosuppression (14). Additionally, abscesses can be difficult to differentiate from malignancies (7), and may be confused as metastasis of an existing cancer (144). This is particularly true for CNS infections in patients with cancers that frequently metastasize to the brain, which can delay diagnosis and may affect prognosis (144).

HIV

Human Immunodeficiency syndrome (HIV) is a risk factor for nocardiosis owing to its impact on cell-mediated immunity (48). Although HIV may be the primary risk factor in many cases, in one study, half of the patients also had chronic lung disease (115). Reported all-cause mortality from older studies was 63% (111) and 67% (114). More recent reports indicate that nocardiosis is less frequent in HIV-positive persons possibly as a result of prophylactic

trimethoprim-sulfamethoxazole to prevent *Pneumocystis* infections (126). However, this prophylaxis may not provide adequate protection against nocardiosis (5, 12).

There are a few estimates of nocardiosis prevalence among HIV-infected individuals. A few articles that are frequently referenced report cases from the 1980's (111, 114, 145) when the demographics, care, and prognosis was vastly different for HIV-positive patients compared to today (127). These estimates range from approximately 0.3% (114, 145)-1.8% (111). In Spain, a report found an incidence rate of 0.38% (115), while one study in Côte d'Ivoire found a nocardiosis prevalence of 4% among patients who died of AIDS (32).

Injection drug use is commonly reported among cases with HIV and nocardiosis. In Uttamdani *et al*, 53% of HIV-positive nocardiosis cases were injection drug users (IDU), compared to 30% among the HIV-positive patients who received treatment at the same time (111). Cases also frequently had onset of AIDS concurrent with the nocardiosis infection or within the previous six months (60%) (111).

Pulmonary nocardiosis can be mistaken for tuberculosis (7), and tuberculosis and HIV are frequent co-infections (146). Among ten patients who were diagnosed post-mortem with nocardiosis, 40% had been incorrectly diagnosed with tuberculosis prior to death (32). Of HIV-positive patients presenting to a chest clinic for suspect pulmonary tuberculosis in Sudan, 1.2% were diagnosed with nocardiosis (29); 2.9% of HIV-negative patients at the same chest clinic also had nocardiosis, but 94% of patients had a risk factor for nocardiosis (29). Another study that also evaluated patients with suspect pulmonary tuberculosis in Ghana found 16.7% were co-infected with HIV and *Nocardia* spp. while 8.3% were co-infected with HIV and tuberculosis (147).

Mortality

The mortality rate ranges widely based on the form of disease, the immune status of the patient, and the era of the publication (48). Most reviews focus on all-cause mortality rather than deaths definitively due to nocardiosis. Factors that are associated with mortality include acute disease (64, 68, 71, 110), involvement of two or more organs (42, 71, 110), severe immunosuppression (71), and greater disease severity (68).

Primary cutaneous disease without dissemination has the lowest risk of death (4). Most individuals with primary cutaneous nocardiosis recover fully (3, 43, 53), although there have been some cases in which primary cutaneous infection disseminates and results in death (3). Patients with bacteremia have a mortality rate of ~50% (110), and the rate among patients with disseminated infections range from 44% (42) -85% (71). CNS involvement, whether primary or secondary infection, has a poor prognosis and mortality of almost 50% (6).

Underlying conditions are also associated with higher mortality rates. Patients with malignancies have a mortality rate greater than 60% (13). Transplant recipients reportedly have the worst outcomes compared to other immunocompromised and immunocompetent patients (28). Of 47 transplant patients, fewer than 60% survived at 12 months, while immunocompetent patients had a survival rate of greater than 90% (28). Another study reported a similarly high all-cause mortality rate of 37% (129). Other studies report better survival outcomes of 82% (141) and 6-month survival at 86% (11). Although transplant recipients are severely immunosuppressed and at greater risk of mortality (148), patients with nocardiosis have poorer outcomes compared to other transplant recipients, with a comparative mortality rate of 16.2% vs. 1.3% (142).

Finally, mortality may have decreased over time. Cases in the literature before 1950 had a mortality rate of 70%, which dropped to 44% between 1950 and 1979 and 26% between 1980 and 1994 (42). This finding could also be due to publication bias.

G. Prevention

Nocardia sp. are ubiquitous in the soil, so there are few techniques to prevent infection (4). Since a majority of primary cutaneous infections reported a traumatic injury to the skin (3, 53), covering skin or open wounds to avoid direct soil contact may prevent cutaneous nocardiosis. Wearing shoes may prevent actinomycetoma by preventing small inoculation injuries to the feet (4); however this has not been systematically examined (149).

TMP-SMX is given to immunocompromised individuals to prevent *Pneumocystis* infection (5). Some authors have suggested that this use may provide ancillary protection

against nocardiosis (110, 126, 150); however, infections concurrent with prophylactic use (5, 12, 141) have led to dispute over its effectiveness for this purpose (142).

Disinfection of a ward following a nosocomial outbreak may be warranted to prevent future infections (118, 124). Antimicrobial treatment of central venous catheters may prevent the introduction of *Nocardia* spp. to an immunocompromised person via biofilm growth (125). There are no other specific recommendations to prevent *Nocardia* spp. nosocomial transmission. However, this may need further evaluation to determine the clinical importance when *Nocardia* spp. are found in healthcare settings (37).

III. Limitations of existing literature and currently available data

There are several limitations in the existing literature that preclude providing an accurate estimate of nocardiosis incidence, a generalizable description of persons at risk and risk factors, or evaluation of geospatial associations of nocardiosis in the United States. First, most publications are case reports or case series with literature reviews. These publications have a definite value added to the medical community in that they comprehensively describe a case's history, the clinical and microbiological findings, treatment, and outcomes. Additionally, these publications provide detailed descriptions of interesting and new presentations, such as nocardiosis following knee surgery (95), infections with newly identified *Nocardia* species (151), or unique presentations (152).

A primary limitation to these articles is publication bias. Cases that are reported in the literature are interesting or unique in some way to warrant the time to be reported and published (153). They are also limited in generalizability, since the case series are typically described from a single facility where patient demographics, geographic influences, and even underlying conditions lack variability (5, 126, 154).

Second, there are a few published multisite studies, but they are not representative of the U.S. population. Some of the studies target high-risk patients at specialty facilities, such as organ transplant recipients at transplant hospitals in Western Europe (8), or patients with cystic fibrosis (130, 155). Some national laboratories have published reports of specimens received for identification, along with associated epidemiologic information (2, 21, 55, 156); however, these are likely limited by reporting bias due to non-random specimen submission (2, 157), and selection bias due to submission for severe or unique cases (157).

For example, following a 10-year report by CDC describing 765 *Nocardia* isolates originating from humans (2), two other studies described 2,650 isolates from six clinical reference laboratories across the United States (16, 17). This demonstrates that the CDC publication lacks national representativeness of nocardiosis cases in the United States, which cannot be remedied by the use of current epidemiologic surveillance data because nocardiosis is not under national surveillance (158).

Third, many publications describe the current incidence of nocardiosis to be approximately 1,000 cases per year, referencing a survey of infectious disease physicians from 1972-74 (1). Yet, this estimate is likely a substantial underestimate for several reasons. Improvements in microbiological and molecular methods have improved the ability to accurately identify and differentiate *Nocardia* species (21, 159). The genus continues to expand and change taxonomically with the assistance of these new techniques (15), which may prevent misdiagnoses. The population at risk has also increased because the number of adults living with immunocompromising conditions has grown (20). Survival has improved among people with immunocompromising conditions, including HIV (127) and cancer (14). In addition, three times the number of transplants were performed in 2018 compared to 1988 (based on OPTN data as of January 17, 2019). Finally, the population of older adults has increased in the United States (19), who are also at greater risk of infections in general (160) and nocardiosis in particular (65).

There are also limitations to the available data. Because nocardiosis is rare, prospective cohort studies are usually not feasible, and the logistics and expense of multi-site studies can be challenging. These reasons likely drive the popularity of facility-based retrospective studies using medical chart or record review (5, 11, 14). Medical records could not be evaluated previously on a large scale for nocardiosis, such as using national hospitalization discharge databases (105), because nocardiosis was combined with other etiologic agents in the same code within the International Classification of Diseases 9th revision-clinical modification (ICD-9-CM). Nocardiosis was given a distinct diagnosis code in the 10th revision (ICD-10-CM) (161), which went into effect on October 1, 2015 for all medical billing in the U.S..

Although nocardiosis diagnoses are collected as a distinct diagnosis code, analyses are still limited. The cost of several large population-based administrative data sources, such as IBM's MarketScan (162), Chronic Conditions Warehouse via the Centers for Medicare and Medicaid Services (163), and databases from the Healthcare Cost Utilization Project (HCUP) (105), can be prohibitively expensive. Additionally, compiled and cleaned databases can take a few years to complete and make available to researchers, which may be further limited by data sharing agreements. HCUP data are visit-based, which can limit the interpretations of the data,

while Medicare data are person-based yet are expensive, complicated, and have strict access and data use agreements. With limited population-level data availability, potential analyses are limited until a future time when there are sufficient data. However, analyses using the currently available data will establish a baseline on which future studies can build.

IV. How research will enhance field

A. Problem statement

There are limited population-based data in the literature regarding nocardiosis. The disease is potentially increasing, as the number of people who are potentially at risk or have pre-disposing risk factors continues to rise (19, 20, 127, 160). Information that is published is often based on case series from specific facilities, which may limit the generalizability due to population differences based on geographic, social, and environmental characteristics. The published multi-center studies are often limited by a narrow scope of the patients (8, 164) or non-spatially representative selection of participating facilities (27, 30, 77, 143). The results from these studies may have high internal validity to the risk group or site locations but may lack generalizability to other populations and are not representative of nocardiosis in the United States.

Epidemiologic studies published by national reference laboratories (2, 156) may be biased also. Selection bias may be present in laboratory surveillance (157), since isolates may be sent for seriously ill patients, those who failed treatment, or had a unique presentation. Reporting bias (e.g., selective submission) may be present if state or provincial laboratories do not send specimens to the reference laboratories for diagnosis (2, 157).

A population-based analysis of nocardiosis to describe clinical characteristics, estimate survival rates, and evaluate known nocardiosis risk factors and spatial characteristics will contribute the first U.S.-representative description of nocardiosis in the literature. The findings may further improve clinical recognition of nocardiosis based on case characteristics and underlying risk factors that are associated with infection. Improved clinical recognition may prompt appropriate and targeted diagnostics, which ultimately improves the rapid provision of

appropriate antimicrobials and overall outcomes (15). Finally, this approach may guide future research activities from findings that may warrant further exploration.

V. Statement of purpose

A. Purpose of the research

The purpose of my research is to evaluate the clinical and spatial characteristics of nocardiosis in the United States using population-level data. This will be the first nationally-representative description of nocardiosis in the country, and the first using medical billing data for nocardiosis.

B. Justification

This research will address limitations in the literature. First, few large-scale case descriptions exist that are not limited by reporting bias or limited generalizability of case reports (153). Second, many studies describe cases from one or a few facilities, which limits the generalizability of the descriptions (5, 126, 154). Third, even large-scale reports may have reporting bias (2, 16). Finally, many more variables and more complete data are available through medical coding compared to laboratory surveillance data. This is the first population-based analysis of nocardiosis clinical characteristics, risk factors, costs, and incidence estimates. It will also establish a baseline against which future studies can be compared to evaluate disease trends.

Additionally, this will be the first evaluation of the geographic distribution of nocardiosis in the United States using a population-based approach. Current literature indicates there may be some geographic differences in distribution of either disease or nocardia species (2, 38, 165); however, it is not possible to determine if differences are associated with the disease, the etiologic agent, or due to reporting or selection bias. Using both spatially and nationally representative data, these biases are reduced.

C. Research questions and hypotheses

The first research question is: who is affected by nocardiosis? I hypothesize that nocardiosis will occur more frequently among Medicare Fee-For-Service (FFS) recipients who have known nocardiosis risk factors or other co-morbidities. The first aim is to describe the disease and patient characteristics, including demographics, diagnoses, severity, treatment, cost, and insurance payer type. The second aim is to describe risk factors and chronic conditions and evaluate the impact of known nocardiosis risk factors on patient outcomes.

The second research question is: what is the incidence of nocardiosis in the United States? I hypothesize that the incidence will be substantially greater than the frequently cited incidence rate of 1,000 cases per year (1), and the rate will be greater among Medicare beneficiaries and persons with more comorbidities.

The third research question is: what factors are associated with mortality among each study population? As a subset of this research question is which comorbidity measure is the most predictive of mortality among nocardiosis-associated hospitalizations in the US?

Chapter 2: Methods

I. Study design

This study is a secondary analysis of administrative discharge and beneficiary data to evaluate patient, clinical, and spatial characteristics of nocardiosis in the United States since the implementation of ICD-10-CM coding in October 2015. The first population studied were beneficiaries receiving Fee-for-Service (FFS) Medicare through the Centers for Medicare and Medicaid Services (CMS); the 100% FFS data available through the Chronic Condition Warehouse (CCW) Virtual Research Data Center (VRDC) from October 2015- March 2018 was used (163). The 100% FFS Medicare data are person-based records of all Medicare beneficiaries who receive FFS care in the United States; all files are linked using a unique beneficiary ID without direct identifiers; access was allowed under a CDC-CMS Interagency Agreement (IAA) and use was restricted under a strict data use agreement.

The second population studied was 100% of inpatient and ambulatory surgery discharges from participating states available through the State Inpatient Databases (SID) and the State Ambulatory Surgery and Services Databases (SASD) from HCUP, available from October 2015- December 2017. The HCUP files are visit-based records of hospitalizations or surgical discharges and are de-identified files available to CDC through an IAA with restricted use under a data use agreement.

A. Subjects and settings

Chronic Condition Warehouse (CCW) Medicare data

The Medicare inpatient, outpatient, carrier (physician billed) claims data were combined with the Master Beneficiary summary dataset containing demographic and coverage information, and the chronic condition files containing pre-coded chronic conditions (163). Access to the CCW VRDC ended on October 31, 2018; all analyses of this source were completed on or before that date. Analysis errors cannot be remedied, nor could additional analyses be performed after that date.

Case Definition

To create the nocardiosis-associated numerator, the following research identifiable files (RIF) were utilized for October 1, 2015- March 30, 2018 unless otherwise stated.

- For outpatient institutional visits:
    - RIF outpatient claims
- For clinician billing accompanying an institutionalized visit:
    - RIF carrier files
- For inpatient institutional visits, due to changing data structure and organization:
    - MedPAR (only available October 1, 2015- December 31, 2016)
    - RIF Inpatient claims (January 1, 2017- March 30, 2018)
- For Parts A-D coverage, HMO coverage, and date of death:
    - Master beneficiary summary file (MBSF)
- For select chronic conditions identified by the CCW:
    - MBSF chronic conditions
    - MBSF other chronic conditions (October 1, 2015- December 31, 2016).

CMS beneficiaries were considered a nocardiosis "case" if they had at least one inpatient or outpatient ICD-10-CM Claim Diagnosis of A43 (nocardiosis) (161). The CCW inclusion criteria for chronic conditions were used to define inclusion of carrier file visits (166). That is, a carrier visit must be accompanied by an institutional claim (i.e., inpatient or outpatient) or a beneficiary had more than two carrier visits with any-listed diagnosis of A43 more than 30 days apart.

Repeated visits

All visits by the same beneficiary with a nocardiosis diagnosis within 30 days were classified as 'related'. Related visits accounted for multiple billing claims, transfers, and provider claims during an institutionalized visit. Analyses of demographics were performed on unrelated visits, while evaluation of costs and presence of co-morbidities were performed on the complete dataset containing all encounters with any-listed nocardiosis that met the inclusion criteria.

Denominator

Beneficiaries with any Health Maintenance Organization (HMO) coverage were excluded from the denominator because they do not have a claims history during their HMO enrollment . After removing all beneficiaries with any HMO coverage, a Medicare population denominator in person-months was calculated for beneficiaries with Medicare FFS enrollment between October 1, 2015- March 30, 2018. State person-month denominators were the summed person-months by the beneficiary state of residence at the start of each calendar year. Beneficiaries may contribute person-time for multiple states, but not in the same years.

Healthcare Cost and Utilization Project (HCUP)

The SID and SASD available from HCUP includes 100% of inpatient discharge records from participating states (105). The SID data containing ICD10 discharge records are available from 29 states in 2015 (October-December), 26 states in 2015-16, and 13 states from 2015-17. The estimated US population included in the inpatient analysis in 2016 is 152,453,663, 47.2% of the total estimated US population in 2016 (167). The SASD data are available from 14 states in 2015 (October-December) and 15 states in 2016; 7 states have data available from October 2015- December 2017. The estimated US population included in the ambulatory visits analysis in 2016 is 92,675,765, which is 28.7% of the total estimated 2016 population (167).

HCUP data are visit-based, thus these data cannot evaluate person-level characteristics; the same person may make multiple visits, which will appear as separate records. However, SID and SASD include people of all ages from all payers, which can be a useful contrast to the older FFS Medicare group described above.

Case Definition

A nocardiosis-associated visit was defined as the presence of the ICD-10-CM claim diagnosis of A43 (nocardiosis) (161) listed anywhere in up to 25 diagnosis variables (168, 169). By searching for ICD-10-CM codes, the visits will be restricted to those that occurred on or after October 1, 2015.

The primary diagnosis, which is located in the first diagnosis variable, will be analyzed separately to determine the frequency that nocardiosis is the principal diagnosis for a visit. SID and SASD visits were evaluated on the same variables as the Medicare FFS when available, as well as insurance type, urban/rural, and chronic disease risk factors listed on the visit record. The study will also evaluate form of nocardiosis, associated risk factors, co-morbidities, medical costs, healthcare payer, and calculate nocardiosis-associated hospitalization rate and rate ratios by demographic groups.

Denominator

Rates were calculated using bridged-race population estimates from the National Center for Health Statistics as the population denominator (167). The census population estimates were included for each year that a state participated. These denominators were used to calculate both person-year denominators and hospitalization rates per 100,000 person-years.

B. Human Subjects

The CCW analysis was determined to be non-human subjects research by the CDC Human Subjects Protection Office, and the project was approved by CMS RESDAC. The HCUP data analysis was also determined to be non-human subjects research by the CDC Human Subjects Protection Office. The project was approved by the CDC Data Hub within the Center for Surveillance, Epidemiology, and Laboratory Services, the administrator of HCUP data at CDC.

II. Definitions and measures

Any strata cell sizes <10 were restricted and analyses were not done based on data use agreements for both data sources. Definitions for specific variables of interest are described below. The definitions apply to both datasets unless indicated.

a) Disease Type

Pulmonary, cutaneous, and disseminated nocardiosis were defined first using specific ICD-10-CM codes for pulmonary (A430) and cutaneous disease (A431) as listed in diagnosis

fields for each claim (161). Then, diagnosis and procedure ICD-10-CM codes indicating pulmonary, cutaneous, disseminated, or CNS disease were searched within each claim (Table 2.1). Disease form was then assigned to each claim; 'not specified' was assigned when disease form could not be determined. The most severe disease form was kept for each beneficiary; when more than one form was identified, the claim was categorized as disseminated disease (170). Erroneously, primary CNS infection was not evaluated in Medicare FFS data and could not be remedied due to data access restrictions. Primary CNS was evaluated in HCUP data.

Risk Factors and Co-morbidity Measures

CCW Medicare data

The earliest CCW Medicare claims data began on January 1, 1999. The MEDPAR, RIF outpatient and carrier, and the MBSF files from January 1, 1999 - September 30, 2015 were used to find chronic conditions and known nocardiosis risk factors existing at any time between Medicare FFS entrance or January 1, 1999 and the nocardiosis diagnosis. Twenty-two conditions were selected as nocardiosis-specific risk factors; these conditions have been described frequently in the literature as occurring or associated with nocardiosis, and some are associated with poorer outcomes in nocardiosis case series (6, 8, 14, 65, 129). Nine of the selected risk factor conditions were already coded in MBSF Chronic Conditions and Other Chronic Conditions datasets (166). The ICD-10-CM (161) and ICD-9-CM (9) diagnosis and procedure codes for the remaining conditions were compiled from the the Charlson co-morbidity index (CCI) (171), the American Thoracic Society (172), additional literature searches, and reviewed by committee member H.W. (Appendix Table A.1).

For years 1999-2016, the select pre-defined and pre-coded conditions available in the MBSF Chronic Conditions files were used (i.e., diabetes, chronic obstructive pulmonary disease, chronic kidney disease, cancer, anemia, alcohol addiction, tobacco use, HIV/AIDS, and cystic fibrosis). The Chronic Conditions files were not available after 2016, so the pre-defined ICD-10-CM codes were used to search all Medicare claims records for each nocardiosis case in 2017 and 2018for those same conditions. The extensive period was included for risk factors due to

reports of nocardiosis onset more than three years after solid organ transplant (8, 11), and the potential for many of the risk factors to be long term chronic conditions.

To calculate the CCI score, the conditions for the CCI were searched in the claims files of nocardiosis cases in the 12 months prior to the first nocardiosis diagnosis using the Quan *et al* modified codes (171). The Charlson weights were used (173).

HCUP

The same risk factor and CCI codes (171) were used as discussed above and listed in Appendix Table A.1; however, because the datasets are visit-based and not person-based, the risk factors could only be applied to diagnoses or procedures listed during a single nocardiosis-associated visit, rather than in the 12 months or more prior(171). Both analyses of risk factors and CCIs will substantially underestimate the presence of these selected conditions if the existing chronic conditions are not reported during the visit, and will inflate the count if the same patients with several conditions have many repeated visits.

In addition to the Charlson comorbidity index and nocardiosis-specific risk factors, the Elixhauser comorbidity index and the Chronic Condition Indicator were evaluated using the HCUP data. These measures have been developed or optimized for administrative data in general (174, 175) and particularly for HCUP (176). The Elixhauser algorithm contains 30 comorbidities that are associated with longer length of stay, hospital charges, and mortality; however, the authors who developed this measure do not recommend collapsing it into a single count as it can differ by age and other patient characteristics (174). Instead, the Elixhauser conditions are included in a regression model with demographic factors to create scores to estimate readmission and mortality.

The Chronic Condition Indicator classifies each diagnosis code into a chronic or non-chronic condition and is an expansion of Hwang *et al's* methodology for inclusion of more ICD-9-CM codes (176, 177). The indicator is then summed across all diagnoses listed for a visit to get the total count of chronic conditions. Both comorbidity measures are beta versions for ICD-10-

CM codes, both measures have been used in published reports using ICD-9-CM codes, although Elixhauser has been used more extensively (178, 179).

The various comorbidity measures can be compared to evaluate predictors of death and disseminated nocardiosis, which has not been done before for nocardiosis. Often, these measures are used to evaluate outcomes of all patients in a specific setting (e.g., ICU) (180), and are frequently used to evaluate cardiovascular disease (179), but rarely infectious diseases. However, due to the opportunistic nature of nocardiosis, comorbidity measures may be appropriate to assist with predicting mortality.

Costs/Charges

CCW Medicare data

Among Medicare FFS, costs per visit and per beneficiary for all nocardiosis-associated visits were calculated by summing the following CCW variables: 'claim payment amount'; 'indirect medical education and provider payments'; 'Part A' and 'Part B coinsurance' amounts; and 'blood deductible' from inpatient, outpatient, and carrier visits. For inpatient visits, 'claim per diem' amount was multiplied by the days of hospitalization and added to the previously listed costs (181).

HCUP

Costs for nocardiosis-associated visits in SID and SASD were converted from the variable total charges using the HCUP cost-to charge ratio files to represent the actual amounts paid versus the amount billed (182).

Mortality

Definitions: CCW Medicare data: For Medicare FFS beneficiaries classified as nocardiosis cases, death was counted if it occurred within 365 days of the first nocardiosis-associated visit, or 12-month all-cause mortality.

HCUP: Death was counted for SID and SASD visits if the patient died during hospitalization or "expired" was reported in the visit record (105).

1 Table 2.1: ICD-10-CM codes used to define disease type

Name	**ICD-10-CM codes**	**Additional Rules**
Cutaneous	**A431**, R21, H16,H15,h43,H04, H10,B42,K04,L02, L03, R22, L04,L08,L10, L11,L29, L52, l92,L97,L98,L99,R238, G245, H2005,H5314,L03213	-
Pulmonary	**A430**, R91,J15,J16,J17,J18, J85,J86,J90,J91,J92,J93, J94, J96, R05,R06,R942,R093,R042,R072,R0902,R0989	-
Disseminated	R4781,R29810,h4400,h4419,R7881,L0221,G9389,h31,h33,I 88,J01,J32,M71,H16,J36,J39,K63,M86,N15,N30,R11,R61,R6 5,R93,R270,R471,R579,E278,K046, K047,K651,R060,,D733,K750	Presence of >1 form of nocardiosis • A43.1 + A43.0 on one or more record for a beneficiary • Diagnosis claims for >1 form identified from specified ICD-10-CM codes
Mycetoma	B471	-
Neurological involvement	R51,R56,R40,R46,R41,R42,R43,R44,R45,R90,G04,G05,G07, G934,G939,R940,G060,G062	If no other form of nocardiosis listed, then = primary CNS infection

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Chapter 3: Data Analysis and Results

I. Analysis

D. Methods and Rationale

Descriptive analyses were performed on the CCW Medicare data and the HCUP data. Analysis of the CCW Medicare data evaluated person-level characteristics and characteristics aggregated to the state of residence. The data were evaluated by demographics, Medicare coverage, chronic conditions and risk factors, duration of hospitalization, costs, diagnoses, procedures, and disposition. Analysis of the HCUP data will evaluate visit-level characteristics, length of stay, urban/rural residence, and disposition. All cell sizes $\leq$10 were suppressed per the data use agreements with both HCUP and the CCW.

Both person-level and visit-level analyses are presented using frequencies and percents or means and standard deviations, as appropriate. Medians are not allowed to be presented from the CCW Medicare data per the data use agreement, as the value could potentially be a result for a single person. For consistency in reporting, means will be presented for HCUP as well unless the data are substantially skewed, in which case medians and ranges are also reported. To evaluate common diagnoses, diagnosis codes from all visits were appended for each case and searched; the 50 most common diagnoses were identified.

Correlations were calculated using Pearson's correlation coefficients to evaluate bivariate associations and collinearity; Spearman's rank correlation was used to evaluate correlation between categorical variables. Disease incidence was calculated from the Medicare FFS using the number of cases divided by the total person-years of beneficiaries who had Medicare coverage, no HMO coverage, and occurred between October 1, 2015 and March 31, 2018. Average annual visit rate per 100,000 persons were calculated from HCUP data, Poisson regression with a robust error variance was used to calculate rate ratios from HCUP data, a modified Poisson which does not overestimate the confidence intervals (183).

Mortality

Kaplan-Meier survival curves evaluated all-cause mortality after the first-listed nocardiosis diagnosis within the CCW, the curves are shown through 12 months following the first diagnosis (184). Multi-collinearity was evaluated with Pearson's correlation. Differences in survival curves were assessed using the log rank test assuming no differences earlier in the year (185). Additionally, Cox proportional hazards models were calculated to evaluate the statistical association of demographic and co-morbidities on time to death (186). The smallest Akaike Information Criterion (AIC) was used to select the final model (185).

The ability of each of the comorbidity measures to predict mortality would be a useful factor when interpreting the associations of these indexes for nocardiosis cases, and to build a mortality model. Such an evaluation must be restricted to the HCUP SID data because of the larger sample size compared to SASD, and the implementation of the four different measures in HCUP and not in Medicare data. To evaluate whether the measures are collinear, and therefore a comparison between them would be inappropriate, correlations were assessed with Pearson's pairwise correlation and then collinearity was assessed using the variance inflation factor and tolerance.

Demographic variables are potential confounders of mortality and were evaluated for inclusion in the baseline model, to which the comorbidity measures would be added. The demographic variables included in the baseline model were age, race, region, urban residence, median income from patient zip code compared to the state, and sex; age was categorized due to a skewed distribution. There was no variable of hospital type for a hospital-level indicator, so urban/rural was used as a proxy.

Each comorbidity measure was added individually to the baseline model with the outcome 'died'; performance of each model was compared using the AIC and c-statistic as has been done previously (187, 188). A single comorbidity measure was selected with the lowest AIC and highest c-statistic. This model serves as the base to build the logistic regression model to explain mortality.

There are many comorbid conditions that are potential moderators of nocardiosis-associated mortality. Only comorbidities that were potentially associated with mortality ($p<0.2$)

on bivariate analysis and were not in the retained measure were included. Conditions that were present in the retained measure and another comorbidity measure were also evaluated if the frequency varied substantially between measures (e.g., renal disease between Charlson and Risk Factor measures), since some use a different combination of ICD codes. The conditions that were present in more than one measure and had a p-value of <0.20 were further evaluated for correlation using Spearman's rank-order coefficient for categorical variables; conditions that were not highly correlated with the similar condition in the retained measure were included in the multivariable model building. Comorbidities that met the above criterion on bivariate analysis were excluded from the model if cell sizes were less than 10. The AIC and Hosmer-Lemeshow Goodness of Fit criteria were used to evaluate fit, and the highest Hosmer-Lemeshow Goodness of Fit result was selected as the final model.

State Aggregated Analyses

Characteristics of the nocardiosis cases in the CCW Medicare data and visits in the HCUP data were aggregated to the state of residence of the case or of the patient who made the visit. Medicare CCW data collects state of residence during each month of the year; to account for Medicare recipients who move between states (*e.g.*, snowbirds), the monthly state of residence was used to calculate the cumulative person-years per state. This cumulative population was used as the denominator to calculate incidence for each state.

The SID contains 100% of the inpatient discharges from each participating state, although each state has participated for varying amounts of time during the 2.25-year study period. The post-censal population estimates (167) for each year a state participated in SID was used to calculate cumulative person-years as the denominator, which was used to calculate the average annual hospitalization rates for each state or jurisdiction. Standard errors were not calculated because the SID and Medicare CCW contain complete data.

Analytical Tools

SAS Enterprise Guide 7.1 (Cary, NC, USA) was used for all analyses within the CCW Virtual Research Data Center. The HCUP data were analyzed in SAS 9.4 (Cary, NC, USA) (alpha =0.05). QGIS 2.18.1 (Boston, MA) was used to map the aggregated state-level incidence and hospitalization rate.

II. Results

A. Patient demographics

Medicare

Between October 1, 2015 and March 31, 2018, 3,167 individual Medicare FFS cases met the inclusion criteria for nocardiosis. This was a rate of 3.3 incident cases per 100,000 case years. A disproportionate number of cases were identified in the last quarter of 2015 compared to the other periods.

While 70.2% of nocardiosis cases were between ages 65 and 84, 19.5% were younger than 65 (Table 3.1). This is consistent with overall enrollment in Medicare FFS, which the average enrollment by these age groups between 2015 and 2017 was 71.6% and 16.6%, respectively (Table 3.1)(189). The ratio of males to females is about 1.1: 1, and a majority were White (83.3%).

Cases with dual Medicare and Medicaid coverage were younger compared to those without. This finding was consistent with the entire Medicare FFS population in which 44.3% with dual coverage were younger than 65 compared to 10.1% without dual coverage (190, 191). Dual coverage differed by race as well (57.3% white with dual coverage, and 89.4% without). These discrepancies were almost the same proportions as in the entire Medicare FFS population except for Hispanic cases, in which the proportion with dual coverage and nocardiosis was 8.3%, compared to 14.0% in the full population (190, 191). Disease type did not differ substantially by dual coverage, thus being lower income may not have an impact on type of infection, and by proxy, severity.

The original reason for enrollment differed between nocardiosis cases and all Medicare cases. A greater proportion of Medicare cases with nocardiosis received Medicare coverage because of disability and/ or End Stage Renal Disease (ESRD) compared to all of Medicare (32.5% vs 17.1%). A higher frequency of nocardiosis cases were sicker and joined Medicare at a younger age than all FFS Medicare cases. There were more disseminated infections in cases with ESRD (χ^2=9.8, df=3, p=0.0201), and the proportion of disseminated infections were seven percentage points higher than among those without ESRD (58.0% vs 51.0%), thus a deeper look into the characteristics of these cases is warranted. Males with nocardiosis had a higher

occurrence of ESRD than females (68.7% with ESRD, 50.3% without) (χ^2=36.7, df=1, p<.0001). This discrepancy was also seen in the entire Medicare FFS population; however the difference was less extreme with males comprising 57.7% of ESRD cases and only 46.4% without ESRD (χ^2=1503.2, df=1, p<.0001) (192). Age was also highly skewed to younger age groups for those with ESRD, while the majority of cases without ESRD were 65-84 years old; 61.9% of ESRD cases were younger than 65 compared to 17% without ESRD. This discrepancy was similar to all Medicare FFS but at a smaller magnitude (53.7% were younger than 65 with ESRD, 16.2% without) (192).

There were also racial disparities among cases with ESRD (χ^2=265.6, df=4, p<.0001); African Americans were disproportionately affected (29.3% of cases with ESRD vs 5.4% without), although the expected counts of ESRD were greater among all non-White race categories. Yet again, the similar disparity was found among all Medicare cases. These differences in cases with nocardiosis compared to all Medicare cases indicate a relationship between males and younger cases with ESRD and nocardiosis.

State Inpatient Databases

From the 29 states participating in the State Inpatient Databases (SID) from October 2015-December 2015, 274 nocardiosis-associated hospitalizations were identified, in 2016, 898 visits were identified from 26 participating states, and 454 visits from 13 states in 2017 for a total of 1,626 visits (Table 3.1). The nocardiosis-associated hospitalization rate was 1.02/100,000 population. The hospitalization rate was greatest in the 65-74-year-old age group and is 11.1 times higher (95% CI: 9.6-12.75) compared to patients 0-49 years of age. The rate almost doubled in patients 55-59 years old compared to 50-54-year-old patients (0.69 vs. 0.35/100,000).

Visits occurred among more men than women (61.6% vs 38.4%) and 51.8% were in adults 65 and older (Table 3.1). There were few visits among adults 85 and older (n=97) of which 53.6% were females, yet in the 2016 population from these participating states, 65% of people 85 and older were women (167).

A larger percentage of nocardiosis-associated visits were reported in the Western census region (37.7%, n=613), although 19.1% of the population represented in these data are from the West. The second largest was from the South (32.4%, n=526), while states in the South represented 38.1% of the population in SID. The Northeast had the lowest with 11.1% (n=181), while the proportion of the population in SID from the study period from the Northeast was 24.6%. Interestingly, the majority of visits among persons younger than 65 occurred in the South and West (73%, n=578), which was a greater proportion of all visits in the South than the other regions (54.9%). When looking at more granular age groups, 47.1% (n=72) of visits in persons under 35 were in the West and the majority of older age groups occurred in the West, while 37.9% (n=241) of visits of persons 35-64 were in the South

Residence in an urban setting was listed for 87.0%, the remainder were in rural or micropolitan areas (193), compared to 78.0% urban dwellers in the total population in the participating states (194). The Midwest was more rural, with 67.7% of visits from residents of rural areas. Median household income state quartile for patient's ZIP code was relatively evenly distributed among the quartiles (22.1%, 26.5%, 26.0%, and 25.5%), but almost 85% of those in rural areas fell into the bottom two income quartiles.

Medicare was the predominant primary payer among the nocardiosis-associated visits (n=317, 64.7%), followed by private insurance and then Medicaid. There were too few self-payers and other insurance coverage to report. Payer type for visits among patients younger than 65 was Medicare (35.5%), Medicaid (23.3%), and Private insurance (37.7%); 60.4% of Medicaid coverage was among adults 35-64, and Medicare was the payer among 23% of visits in the same age group. Of visits with a primary payer of Medicare, 16 (17.2%) had secondary Medicaid coverage and 60 (64.5%) had private insurance.

State Ambulatory Surgery and Services Databases

In SASD, there were 86 nocardiosis-associated surgical or ambulatory visits identified from 14 states in 2015, 471 from 15 states in 2016, and 254 from seven states in 2017 for 811 visits. The nocardiosis-associated visit rate was 0.38/100,000 population.

Visit counts were similar by sex except among persons younger than 35, of which females accounted for 52 of 71 (73.2%) visits. Among adults 35-64, 45.2% of visits were made by females; in all other age groups, females accounted for close to 50%. Visits had similar breakdown by age groups compared to SID (Table 3.1); a majority of visits occurred among adults between 50 and 74 years old. Regionally, 437 (53.8%) visits were reported in the South, 312 (38.4%) were out of the Midwest, although the populations from both the South and Midwest were predominately represented in SASD (42.9% and 32.0%, respectively). Only 52 (6.4%) were reported out of the West despite a population proportion of 16.3%.

Rural residence may be associated with different types of exposures compared to urban residence; here, 606 (74.7%) of visits occurred among persons who resided in urban areas. Urban residence was only 63.5% among visits in the Midwest, and 83.1% in the South. Urbanity also varied by type of nocardiosis; 27.5% of visits for pulmonary infections resided in rural areas, and only 17% and 19% of visits for disseminated or cutaneous infections were reported with rural residence.

Medicare was the primary payer for 32.6% of visits among persons younger than 65, and an additional 188 (51.5%) had private insurance. Of the visits with Medicare as the primary payer, 176 (62.0%) had private insurance as well.

Table 3.1: Demographic characteristics of all Medicare FFS beneficiaries, Medicare FFS nocardiosis cases, and nocardiosis-associated visits from the State Inpatient Databases (SID) and State Ambulatory Surgery and Services Databases (SASD)±

Characteristics	All Medicare FFS (N=38,434,496)	Medicare FFS (N=3,167)	SID (N=1,626)			SASD (N=811)		
	n (%)	n (%)	n (%)	Rate	Rate ratio (95% CI)	n (%)	Rate	Rate ratio (95% CI)
Age (Mean [SD]) *	NA	71.6 (11.5)	61.6 (17.3)			62.0 (16.9)		
0-49	NA	NA	302 (18.7)	0.12	Reference	123 (15.2)	0.11	Reference
50-64	NA	NA	476 (29.5)	0.61	4.9 (4.25,5.65)	226 (27.9)	0.52	4.9 (4.0, 6.06)
< 65	6,383,276 (16.6)	618 (19.5)	778 (48.2)			349 (43.0)		
65-74	18,307,981 (47.6)	1285 (40.6)	494 (30.6)	1.37	11.06 (9.6,12.75)	246 (30.3)	1.23	11.61 (9.46,14.25)
75-84	9,235,317 (24.0)	938 (29.6)	246 (15.2)	1.37	11.02 (9.32, 13.02)	163 (20.1)	1.61	15.22 (12.17,19.02)
85+	4,507,923 (11.7)	326 (10.3)	97 (6.0)	1.20	9.67 (7.7, 12.14)	30 (3.7)	0.66	6.19 (4.18,9.18)
Female	20,538,791 (53.4)	1,519 (48.0)	624 (38.4)	0.31	Reference	408 (50.3)	0.38	Reference
Male	17,895,705 (46.6)	1,648 (52.0)	1,001 (61.6)	0.52	1.66 (1.5,1.84)	403 (49.7)	0.38	1.02 (0.89,1.17)
Race/Ethnicity (190)								
White	29,759,289 (77.4)	2639 (83.3)	1,149 (76.0)	0.56	Reference	593 (87.1)	0.48	Reference
Black	3,755,377 (9.8)	244 (7.7)	149 (9.9)	0.34	0.6 (0.5, 0.71)	65 (9.5)	0.27	0.57 (0.44,0.73)
Asian	1,140,792 (3.0)	64 (2.0)	42 (2.8)	0.26	0.46 (0.34,0.62)	11	0.14	0.29 (0.16,0.53)
Hispanic	2,640,205 (6.9)	63 (2.0)	121 (8.0)	0.27	0.48 (0.4,0.58)	-	-	-
Other	558,460 (1.5)	157 (5.0)	35 (2.3)			-	-	-
Unknown	580,373 (1.5)		-			-		

±All Medicare FFS beneficiaries (190) Oct 1, 2015 and Dec 31, 2017, Medicare FFS nocardiosis cases: Oct 1, 2015 and March 31, 2018, SID and SASD: Oct 1, 2015 -Dec 31, 2017; * 11 records missing age in SID, 115 records missing race in SID; - Suppressed counts when cell size <11;

B. Characteristics of illness

Medicare

Using the ICD-10-CM codes for nocardiosis, pulmonary nocardiosis (A43.0) was the most frequently listed diagnosis for cases, followed by unspecified nocardiosis (A43.9) (Table 3.2). However, these values do not account for the numerous listings of the nocardiosis diagnosis or symptoms on repeated visits. From 40,205 separate visit records, 50.9% had pulmonary nocardiosis (A43.0), and 43.8% were unspecified nocardiosis (A43.9); 1.8% in each group were also reported along with other ICD-10-CM nocardiosis codes.

Applying the definitions for each of the main forms of disease (Table 2.1), disseminated disease was the most frequently identified form of nocardiosis (Table 3.2); 700 of these 1,635 cases had evidence of neurologic involvement or deficit. However, all neurologic involvement was classified as disseminated without accounting for primary neurologic nocardiosis. Only 239 cases (7.5%) had disease that could not be properly classified by disease type and remain "unspecified nocardiosis".

Evaluation of all listed diagnoses on a record, the most prevalent diagnoses were chronic conditions including hypertension (n=371) and hyperlipidemia (n=244). Lung findings were common and reported in multiple diagnosis codes. Pneumonia (n=222) and pulmonary mycobacterial infection (n=205) were both common findings. Symptoms included cough (n=124) and shortness of breath (n=76). Signs included acute respiratory failure with hypoxia (n=108), pleural effusion (n=79), solitary pulmonary nodule (n=72, and other nonspecific abnormal findings of the lung field (n=166). Neurological signs of infection were only identified by one code for intracranial abscess and granuloma (n= 110), and sepsis was reported 112 times.

Several potential indicators of severe disease were also reported. These included acute kidney failure (n=205), hypoosmolality and hyponatremia (n=141), hyperkalemia (n=77), and acidosis (n=68). There were few common procedures identified. There were 84 procedures reported that drained various parts of the lung, and the same count for short term mechanical ventilation.

The diseases identified most often were 'other bacterial diseases' (ICD-10-CM codes A30-A49). Mycobacterial infections were the most reported in 470 visits, 375 of which were pulmonary mycobacterial infections. Bacterial sepsis was reported for 306 (8.9%), and actinomycosis was not common (n=54). 'Mycoses' comprised 428 of the infectious diseases (ICD-10-CM codes B35-B49); aspergillosis was reported in 216 cases and candidiasis in 170. Cytomegalovirus was reported in 92 cases (2.7%), HIV in 35 (1.0%), and *Pneumocystosis* in only 14 (0.4%).

On average, each nocardiosis case had 3.7 (SD: 8.9) non-nocardiosis infectious diseases listed, and 23.4% of all nocardiosis-associated visits reported one or more other infectious diseases. Because many cases had more than one visit, the change in infectious diseases listed on the first and the last visit records was evaluated under the assumption that more infectious agents would be listed on the first visit as differential diagnoses; the change was negligibly smaller, with an average negative change of 0.051 (SD: 0.71). On the first visit, only 23.7% (n=752) of cases had one and 8.7% (n=276) had two or more infectious diseases listed. At the final visit, this was reduced slightly to 21.6% (n=683) and 7.8% (n=247), respectively.

Table 3.2: Counts of Nocardiosis disease form based on ICD-10-CM A43 and expanded definition for Medicare FFS nocardiosis cases, and nocardiosis-associated visits from the State Inpatient Databases (SID) and State Ambulatory Surgery and Services Databases (SASD)±

	Medicare FFS (N=3,167) n (%)		**SID** (N=1,626) n (%)		**SASD** (N=811) n (%)	
Nocardiosis disease form	**ICD-10-CM A43**	**ICD-10-CM +^**	**ICD-10-CM A43**	**ICD-10-CM +^**	**ICD-10-CM A43**	**ICD-10-CM +**
Not specified	1290 (40.7)	239 (7.5)	222 (13.7)	21 (4.3)	400 (49.3)	304 (37.5)
Other	220 (6.9)	NA	312 (19.2)	NA	41 (5.1)	NA
Cutaneous	187 (5.9)	201 (6.3)	107 (6.6)	61 (3.8)	24 (3.0)	37 (4.6)
Pulmonary	1537 (48.5)	1092 (34.5)	1128 (69.4)	739 (45.5)	357 (44.0)	349 (43.0)
Disseminated	NA	1635 (51.6)	NA	683 (42.0)	NA	100 (12.3)
Neurologic*	NA	700 (22.1)	NA	61 (3.8)	NA	21 (4.6)

± Medicare FFS nocardiosis cases: Oct 1, 2015 and March 31, 2018, SID and SASD: Oct 1, 2015 -Dec 31, 2017;
^ICD-10-CM+= the ICD-10-CM code A43 for nocardiosis plus the additional codes listed in Table 2.1;
*Neurologic nocardiosis include only signs/symptoms not denoting disseminated infection (Table 2.1), it was not separated from disseminated disease in Medicare;
NA- Not applicable- there is no specific ICD-10-CM code for disseminated or neurologic nocardiosis, and Other was not used as a valid category when applying additional ICD codes.

There were 296 cases with both pulmonary nocardiosis (A43.0) and pulmonary mycobacterial infection (A31.0) listed on their visit records, which is 27.1% of cases with pulmonary nocardiosis and 78.9% of those with pulmonary mycobacterial infections. Per the definitions to classify diagnosis claims into disease types (Chapter 2), 55.4% of cases were classified with pulmonary infections and 44.5% were classified with disseminated infections.

State Inpatient Databases

Based on the ICD-10-CM codes, pulmonary nocardiosis was the most frequently reported nocardiosis-associated diagnosis. Nocardiosis was the primary diagnosis in 349 visits (21.5%), of which 256 (73.4%) were pulmonary nocardiosis. More than one nocardiosis ICD-10-CM code was used on 128 visits, most of which were pulmonary combined with at least one other nocardiosis code; 82% of these visits, 'Nocardiosis, other' was the second code.

With the application of the additional definitions accounting for nocardiosis-associated diagnostic codes (with the exception that all neurologic signs were separated from the disseminated definition), pulmonary infection was identified most often, then disseminated infections (Table 3.2). Eye infections were too infrequent to report. Neurologic signs and symptoms were identified in 386 visits (23.7%), although most visits were also classified as disseminated infections. Neurologic nocardiosis occurred at a greater frequency among males than seen in the overall nocardiosis cohort (n=43/61, 70.5%), although the gender difference among neurologic infections was not statistically significant (χ^2: 2.12, df=1, p=0.146). People of White race accounted for 488 disseminated infection visits (78.7%) and 518 pulmonary visits (74.3%). Black/African Americans accounted for 58 disseminated infection visits (9.4%) and 70 pulmonary visits (10.0%). Pulmonary infections were more frequent compared to disseminated and other forms in the Northeast (50.8% vs 35.4%) and West (49.3% vs 41.0%) regions, whereas in the South and Midwest, disseminated and pulmonary forms occurred at a similar frequency; and the difference in disease type by region was statistically significant (χ^2: 18.97, df=6, p=0.0042).

Combining the diagnoses into categories using the Clinical Classifications Software (CCS), the most frequent category for all visits was pneumonia (1,217, 74.8%); other pulmonary codes

were also common: respiratory failure, insufficiency, or arrest (593, 36.5%); and pleurisy, pneumothorax, or pulmonary collapse (303, 18.6%). Septicemia was present in 257 visits (15.8%), while skin and subcutaneous tissue infections were present in 208 (12.8%) visits. Disorders affecting fluid and electrolytes were common (739, 45.5%), along with other disorders of deficiency: anemias (691, 42.5%); nutritional deficiencies (515, 31.7%); and other nutritional, endocrine, and metabolic disorders (538, 33.1%).

Of the categorized procedures reported, diagnostic bronchoscopy and biopsy of bronchus were listed for 374 visits (23.0%), followed by respiratory intubation and mechanical ventilation (228, 14.0%). Incision of pleura, thoracentesis, and chest drainage were performed during 154 visits (9.5%), and blood transfusions were performed during 199 visits (12.2%).

Of all listed individual diagnoses (n=31,534), almost 89% of visits had 'Factors influencing health status and health services' (ICD-10-CM Z00-Z99) accounting for 5,490 separate diagnoses. On average, 3.8 diagnoses in this category were reported per visit (SD: 2.2). Long-term current drug therapy was the most common subgroup within this category, of which systemic steroids were listed in 265 visits (16.3%). Other frequently listed diagnoses in this category included history of nicotine dependence (n=471), dependence on supplemental oxygen (n=184); 'do not resuscitate' orders were listed for 194 visits.

There were 4,112 endocrine system diagnoses listed in 1,404 visits (86%). Disorders of fluid, electrolyte, and acid-base balance (ICD-10-CM code E87) were the most frequent subcategory (n=1,1163 diagnoses). Disorders of endocrine glands, including hypothyroidism and other disorders of the thyroid (n=294), were somewhat frequent, as was malnutrition and other nutritional deficiencies (n=482).

Various forms of circulatory diseases were reported in 1,284 visits listing 3,367 diagnoses; hypertensive diseases were the most common (n=976 diagnoses), followed by ischemic heart disease (n=466), and atrial fibrillation (n=420). Respiratory diagnoses were reported from 1,193 visits for 2928 separate diagnoses; bacterial pneumonia was reported in 342 visits, pleural effusion in 204 visits, and respiratory failure in 540 visits. Kidney disease was reported 1,100 times from 717 visits, of which 484 visits had a diagnosis of acute renal failure.

Fewer diagnoses of disorders that affect the blood, blood-forming organs, and immune mechanism were reported (n=1,737), but these were reported from 1,035 visits. Non-nutritional anemias were the most common (n=826) from 740 separate visits. Neoplasms were reported from 386 visits, of which lymphoma and leukemia were the most common (228 of 517 diagnoses). Additionally, 522 skin disease diagnoses were reported from 345 (21.2%) visits, and the majority were infections of the skin (n=231) including cellulitis, acute lymphangitis, cutaneous abscesses, and acute lymphadenitis. Only 44 of the skin disease visits (28.2%) were among patients with listed cutaneous nocardiosis; 71.2% were among patients with disseminated disease, which may indicate hematogenous spread from a cutaneous lesion.

There were 1456 non-nocardiosis infectious disease diagnoses that were listed on 922 (56.7%) visit records. Mycoses comprised 30% of diagnoses, including aspergillosis (n=145) and Candidiasis (n=207). Mycobacterium infections were uncommonly reported. CMV was listed 62 times. Systemic inflammatory response syndrome/sepsis was listed for 156 separate symptom diagnoses and 313 that were under infectious agent diagnoses from 334 visits. By presentation of disease, 68.6% were in patients with disseminated disease and 26.6% were in pulmonary nocardiosis.

Various symptoms, signs, and diagnostic findings were reported from 1,091 visits accounting for 2,139 diagnoses. Most symptoms fell into the ICD-10-CM category of “General Symptoms and Signs” (n=735); although there were no prominent symptoms or signs; from these, 101 diagnoses were malaise and fatigue, 69 with cachexia, and 58 with fever.

State Ambulatory Surgery and Services Databases

The most frequently listed ICD-10-CM code was ‘Nocardiosis, not specified’ (A43.9) (Table 3.2), followed by pulmonary nocardiosis (A43.1). Nocardiosis was the primary diagnosis for 365 (45.0%) visits. Pulmonary infections were identified most frequently when applying the definitions in Table 2.1, followed closely by nonspecific nocardiosis. Disseminated infections were only identified from 12.3% of visits, and eye infections were too infrequent to report. Disseminated infection visits occurred more often among males (61% vs 39% in females); almost 60% (n=209) of the pulmonary visits occurred among adults 65 and older, while 52% of

disseminated and 57% of cutaneous nocardiosis visits occurred among patients under 65 years old. Regionally, 61 (61%) disseminated infection visits occurred in the South.

The most frequently listed CCS for all visits was pneumonia (404, 49.8%), then bacterial infection (393, 48.5%). Of all listed individual diagnoses (n=3,575), about 48% of visits had 'Factors influencing health status and health services' (ICD-10-CM Z00-Z99) accounting for 939 separate diagnoses. Most of these diagnoses fell into the category of health history that influences health status. There were few diagnoses listed that could be readily classified into meaningful groups.

C. Characteristics of Visits

Medicare

The types of claim records for the 3,167 cases were: 1,813 cases had 7,755 outpatient visits, 1,404 cases had 2,343 inpatient visits, and 2,707 cases had 30,107 separate carrier records. Of the 2,792 cases with more than one visit or record, the mean number of records per person was 14.3 (SD: 17.2). In- and outpatient visits varied in frequency by sex: females received outpatient care at a greater frequency than inpatient care (55.4% of outpatient visits vs 40.4% of inpatient). Cases in people younger than 65 had a greater percentage that received inpatient care than outpatient care (24.2 vs 17.4%).

When looking at the number of visits by disease type, cases with disseminated infection had the greatest number of visits (28,476) for an average of 17.4 encounters per case, and 74.6% of these encounters were readmission or encounter within 30 days of a previous visit. Cases with pulmonary infections had 9,333 encounters (mean= 8.5), of which 64.1% were readmission or repeat encounters. Cutaneous cases had 1,350 visits (mean= 6.7 encounters), and unspecified nocardiosis had 1,046 encounters (mean= 4.4 encounters).

The average length of stay among inpatient visits was on average four days longer, compared to the average duration of care, which includes total follow up time including both inpatient and outpatient care (Table 3.4).

The mean cost per case was $38,890 (SD: $168,134) for a total cost of more than $123 million during the study period (Table 3.3). The average cost per visit was low since it included

outpatient, inpatient, and carrier visits, although with a wide standard deviation. Mean costs per case differed by age group, with the highest among cases less than 65 years old ($65,196 [SD: $261,119]) and lowest among those 85 and older ($15,868 [SD: $33,180]); however, the standard deviations were wide, demonstrating a large variation in the amount paid for each case.

Table 3.3: Visit characteristics for Medicare FFS nocardiosis cases, SID and SASD

Visit characteristics	Medicare FFS	SID	SASD
Total visit records	40,205	1626	811
Duration of care (Mean days, SD)±	8.7 (19.1)	0.82 (5.1)	0.4 (5.0)
Length of all inpatient stays† (Mean days, SD)	12.7 (13.5)	12.7 (14.7)	0.4 (3.1)
Outcome			
Died	881 (27.8)	102 (6.3)	0
Time to death, days (Mean, SD)*	269.1 (262.0)	20.1 (17.9)	-
Total cost**	$123,164,077	$44,033,097	$2,560,033
Cost/visit (Mean, SD)	$3,063 ($44,836)	$35,226 ($69,202)	$3,427 ($10,032)

±Duration of total follow up from first to last nocardiosis-associated visit, including outpatient and inpatient visits.
†Duration of hospitalization only
*for SID, this is calculated from length of stay for visits where a death was reported
** SASD, this is total charges due to no cost-to-charge ratio data

Disseminated infections had the highest average costs ($64,133 [SD: $226,704]); average costs for pulmonary infections ($15,258 [SD: $54,160]) and cutaneous infections ($6,096 [SD: $24,108]) were substantially lower with less extreme variation within groups. The costs were larger in each subsequently larger CCI group, with the highest among cases with a CCI score of six or more, but again, there was substantial variation within groups. When evaluated by specific nocardiosis-specific risk factors, cases with HIV ($5,802, SD: $65,937), stem cell transplant ($6,029, SD: $46,658), and solid organ transplant ($3,686, SD: $53842) had higher costs per visit than the overall average per visit.

State Inpatient Databases

Most hospitalizations were either emergency (974, 60.0%) or urgent (420, 25.9%), and 69.8% were not transfers from another healthcare facility. Length of inpatient stay was similar to Medicare (Table 3.3); since length of stay was skewed, means and medians are both reported in Appendix Table 3.1. Median visit length was shorter for each older age group, and was consecutively longer with more chronic conditions or risk factors, regardless of the co-morbidity measure

Costs were calculated for 1,520 visits using the cost to charge ratio for SID. Costs represent the actual costs incurred for services and exclude physician fees, whereas charges are the total amount billed by a hospital. The conversion could not be done for all visits because of missing hospital identifiers in all records from four states in all years (Iowa, Minnesota, Nebraska, and South Carolina) accounting for 166 visits (10.2%), as well as 49 visits (3%) in 2017 from Georgia, Mississippi, Washington, and West Virginia.

The overall and average costs during the study period is in Table 3.4; the median was $18,813 (IQR: $28,895). The average costs per CCI category (Appendix Table A.2) did not reflect the same pattern as the Medicare data, which showed higher average costs with each increasing CCI category; however, the median costs from SID did follow this pattern. The median costs for visits with disseminated ($26,125, IQR: $43,991) and neurologic nocardiosis ($26,751, IQR: $37,995) were more than twice the amount of cutaneous nocardiosis ($10,933, IQR: $13,864). Costs for pulmonary nocardiosis was between these ($16,382, IQR: $21,164.

Costs were evaluated for some common risk factor comorbidities; median costs for visits with renal failure listed was higher ($21,335, IQR $32,625]) than those without ($16,478, IQR $24,637), visits with malnutrition also had much higher costs ($29,438, IQR: $45,530) than those without ($16,515, IQR: $24,725), as well as those with history of solid organ transplant ($22,058 IQR $36,591) than those without ($17,399 (IQR $26,865).

Because SID and SASD data are visit-based, there is not an equivalent analysis of readmissions or person-based versus visit-based characteristics. However, because 14 of the 29 participating states provide a variable that links visits together at the patient level, the number of repeated visits by the same person during the same year could be evaluated for 722 (44.4%)

SID and 133 (16.4%) SASD visits, which are combined for this brief description. These visits represented 549 unique individuals, of which 374 (68.1%) had only a single visit; the average number of visits per person was 1.6 (SD 1.1) with a maximum of 10 visits. Among those with more than one visit, the average time between visits was highly skewed (35 days, SD 69), and the median was 5 days (IQR 35).

State Ambulatory Surgery and Services Databases

The primary reason for the visit was pneumonia (169, 27.8%). While 97.2% of all SASD visits were classified as elective, 46.7% (326) were referred by their clinician. Charges instead of costs were calculated for all nocardiosis-associated SASD visits due to the absence of cost-to-charge ratios. The average charges were similar to Medicare costs despite charges overestimating the true costs (Table 3.3). The overall median charge was $745 per visit (IQR: $2,645); almost 10% of the values were extreme outliers, which is clear in the drastic difference between the mean and the median. Median charges were larger each year, but these were not statistically significantly different ([2015: $337, IQR: $723]; [2016: $655, IQR: $1,951]; [2017: 736, IQR: $2,357]; χ^2=2.05, df=2, p=0.36). Charges appeared lower with each older age group, with a median of $871 (IQR $2,930) in people under age 65 to $379 (IQR $464) in those 85 and older. The number of chronic conditions measure was more evenly distributed into categories (Figure 1), and thus was selected to evaluate chronic conditions on charges. The median charges were statistically significantly different between the categorized comorbidity counts, in which the median charges showed a positive change in each greater chronic condition category from 0 conditions to 6 or more ([$518, IQR: $1,281], [$1,506, IQR: $5,358], χ^2=46.35, df=4, p<0.0001).

D. Risk Factors and Chronic Conditions

Medicare

Several chronic conditions that were investigated were highly prevalent among nocardiosis cases, although counts varied based on the definitions of each comorbidity measure (Table 3.4). For example, experiencing renal disease at any time during Medicare coverage was

highly prevalent (68%), although dropped by more than half when limiting to reported renal disease in the previous 12 months.

Conditions that comprise many nocardiosis case reports (e.g., cystic fibrosis and HIV), as well as cytomegalovirus infection, which has been associated with nocardiosis mortality, are not common among this Medicare population (Table 3.4). Prevalent conditions that cannot easily be discerned as being caused by the acute illness or other underlying conditions included anemia, malnourishment, weight loss, and fluid disorders.

Of the cases with history of solid organ transplant (SOT), heart transplants were the most frequently identified (889, 66.2%), followed by kidney (353, 26.3%), liver/pancreas (338, 25.2%), and lung (146, 10.9%); these add up to more than 100% because some cases had more than one organ transplant reported. Almost half of kidney transplants occurred in cases younger than 65, which is likely due to Medicare availability to persons suffering from end stage renal disease (195). While only 33.5% of cases with transplant history and 35.7% of kidney transplants were women, other transplanted organs were slightly more common in women than men (lung: 55.5%, heart 61.8%, and liver/pancreas 53.6%).

Some chronic conditions were associated with the form of nocardiosis. COPD was significantly greater in cases with pulmonary nocardiosis (62.2%) compared to disseminated (52.8%) and cutaneous disease (20.2%) (χ^2=120.9, df=2, p <.0001). Diabetes, which can cause both skin and systemic problems, was greater among both cutaneous and disseminated nocardiosis cases (χ^2=30.1, df=2, p <.0001). Systemic conditions that cause immunosuppression, including malignancy, renal disease, and SOT, were greater in cases with disseminated infection compared to pulmonary or cutaneous forms. Malignancy among disseminated infections was 24.8% compared to 17.5% in pulmonary cases (χ^2=28.5, df=2, p <.0001); renal disease was present in 30.8% of disseminated infections and 23.1% of pulmonary (χ^2=22.3, df=2, p <.0001); SOT was present in 45% of disseminated infections and 40.3% of pulmonary (χ^2=7.2, df=2, p 0.0271).

458 Table 3.4: Counts of comorbid conditions by comorbidity measure identified for Medicare FFS
459 nocardiosis cases, and nocardiosis-associated visits from the State Inpatient Databases (SID) ±

	Medicare (N=3,080)	Medicare (N=3,167)	SID (N=1626)		
Conditions	**Charlson n (%)**	**Risk factors n (%)**	**Charlson n (%)**	**Risk factors n (%)**	**Elixhauser n (%)**
Congestive heart failure	608 (19.7)		338 (20.8)		267 (16.4)
Peripheral Vascular Disease	434 (14.1)		101 (6.2)		93 (5.7)
Cerebrovascular Disease	239 (7.8)		92 (5.7)		
Hypertension					910 (56.0)
Rheumatologic Disease	248 (8.1)		117 (7.2)		124 (7.6)
COPD	1,642 (53.3)		721 (44.3)		
Paralysis	47 (1.5)		50 (3.1)		74 (4.6)
Diabetes	1,241 (40.3)	1,431 (45.2)	416 (25.6)	477 (29.3)	472 (29.0)
Liver (mild-severe)	178 (5.8)		123 (7.6)		104 (6.4)
Renal disease	839 (27.2)	2,136 (67.5)	477 (29.3)	835 (51.4)	437 (26.9)
Malignancy	643 (20.9)	1,554 (49.1)	289 (17.8)	464 (28.5)	159 (9.8)
Metastatic tumor	117 (3.8)		58 (3.6)		50 (3.1)
HIV	29 (0.9)	56 (1.8)	59 (3.6)	64 (3.9)	14 (0.9)
Chronic lung disease		2,437 (77)		727 (44.7)	652 (40.1)
Respirator use		142 (4.5)		25 (1.5)	
Anemia		2,369 (74.8)		615 (37.8)	601 (37.0)
Malnutrition		598 (18.9)		381 (23.4)	
Bowel disease		116 (3.7)		23 (1.4)	
Hemodialysis		389 (12.3)		80 (4.9)	
Organ transplant		1,343 (42.5)		417 (25.7)	
Stem cell transplant		95 (3)		36 (2.2)	
History of immuno-suppression therapy		121 (3.8)		0	
Cell-mediated immunosuppression		1,052 (33.2)		161 (9.9)	
Chronic steroid use		410 (13.0)		0	
Ectopic Cushing's		112 (3.5)		-	
Cystic fibrosis		261 (8.2)		80 (4.9)	
CMV		194 (6.1)		59 (3.6)	
Alcohol abuse		193 (6.1)		46 (2.8)	45 (2.8)
Smoking		769 (24.3)		149 (9.2)	
Drug abuse					54 (3.3)
Weight loss					418 (25.7)
Obesity					102 (6.3)
Fluid/electrolyte disorder					794 (48.8)
Other neurologic conditions					183 (11.3)
Hypothyroidism					274 (16.9)
Coagulopathy					268 (16.5)

Some chronic conditions were associated with the form of nocardiosis. COPD was significantly greater in cases with pulmonary nocardiosis (62.2%) compared to disseminated (52.8%) and cutaneous disease (20.2%) (χ^2=120.9, df=2, p <.0001). Diabetes, which can cause both skin and systemic problems, was greater among both cutaneous and disseminated nocardiosis cases (χ^2=30.1, df=2, p <.0001). Systemic conditions that cause immunosuppression, including malignancy, renal disease, and SOT, were greater in cases with disseminated infection compared to pulmonary or cutaneous forms. Malignancy among disseminated infections was 24.8% compared to 17.5% in pulmonary cases (χ^2=28.5, df=2, p <.0001); renal disease was present in 30.8% of disseminated infections and 23.1% of pulmonary (χ^2=22.3, df=2, p <.0001); SOT was present in 45% of disseminated infections and 40.3% of pulmonary (χ^2=7.2, df=2, p 0.0271).

The weighted score or unweighted count of each comorbidity measure was categorized to evaluate these nocardiosis cases by demographics and other covariates. While 70% of cases had a weighted score of three or fewer CCI comorbidities (Figure 3.1), the average score in the highest CCI category of 6+ was 7.9 (SD: 2.1). Meanwhile, the unweighted risk factors, which were identified from nocardiosis case reports in the literature (Appendix Table A.1), had an average count of almost twice the CCI score. Almost 75% of cases had more than three nocardiosis risk factor conditions.

Some demographic characteristics vary between the CCI categories. Age appears inverse to CCI score and number of risk factors; a greater proportion of cases younger than 65 have higher CCI scores (χ^2=79.7, df=9, p<.0001) (Appendix Table A.2). Females had lower CCI scores; only 22.3% had a score of four or greater, while almost 40% of men did (χ^2=136.7, df=3, p<.0001). Race also appears to vary by CCI category; the proportion of cases among Black/African Americans was larger in the two highest CCI categories (χ^2=269.5, df=12, p<.0001). 96% of ESRD had four or more nocardiosis risk factors, and also had a greater CCI score (χ^2=187.0, df=3, p<.0001), as did those with dual Medicare/Medicaid coverage.

More severe forms of nocardiosis occurred in cases with a higher CCI score; cutaneous infections were higher than expected in the lower CCI categories, and disseminated infections were higher in the two highest CCI categories (χ^2=52.8, df=9, p<.0001) (Appendix Table A.2).

Disseminated nocardiosis also made up a greater proportion of the cases with more than three risk factors compared to lower categories, accounting for 79.4% of disseminated cases (n=1,298) (χ^2=134.7, df=9, p<.0001). Three-quarters of cases with history of transplant had six or more risk factors.

State Inpatient Databases

Hypertension, chronic lung disease, COPD, renal disease, and fluid/electrolyte imbalance were present in almost half or more of visits (Table 3.4). Some conditions in the comorbidity measures that were commonly present in these visits, including coagulopathy, anemia, and weight loss, may be associated with the acute *Nocardia* infection or truly be an underlying factor. Conditions that are frequently associated with nocardiosis in the literature (i.e., HIV, cystic fibrosis, CMV, alcohol, and drug abuse) were infrequently listed on visits (8, 111, 114, 155, 196).

Among the visits with history of SOT, specific organ transplant information was not able to be elicited. However, 336 (80.6%) had renal disease and 79 (18.9%) had chronic pulmonary disease, 59 visits reported both conditions. Almost 69% of visits with SOT were among males, and 64.8% of visits occurred in those younger than 65. Most of the infections were either pulmonary (48.2%) or disseminated (38.6%).

Two additional comorbidity measures were included in the SID analysis, the HCUP chronic condition indicator (197) and Elixhauser comorbidity index (198). These were included because SID visit data only contains comorbidities during the single visit record and fails to capture comorbidities present during the 12 months or more before onset, as defined by the Charlson Comorbidity Index (171) or the nocardiosis risk factors measure (Appendix Table A.1).

The distribution and average scores for each measure are shown in Figure 3.1. The unweighted count of nocardiosis risk factors and the weighted CCI produced lower scores, 66% of visits had fewer than four risk factors, while 70% had a CCI score less than four. The mean number of chronic conditions from the Chronic Condition Indicator Tool was nearly five times larger (Figure 3.1), and 70% of visits reported six or more conditions.

Evaluating demographics by categorized measure, age was variable for each measure. Females had fewer comorbidities than males in all comorbidity measures. The largest difference was identified among the CCI, in which 22% of visits among females reported a CCI score of four or more compared to 35% of visits among men (χ^2: 37.6, df=3, p<.0001) (Appendix Table A.2).

The categorized measures by disease form also vary by measure. Most visits reporting cutaneous infection have fewer than four conditions using the risk factors, CCI, and Elixhauser measures. Meanwhile, 57% and 68% of reports with disseminated infection have fewer than four conditions among risk factors and CCI measures. Although the number of chronic conditions is heavily skewed to the highest category of six or more conditions, a greater proportion of disseminated infection visits are in this highest category (79%) than pulmonary infection visits (70%) or cutaneous infections (51%). A similar trend was also seen for the count of Elixhauser conditions.

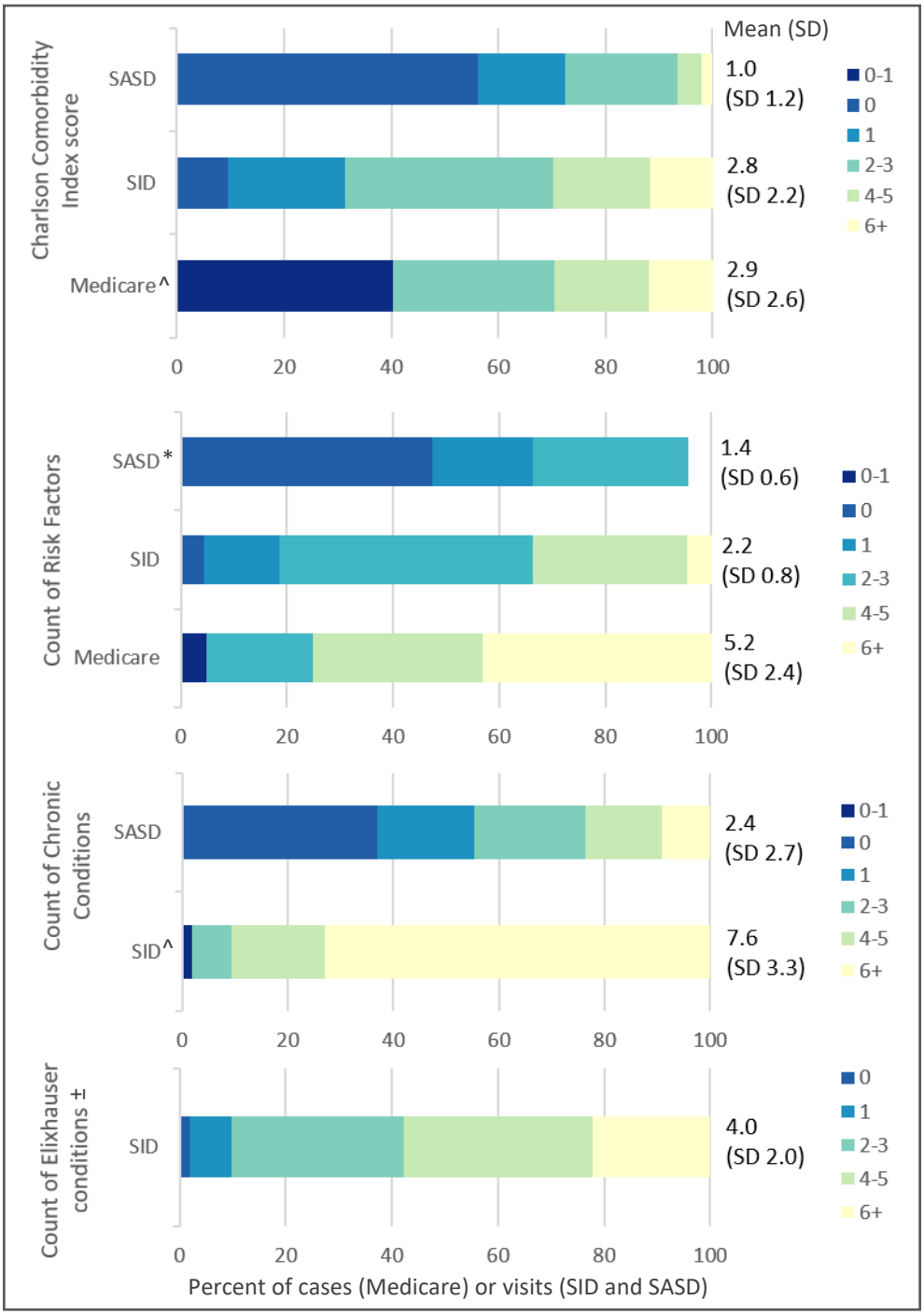
The calculated Elixhauser readmission and mortality scores are more useful values than the count of conditions alone for this measure (174). The average estimated readmission score was 28.3 (SD: 17.1), and the Elixhauser mortality score was 13.4 (SD: 11.6). The average readmission score was highest among visits reporting neurologic nocardiosis (31.5, SD: 16.8 [Median: 33, IQR: 20), followed by disseminated (30.2, SD: 17.3 [Median: 30, IQR: 24]). The average readmission score for visits with pulmonary infections was 26.7 (SD: 15.9 [Median: 25, IQR: 22]), and the score for cutaneous nocardiosis visits was only 20.9 (SD: 18.6 [Median: 16, IQR: 29]); the estimated readmission was statistically significant by disease form (χ^2=34.2, df=4, p<.0001).

State Ambulatory Surgery and Services Databases

The application of various comorbidity measures to the SASD visit records had limited utility since many of the conditions had numbers too low to report. It is unlikely that the patients who were seen on these visits lacked chronic conditions to the extent shown in Figure 3.1, but rather is likely indicative of limited reporting of diagnoses on such visits; almost 85% of records had fewer than 10 diagnoses, whereas 50% of SID records had 20 or more diagnoses.

Additionally, Elixhauser was not run on SASD since it is not validated or recommended for use in SASD.

Among conditions with sufficient counts, COPD was reported in 133 (16.4%), 85 had a malignancy (10.5%), and 121 had renal disease (14.9%). Among SASD visits with a history of solid organ transplant (n=171, 21.1%), 67.8% were among males, and almost 77% were among individuals younger than 65. Eighty-five (49.7%) visits with transplant history had pulmonary nocardiosis, and 55 (32.2%) were not specified.



556 Figure 3.1. Percent of nocardiosis cases or visits with categorized count or score by comorbidity
557 measure, among Medicare FFS cases, State Inpatient Databases [SID] visits, and State
558 Ambulatory Surgery and Services Databases [SASD] visits

559 ^ All comorbidity measures are grouped into a single category of '0-1' conditions for Medicare data, SID
560 data are collapsed into the '0-1' category when the counts are too small to report individually. * The
561 count of risk factors for SASD in categories 4-5 and 6+ are too small to report separately. ±Elixhauser
562 comorbidity index is not validated for use in SASD data, so was not run for SASD.

E. Predictors of Mortality

Medicare

Of the 3,167 cases, 881 (27.8%) died at any point during the study period, with an overall average time to death of 269.1 days (SD: 262.0) from the first nocardiosis-associated visit, although 19.5% died within 12 months (Figure 3.2). Dual Medicare coverage, Part B coverage, end stage renal disease, and the original reason for entitlement were similar by death status (Table 3.5).

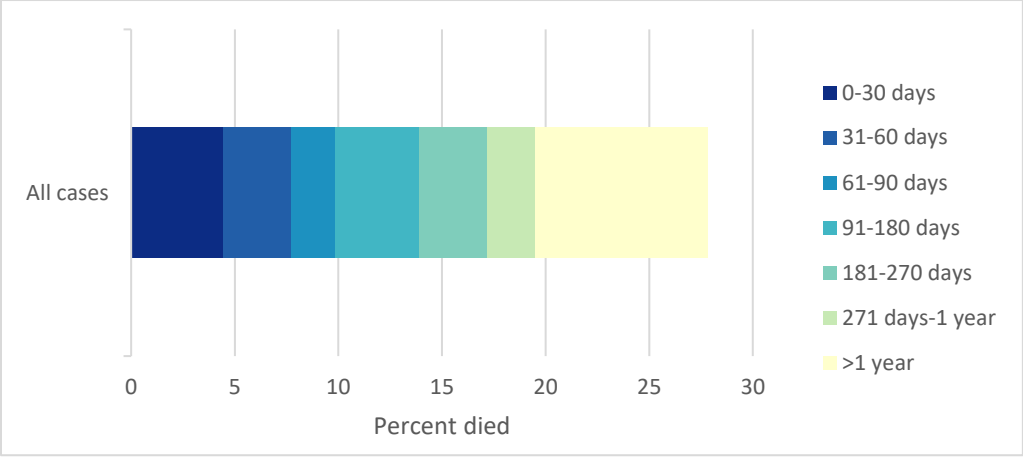


Figure 3.2: Percentage died at each time point following the first nocardiosis-associated visit among Medicare FFS nocardiosis cases

Up to 716 cases (22.6%) had their first visit after April 2017 and were censored prior to the 12-month cut off as shown in the Kaplan-Meier survival curves (Figures 3.3-3.5) but may have subsequently died. Among survivors, the average time from the first nocardiosis visit until the last known visit during the study period was 320.5 days (SD: 90.0).

Males had a higher frequency of death compared to females (31.9% vs 23.4%), which was also borne out by age groups. Older cases also had a greater frequency of death compared to each younger age group (39.7%, 29.9%, 25.4%), except cases younger than 65 (48.1%).

Cases with a greater number of comorbidities also had a higher frequency of mortality; 26.2% of all deaths occurred among cases with a CCI score $\geq$ 6, which only constituted 14.3% of the included cases. In this group, 50.9% of cases died compared to 16.3% of cases with a CCI score $\leq$ 1, which comprised 39.2% of all cases. Additionally, this group had a greater frequency

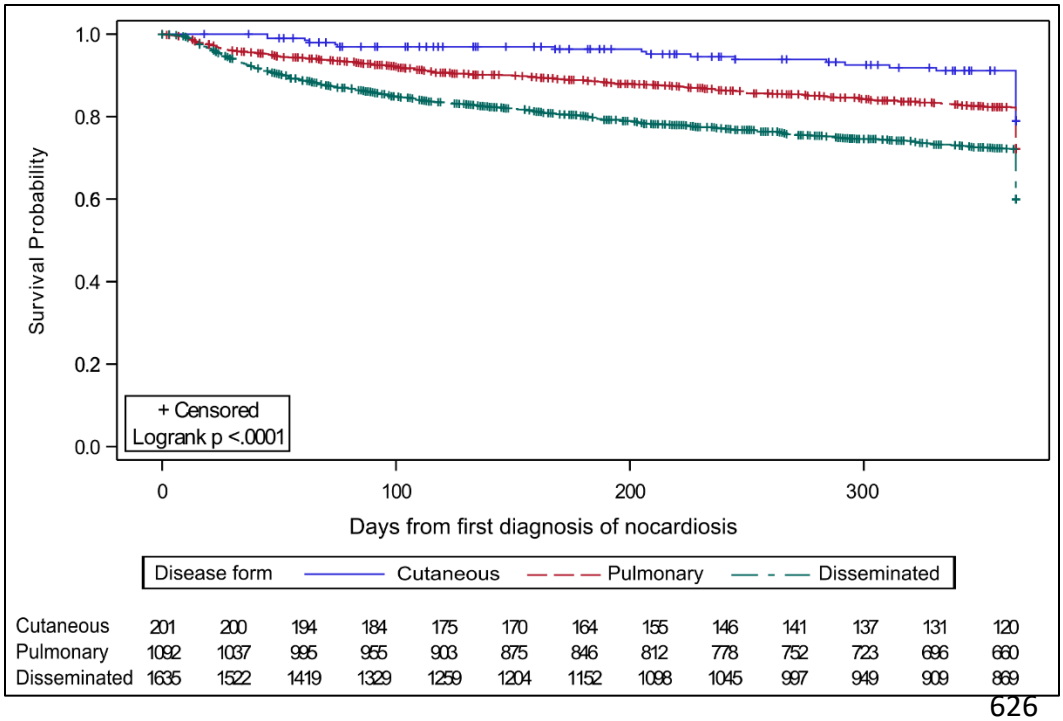
of either being censored or dying within 30 and 60 days of their first visit compared to the other CCI categories (9.0% vs 4.0-5.7%, 7.9% vs. 3.6-5.3%, respectively). Risk factors were evaluated separately from CCI; 75.1% of cases had four or more nocardiosis risk factors, of which 31% died.

Deaths occurred more frequently among cases with disseminated disease regardless of the CCI category, although the mortality rate positively changed with each increase in CCI category (22.7%, 35.4%, 37.4%, and 53.8%) which gives an overall mortality of 34.6% among disseminated cases. Mortality among cases with pulmonary disease followed this same pattern (12.3%, 23.5%, 31.0%, and 51.1%) for an overall mortality rate of 23.4%. CCI classification of cases with skin or unspecified disease cannot be reported due to small cell size.

Kaplan-Meier survival curves were developed to compare survival over time by nocardiosis disease type, CCI, and risk factor categories. There was a high percentage of censoring in each analysis (70.9%, 72.2%, and 72.2% respectively). There was evidence of a statistically significant difference between the survival curves for nocardiosis disease form (χ^2: 61.54, degrees of freedom [df]: 2, $p<0.0001$) (Figure 3.3). The three main disease forms have clearly delineated survival curves. Survival remains at or near 100% until approximately 50 days for cases with skin infections.

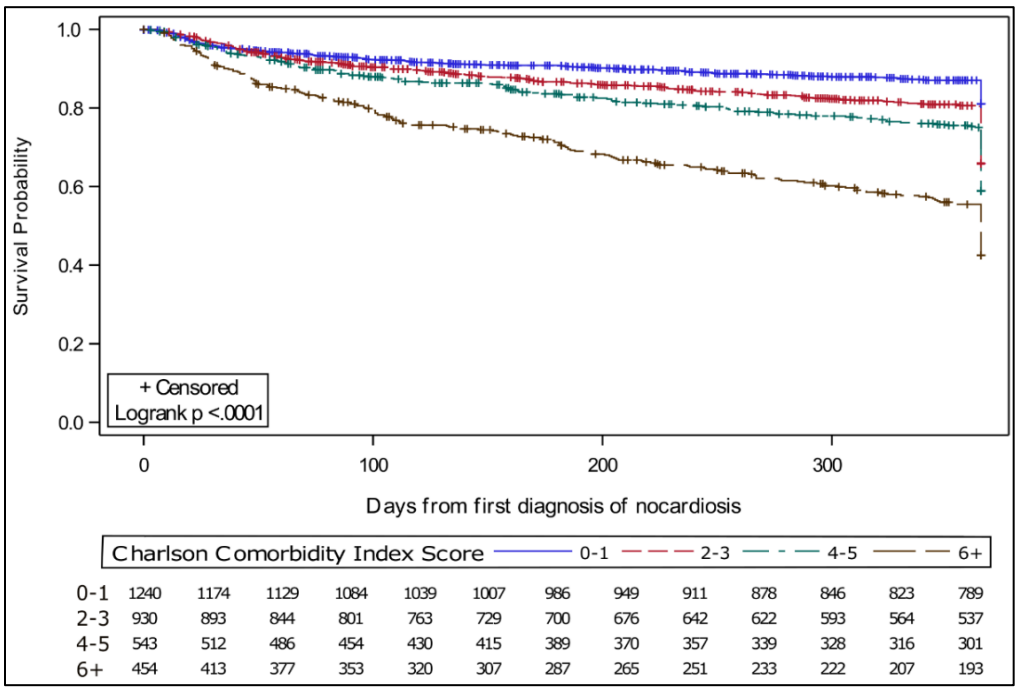
The survival curves for the categorized CCI scores demonstrate a statistically significantly different all-cause mortality between these groups (χ^2: 235.10, df: 3, $p<0.0001$) (Figure 3.4). The survival probability of cases with a score $\geq$6 appears to separate from the other groups around 25 days, and the rest of the categories separate from each other after 50 days. Similarly, the survival curves for number of known nocardiosis risk factors (0-1, 2-3, 4-5, and 6+) significantly differ (χ^2: 47.44, df=3, $p<0.0001$), although the visual differences are less distinct compared to the CCI survival curves (Figure 3.5).

Average time to death was calculated for CCI separately from the biased Kaplan-Meier estimates. The average was shortest among CCI group 4 (217.9, SD: 213.1), while the next shortest was CCI group 1 (mean 243.0, SD: 260.6), and the longest was CCI group 2 (mean 312.2, SD: 281.9).



626

627 Figure 3.3: Kaplan Meier survival curves of Medicare nocardiosis cases for all-cause mortality by
628 type of nocardiosis, October 1 2015- March 31, 2018; logrank testing for homogeneity between
629 curves, n=3167



630
631 Figure 3.4: Kaplan Meier survival curves of Medicare nocardiosis cases for all-cause mortality by
632 Charlson Comorbidity Index score, October 1 2015- March 31, 2018; logrank testing for
633 homogeneity between curves, n=3167
634

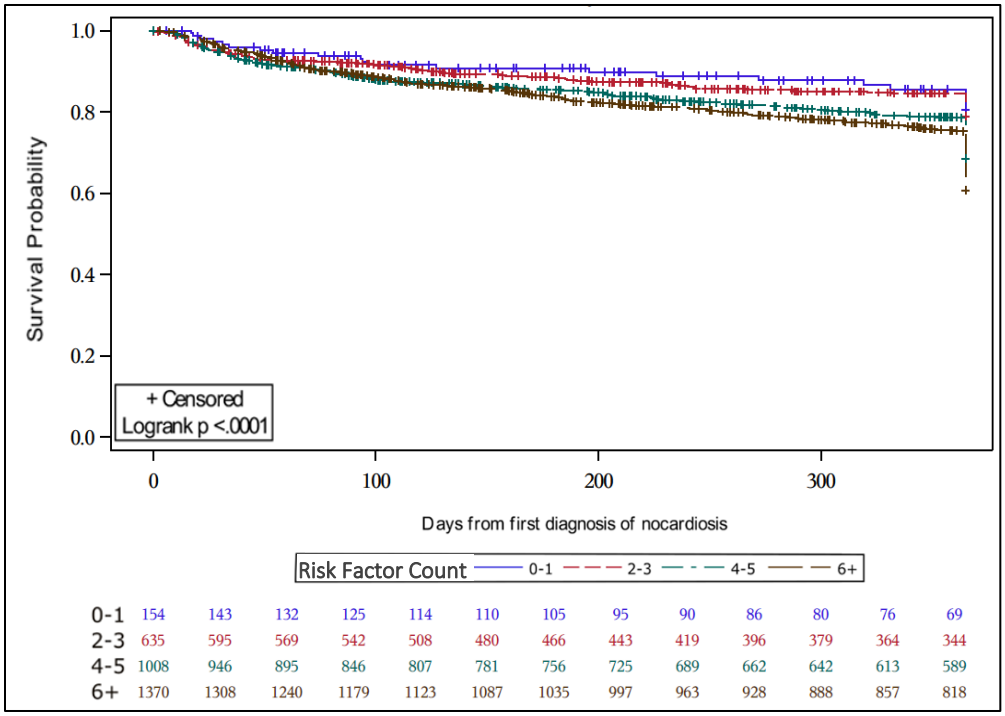


Figure 3.5: Kaplan Meier survival curves of Medicare nocardiosis cases for all-cause mortality by number of risk factors, October 1, 2015- March 31, 2018; logrank testing for homogeneity between curves, n=3167

In the adjusted Cox regression model of nocardiosis cases, age had a small impact with a 2% increase in mortality rate for each additional year of age, while females had a 19% lower mortality rate than men (Table 3.5). Cases with higher CCI scores had a higher adjusted mortality rate; cases with a CCI score of 2-3 had a 78% higher mortality rate compared to those with a score $\leq$1, while this increased to two to almost four times the mortality rate for cases with CCI score of 4-5 and $\geq$6, respectively. Both pulmonary and disseminated infections were also associated with a higher adjusted mortality rate compared to cases with only “not specified” nocardiosis.

Table 3.5: Descriptive characteristics and adjusted Cox proportional hazards model of Medicare FFS nocardiosis cases between Oct 1, 2015 and March 31, 2018, by death or censoring status

Variables	Descriptive Statistics		Adjusted Cox proportional hazards model	
	Died n=881 n (%)	**Censored or alive** n=2286 n (%)	HR (95% CI)	p ***value***
Female	355 (40.3)	1164 (50.9)	0.81 (0.70, 0.93)	0.0026
Male	526 (59.7)	1122 (49.1)		
Age (mean, SD)	72.1 (11.7)	70.4 (11.4)	1.02 (1.01, 1.03)	<0.0001
No Part B coverage	17 (1.9)	25 (1.1)	2.07 (1.28, 3.35)	0.0027
ESRD	89 (10.1)	211 (9.2)	0.85 (0.67, 1.08)	0.17
Original reason for entitlement				
OASI	586 (66.5)	1552 (67.9)	-	-
DIB	237 (26.9)	514 (22.5)	-	-
ESRD	30 (3.4)	103 (4.5)	-	-
DIB/ESRD	28 (3.2)	117 (5.1)	-	-
Dual coverage	182 (20.7)	418 (18.3)	-	-
CCI weighted score (mean, SD)	4.1 (3.0)	2.5 (2.3)	-	-
0-1	202 (22.9)	1038 (45.4)	Reference	-
2-3	262 (29.7)	668 (29.2)	1.78 (1.48, 2.14)	<0.0001
4-5	186 (21.1)	357 (15.6)	2.26 (1.84, 2.77)	<0.0001
6+	231 (26.2)	223 (9.8)	3.72 (3.06, 4.53)	<0.0001
Risk factors (mean, SD)	5.2 (2.4)	5.2 (2.4)		
0-1	22 (2.5)	132 (5.8)	-	-
2-3	112 (12.7)	523 (22.9)	-	-
4-5	274 (31.1)	734 (32.1)	-	-
6+	473 (53.7)	897 (39.2)	-	-
Nocardiosis disease form				
Not specified	30 (3.4)	209 (9.1)	Reference	-
Cutaneous	31 (3.5)	170 (7.4)	1.24 (0.75, 2.06)	0.39
Pulmonary	255 (28.9)	837 (36.6)	2.05 (1.40, 2.99)	0.0002
Disseminated	565 (64.1)	1070 (46.8)	2.99 (2.07, 4.32)	<0.0001

Abbreviations: SD=Standard Deviation, ESRD=end stage renal disease, OASI=old-age and survivor's insurance, DIB=disability insurance benefit, CCI=Charlson comorbidity index, HR=hazard rate; CI= confidence interval

State Inpatient Databases and State Ambulatory Surgery Databases

Inpatient visit outcomes were captured by disposition of the patient. While 39.7% were routine discharges, 29% were discharged to some other facility, including short term care

facilities. An additional 24.3% were transferred to receive home health care, and 102 (6.3%) died during the hospitalization. Little outcome information was available for surgical and ambulatory visits: 789 (99.3%) visits were listed as routine discharge, and the disposition for 16 visits was missing. No deaths were reported from these visits.

Disseminated nocardiosis visits had the highest average Elixhauser mortality score (15.2, SD: 11.7 [Median: 14, IQR: 29), followed by visits with neurologic infection (15.1, SD: 13.2 [Median: 14, IQR: 18). Cutaneous infection visits had the lowest mortality score (7.3, SD: 11.2 [Median: 6, IQR: 13). The differences in median ranks also differed significantly (χ^2=57.2, df=4, p<.0001).

Looking specifically at patients using the 'visitlink' variable, 66% of repeated visits were among males. There were 54 deaths among 549 unique individuals for a mortality rate of 9.8%. Visits with disseminated infections had the highest mortality at 10.8% (n=74/683), while pulmonary infections had a mortality rate of 3.4% (n=25/737); the mortality for the other groups was too small to report. Length of stay was longer among visits where death was reported (Appendix Table A.2). Mortality rates were lowest in the category with the fewest comorbidities in each of the comorbidity measures, in which they ranged from 0-4%, and were larger in each subsequent category; in the category of $\geq$6, the range of mortality rates were 7.7-12.2%.

Comparison of comorbidity measures as predictors of in-hospital mortality and predictor of mortality

None of the comorbidity measure pairs suffers from collinearity (Appendix Table A.4). A baseline model was first selected to include demographic variables that are potential confounders; although two potential confounders, race and urban residence, did not affect other potential confounders and were excluded from the baseline model. Region and median income were also excluded due to affecting the Global Score test of the model. Each comorbidity measure was added to the baseline model, and the AIC and c-statistics are reported for each model in Appendix Table A.5. The Elixhauser mortality score provided the most predictive model of the four measures; surprisingly, the weighted Charlson Comorbidity

Index measure performed worse than the non-weighted measures of known nocardiosis risk factors and the number of chronic conditions (Appendix Table A.5).

On bivariate analysis, chronic steroid use, reliance on a respirator, and CMV infection were statistically significantly associated with death, but the cell sizes were <10 and thus were not included in the multivariable model. All variables in that were included in the initial model were retained for the highest AIC and c-statistic.

Table 3.6: Crude and Adjusted Odds Ratios (OR) from a Multivariable Logistic Regression Model on the Outcome of Death During a Nocardiosis-Associated Hospitalization Using SID

	Died during hospitalization				
Variable^	N (%) (n=102)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Male	56 (54.5)	Reference		Reference	
Female	46 (45.1)	1.34 (0.90, 2.01)	0.1549	1.57 (1.02, 2.41)	**0.0387**
Age					
0-64	35 (34.3)	Reference		Reference	
65-75	34 (33.3)	1.6 (0.98, 2.6)	0.8294	1.50 (0.90, 2.51)	0.8999
75+	33 (32.4)	2.3 (1.4, 3.8)	0.0063	2.13 (1.26, 3.58)	**0.0184**
Length of Stay					
Above median	76 (74.5)	Reference		Reference	
Below median=8	26 (25.5)	2.6 (1.7, 4.1)	<.0001	1.53 (0.93, 2.52)	0.096
Disseminated nocardiosis*	74 (72.6)	3.96 (2.53, 6.19)	<.0001	3.06 (1.92, 4.90)	**<.0001**
Elixhauser Mortality score	102 (100)	1.06 (1.04, 1.08)	<.0001	1.03 (1.01, 1.06)	**0.0019**
Cerebrovascular disease *	17 (16.7)	3.86 (2.18, 6.82)	<.0001	2.31 (1.25, 4.27)	**0.0074**
Malignancy*	41 (40.2)	1.75 (1.16, 2.64)	0.0079	1.41 (0.91, 2.2)	0.13
Malnutrition*	44 (43.1)	2.668 (1.77, 4.02)	<.0001	1.52 (0.94, 2.46)	0.091

^Final model AIC: 680.709, Hosmer-Lemeshow Goodness of Fit: χ^2= 11.5, df=8, p= 0.17

*Reference is absence of risk factor or of disseminated disease

The final multivariable model estimated the odds of death among visits with disseminated nocardiosis to be three times greater than the odds among visits reporting other forms of nocardiosis, when controlling for demographics, length of stay, and comorbid conditions (Table 3.6). Similarly, visits in which cerebrovascular disease (CVD) was reported also had a 2.3 times greater odds of death compared to those visits without CVD, controlling for factors in Table 3.6. For each additional point of the Elixhauser comorbid score, there is a 3% positive change in the odds of death, when controlling for other factors.

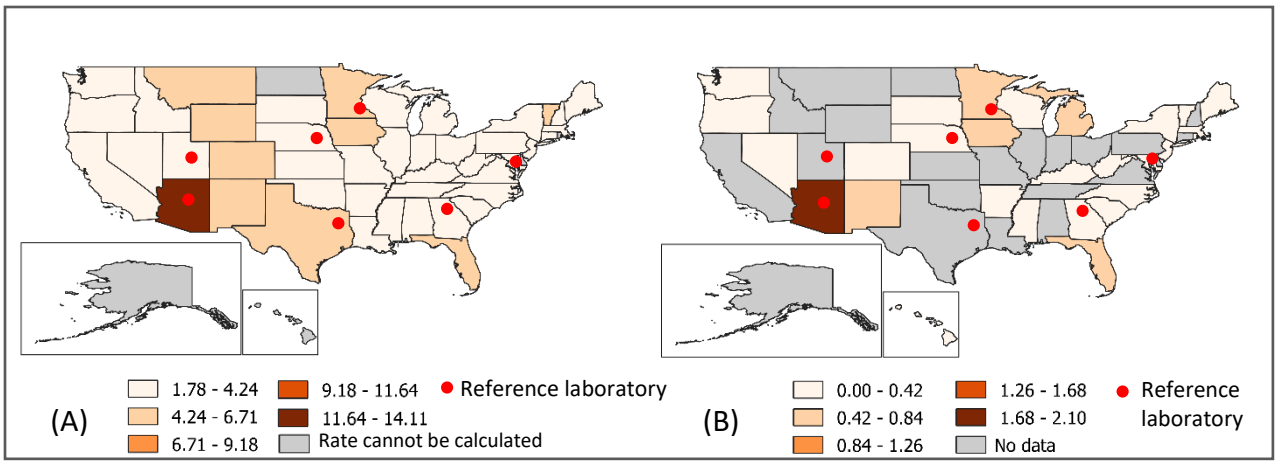
E. State Aggregated Characteristics

Medicare and State Inpatient Databases

Four states contributed 34.5% of all nocardiosis cases from Medicare, which were Arizona, California, Florida, and Texas, although these states comprised 24% of the Medicare population during the study time. Arizona had the highest incidence rate (14.1/100,000 person years), which was 2.4 times larger than the next highest state rate (Montana: 5.9/100,000 person years). The median incidence rate per state was 3.2 (IQR 1.5). There were nine states with rates greater than 4.2/100,000 (Figure 3.6A).

In SID, three states contributed 44.9% of nocardiosis-associated hospitalizations (Arizona, Florida, and Minnesota), but only comprised 20% of the study population. Arizona had the highest hospitalization rate in SID as well (2.1 hospitalizations per 100,000 person years), which was almost two times larger than the next highest calculated rate in Washington DC (1.1 hospitalizations per 100,000 person years). The median hospitalization rate from the participating states was 0.31 per 100,000 person years (IQR 0.25), and six states have rates greater than the median (Figure 3.6B). From both data sources, Arizona, Iowa, Florida, Minnesota, and New Mexico each had incidence and hospitalization rates in the upper quartiles, and the Arizona rates were both extreme outliers of the respective distributions.

The *Nocardia* spp. reference laboratories are shown on the maps in Figure 3.6. In theory, the presence of such expertise could drive additional recognition or diagnosis of nocardiosis; however, this does not appear to be an impact in any state other than Arizona, in which case there is likely another explanation.



724 Figure 3.6. (A) Nocardiosis incidence per 100,000 person years calculated from 100% FFS
725 Medicare data, Oct 2015-March 2018; (B) Nocardiosis hospitalization rate per 100,000 person
726 years calculated for 26 states in SID, Oct 2015-December 2017
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Chapter 4: Discussion

I. Discussion of findings

Evaluating nocardiosis cases using population-level data provides a description of the disease that can be generalized to a broad population in the US, constituting all Medicare FFS beneficiaries and all residents of 29 states, or 47% of the US population (167). The comprehensive literature review will serve as a large component of an invited review of the disease, the last of which was published in 2006 (6).

The results from this work will contribute to the existing literature to replace existing incidence and mortality estimates, which have been limited in scope (13) or dated (1, 48). These findings will serve as a baseline from which to build additional research studies, and has identified locations in which to target activities, such as Arizona. The use of administrative discharge data, particularly the longitudinal Medicare data, allowed for an evaluation of preexisting conditions, the extent of healthcare use, and the time to death.

This comprehensive description of case characteristics has found that cases are more often male, older, and sicker. The male to female ratio is 87:100 in Medicare FFS (190), but 108 per 100 females among nocardiosis cases. The same trend is found among nocardiosis visits (160 males/100 females) compared to the US population (97 males/100 females) (199). Medicare cases are slightly younger than the full Medicare population, while the nocardiosis-associated visits in SID are among patients much older than the estimated median age of the US population of 37.8 ± 0.1 and with a greater proportion covered by Medicare (63%) than the population (18.1% ± 0.1) (199). In Medicare data, 60.7% of all ESRD prevalent cases in 2016 were covered by primary payer FFS Medicare (200), and enrollments for disability and ESRD are higher among the nocardiosis cases.

Duration of hospitalization and costs were higher for nocardiosis cases and nocardiosis-associated visits than the national average, indicating nocardiosis cases require extensive and lengthy care and support. The average length of stay among all US adults was 4.6 days and increased to 5.1 days in adults over age 45 (201); the average length was almost three times this duration in both Medicare and SID data. The average hospitalization cost in SID was

$35,226, which was three times greater than the national average cost per hospitalization $11,700 (201).

For the most part, these findings are consistent with the existing literature, although a wider gap by sex was found among nocardiosis visits of all ages in SID compared to Medicare. Additionally, beneficiaries who were older, were male, or never had Part B Medicare coverage had a greater hazard of dying. Females were associated with a lower hazard of dying, which may indicate less severe disease. Case series disproportionately report disease occurrence among males, with ratios ranging from 2-3: 1 (65, 109). However, in laboratory and facility surveillance studies, this difference is less extreme (5). Males receive a greater proportion of transplants (109) and have greater incidence of most cancers (202), both of which are important risk factors for nocardiosis and poor outcomes (13, 129). Consequently, males may have more severe nocardiosis, may have more repeat visits, and subsequently greater mortality. Additionally, because of worse outcomes, they may be more likely to be recognized and published in the literature.

Medicare beneficiaries younger than 65 are more likely to have lower income, poorer health, and have limited access to care compared to beneficiaries 65 and older (203). Never having Medicare Part B outpatient coverage is an indicator of low income, since Part B coverage is an additional cost (204). Lower income is associated with higher mortality, particularly among preventable conditions (205), and nocardiosis occurs less often in healthy individuals (6). Limited access may delay diagnosis, which along with poor health can lead to poorer outcomes from nocardiosis (4).

Disseminated nocardiosis and greater number of co-morbidities were associated with a lower survival and had a greater hazard of dying. The drop in survival among beneficiaries with skin infections may indicate dissemination or complications of disease that we were unable to capture in the coding. Mortality does occur infrequently among cutaneous nocardiosis, but is typically associated with an underlying condition (53) or subsequent dissemination (42). Higher mortality among both pulmonary and disseminated infections is supported in the nocardiosis literature (5, 42). In future, a comparison to matched controls could determine if there are

important differences in nocardiosis cases and controls. Such differences may be useful to raise the clinical specter for opportunistic infections, including nocardiosis-like illness.

Higher scores on the Charlson Co-morbidity index have been linked to poorer outcomes and higher mortality (206, 207), which are consistent with our findings. The score is weighted to account for greater debilitation from certain conditions, including malignancies and liver disease (171). The less distinct drop in survival among the nocardiosis risk factor categories compared to the CCI categories is likely due to a lack of weighting on the risk factors. This demonstrates that the weights applied in the CCI may predict mortality. This finding was not borne out in the SID analysis, as the CCI was found to be the worst performing comorbidity measure to estimate mortality, and may be the limitation of the CCI in visit-based analysis without capturing conditions that are present in the past year. The Elixhauser measure should be selected or at least evaluated in future analyses of nocardiosis cases.

The incidence and mortality estimates are more robust given the current aging population (19). The existing incidence rate was calculated by Beaman in 1976 based on a survey with low response rate (1); although he described the limitations of this estimate of 1,000 incident cases per year, the number nevertheless has since been reported and referenced repeatedly as the national incidence of nocardiosis. Beaman's count gives an incidence rate of 0.47/100,000 (208). The incidence in the Medicare population alone is seven times this estimate, which is a more accurate estimate to use. To reference the US population instead, the SID hospitalization rate of 1.02/100,000 population is still more accurate.

Evaluating nocardiosis rates at the state level may suggest the influence of environmental factors (e.g., dust storms or soil composition that is preferred by more virulent *Nocardia* species), population factors (e.g., older population), or behavioral factors (e.g., more soil exposure) based on geography. These findings could also be an artifact due to disease awareness by clinicians in certain areas, such as areas where there is a clinical laboratory expert or reference laboratory. However, Arizona is the only state with an elevated rate and the presence of a reference laboratory with a *Nocardia* spp. focus, which dispels this myth. Additionally, reference laboratories that publish summaries of their data receive samples from a majority of US states, so their influence extends beyond their state borders (2, 17). Of course,

the geographic location of a hospitalization does not indicate where the exposure occurred, and thus other data are needed to investigate any geographic influence on nocardiosis.

II. Addressing the Study Design Approach

Although the Medicare and HCUP analyses are separate, and despite a majority of Medicare beneficiaries among the HCUP nocardiosis-associated visits, both data sources add to the story of nocardiosis in the US by capturing both older adults and a population of younger adults who are also at risk of nocardiosis. However, the downside of using HCUP is the inability to apply the comorbidity measures over time, and thus likely underestimate the prevalence of some comorbid conditions. This could affect the selection of the Elixhauser comorbidity measure over the other measures as well as the mortality estimates.

III. Limitations

A major limitation to these analyses is that these are administrative discharge records, and do not indicate a laboratory confirmation. The sensitivity of discharge records has not been evaluated for nocardiosis, nor can that be done given these data. This is especially a concern in using ICD-10-CM codes for a disease that did not have an individual code in ICD-9-CM (9); however, the benefit to using a new code as a crosswalk was not needed between the two coding systems. However, crosswalk coding was needed to apply ICD-9-CM and unvalidated ICD-10-CM codes to collect the comorbid conditions (171, 175, 176, 209-221). Promising findings from a study done among medical coders found that a majority felt minimum training would be needed to transition to ICD-10-CM, and that the instructions and clinical descriptions were clearer than ICD-9-CM (222); these results are promising that the beta versions of these codes will not change drastically to be validated.

The application of ICD-10-CM coding to define the form of nocardiosis disease is not validated, and the high number of disseminated infections could be due to medical coding errors (e.g., listing various A43.X codes for a patient with only a single form), which could cause misclassification error.

Medians cannot be reported per data use requirements to use the CCW. This allows for extreme values to affect the estimated measures of central tendency, which was evident among many of the covariates evaluated by the large standard deviations. This limits the results

of the survival analysis by underestimating the means of the Kaplan-Meier curves due to high level of censoring and are thus not reported here. Median estimates were not allowed to be outputted for the survival curves because of the data use agreement restrictions, so median times can only be made by visual inspection of the survival curves.

One-year all-cause mortality is limited to beneficiaries who did not change coverage to Medicare Advantage and for whom date of death was appropriately captured. Additionally, beneficiaries who had their first nocardiosis-associated visit <12 months before March 30, 2018, may be incorrectly censored if they died after the end of the study period but within one year of their first visit.

Additional limitations with the survival analysis additionally include lack of comparison of these findings to a control group, which does not allow comparisons against the rest of the Medicare population. Similarly, no control group was developed for the HCUP data since it is visit-based and thus a control group may not be mutually exclusive from the nocardiosis-associated visit group. A control that is appropriately matched to reduce bias and is of ample sample size should be applied in future.

IV. Strengths and Weaknesses

Loss of data access early on in the dissertation process led to several weaknesses of this product. The lack of a control group for the Medicare survival analysis weakens the findings of the survival analysis and fails to give the findings context. A control group was developed, but there was a critical error in the code that could not be fixed due to loss of data access, rendering the comparison unpresentable. Loss of data access was a common theme with the Medicare data, which was substantially more robust than the HCUP data.

A strength of the work is that these are large datasets compared to the existing literature, and results can be generalized to those beyond the walls of a hospital, which will add to the nocardiosis literature. The databases are complex, particularly the Medicare data, and required merging of many datasets that changed definitions and data structure over time. This work provides a template for using administrative data (aka “Big Data”) containing 100% of records for public health research on rare conditions.

Other mechanisms to understand a disease may not exist for some rare conditions, such as national surveillance systems, registries, or surveys. Also, easier to access sample data, such as the 5% Medicare FFS databases, may not have sufficient sample size from which to conduct meaningful analyses of rare conditions. Although a highly sensitive and representative case-based surveillance program with data on individual characteristics would be the ideal source from which to describe nocardiosis and predict poor outcomes; however, that level of detail will likely never be available. Utilizing robust administrative data may be the best data source available at this time for a rare disease like nocardiosis, despite their complexity, challenges with access, and for HCUP, the limited answers the data can provide for a disease that requires extended care.

V. Public Health Impact

This is the largest survival analysis of nocardiosis cases. The data are from a population-level, longitudinal data source, which reduces biases that can be present in facility or surveillance-based analyses. The findings may provide clarity regarding characteristics that place patients with nocardiosis at greater risk of mortality. The findings from the Medicare data are generalizable to the entire Medicare FFS population, while the HCUP data are generalizable to the entire population of the participating states, which constitutes almost 50% of the US population. These findings may assist with identifying infections in patients who present with the identified risk factors and may provide additional insight into which patients have a greater odds of dying.

VI. Future Directions

Building off this work in the future, the sensitivity of the nocardiosis ICD-10-CM code should be validated against hospitalization records of known nocardiosis cases. If found to be sufficiently sensitive, these data should be re-analyzed over time to evaluate trends, particularly as the population grows older and sicker (19, 20, 127, 160). It might be possible to evaluate the impact of ICD-10-CM implementation, since the presented analyses included data from the first date of the conversion from 9 to 10. The comorbidity measures may also be affected, and hopefully will be validated in the coming years.

Future re-analysis of these data will be of interest to evaluate the effect of the coronavirus (COVID-19) pandemic on nocardiosis as well as other opportunistic infections. The same people may be at risk for both diseases, since older adults and people with underlying conditions are associated with severe coronavirus disease and death (223, 224), and many of these conditions overlap with nocardiosis risk factors (225), including solid organ transplant (224), cancer (226), chronic kidney disease (227), and COPD (228). Transmission mitigation measures implemented for COVID-19 would not prevent exposure to the soil-borne pathogen *Nocardia* spp. (6); however, the enormous burden of COVID-19 in older and sicker people may decrease the incidence of nocardiosis over the duration of the pandemic.

States with highest incidence and hospitalization rates can be targeted for future research activities. These activities may include studies to understand why there are more cases in those states, or even if there are more cases. The latter may be done by developing partnerships with laboratories in these states to compare clinical diagnoses with laboratory diagnoses. Studies in these states may also be able to identify specific populations for which focused messaging on early healthcare seeking may prevent severe outcomes.

It was not possible to evaluate the geospatial impact of nocardiosis from these data due to lack of granularity. The development of a dataset with greater geographic granularity of cases and environmental sampling locations may add to the understanding of the pathogen and the disease. Disease severity may be affected by the infecting *Nocardia* species, and one study suggests that species have variable environmental preferences (41), thus investigating the environmental and climatic characteristics may provide predictions of more severe disease by geography.

VII. Conclusion

The use of administrative data has offered an opportunity to provide generalizable results on a rare disease. Nocardiosis cases were found to be more often male, older, and sicker than the general Medicare and overall US populations, which is consistent with the literature. Infections also require longer care and greater cost, on average, than the US population. The calculated incidence rate was much larger than has previously been reported, and accounts for

928 the changes in the US population and advances in medical care over the last 45 years. Mortality
929 was associated with disseminated nocardiosis, cerebrovascular disease, and the presence of
930 additional comorbid conditions, when controlling for other demographic and comorbid factors.
931 Higher mortality among Medicare nocardiosis cases was associated with being older, male,
932 having disseminated nocardiosis, and having a greater number of co-morbidities.
933 These findings will contribute to the nocardiosis literature, and future studies can be
934 developed to further add to these findings or to help explain them. Yet, the difficulty with
935 access and the high cost of the 100% Medicare data are limitations in their use for public health
936 research, particularly when the data collection is federally funded, as were these analyses.
937

References

1. Beaman BL, Burnside J, Edwards B, Causey W. Nocardial infections in the United States, 1972-1974. J Infect Dis. 1976 Sep;134(3):286-9.
2. Uhde KB, Pathak S, McCullum I, Jr., Jannat-Khah DP, Shadomy SV, Dykewicz CA, et al. Antimicrobial-resistant *Nocardia* isolates, United States, 1995-2004. Clin Infect Dis. 2010 Dec 15;51(12):1445-8.
3. Smego RA, Jr., Gallis HA. The clinical spectrum of *Nocardia brasiliensis* infection in the United States. Rev Infect Dis. 1984 Mar-Apr;6(2):164-80.
4. McNeil MM, Brown JM. The medically important aerobic actinomycetes: epidemiology and microbiology. Clin Microbiol Rev. 1994 Jul;7(3):357-417.
5. Steinbrink J, Leavens J, Kauffman CA, Miceli MH. Manifestations and outcomes of *Nocardia* infections: Comparison of immunocompromised and nonimmunocompromised adult patients. Medicine (Baltimore). 2018 Oct;97(40):e12436.
6. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ, Jr. Clinical and laboratory features of the *Nocardia* spp. based on current molecular taxonomy. Clin Microbiol Rev. 2006 Apr;19(2):259-82.
7. Wilson JW. Nocardiosis: updates and clinical overview. Mayo Clin Proc. 2012 Apr;87(4):403-7.
8. Coussement J, Lebeaux D, van Delden C, Guillot H, Freund R, Marbus S, et al. *Nocardia* infection in solid organ transplant recipients: A multicenter European case-control study. Clin Infect Dis. 2016 Aug 1;63(3):338-45.
9. National Center for Health Statistics. ICD-9-CM. 2015.
10. Hofflin JM, Potasman I, Baldwin JC, Oyer PE, Stinson EB, Remington JS. Infectious complications in heart transplant recipients receiving cyclosporine and corticosteroids. Ann Intern Med. 1987 Feb;106(2):209-16.
11. Peleg AY, Husain S, Qureshi ZA, Silveira FP, Sarumi M, Shutt KA, et al. Risk factors, clinical characteristics, and outcome of *Nocardia* infection in organ transplant recipients: a matched case-control study. Clin Infect Dis. 2007 May 15;44(10):1307-14.
12. Shannon K, Pasikhova Y, Ibekweh Q, Ludlow S, Baluch A. Nocardiosis following hematopoietic stem cell transplantation. Transpl Infect Dis. 2016 Apr;18(2):169-75.
13. Torres HA, Reddy BT, Raad, II, Tarrand J, Bodey GP, Hanna HA, et al. Nocardiosis in cancer patients. Medicine (Baltimore). 2002 Sep;81(5):388-97.
14. Wang HL, Seo YH, LaSala PR, Tarrand JJ, Han XY. Nocardiosis in 132 patients with cancer: microbiological and clinical analyses. Am J Clin Pathol. 2014 Oct;142(4):513-23.
15. Conville PS, Brown-Elliott BA, Smith T, Zelazny AM. The complexities of *Nocardia* taxonomy and identification. J Clin Microbiol. 2018 Jan;56(1).
16. Brown-Elliott BA, Biehle J, Conville PS, Cohen S, Saubolle M, Sussland D, et al. Sulfonamide resistance in isolates of *Nocardia* spp. from a US multicenter survey. J Clin Microbiol. 2012 Mar;50(3):670-2.
17. Schlaberg R, Fisher MA, Hanson KE. Susceptibility profiles of *Nocardia* isolates based on current taxonomy. Antimicrob Agents Chemother. 2014;58(2):795-800.
18. Salinas-Carmona MC, Rosas-Taraco AG, Welsh O. Systemic increased immune response to *Nocardia brasiliensis* co-exists with local immunosuppressive microenvironment. Antonie van Leeuwenhoek. 2012 Oct;102(3):473-80.
19. Ortman JM, Velkoff VA, Hogan H. An Aging Nation: The Older Population in the United States, Current Population Reports, P25-1140. U.S. Census Bureau. Washington, DC. ; 2014.
20. Harpaz R, Dahl RM, Dooling KL. Prevalence of immunosuppression among US adults, 2013. JAMA. 2016 Dec 20;316(23):2547-8.

21. Lebeaux D, Bergeron E, Berthet J, Djadi-Prat J, Mouniee D, Boiron P, et al. Antibiotic susceptibility testing and species identification of *Nocardia* isolates: a retrospective analysis of data from a French expert laboratory, 2010-2015. Clin Microbiol Infect. 2018 Jun 20.
22. Goodfellow M, Maldonado LA. Genus *Nocardia* Trevisan 1889,9. In: Goodfellow M, Kämpfer P, Busse HJ, Trujillo ME, Suzuki K, Ludwig W, et al., editors. Bergey's manual of systematic bacteriology. 2nd ed ed. New York, NY: Springer; 2012. p. 376–419.
23. Goodfellow M. Numerical taxonomy of some nocardioform bacteria. J Gen Microbiol. 1971 Nov;69(1):33-80.
24. Wallace RJ, Jr., Steele LC, Sumter G, Smith JM. Antimicrobial susceptibility patterns of *Nocardia asteroides*. Antimicrob Agents Chemother. 1988 Dec;32(12):1776-9.
25. Bell M, McNeil MM, Brown JM. *Nocardia* species (Nocardiosis). antimicrobe 2017 [cited 2018 November 11]; Available from: http://www.antimicrobe.org/b117.asp#top
26. Conville PS, Witebsky FG. Organisms designated as *Nocardia asteroides* drug pattern type VI are members of the species *Nocardia cyriacigeorgica*. J Clin Microbiol. 2007 Jul;45(7):2257-9.
27. Hashemi-Shahraki A, Heidarieh P, Bostanabad SZ, Hashemzadeh M, Feizabadi MM, Schraufnagel D, et al. Genetic diversity and antimicrobial susceptibility of *Nocardia* species among patients with nocardiosis. Sci Rep. 2015 Dec 7;5:17862.
28. Woodworth MH, Saullo JL, Lantos PM, Cox GM, Stout JE. Increasing *Nocardia* incidence associated with bronchiectasis at a tertiary care center. Ann Am Thorac Soc. 2017 Mar;14(3):347-54.
29. Alnaum HM, Elhassan MM, Mustafa FY, Hamid ME. Prevalence of *Nocardia* species among HIV-positive patients with suspected tuberculosis. Trop Doct. 2011 Oct;41(4):224-6.
30. Cattaneo C, Antoniazzi F, Caira M, Castagnola C, Delia M, Tumbarello M, et al. *Nocardia* spp infections among hematological patients: results of a retrospective multicenter study. Int J Infect Dis. 2013 Aug;17(8):e610-4.
31. Jiang Y, Huang A, Fang Q. Disseminated nocardiosis caused by *Nocardia otitidiscaviarum* in an immunocompetent host: A case report and literature review. Exp Ther Med. 2016 Nov;12(5):3339-46.
32. Lucas SB, Hounnou A, Peacock C, Beaumel A, Kadio A, De Cock KM. Nocardiosis in HIV-positive patients: an autopsy study in West Africa. Tuber Lung Dis. 1994 Aug;75(4):301-7.
33. Martinez Tomas R, Menendez Villanueva R, Reyes Calzada S, Santos Durantez M, Valles Tarazona JM, Modesto Alapont M, et al. Pulmonary nocardiosis: risk factors and outcomes. Respirology. 2007 May;12(3):394-400.
34. Minero MV, Marin M, Cercenado E, Rabadan PM, Bouza E, Munoz P. Nocardiosis at the turn of the century. Medicine (Baltimore). 2009 Jul;88(4):250-61.
35. Nenoff P, van de Sande WW, Fahal AH, Reinel D, Schofer H. Eumycetoma and actinomycetoma--an update on causative agents, epidemiology, pathogenesis, diagnostics and therapy. J Eur Acad Dermatol Venereol. 2015 Oct;29(10):1873-83.
36. Ni N, Srinivasan M, McLeod SD, Acharya NR, Lietman TM, Rose-Nussbaumer J. Use of adjunctive topical corticosteroids in bacterial keratitis. Curr Opin Ophthalmol. 2016 Jul;27(4):353-7.
37. Rahdar HA, Azadi D, Shojaei H, Daei-Naser A. Molecular analysis and species diversity of *Nocardia* in the hospital environment in a developing country, a potential health hazard. J Med Microbiol. 2017 Mar;66(3):334-41.
38. Saubolle MA, Sussland D. Nocardiosis: review of clinical and laboratory experience. J Clin Microbiol. 2003 Oct;41(10):4497-501.
39. Stapleton F, Keay LJ, Sanfilippo PG, Katiyar S, Edwards KP, Naduvilath T. Relationship between climate, disease severity, and causative organism for contact lens-associated microbial keratitis in Australia. Am J Ophthalmol. 2007 Nov;144(5):690-8.

40. Bonifaz A, Tirado-Sanchez A, Calderon L, Saul A, Araiza J, Hernandez M, et al. Mycetoma: experience of 482 cases in a single center in Mexico. PLoS neglected tropical diseases. 2014 Aug;8(8):e3102.
41. Kachuei R, Emami M, Mirnejad R, Khoobdel M. Diversity and frequency of *Nocardia* spp. in the soil of Isfahan province, Iran. Asian Pac J Trop Biomed. 2012 Jun;2(6):474-8.
42. Beaman BL, Beaman L. *Nocardia* species: host-parasite relationships. Clin Microbiol Rev. 1994 Apr;7(2):213-64.
43. Tarchini G, Ross FS. Primary lymphocutaneous nocardiosis associated with gardening: A case series. World J Clin Infect Dis. 2013;3(4):86-9.
44. Angelika J, Hans-Jurgen G, Uwe-Frithjof H. Primary cutaneous nocardiosis in a husband and wife. J Am Acad Dermatol. 1999 Aug;41(2 Pt 2):338-40.
45. Welsh O, Morales-Toquero A, Vera-Cabrera L, Vazquez-Martinez O, Gomez-Flores M, Ocampo-Candiani J. Actinomycetoma of the scalp after a car accident. Int J Dermatol. 2011 Jul;50(7):854-7.
46. Exmelin L, Malbruny B, Vergnaud M, Prosvost F, Boiron P, Morel C. Molecular study of nosocomial nocardiosis outbreak involving heart transplant recipients. J Clin Microbiol. 1996 Apr;34(4):1014-6.
47. Chen B, Tang J, Lu Z, Wang N, Gao X, Wang F. Primary cutaneous nocardiosis in a patient with nephrotic syndrome: A case report and review of the literature. Medicine (Baltimore). 2016 Jan;95(3):e2490.
48. Lerner PI. Nocardiosis. Clin Infect Dis. 1996 Jun;22(6):891-903; quiz 4-5.
49. Sherber NS, Olivere JW, Martins CR. An 80-year-old man with a nonhealing glabellar lesion. Primary cutaneous nocardiosis. Arch Pathol Lab Med. 2006 Oct;130(10):e100-1.
50. Sinnott JTt, Holt DA, Alverez C, Greene J, Sweeney MS. *Nocardia brasiliensis* cellulitis in a heart transplant patient. Tex Heart Inst J. 1990;17(2):133-5.
51. Schiff TA, McNeil MM, Brown JM. Cutaneous *Nocardia farcinica* infection in a nonimmunocompromised patient: case report and review. Clin Infect Dis. 1993 Jun;16(6):756-60.
52. Bhalodia AM, Lertzman BH, Kantor GR, Granick MS. Localized cutaneous *Nocardia brasiliensis* mimicking foreign body granuloma. Cutis. 1998 Mar;61(3):161-3.
53. Parvu M, Schleiter G, Stratidis JG. Skin Infections caused by *Nocardia* species a case report and review of the literature of primary cutaneous nocardiosis reported in the United States. Infect Dis Clin Pract. 2012;20:237-41.
54. Ng CS, Hellinger WC. Superficial cutaneous abscess and multiple brain abscesses from *Nocardia asteroides* in an immunocompetent patient. J Am Acad Dermatol. 1998 Nov;39(5 Pt 1):793-4.
55. Georghiou PR, Blacklock ZM. Infection with *Nocardia* species in Queensland. A review of 102 clinical isolates. Med J Aust. 1992 May 18;156(10):692-7.
56. Hawrot AC, Carter EL. Simultaneous chronic cutaneous infection with *Mycobacterium marinum* and *Nocardia asteroides*. J Am Acad Dermatol. 2005 Apr;52(4):703-4.
57. Beer KD, Blaney DD, Kadzik M, Asiedu KB, Shieh W, Bower W, et al. A Call to Action for Mycetoma. Current Fungal Infection Reports. 2018;12:99.
58. Rodriguez-Nava V, Couble A, Molinard C, Sandoval H, Boiron P, Laurent F. *Nocardia mexicana* sp. nov., a new pathogen isolated from human mycetomas. J Clin Microbiol. 2004 Oct;42(10):4530-5.
59. Fahal A, Mahgoub el S, El Hassan AM, Abdel-Rahman ME. Mycetoma in the Sudan: an update from the Mycetoma Research Centre, University of Khartoum, Sudan. PLoS neglected tropical diseases. 2015 Mar;9(3):e0003679.
60. Ahmed AA, van de Sande W, Fahal AH. Mycetoma laboratory diagnosis: Review article. PLoS neglected tropical diseases. 2017 Aug;11(8):e0005638.
61. Reis CMS, Reis-Filho EGM. Mycetomas: an epidemiological, etiological, clinical, laboratory and therapeutic review. An Bras Dermatol. 2018 Jan-Feb;93(1):8-18.

62. Zijlstra EE, van de Sande WW, Fahal AH. Mycetoma: A Long Journey from Neglect. PLoS neglected tropical diseases. 2016 Jan;10(1):e0004244.
63. Maggiorelli C, Di Pierro I, Manta C, Maccari U, Galanti I, Scala R. *Nocardia* and lungs in COPD: Beyond immuno-deficiencies. COPD. 2015 Jun;12(3):315-9.
64. Fujita T, Ikari J, Watanabe A, Tatsumi K. Clinical characteristics of pulmonary nocardiosis in immunocompetent patients. J Infect Chemother. 2016 Nov;22(11):738-43.
65. Kurahara Y, Tachibana K, Tsuyuguchi K, Akira M, Suzuki K, Hayashi S. Pulmonary nocardiosis: a clinical analysis of 59 cases. Respir Investig. 2014 May;52(3):160-6.
66. Rosett W, Hodges GR. Recent experiences with nocardial infections. Am J Med Sci. 1978 Nov-Dec;276(3):279-85.
67. Schoen L, Santoro JD, Milla C, Bhargava S. Pulmonary nocardiosis in an immunocompetent patient with cystic fibrosis. Case Rep Pulmonol. 2015;2015:984171.
68. Chen YC, Lee CH, Chien CC, Chao TL, Lin WC, Liu JW. Pulmonary nocardiosis in southern Taiwan. J Microbiol Immunol Infect. 2013 Dec;46(6):441-7.
69. Hui CH, Au VW, Rowland K, Slavotinek JP, Gordon DL. Pulmonary nocardiosis re-visited: experience of 35 patients at diagnosis. Respir Med. 2003 Jun;97(6):709-17.
70. Martinez R, Reyes S, Menendez R. Pulmonary nocardiosis: risk factors, clinical features, diagnosis and prognosis. Curr Opin Pulm Med. 2008 May;14(3):219-27.
71. Presant CA, Wiernik PH, Serpick AA. Factors affecting survival in nocardiosis. Am Rev Respir Dis. 1973 Dec;108(6):1444-8.
72. Olson ES, Simpson AJ, Norton AJ, Das SS. Not everything acid fast is *Mycobacterium tuberculosis*--a case report. J Clin Pathol. 1998 Jul;51(7):535-6.
73. Benes J, Viechova J, Picha D, Horova B, Zatloukal P. Disseminated *Nocardia asteroides* infection in an immunocompetent woman following an arm injury. Infection. 2003 Mar;31(2):112-4.
74. Koll BS, Brown AE, Kiehn TE, Armstrong D. Disseminated *Nocardia brasiliensis* infection with septic arthritis. Clin Infect Dis. 1992 Sep;15(3):469-72.
75. Puri S, Hadayer A, Breaux A, Barr CC. Disseminated nocardiosis with retinal abscess in a patient treated for bullous pemphigoid. Am J Ophthalmol Case Rep. 2018 Jun;10:145-7.
76. Tabrizi SJ. *Nocardia* pericarditis. Bmj. 1994 Dec 3;309(6967):1495-7.
77. Lai CC, Liu WL, Ko WC, Chen YH, Tan HR, Huang YT, et al. Multicenter study in Taiwan of the in vitro activities of nemonoxacin, tigecycline, doripenem, and other antimicrobial agents against clinical isolates of various *Nocardia* species. Antimicrob Agents Chemother. 2011 May;55(5):2084-91.
78. Khan M, Adnan MM, Shahbaz N, Hamza M, Mujeeb SA. *Nocardia mikamii* a Novel Species Causing Disseminated Nocardiosis: A Literature Review of Disseminated Nocardiosis. Int Sch Res Notices. 2014;2014:869153.
79. Beaman BL, Boiron P, Beaman L, Brownell GH, Schaal K, Gombert ME. *Nocardia* and nocardiosis. J Med Vet Mycol. 1992;30 Suppl 1:317-31.
80. Lalitha P. *Nocardia* keratitis. Curr Opin Ophthalmol. 2009 Jul;20(4):318-23.
81. Sharma N, O'Hagan S. The role of oral co-trimoxazole in treating *Nocardia farcinica* keratitis: a case report. J Ophthalmic Inflamm Infect. 2016 Dec;6(1):21.
82. Epstein S, Holden M, Feldshuh J, Singer JM. Unusual Cause of Spinal Cord Compression: Nocardiosis. N Y State J Med. 1963 Dec 1;63:3422-7.
83. Raszka D, Popelka S, Jr., Hert J, Jahoda D, Landor I, Vavrik P. Rare case of osteomyelitis of tibial shaft caused by *Nocardia cyriacigeorgica*. Folia Microbiol (Praha). 2018 Jul;63(4):525-32.
84. Tokumoto JI, Jacobs RA. Case report: *Nocardia* osteomyelitis. Am J Med Sci. 1994 Jun;307(6):428-33.

85. Vander Heiden T, Stahel PF, Clutter S, Price C, Peterson SL, Morgan SJ. *Nocardia* osteomyelitis: a rare complication after intramedullary nailing of a closed tibial shaft fracture. J Orthop Trauma. 2009 Mar;23(3):232-6.
86. Vanegas S, Franco-Cendejas R, Cicero A, Lopez-Jacome E, Colin C, Hernandez M. *Nocardia brasiliensis*-associated femorotibial osteomyelitis. Int J Infect Dis. 2014 Mar;20:63-5.
87. Baraboutis IG, Argyropoulou A, Papastamopoulos V, Psaroudaki Z, Paniara O, Skoutelis AT. Primary sternal osteomyelitis caused by *Nocardia nova*: case report and literature review. Braz J Infect Dis. 2008 Jun;12(3):257-9.
88. Talpada M, Rauf SJ, Walling DM. Primary *Nocardia* osteomyelitis as a presentation of AIDS. AIDS Read. 2002 Feb;12(2):75-8.
89. Moore SL, Jones S, Lee JL. *Nocardia* osteomyelitis in the setting of previously unknown HIV infection. Skeletal Radiol. 2005 Jan;34(1):58-60.
90. Moore M, Lane CW, Gaul LE. Nocardiosis of the knee caused by *Nocardia brasiliensis*; report of first case in a native of the United States. AMA Arch Derm Syphilol. 1954 Sep;70(3):302-10.
91. Nizam I, Kohan L, Kerr D. *Nocardia nova* septic arthritis following total knee replacement: a case report. J Orthop Surg (Hong Kong). 2007 Dec;15(3):390-2.
92. Ozan F, Koyuncu S, Kizilay C, Ozgenc O. The *Nocardia farcinica* infection developing after total knee arthroplasty surgery. Acta Orthop Traumatol Turc. 2013;47(3):212-7.
93. Hadeed MM, MacDonell JR, Dempsey IJ, Moore CC, Browne JA. Chronic *Nocardia cyriacigeorgica* periprosthetic knee infection successfully treated with a two-stage revision: A case report. JBJS Case Connect. 2017 Oct-Dec;7(4):e74.
94. Laurent F, Rodriguez-Villalobos H, Cornu O, Vandercam B, Yombi JC. *Nocardia* prosthetic knee infection successfully treated by one-stage exchange: case report and review. Acta Clin Belg. 2015 Aug;70(4):287-90.
95. Gupta AK, Moorman CT, 3rd. *Nocardia nova* infection after primary anterior cruciate ligament reconstruction with tibialis anterior allograft. Am J Sports Med. 2010 Jul;38(7):1483-6.
96. Yong EX, Cheong EY, Boutlis CS, Chen DB, Liu EY, McKew GL. *Nocardia* septic arthritis complicating an anterior cruciate ligament repair. J Clin Microbiol. 2015 Aug;53(8):2760-2.
97. Wallace RJ, Brown BA, Brown JM, McNeil M. Taxonomy of *Nocardia* species. Clin Infect Dis. 1994 Mar;18(3):476-7.
98. Tremblay J, Thibert L, Alarie I, Valiquette L, Pepin J. Nocardiosis in Quebec, Canada, 1988-2008. Clin Microbiol Infect. 2011 May;17(5):690-6.
99. Welsh O, Vera-Cabrera L, Salinas-Carmona MC. Current treatment for *Nocardia* infections. Expert Opin Pharmacother. 2013 Dec;14(17):2387-98.
100. Mamelak AN, Obana WG, Flaherty JF, Rosenblum ML. Nocardial brain abscess: treatment strategies and factors influencing outcome. Neurosurgery. 1994 Oct;35(4):622-31.
101. Ricci JA, Weil AA, Eberlin KR. Necrotizing Cutaneous Nocardiosis of the Hand: A Case Report and Review of the Literature. J Hand Microsurg. 2015 Jun;7(1):224-7.
102. Suleiman SH, Wadaella el S, Fahal AH. The Surgical Treatment of Mycetoma. PLoS neglected tropical diseases. 2016 Jun;10(6):e0004690.
103. Singh A, Chhina D, Soni RK, Kakkar C, Sidhu US. Clinical spectrum and outcome of pulmonary nocardiosis: 5-year experience. Lung India. 2016 Jul-Aug;33(4):398-403.
104. CLSI. Susceptibility testing of mycobacteria, *Nocardia* spp., and other aerobic actinomycetes. 3rd Ed. CLSI Standard M24. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
105. Healthcare Cost and Utilization Project (HCUP). HCUP State Inpatient Databases (SID). 2001-2015. Rockville, MD: Agency for Healthcare Research and Quality.

106. Blosser SJ, Drake SK, Andrasko JL, Henderson CM, Kamboj K, Antonara S, et al. Multicenter Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry Study for Identification of Clinically Relevant *Nocardia* spp. J Clin Microbiol. 2016 May;54(5):1251-8.
107. Girard V, Mailler S, Polsinelli S, Jacob D, Saccomani MC, Celliere B, et al. Routine identification of *Nocardia* species by MALDI-TOF mass spectrometry. Diagn Microbiol Infect Dis. 2017 Jan;87(1):7-10.
108. Xiao M, Pang L, Chen SC, Fan X, Zhang L, Li HX, et al. Accurate identification of common pathogenic *Nocardia* species: evaluation of a multilocus sequence analysis platform and matrix-assisted laser desorption ionization-time of flight mass spectrometry. PLoS One. 2016;11(1):e0147487.
109. Arduino RC, Johnson PC, Miranda AG. Nocardiosis in renal transplant recipients undergoing immunosuppression with cyclosporine. Clin Infect Dis. 1993 Apr;16(4):505-12.
110. Kontoyiannis DP, Ruoff K, Hooper DC. *Nocardia* bacteremia. Report of 4 cases and review of the literature. Medicine (Baltimore). 1998 Jul;77(4):255-67.
111. Uttamchandani RB, Daikos GL, Reyes RR, Fischl MA, Dickinson GM, Yamaguchi E, et al. Nocardiosis in 30 patients with advanced human immunodeficiency virus infection: clinical features and outcome. Clin Infect Dis. 1994 Mar;18(3):348-53.
112. Berkey P, Bodey GP. Nocardial infection in patients with neoplastic disease. Rev Infect Dis. 1989 May-Jun;11(3):407-12.
113. Simpson GL, Stinson EB, Egger MJ, Remington JS. Nocardial infections in the immunocompromised host: A detailed study in a defined population. Rev Infect Dis. 1981 May-Jun;3(3):492-507.
114. Kim J, Minamoto GY, Grieco MH. Nocardial infection as a complication of AIDS: report of six cases and review. Rev Infect Dis. 1991 Jul-Aug;13(4):624-9.
115. Pintado V, Gomez-Mampaso E, Fortun J, Meseguer MA, Cobo J, Navas E, et al. Infection with *Nocardia* species: clinical spectrum of disease and species distribution in Madrid, Spain, 1978-2001. Infection. 2002 Dec;30(6):338-40.
116. Goodfellow M, Williams ST. Ecology of actinomycetes. Annu Rev Microbiol. 1983;37:189-216.
117. Orchard VA, Goodfellow M. Numerical classification of some named strains of *Nocardia asteroides* and related isolates from soil. J Gen Microbiol. 1980 Jun;118(2):295-312.
118. Houang ET, Lovett IS, Thompson FD, Harrison AR, Joekes AM, Goodfellow M. *Nocardia asteroides* infection--a transmissible disease. J Hosp Infect. 1980 Mar;1(1):31-40.
119. Predicala BZ, Urban JE, Maghirang RG, Jerez SB, Goodband RD. Assessment of bioaerosols in swine barns by filtration and impaction. Curr Microbiol. 2002 Feb;44(2):136-40.
120. Vuotto F, Faure K, Queyre V, Dessein R, Pasquet A, Lambert M, et al. Vascular nosocomial *Nocardia farcinica* infection after arterial stenting in an immunocompetent patient. Can J Infect Dis Med Microbiol. 2011 Spring;22(1):e10-1.
121. Bross JE, Gordon G. Nocardial meningitis: case reports and review. Rev Infect Dis. 1991 Jan-Feb;13(1):160-5.
122. Kachi S, Okazaki M, Takeda H, Igarashi H, Kobayashi O, Watanabe H, et al. Outbreak of *Nocardia farcinica* infection with the same pattern in randomly amplified polymorphic DNA analysis. J Hosp Infect. 2006 Apr;62(4):502-6.
123. Mrozek N, Hamizi S, Gourdon F, Laurichesse H, Beytout J, Lesens O. [Potential nosocomial disseminated infection due to *Nocardia asteroides* after a prosthesis insertion in an immunocompetent patient]. Rev Med Interne. 2008 Dec;29(12):1034-7.
124. Wenger PN, Brown JM, McNeil MM, Jarvis WR. *Nocardia farcinica* sternotomy site infections in patients following open heart surgery. J Infect Dis. 1998 Nov;178(5):1539-43.
125. Al Akhrass F, Hachem R, Mohamed JA, Tarrand J, Kontoyiannis DP, Chandra J, et al. Central venous catheter-associated *Nocardia* bacteremia in cancer patients. Emerg Infect Dis. 2011 Sep;17(9):1651-8.

126. Lederman ER, Crum NF. A case series and focused review of nocardiosis: clinical and microbiologic aspects. Medicine (Baltimore). 2004 Sep;83(5):300-13.
127. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, Buchacz K, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One. 2013;8(12):e81355.
128. Kageyama A, Yazawa K, Ishikawa J, Hotta K, Nishimura K, Mikami Y. Nocardial infections in Japan from 1992 to 2001, including the first report of infection by *Nocardia transvalensis*. Eur J Epidemiol. 2004;19(4):383-9.
129. Santos M, Gil-Brusola A, Morales P. Infection by *Nocardia* in solid organ transplantation: thirty years of experience. Transplant Proc. 2011 Jul-Aug;43(6):2141-4.
130. Betran A, Villuendas MC, Rezusta A, Pereira J, Revillo MJ, Rodriguez-Nava V. Clinical significance, antimicrobial susceptibility and molecular identification of *Nocardia* species isolated from children with cystic fibrosis. Braz J Microbiol. 2016 Jul-Sep;47(3):531-5.
131. Iwasaki A, Foxman EF, Molony RD. Early local immune defences in the respiratory tract. Nat Rev Immunol. 2017 Jan;17(1):7-20.
132. Rosen LB, Rocha Pereira N, Figueiredo C, Fiske LC, Ressner RA, Hong JC, et al. *Nocardia*-induced granulocyte macrophage colony-stimulating factor is neutralized by autoantibodies in disseminated/extrapulmonary nocardiosis. Clin Infect Dis. 2015 Apr 1;60(7):1017-25.
133. Andrejak C, Nielsen R, Thomsen VO, Duhaut P, Sorensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax. 2013 Mar;68(3):256-62.
134. Filice GA. Inhibition of *Nocardia asteroides* by neutrophils. J Infect Dis. 1985 Jan;151(1):47-56.
135. Filice GA, Beaman BL, Krick JA, Remington JS. Effects of human neutrophils and monocytes on *Nocardia asteroides*: failure of killing despite occurrence of the oxidative metabolic burst. J Infect Dis. 1980 Sep;142(3):432-8.
136. Deem RL, Doughty FA, Beaman BL. Immunologically specific direct T lymphocyte-mediated killing of *Nocardia asteroides*. J Immunol. 1983 May;130(5):2401-6.
137. Clark NM, Reid GE, Practice ASTIDCo. *Nocardia* infections in solid organ transplantation. Am J Transplant. 2013 Mar;13 Suppl 4:83-92.
138. Filice GA. Nocardiosis in persons with human immunodeficiency virus infection, transplant recipients, and large, geographically defined populations. J Lab Clin Med. 2005 Mar;145(3):156-62.
139. Peraira JR, Segovia J, Fuentes R, Jimenez-Mazuecos J, Arroyo R, Fuertes B, et al. Pulmonary nocardiosis in heart transplant recipients: treatment and outcome. Transplant Proc. 2003 Aug;35(5):2006-8.
140. Husain S, McCurry K, Dauber J, Singh N, Kusne S. *Nocardia* infection in lung transplant recipients. J Heart Lung Transplant. 2002 Mar;21(3):354-9.
141. Poonyagariyagorn HK, Gershman A, Avery R, Minai O, Blazey H, Asamoto K, et al. Challenges in the diagnosis and management of *Nocardia* infections in lung transplant recipients. Transpl Infect Dis. 2008 Dec;10(6):403-8.
142. Coussement J, De Greef J, Dureault A, Lebeaux D. Can we kill two birds with this stone? Anti-pneumocystis prophylaxis to prevent *Nocardia* infection in hematopoietic stem cell transplant recipients. Biol Blood Marrow Transplant. 2018 Sep;24(9):1952-3.
143. Haussaire D, Fournier PE, Djiguiba K, Moal V, Legris T, Purgus R, et al. Nocardiosis in the south of France over a 10-years period, 2004-2014. Int J Infect Dis. 2017 Apr;57:13-20.
144. Abel S, Hasan S, Kujawski B, Talwar A, Betler J, Wegner R, et al. Cryptic *Nocardia nova* brain abscess postradiation treatment and neurosurgery in a patient with small cell lung cancer: A case report and review of the literature. Adv Radiat Oncol. 2016 Oct-Dec;1(4):290-3.

145. Holtz HA, Lavery DP, Kapila R. Actinomycetales infection in the acquired immunodeficiency syndrome. Ann Intern Med. 1985 Feb;102(2):203-5.
146. Mendez-Samperio P. Diagnosis of tuberculosis in HIV co-infected individuals: Current Status, challenges and opportunities for the future. Scand J Immunol. 2017 Aug;86(2):76-82.
147. Sakyi SA, Danquah KO, Ephraim RD, Enimil A, Frimpong V, Ahenkorah Fondjo L, et al. Evaluating the contribution of *Nocardia* spp. and *Mycobacterium tuberculosis* to pulmonary infections among HIV and non-HIV patients at the Komfo Anokye Teaching Hospital, Ghana. Can J Infect Dis Med Microbiol. 2018;2018:2910198.
148. Gondos A, Brenner H. Relative survival of transplant patients: quantifying surplus mortality among renal transplant recipients compared with the general population. Transplantation. 2011 Oct 27;92(8):913-7.
149. Tomczyk S, Deribe K, Brooker SJ, Clark H, Rafique K, Knopp S, et al. Association between footwear use and neglected tropical diseases: a systematic review and meta-analysis. PLoS neglected tropical diseases. 2014;8(11):e3285.
150. Molina A, Winston DJ, Pan D, Schiller GJ. Increased Incidence of Nocardial Infections in an Era of Atovaquone Prophylaxis in Allogeneic Hematopoietic Stem Cell Transplant Recipients. Biol Blood Marrow Transplant. 2018 Aug;24(8):1715-20.
151. Santos RP, Almeida J, Almeida FT, Duarte MDL. Cutaneous nocardiosis by a new pathogenic species: *Nocardia grenadensis*. BMJ Case Rep. 2018 Jun 4;2018.
152. Sherbuk J, Saly D, Barakat L, Ogbuagu O. Unusual presentation of disseminated *Nocardia abscessus* infection in a patient with AIDS. BMJ Case Rep. 2016 Jul 20;2016.
153. Nissen T, Wynn R. The clinical case report: a review of its merits and limitations. BMC Res Notes. 2014 Apr 23;7:264.
154. Oszoyoglu AA, Kirsch J, Mohammed TL. Pulmonary nocardiosis after lung transplantation: CT findings in 7 patients and review of the literature. J Thorac Imaging. 2007 May;22(2):143-8.
155. Mei-Zahav M, Livnat G, Bentur L, Mussaffi H, Prais D, Stafler P, et al. The spectrum of *Nocardia* lung disease in cystic fibrosis. Pediatr Infect Dis J. 2015 Aug;34(8):909-11.
156. Valdezate S, Garrido N, Carrasco G, Medina-Pascual MJ, Villalon P, Navarro AM, et al. Epidemiology and susceptibility to antimicrobial agents of the main *Nocardia* species in Spain. J Antimicrob Chemother. 2017 Mar 1;72(3):754-61.
157. Laupland KB, Ross T, Pitout JD, Church DL, Gregson DB. Investigation of sources of potential bias in laboratory surveillance for anti-microbial resistance. Clin Invest Med. 2007;30(4):E159-66.
158. CDC. Surveillance Case Definitions for Current and Historical Conditions. National Notifiable Diseases Surveillance System (NNDSS) 2017 [cited 2019 March 12]; Available from: https://wwwn.cdc.gov/nndss/conditions/
159. Laurent F, Provost F, Couble A, Casoli E, Boiron P. Genetic relatedness analysis of *Nocardia* strains by random amplification polymorphic DNA: validation and applications. Res Microbiol. 2000 May;151(4):263-70.
160. Gavazzi G, Krause KH. Ageing and infection. Lancet Infect Dis. 2002 Nov;2(11):659-66.
161. National Center for Health Statistics. 2018 release of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). 2018.
162. IBM MarketScan Research Databases. [cited; Available from: https://www.ibm.com/us-en/marketplace/marketscan-research-databases
163. Chronic Conditions Warehouse. In: Center for Medicare and Medicaid Services, editor.; 2018.
164. Rodriguez-Nava V, Durupt S, Chyderiotis S, Freydiere AM, Karsenty J, de Montclos M, et al. A French multicentric study and review of pulmonary *Nocardia* spp. in cystic fibrosis patients. Med Microbiol Immunol. 2015 Aug;204(4):493-504.

165. Smego RA, Jr., Castiglia M, Asperilla MO. Lymphocutaneous syndrome. A review of non-sporothrix causes. Medicine (Baltimore). 1999 Jan;78(1):38-63.
166. Center for Medicare and Medicaid Services. Condition Categories. 2018 [cited 2018 August 5]; Available from: https://www.ccwdata.org/web/guest/condition-categories
167. National Center for Health Statistics (NCHS). Vintage 2016 postcensal estimates of the resident population of the United States (April 1, 2010, July 1, 2010-July 1, 2016), by year, county, single-year of age (0, 1, 2, .., 85 years and over), bridged race, Hispanic origin, and sex. Prepared under a collaborative arrangement with the U.S. Census Bureau. Available from: http://www.cdc.gov/nchs/nvss/bridged_race.htm as of June 26, 2017, following release by the U.S. Census Bureau of the unbridged Vintage 2016 postcensal estimates by 5-year age group on June 22, 2017. [cited; Available from:
168. Healthcare Cost and Utilization Project (HCUP). HCUP State Inpatient Databases (SID). 2001-2015. Rockville, MD: Agency for Healthcare Research and Quality.
169. Healthcare Cost and Utilization Project (HCUP). HCUP State Ambulatory Surgery and Services Databases (SASD), 2015-2016. Rockville, MD: Agency for Healthcare Research and Quality.
170. Matulionyte R, Rohner P, Uckay I, Lew D, Garbino J. Secular trends of nocardia infection over 15 years in a tertiary care hospital. J Clin Pathol. 2004 Aug;57(8):807-12.
171. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical care. 2005 Nov;43(11):1130-9.
172. American Thoracic Society. ICD-10-CM Coding for Interstitial Lung Diseases. 2015 November 2016 [cited 2018 September 10]; Available from: https://www.thoracic.org/about/newsroom/newsletters/coding-and-billing/2015/september/icd-10-cm-coding.php
173. National Cancer Institute. Comorbidity SAS Macro (2014 version). 2017.
174. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Medical care. 1998 Jan;36(1):8-27.
175. Healthcare Cost and Utilization Project (HCUP). Elixhauser Comorbidity Software for ICD-10-CM (beta version). HCUP Tools and Software 2018 11/5/18 [cited 2020 July 7]; Available from: https://www.hcup-us.ahrq.gov/toolssoftware/comorbidityicd10/comorbidity_icd10.jsp
176. Healthcare Cost and Utilization Project (HCUP). Chronic Condition Indicator (CCI) for ICD-10-CM (beta version). HCUP Tools and Software 2018 11/25/18 [cited 2020 July 7]; Available from: https://www.hcup-us.ahrq.gov/toolssoftware/chronic_icd10/chronic_icd10.jsp
177. Hwang W, Weller W, Ireys H, Anderson G. Out-of-pocket medical spending for care of chronic conditions. Health affairs (Project Hope). 2001 Nov-Dec;20(6):267-78.
178. Chi MJ, Lee CY, Wu SC. The prevalence of chronic conditions and medical expenditures of the elderly by chronic condition indicator (CCI). Archives of gerontology and geriatrics. 2011 May-Jun;52(3):284-9.
179. Sharabiani MT, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. Medical care. 2012 Dec;50(12):1109-18.
180. Johnston JA, Wagner DP, Timmons S, Welsh D, Tsevat J, Render ML. Impact of different measures of comorbid disease on predicted mortality of intensive care unit patients. Medical care. 2002 Oct;40(10):929-40.
181. ResDAC. Claim Pass Thru Per Diem Amount; Inpatient (Fee-for-Service) Data Dictionary. 2018 [cited; Available from: https://www.resdac.org/cms-data/variables/claim-pass-thru-diem-amount
182. Cost-to-Charge Ratio Files.Healthcare Cost and Utilization Project (HCUP). September 2018. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/db/state/costtocharge.jsp.

183. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004 Apr 1;159(7):702-6.
184. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association. 1958;53:457-81.
185. Kleinbaum DG, Klein M. Survival Analysis. 3rd ed. New York: Springer; 2012.
186. Cox D. Regression models and life-tables. Journal of the Royal Statistical Society Series B. 1972;34:187-220.
187. Baldwin LM, Klabunde CN, Green P, Barlow W, Wright G. In search of the perfect comorbidity measure for use with administrative claims data: does it exist? Medical care. 2006 Aug;44(8):745-53.
188. Tang J, Wan JY, Bailey JE. Performance of comorbidity measures to predict stroke and death in a community-dwelling, hypertensive Medicaid population. Stroke. 2008 Jul;39(7):1938-44.
189. MDCR ENROLL AB 10. Original Medicare Enrollment: Part A and/or Part B Enrollees, by Age Group, Calendar Years 2012-2017. In: Center for Medicare and Medicaid Services, editor.; 2017.
190. Center for Medicare and Medicaid Services. MDCR ENROLL AB 10. Original Medicare Enrollment: Part A and/or Part B Enrollees, by Age Group, Calendar Years 2012-2017. 2017.
191. Center for Medicare and Medicaid Services. MDCR ENROLL AB 44. Medicare-Medicaid Enrollment (MME): Original Medicare Enrollees by Type of Eligibility, by Demographic Characteristics, Calendar Year 2015, 2016, 2017. 2017.
192. Center for Medicare and Medicaid Services. MDCR ENROLL AB 12. Original Medicare Enrollment: Part A and/or Part B Enrollees, by Type of Entitlement and Demographic Characteristics, Calendar Year 2015, 2016, 2017. 2017.
193. Office of Management and Budget, 2010 Standards for Delineating Metropolitan and Micropolitan Statistical Areas; Part IV, Notice In: Office of Management and Budget, editor.: Federal Register. p. 37246 -52.
194. US Census Bureau. Explore Census Data. [cited 7 July 2020]; Available from: https://data.census.gov/cedsci/
195. Social Security Act (SSA). Special provisions relating to coverage under Medicare program for end stage renal disease. In: Social Security Administration, editor. Title II §226a.
196. McGuinness SL, Whiting SE, Baird R, Currie BJ, Ralph AP, Anstey NM, et al. Nocardiosis in the Tropical Northern Territory of Australia, 1997-2014. Open Forum Infect Dis. 2016 Oct;3(4):ofw208.
197. Tucker FC, Hirsch EF. Nocardiosis, with a report of three cases of actinomycosis due to Nocardia asteroides. J Infect Dis. 1949 Jul-Aug;85(1):72-86.
198. Yamamura H, Tamura T, Sakiyama Y, Harayama S. Nocardia amamiensis sp. nov., isolated from a sugar-cane field in Japan. Int J Syst Evol Microbiol. 2007 Jul;57(Pt 7):1599-602.
199. US Census Bureau. American Community Survey 5-Year Estimates Subject Table S0101, AGE AND SEX, 2017. 2020.
200. United States Renal Data System. 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD; 2018.
201. Statistical Brief #246. Healthcare Cost and Utilization Project (HCUP). Overview of U.S. Hospital Stays in 2016: Variation by Geographic Region. Rockville, MD: Agency for Healthcare Research and Quality; December 2018.
202. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. Oncologist. 2007 Jan;12(1):20-37.

203. Cubanski J, Neuman T, Damico A. Medicare's Role for People Under Age 65 with Disabilities. Aug 12, 2016 [cited 2019 March 3]; Available from: https://www.kff.org/medicare/issue-brief/medicares-role-for-people-under-age-65-with-disabilities/
204. Income-Related Monthly Adjustment Amounts for Medicare Part B and Prescription Drug Coverage Premiums. Final rule. Fed Regist. 2018 Nov 7;83(216):55626-32.
205. Phelan JC, Link BG, Diez-Roux A, Kawachi I, Levin B. "Fundamental causes" of social inequalities in mortality: a test of the theory. J Health Soc Behav. 2004 Sep;45(3):265-85.
206. Birim O, Maat AP, Kappetein AP, van Meerbeeck JP, Damhuis RA, Bogers AJ. Validation of the Charlson comorbidity index in patients with operated primary non-small cell lung cancer. Eur J Cardiothorac Surg. 2003 Jan;23(1):30-4.
207. Formiga F, Moreno-Gonzalez R, Chivite D, Franco J, Montero A, Corbella X. High comorbidity, measured by the Charlson Comorbidity Index, associates with higher 1-year mortality risks in elderly patients experiencing a first acute heart failure hospitalization. Aging Clin Exp Res. 2018 Aug;30(8):927-33.
208. US Census Bureau. Current Population Reports, Series P-23, No. 67, "Population Estimates by Race, for States: July 1, 1973 and 1975". February 1978 ed. Washington, DC: US Government Printing Office; 1978.
209. CMS Chronic Conditions Data Warehouse (CCW). Chronic Obstructive Pulmonary Disease and Bronchiectasis. CCW Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19139608/ccw-cond-algo-copd.pdf
210. CMS Chronic Conditions Data Warehouse (CCW). Colorectal Cancer. CCW Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19139608/ccw-cond-algo-colorectalcancer.pdf
211. CMS Chronic Conditions Data Warehouse (CCW). Endometrial Cancer. CCW Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19139608/ccw-cond-algo-endometrial.pdf
212. CMS Chronic Conditions Data Warehouse (CCW). Breast Cancer. CCW Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19139608/ccw-cond-algo-breastcancer.pdf
213. CMS Chronic Conditions Data Warehouse (CCW). Lung Cancer. CCW Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19139608/ccw-cond-algo-lungcancer.pdf
214. CMS Chronic Conditions Data Warehouse (CCW). Prostate Cancer. CCW Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19139608/ccw-cond-algo-prostatecancer.pdf
215. CMS Chronic Conditions Data Warehouse (CCW). Tobacco Use. Other Chronic or Potentially Disabling Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19140001/oth-cond-algo-tobacco.pdf
216. CMS Chronic Conditions Data Warehouse (CCW). Cystic Fibrosis and Other Metabolic Developmental Disorders. Other Chronic or Potentially Disabling Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19140001/oth-cond-algo-cysticfibrosis.pdf
217. CMS Chronic Conditions Data Warehouse (CCW). Diabetes. CCW Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19139608/ccw-cond-algo-diabetes.pdf
218. CMS Chronic Conditions Data Warehouse (CCW). Human Immunodeficiency Virus and/or Acquired Immunodeficiency Syndrome (HIV/AIDS). Other Chronic or Potentially Disabling Condition

Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19140001/oth-cond-algo-hivaids.pdf
219. CMS Chronic Conditions Data Warehouse (CCW). Chronic Kidney Disease. CCW Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19139608/ccw-cond-algo-ckd.pdf
220. CMS Chronic Conditions Data Warehouse (CCW). Anemia. CCW Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19139608/ccw-cond-algo-anemia.pdf
221. CMS Chronic Conditions Data Warehouse (CCW). Alcohol Use Disorders. Other Chronic or Potentially Disabling Condition Algorithms 11/2017 11/2017 [cited 2018 September 10]; Available from: https://www.ccwdata.org/documents/10280/19140001/oth-cond-algo-alcohol-use.pdf
222. The American Health Information Management Association. ICD-10-CM Field Testing Project: Report on Findings: Perceptions, Ideas and Recommendations from Coding Professionals Across the Nation. 2003 September 23, 2003 [cited 2020 November 6, 2020]; Available from: http://library.ahima.org/doc?oid=61292#.X637qshKg2w
223. Workman MR, Philpott-Howard J, Yates M, Beighton D, Casewell MW. Identification and antibiotic susceptibility of Nocardia farcinica and N. nova in the UK. J Med Microbiol. 1998 Jan;47(1):85-90.
224. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep. 2020 Apr 17;69(15):458-64.
225. Centers for Disease Control and Prevention. Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. Your Health 2020 Nov. 2, 2020 [cited 2020 November 6, 2020]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html
226. Fung M, Babik JM. COVID-19 in Immunocompromised Hosts: What We Know So Far. Clin Infect Dis. 2020 Jun 27.
227. Aziz F, Mandelbrot D, Singh T, Parajuli S, Garg N, Mohamed M, et al. Early Report on Published Outcomes in Kidney Transplant Recipients Compared to Nontransplant Patients Infected With Coronavirus Disease 2019. Transplant Proc. 2020 Nov;52(9):2659-62.
228. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020 May;94:91-5.
229. Ukai Y, Fujimoto N, Fujii N, Shirai M, Wakabayashi M, Uenishi T, et al. Case of muscle abscess due to disseminated nocardiosis in a patient with autoimmune hemolytic anemia, and review of the published work. J Dermatol. 2012 May;39(5):466-9.
230. Wessler JM, Adams DJ, Kunz AN, Babcock JG, Hartman KR. Recurrent Nocardia Sepsis in a Patient With Sickle Cell Anemia Receiving Continuous Deferoxamine. J Pediatric Infect Dis Soc. 2014 Sep;3(3):e35-7.
231. Abreu C, Rocha-Pereira N, Sarmento A, Magro F. Nocardia infections among immunomodulated inflammatory bowel disease patients: A review. World J Gastroenterol. 2015 Jun 7;21(21):6491-8.
232. Sutton BJ, Parks GE, Manavi CK, Palavecino EL, Geisinger KR. Cushing's syndrome and nocardiosis associated with a pulmonary carcinoid tumor: report of a case and review of the literature. Diagn Cytopathol. 2011 May;39(5):359-62.
233. Marciano BE, Spalding C, Fitzgerald A, Mann D, Brown T, Osgood S, et al. Common severe infections in chronic granulomatous disease. Clin Infect Dis. 2015 Apr 15;60(8):1176-83.

234. Ortiz AM, Rabagliati R, Machuca E. Successful treatment of Nocardia asteroides peritonitis in a patient undergoing automated peritoneal dialysis and receiving immunosuppressive therapy. Adv Perit Dial. 2005;21:66-8.
235. Pak S, Mansour T, Yatsynovich Y, Kobalka A. Ventilator-dependent pulmonary nocardiosis in a patient with chronic obstructive pulmonary disease. Lung India. 2018 Jan-Feb;35(1):58-61.
236. de Montmollin E, Corcos O, Noussair L, Leflon-Guibout V, Belmatoug N, Joly F, et al. Retroperitoneal abscesses due to Nocardia farcinica: report of two cases in patients with malnutrition. Infection. 2012 Feb;40(1):93-6.
237. Blue Cross Blue Shield Minnesota. Policy Number: IV-128, Organ Transplantation. Medical and Behavioral Health Policy, Section: Surgery 08/18/2014 [cited 2018 September 12]; Available from: https://www.supercoder.com/webroot/upload/general_pages_docs/document/Organ_Transplantation.pdf

Appendix

Table A.1: ICD-10-CM and ICD-9-CM codes used to identify risk factors from the diagnosis and procedure variables within each claim or visit

Risk Factor/ CCI*	Name	ICD 10-CM^	ICD 9-CM ^	CCW ± Chronic Conditions §	Weight	Reference	
						Presence	Code
RF	Cystic fibrosis	E00,E84,E7119,E7141,E7420,E7421,E7429,D81810,D841,E030,E031,E250,E258,E259,E569,E700,E701,E702,E703,E705,E708,E709,E710, E7111, E712, E713, E721,E722, E723, E724,E725,E728, and CCW codes	243,270,2711,2770,2776,2552,2692,27781,27785, and CCW codes	Oth: Cystic fibrosis	1	(164)	(216)
RF	Anemia	D59.0 - D59.1, and CCW codes	283, and CCW codes	CC: Anemia	1	(229, 230)	(220)
RF	Alcohol abuse	T51,F10, and CCW codes	3050,303,980, and CCW codes	Oth: Alcohol use disorders	1	(196)	(221)
RF	Immuno-modulated inflammatory bowel disease	K50, K51	555, 556		1	(231)	
RF	Bronchiectasis	J47,Q334	494.0,494.1, 494, 748.61,V12.69		1	(28)	(28, 209)
RF	Cell mediated immune suppression	D81-D89	135,2662, 2730,2731, 2732, 2772, 2776, 2791, 2792, 2793, 2794, 2798, 2799,27906, 28989		1	(48)	

RF	Personal history of immuno-suppression therapy	Z92.25	V87.46		1	(8, 11)	
RF	Long term (current) use of systemic steroids	Z79.52	V58.65		1	(63)	
RF	Cytomegaloviral disease	B25	78.5		1	(11)	
RF	Ectopic Cushing's	E24.3	255		1	(232)	
RF	Chronic granulomatous disease	D71	288.1		1	(233)	
RF	Dependence on renal dialysis, and history of	Z99.2, Z92.89	V45.11, V15.89		1	(129, 234)	
RF	Dependence on respirator	Z99.1	V46.1		1	(235)	
RF	Smoking	T65,F17, and CCW codes	3051,98984,V1582, and CCW codes	Oth: Tobacco use	1	(65)	(215)
RF	Malnutrition	E40-E46	260 - 263, 269		1	(236)	
RF	Solid organ transplant, hematopoietic stem cell transplant, history of	Z94,T86,D898,07Y,0BY,0DY,0FY,02Y,0TY,0UY,0WY,BT29,BT39,BT49	E8780, 9968,V5844, V42,4194, 0794, 335,336, 697,3751,556, 528, 505,2795,9968, 4697, 6592,		1	(8, 11)	(237)
RF	Chronic lung disease, Pulmonary alveolar proteinosis, Other interstitial pulmonary disease	J8401,I278, I279, J684, J701, J703,J40,J41,J42,J43,J44,J45,J46,J47,J60,J61,J62,J63,J64,J65,J66, J67, and CCW codes	4168,4169, 5064, 5081, 5088,90,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,516, and CCW codes	CC: COPD	1	(65)	(8, 171, 172, 209)

CCI	Chronic pulmonary disease	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x,J68.4, J70.1, J70.3	416.8, 416.9, 490.x-505.x, 506.4, 508.1, 508.8, 519.1		1		(171)
RF	Chronic kidney disease	N08,N16,N19,N00,N20,N30,N40,N050,N060,N070,B520,C641,C642,C649,C689,D593,E748,I120,I129,I130,I132,I701,I722,K767,N011-N019,N131,N132,N140-N144,N150,N158,N159,N170,N171,N172,N178,N179,N181-N186,N189,N250,N251,N259,N261,N269,Q612,Q613,Q614,Q615,Q618,Q620,Q622,R944,A1811,A5275,D3000,D3001,D3002,D4100,D4101,D4102,D4110,D4111,D4112,D4120,D4121,D4122,E0821,E0822,E0829,E0865,E0921,E0922,E0929,E1021,E1022,E1029,E1065,E1121,E1122,E1129,E1165,E1321,E1322,E1329,I1310,I1311,M1030,M1038,M1039,M3214,M3215,M3504,N1330,N1339,N2581,N2589,Q6102,Q6111,Q6119,Q6210,Q6211,Q6212,Q6231,Q6232,Q6239,M10311,M10312,M10319,M10321,M10322,M10329,M10331,M10332,M10339,M10341,M10342,M10349,M10351,M10352,M10359,M10361,M10362,M1	189,223,580,581,582,583,584,585,586,587,588,591,954,,0160,1899,2494,2504,2714,2741,4401,4421,5724,5804,5809,7532,7944,,23691,28311,40301,40311,40391,40402,40403,40412,40413,40492,40493,58081,58089,75312,75313,75314,75315,75316,75317,75319,75321,75322,75323,75329, and CCW codes	CC: chronic kidney disease, if ESRD=Yes	1	(47)	(219)

		0369,M10371,M10372,M10379, and CCW codes					
CCI	Renal disease	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0,Z49.0-Z49.2, Z94.0, Z99.2	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92,404.93, 582.x, 583.0-583.7, 585.x,586.x, 588.0, V42.0, V45.1, V56.x		2		(171)
RF	Hematopoietic stem cell transplant	Z9484	V4282		1	(12)	
RF	Diabetes mellitus	E08-E13, and CCW codes	249, 250, 357.2, 362.01,362.02,362.03,362.04,362.05,362.06,366.41, and CCW codes	CC: diabetes	1	(105)	(217)
CCI	Diabetes without chronic complications	E10.0, E10.1, E10.6, E10.8,E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	250.0-250.3, 250.8, 250.9		1		(171)
CCI	Diabetes with chronic complications	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7,E13.2-E13.5, E13.7, E14.2-E14.5,E14.7	250.4-250.7, 362.0		2		(171)
RF	HIV/AIDS	B20,Z21,B9735, and CCW codes	969,970,974,975,976,977,07953,042,043,V08, and CCW codes	Oth: HIV/AIDS	1	(29)	(171, 218)
CCI		B20.x-B22.x, B24.x	042.x-044.x		6		

RF	Malignancy (neoplasms)	Z85,C00-C26,C30- C34,C37-C41,C43,C45-C58,C60-C76,C81-C85,C88,C90-C97, and CCW codes	140-172,193,194,200-208,1950-1958,2386,V10, and CCW codes	CC: Cancers	1	(13, 14)	(171, 210-214)
CCI	Any malignancy, including leukemia and lymphoma	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x	140.x-172.x, 174.x-195.8,200.x-208.x, 238.6		2		(171)
CCI	Metastatic solid tumor	C77.x-C80.x	196.x-199.x		6		(171)
CCI	Myocardial infarction	I21.x, I22.x, I25.2	410.x, 412.x		1		(171)
CCI	Congestive heart failure	I09.9,I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x		1		(171)
CCI	Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	093.0, 437.3, 440.x, 441.x, 443.1-443.9, 447.1, 557.1, 557.9, V43.4		1		(171)
CCI	Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x-I69.x	362.34, 430.x-438.x		1		(171)
CCI	Dementia	F00.x-F03.x, F05.1, G30.x,G31.1	290.x, 291.1,291.2,292.82, 294.1, 331.0,331.2,331.82		1		(171)
CCI	Rheumatologic disease	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0	446.5, 710.0-710.4, 714.0-714.2, 714.8, 725.x		1		(171)
CCI	Peptic ulcer disease	K25.x-K28.x	531.x-534.x		1		(171)
CCI	Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x,G82.x, G83.0-G83.4, G83.9	334.1, 342.x, 343.x, 344.0-344.6,344.9		2		(171)

CCI	Mild liver disease	B18.x, K70.0-K70.3, K70.9,K71.3-K71.5, K71.7, K73.x, K74.x,K76.0, K76.2-K76.4, K76.8, K76.9,Z94.4	070.22, 070.23, 070.32,070.33 ,070.44, 070.54, 070.6,070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7		1		(171)
CCI	Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6,K76.7	456.0-456.2, 572.2-572.8		3		(171)
HCUP	End stage renal disease	Z99.2, Z91.15, Z49.31, Z49.32, (3E1M39Z, 5A1D70Z- 5A1D90Z					
* CCI=Charlson comorbidity index ^ If no references are listed for codes, the website ICD10.com was used to search for codes related to the condition. These are likely less robust compared to those created by the CCW or Charlson Co-morbidity Index ± CCW=Chronic conditions warehouse § Cc=CCW chronic conditions § Oth= and Other Chronic or Potentially Disabling Conditions							

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Table A.2: LOS for inpatient visits for SID

Characteristic	Mean days (SD)	Median days (IQR)	Measure of Association †
Overall	12.7 (14.7)	8 (12)	
Age group (years)			χ^2=17.7, df=4, p=0.0014
0-34	12.9 (11.7)	10 (10)	
35-64	14.6 (18.4)	9 (13)	
65-74	12.0 (12.5)	8 (12)	
75-84	10.6 (10.2)	7.5 (10)	
85+	8.9 (9.1)	6 (7)	
Sex			χ^2=2.05, df=1, p=0.15
Male	13.1 (15.5)	9 (12)	
Female	12.1 (13.4)	8 (10)	
Race/ethnicity			χ^2=10.5, df=3, p=0.0150
White	12.3 (14.4)	8 (11)	
Black	14.7 (14.4)	11 (12)	
Hispanic	11.3 (10.7)	8 (10)	
Other‡	15.3 (16.6)	9.5 (16)	
Region			χ^2=18.2, df=3, p=0.0004
Northeast	16.0 (16.4)	11 (14)	
Midwest	12.1(15.9)	7 (10)	
South	14.2 (16.0)	9 (13)	
West	10.8 (10.8)	8 (10)	
Type of nocardiosis			χ^2=132.1, df=4, p<.0001
Disseminated	16.6 (18.3)	12 (15)	
Neurologic	14.2 (13.8)	12 (10)	
Pulmonary	10.0 (10.7)	7 (9)	
Skin	7.5 (6.8)	6 (7)	
Not specified	7.4 (7.6)	5 (7)	
Disposition			χ^2=26.9, df=1, p<0.0001
Discharge alive	12.2 (14.3)	8 (11)	
Died	20.1 (17.9)	16.5 (20)	
Number Chronic conditions			χ^2=38.5, df=4, p<0.0001
0	10.9 (10.4)	6 (16.5)	
1	9.3 (6.4)	7 (7)	
2-3	8.6 (8.2)	6 (9.5)	
4-5	9.6 (9.5)	6 (8)	
6+	14.0 (16.1)	9 (12)	
Charlson CI			χ^2=23.6, df=4, p<0.0001
0	11.5 (15.7)	7 (12)	
1	10.6 (11.7)	7 (11)	
2-3	13.4 (15.9)	8.5 (12)	
4-5	12.8 (13.7)	8 (13)	

6+	15.1 (15.4)	12 (12)	
Risk factors			χ^2=54.1, df=4, p <0.0001
0	9.2 (8.4)	6 (11)	
1	9.8 (11.1)	6 (9)	
2-3	12.3 (14.8)	8 (11)	
4-5	14.0 (14.7)	10 (13)	
6+	20.6 (22.5)	14 (15)	
Elixhauser			χ^2=95.4, df=3, p<0.0001
0	9. 4 (11.2)	6 (11)	
1	9.1 (8.8)	6 (7)	
2-3	10.1 (13.3)	6 (9)	
4-5	13.5 (15.7)	9 (11)	
6+	16.6 (15.8)	12 (16)	

† Using the Kruskal-Wallis H-test

‡ 'Other' race includes Asian/Pacific Islander, Native American, and Other, and were combined due to small numbers

Table A.3: Demographics by Charlson Comorbidity Index for Medicare FFS nocardiosis cases and nocardiosis-associated visits from the State Inpatient Databases (SID)±

	Medicare				SID			
	CCI weighted score				CCI weighted score			
Characteristics	0-1	2-3	4-5	6+	0-1	2-3	4-5	6+
	N=1,240	N=930	N=542	N=454	N=510	N=632	N=294	N=190
Age (Mean)	72.7 (10.5)	71.8 (12.0)	69.5 (12.3)	70.4 (11.5)	56.4 (21.5)	64.1 (14.2)	66.5 (12.7)	59.7 (16.2)
< 65	168 (13.6)	183 (19.7)	151 (27.8)	116 (25.6)	282 (55.3)	282 (44.6)	121 (41.2)	104 (54.7)
65-74	561 (45.2)	335 (36.0)	218 (40.2)	171 (37.7)	124 (24.3)	215 (34.0)	103 (35.0)	52 (27.4)
75-84	374 (30.2)	315 (33.9)	123 (22.7)	126 (27.8)	75 (14.7)	103 (16.3)	43 (14.6)	-
85+	137 (11.1)	97 (10.4)	51 (9.4)	41 (9.0)	29 (5.7)	32 (5.1)	27 (9.2)	-
Female	728 (58.7)	452 (48.6)	195 (35.9)	144 (31.7)	238 (46.7)	250 (39.6)	90 (30.6)	46 (24.2)
Male	512 (41.3)	478 (51.4)	347 (64.0)	310 (68.3)	272 (53.3)	381 (60.4)	204 (69.4	144 (75.8)
Race								
White	1,098 (88.6)	787 (84.6)	403 (74.2)	351 (79.2)	394 (81.4)	455 (77.3)	196 (74.0)	104 (60.1)
Black	39 (3.2)	62 (6.7)	75 (13.8)	68 (15.3)	32(6.6)	47 (8.0)	28 (10.6)	42 (24.3)
Hispanic	0	20 (2.4)	19 (3.5)	24 (5.4)	40(8.3)	51 (8.7)	20 (7.6)	-
Other	17 (1.4)	61 (6.6)	18 (3.3)	-	18 (3.7)	36 (6.1)	21 (7.9)	17 (9.8)
Unknown	0	0	28 (5.2)	-	0	0	0	0
End-stage Renal Disease (ESRD)	-	88 (9.5)	106 (19.5)	99 (21.8)	NA^	NA^	NA^	NA^
Insurance provider								
Dual coverage	188 (15.2)	160 (17.2)	134 (24.7)	118 (26.0)	-	-	-	-
Medicare	NA	NA	NA	NA	250 (49.0)	442 (69.9)	229 (77.9)	109 (57.4)
Medicaid	NA	NA	NA	NA	61 (12.0)	44 (7.0)	13 (4.4)	35 (18.4)
Private Payer	NA	NA	NA	NA	177 (34.7)	135 (21.4)	46 (15.7)	39 (20.5)

Self-pay	NA	NA	NA	NA	-	-	-	0
Nocardiosis disease form								
Not specified	104 (8.4)	76 (8.2)	36 (6.6)	23 (5.1)	26 (5.1)	25 (4.0)	23 (7.8)	-
Cutaneous	94 (7.6)	55 (5.9)	31 (5.7)	21 (4.6)	26 (5.1)	20 (3.2)	-	-
Pulmonary	482 (38.9)	324 (34.8)	155 (28.6)	131 (28.9)	240 (47.1)	297 (47.0)	130 (44.2)	72 (37.9)
Disseminated	560 (45.2)	475 (51.1)	321 (59.1)	279 (61.5)	197 (38.6)	272 (43.0)	125 (42.5)	89 (46.8)
Neurologic	206 (16.6)	199 (21.4)	144 (26.5)	151 (33.2)	21 (4.1)	18 (2.9)	-	15 (7.9)
Costs/visit (mean [SD])	$2,160 ($36,227)	$3,145 ($43,181)	$3,214 ($24,934)	$4,743 ($74,200)	$29,837 ($60,681)	$39,664 ($189,242)	$35,702 ($48,007)	$34,300 ($29,576)
Length of all inpatient stays (Mean days [std])	12.3 (16.5)	12.8 (13.6)	12.1 (11.6)	13.6 (15.8)	10.9 (13.1)	13.4 (15.9)	12.8 (13.7)	15.1 (15.4)

- = Suppressed counts when cell size <11

NA^ ESRD not assigned using ICD codes, so cannot be determined from HCUP data

Table A.4: Pairwise Pearson correlation of continuous co-morbidity variables for nocardiosis-associated visits from the State Inpatient Databases (SID), n=1626

Variable	Chronic conditions	Charlson	Nocardiosis Risk factors	Mortality score
Chronic conditions	1.0			
Charlson	0.398 <.0001	1.0		
Nocardiosis Risk factors	0.453 <.0001	0.389 <.0001	1.0	
Mortality score	0.340 <.0001	0.417 <.0001	0.323 <.0001	1.0

Table A.5: Baseline demographic model estimating mortality and the model performance with the addition of comorbidity measures

	Baseline Model (Age, Sex*)	Baseline + Elixhauser Mortality Score	Number of Chronic Conditions	Number of Nocardiosis Risk Factors	Charlson Comorbidity Index
AIC^	757.200	717.237	739.263	743.794	745.439
C-statistic	0.608	0.718	0.669	0.654	0.641
HF-GOF±	0.357	0.1917	0.158	0.8337	0.97
OR	-	1.058	1.144	1.307	1.169
95% CI	-	1.040, 1.077	1.079, 1.214	1.144, 1.494	1.080, 1.264

*Sex was categorized into: 0-64, 65-75,75+ years old

^AIC= Akaike Information Criterion; intercept only model =763.931

±HF-GOF= Hosmer-Lemeshow Goodness of Fit test

Yellow cells indicate selected comorbidity measure