PRESCRIBING PATTERNS AND TOLERABILITY OUTCOMES OF MULTI-DRUG ANTIBIOTIC THERAPY USED TO TREAT PULMONARY NONTUBERCULOUS MYCOBACTERIAL DISEASE DUE TO *MYCOBACTERIUM AVIUM* COMPLEX IN U.S. MEDICARE BENEFICIARIES WITH BRONCHIECTASIS

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A DISSERTATION

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CERTIFCATE OF APPROVAL

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ABSTRACT OF THE DISSERTATION

Prescribing patterns and tolerability outcomes of multi-drug antibiotic therapy used to treat pulmonary nontuberculous mycobacterial disease due to *Mycobacterium avium* complex in U.S. Medicare beneficiaries with bronchiectasis

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Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that can cause chronic, debilitating pulmonary disease, leading to extensive parenchymal destruction, inflammatory lung tissue damage, airway dilation, and respiratory failure in rare cases. NTM infection disproportionately affects older individuals, post-menopausal women in particular, and those with chronic underlying lung diseases such as bronchiectasis, of which 80% occurs simultaneously with NTM infection. The burden of NTM disease has increased significantly in the past decade worldwide, leading to chronic, debilitating symptoms reducing quality of life and increasing morbidities, mortalities and permanent disabilities.

Mycobacterium avium complex (MAC) are a subset of NTM accounting for up to 90% of NTM infection. Pulmonary MAC disease often requires aggressive, long-term multi-drug antibiotic therapy, which is often associated with substantial, sometimes fatal, side effects with a low chance of cure. The current therapy recommendation of 18 - 24 months of a 3-drug regimen is largely based on limited clinical evidence. Approximately 30% discontinue therapy due to adverse events and many develop recurrent disease after

therapy completion. Yet, little is known about the patterns of MAC therapy use, and data on the safety and tolerability of MAC therapy are mostly from small case-series. Consequently, large, representative population-based data to guide informed treatment decisions are severely lacking.

A better understanding of the current NTM disease treatment is crucial. Three major research gaps related to the epidemiology and outcomes of NTM disease I identified were: 1) the validity of diagnosis-code based case definitions and identification of the optimal NTM case-finding definition; 2) up-to-date knowledge of the prescribing patterns of therapy used to treat pulmonary MAC; and 3) tolerability outcomes of MAC therapy.

In this dissertation work, I addressed these gaps by: 1) validating code-based case definitions for pulmonary NTM in Medicare data using the U.S. Bronchiectasis & NTM Research Registry as a gold standard, and identifying the most optimal NTM-case-finding definition; 2) describing patterns of MAC therapy among first-time MAC therapy users in U.S. Medicare data; and 3) evaluating tolerability of outcomes of MAC therapy in first-time MAC therapy users in U.S .Medicare data.

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LIST OF ABBREVIATIONS

ATS	American Thoracic Society
BRR	U.S. Bronchiectasis & NTM Research Registry
COPD	Chronic obstructive pulmonary disease
CM	Clinical modification
HIV	Human immune deficiency virus
IDSA	Infectious disease society of America
ICD	International classification of diseases
MAC	*Mycobacterium avium* complex
NTM	Nontuberculous mycobacteria
PPV	Positive predictive value

CHAPTER 1. INTRODUCTION & RESEARCH AIMS

1.1. Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that can cause chronic, debilitating pulmonary disease, leading to extensive parenchymal destruction, inflammatory lung tissue damage and airway dilation, and respiratory failure in rare cases. The disease disproportionately affects older females and those with chronic underlying lung diseases such as bronchiectasis. The incidence and prevalence of pulmonary NTM diagnosis have been increasing in the last few decades. In 1981–1983, the prevalence of pulmonary NTM was estimated as 2.4 cases per 100,000 in the U.S.[1] More recent studies reported annual prevalence estimates for pulmonary NTM of 17.3 cases per 100,000 during 1994–1996,[2 3] and 26.7 per 100,000 during 2004–2006 in persons aged 60 years and older.[4]

Mycobacterium avium complex (MAC) are a subset of NTM accounting for up to 90% of all NTM infection.[5 6] Pulmonary MAC disease often requires aggressive, long-term multi-drug antibiotic therapy, which is commonly associated with substantial side effects with a low chance of cure. Pulmonary NTM disease often requires aggressive, long-term, species-specific multi-drug antibiotic therapy, and can be extremely difficult to manage. The recommended standard regimen targeted for pulmonary MAC is an 18–24-month period of treatment with a minimum of 3 antibiotics, including a macrolide, rifamycin and ethambutol.[5 7] However, the current guidelines are based on limited evidence, and data on the safety and tolerability of pulmonary MAC therapy are from several single-site case-series studies. U.S. population-based data on NTM disease, particularly on therapy used for pulmonary NTM are scarce,[5 8] and access to evidence-based therapy is limited

among U.S. patients with MAC pulmonary disease. Population-based data on treatment practices are needed in light of recent clinical practice guidelines.

1.2. Dissertation Overview & Research Aims

The dissertation begins with a review of current literature on pulmonary NTM in Chapter 2 (Review of the literature). In this chapter, I begin by providing an overview of the epidemiology of pulmonary NTM. I discuss the use of administrative data for NTM research and the need for validation of diagnosis code-based case definitions. I also provide background on the current recommendations for treatment of pulmonary MAC disease, and associated treatment burden due to drug-related adverse events. I then discuss the need for a better understanding of patterns of therapy prescribed to treat pulmonary MAC disease as well as tolerability outcomes.

In Chapter 3 (Aim 1), I examine the validity of International Classification of Diseases, 9th revision (ICD-9) Clinical Modification (CM) code-based case definitions of pulmonary NTM infection in Medicare claims data using the U.S. Bronchiectasis and NTM Research Registry (BRR) as a gold standard. I accomplish this aim by using a linkage between Medicare beneficiaries and BRR participants. I evaluate the validity of several diagnosis-code based case definitions for pulmonary NTM infection, and identify the most optimal case-definition for identifying pulmonary NTM cases in Medicare beneficiaries in the high-risk setting of bronchiectasis.

In Chapter 4 (Aim 2), I descriptively assess prescribing patterns of multi-drug antibiotic therapy used to treat MAC pulmonary infection and regimen changes over time among

U.S. Medicare beneficiaries with bronchiectasis. I describe the proportion of new MAC therapy users on: (1) guideline-based standard 3-drug regimen with or without amikacin; (2) macrolide plus rifamycin with or without amikacin; and (3) macrolide plus ethambutol with or without amikacin. I also describe the cumulative duration of each drug regimen as well as the number of regimen changes. Then I illustrate regimen changes over time (at treatment start, 6, 12 and 18 months after treatment start) using alluvial diagrams.

In Chapter 5 (Aim 3), I evaluate the tolerability outcomes of multi-drug antibiotic therapy prescribed to treat pulmonary MAC infection in Medicare beneficiaries with bronchiectasis. The first outcome of interest is adverse events occurring within 12 months of treatment start. The second outcome of interest is regimen change/treatment discontinuation within 12 months of treatment start. I use Cox proportional hazard regression methods to evaluate the hazard rates of the outcomes in: (1) azithromycin-containing regimens versus clarithromycin-containing regimen; (2) rifampin-containing regimens versus rifabutin-containing regimens; and (3) an azithromycin-ethambutol-rifampin regimen versus a clarithromycin-ethambutol-rifabutin regimen. I also use Kaplan-Meier curves to illustrate the survival function of the outcomes over time.

In chapter 6, I conclude with a critical summary of the dissertation's rationale and importance, key study findings, strengths and limitations of the work, as well as public health implications and directions for future research.

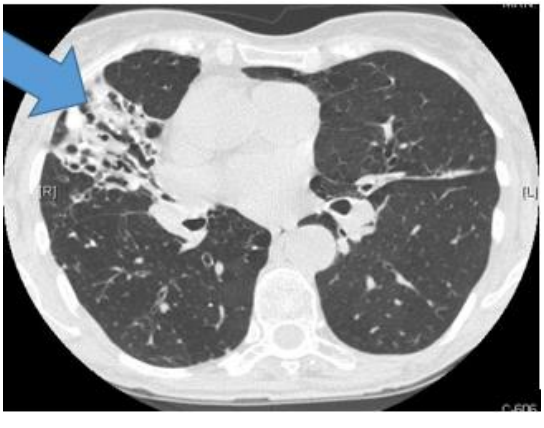
Finally, the Appendices provide documentation from the Oregon Health & Science University Institutional Review Board as well as supplemental materials for the three aims.

CHAPTER 2. REVIEW OF THE LITERATURE

2.1. Epidemiology of pulmonary nontuberculous mycobacterial disease

Nontuberculous mycobacteria (NTM), relatives of *Mycobacterium tuberculosis*, are ubiquitous environmental organisms that cause chronic, debilitating pulmonary disease, primarily in older individuals.[5 9] Patients typically suffer from chronic cough, wheezing, difficulty breathing, fatigue, night sweats, weight loss, depression, social anxiety, hemoptysis, and other symptoms. Though not communicable, NTM infection may cause extensive destruction and, progressive inflammatory damage of lung tissues as well as airway dilation (i.e. bronchiectasis) (**Figure 2.1**), leading to respiratory failure in rare cases.

Figure 2.1. Computed tomography scan of chronic *Mycobacterium avium* complex infection in the right middle lobe with bronchiectasis and inflammatory infiltrate (arrow)



NTM diagnosis involves clinical, radiological and microbiologic assessments (i.e. acid-fast bacilli cultures), and is often difficult due to non-specific symptoms, frequent coinfections, and the need for collection of acid-fast bacilli cultures, which are not routinely collected. NTM disease often requires aggressive, long-term, species-specific multi-drug antibiotic therapy, and can be extremely difficult to manage. NTM therapy is often associated with side effects and has a low chance of long-term cure. Many develop

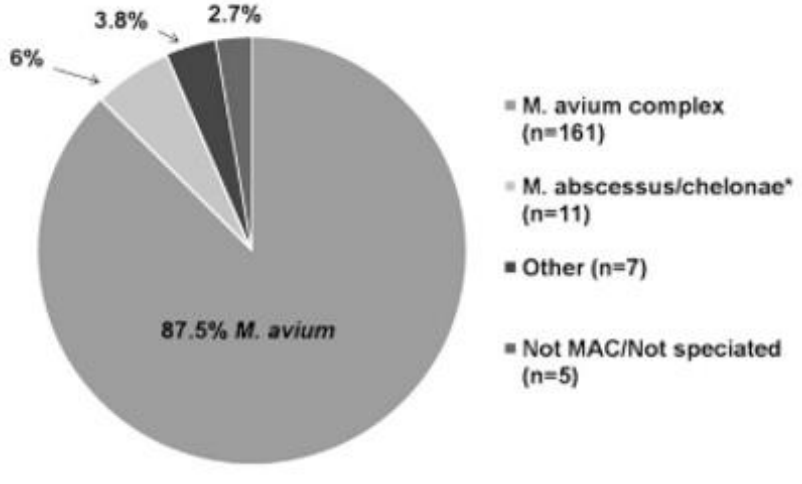
recurrent disease due to reinfection or failure to respond to therapy, necessitating therapy restart. Additionally, many NTM species are resistant to many of the currently available antimicrobial agents, further limiting treatment options. The American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) have published specific criteria for the diagnosis and treatment of NTM lung disease (**Table 2.1**),[5] and more recent official clinical practice guidelines have been published.[7] However, challenges with diagnosis and treatment of pulmonary NTM still remain.

Table 2.1. Clinical and microbiologic criteria for diagnosis of nontuberculous mycobacterial pulmonary disease[5]

Clinical (both required)
1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules; and 2. Appropriate exclusion of other diagnoses
Microbiologic
1. Positive culture results from at least two separate expectorated sputum samples. If the results are non-diagnostic, consider repeat sputum acid-fast-bacilli smears and cultures; or 2. Positive culture result from at least one bronchial wash or lavage; or 3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid-fast-bacilli) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or acid-fast-bacilli) and one or more sputum or bronchial washings that are culture positive for NTM 4. Expert consultation should be obtained when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination 5. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed until the diagnosis is firmly established or excluded 6. Making the diagnosis of NTM lung disease does not, per se, necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients

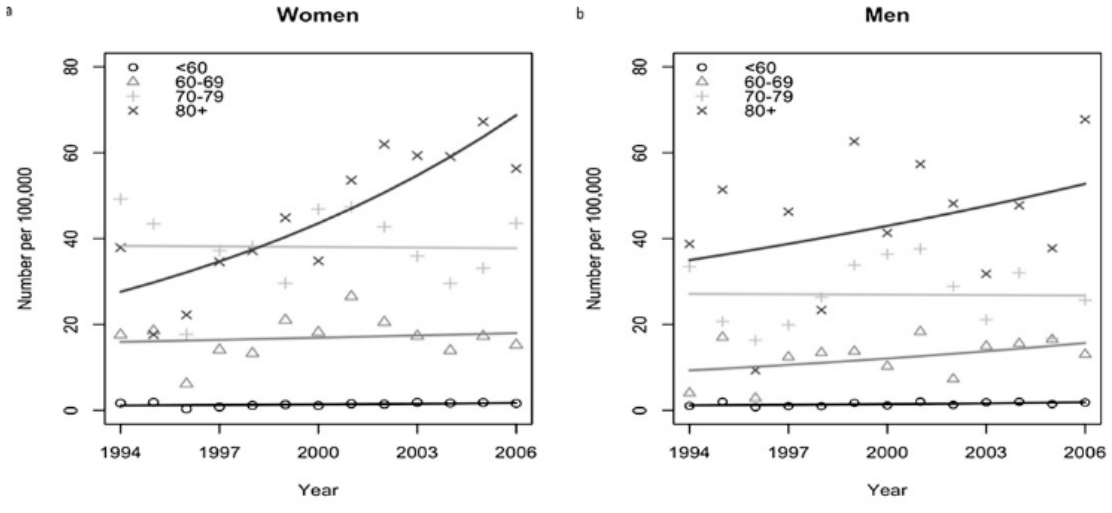
Pulmonary NTM disease primarily affects older individuals, but also affect younger individuals with cystic fibrosis, or individuals with genetic predisposition or underlying lung disease. Pulmonary NTM disease commonly occurs in the setting of chronic underlying lung disease such as chronic obstructive pulmonary disease (COPD) and bronchiectasis where the abnormal lung architecture increases the risk of collecting pathogens from the environment.[4 10] Post-menopausal women without apparent predisposing conditions or smoking history are particularly susceptible to nodular bronchiectatic disease with predominant infection in the anterior mid-lung.[11] Conversely, NTM disease also occurs in men,[12] and in those with a smoking history and/or underlying pulmonary disease like COPD/emphysema, in the form of fibrocavitary disease.[13] Fibrocavitary disease often requires more aggressive treatment than the more indolent nodular bronchiectatic disease, for which half of patients still require treatment within 3 years due to radiographic progression and worsening of symptoms.[11]

Figure 2.2. Mycobacterial etiology of confirmed pulmonary nontuberculous Mycobacteria disease, Oregon 2005–2006[10]



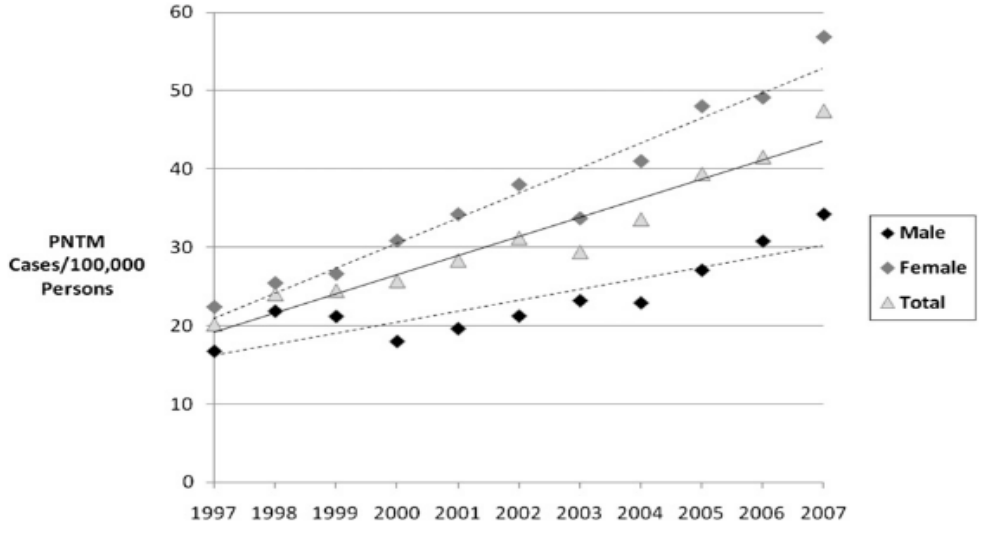
The incidence and prevalence of pulmonary NTM have been increasing in the last few decades. Among NTM species, *Mycobacterium avium* complex (MAC), *M. abscessus* and *M. kansaii* are the most frequently encountered pathogens, and MAC accounts for up to 90% of pulmonary NTM disease (**Figure 2.2**).[5 6 10] In 1981–1983, a U.S. national estimate of NTM prevalence, as defined by an individual with an NTM culture-positive specimen, was estimated as 2.4 cases per 100,000.[1] In 2009, using statewide comprehensive laboratory data, an Oregon study reported an annual prevalence of pulmonary NTM disease in Oregon at 7.2 cases per 100,000 in all age groups, and a prevalence of pulmonary MAC of 13.5 cases per 100,000 in the ≥51 year age group.[3] This study also reported increasing incidence of pulmonary NTM disease meeting the ATS/IDSA disease criteria between 2007 and 2012; incidence increased from 4.8 per 100,000 in 2007 to 5.6 per 100,000 in 2012, and to more than 25 per 100,000 in those aged 80 years and older. A multi-center study using data from four U.S. integrated health care delivery systems including 4.1 million beneficiaries in California, Colorado, Pennsylvania, and Washington, the average annual site-specific prevalence of pulmonary NTM disease ranged between 1.4 and 6.6 per 100,000.[4] Increasing disease burden was most evident among persons aged 60 years and older as the annual prevalence in this group increased from 19.6 per 100,000 during 1994–1996 to 26.7 per 100,000 during 2004–2006 (**Figure 2.3**).

Figure 2.3. Observed annual prevalence with fitted trend from Poisson regression model, by sex between 1994 and 2006 (lines represent age groups in years)[4]



In a study of U.S. Medicare beneficiaries (≥65 years of age), from 1997 through 2007, the investigators used International Classification of Diseases, 9th revision (ICD-9) Clinical Modification (CM) codes to identify cases of pulmonary NTM disease. Similar to earlier studies, this study reported a steadily increasing trend in prevalence of pulmonary NTM between 1997 and 2007, with an annual prevalence of 47 per 100,000 in 2007 (**Figure 2.4**).[14] Lastly, in a 2010 report in Portland, Oregon, the two-year period prevalence, defined by full microbiological and clinical criteria,[5] was estimated at 8.6 per 100,000, and 20.4 per 100,000 in those aged ≥50 years.[10]

Figure 2.4. Annual prevalence of pulmonary NTM cases among a sample of U.S. Medicare Part B enrollees by sex from 1997 to 2007 (PNTM = pulmonary nontuberculous mycobacteria)[14]



Overall, data on the epidemiology of pulmonary NTM suggest that the burden of NTM pulmonary disease has increased significantly in the past decade, especially in the elderly. As the average U.S. population is aging, pulmonary NTM disease is clearly an emerging public health concern.

2.2. Use of administrative data for NTM research and the need for validation of case finding algorithms

Administrative healthcare data such as Medicare claims containing ICD-diagnosis codes can provide a readily available, inexpensive, efficient and powerful tool for case identification in research studies. Such data sources may also provide advantages such as minimal referral bias, minimal missing data and lower costs. With large population coverage and the ability to link between databases using a unique identification number, administrative healthcare data have been used extensively for epidemiologic and health

services research.[15-18] Healthcare reimbursement claims data containing diagnosis codes have provided valuable tools to identify NTM cases in epidemiologic studies to estimate prevalence and incidence measures, disease trends and geographic distribution in the U.S.[14 19-24] and in other parts of the world.[25] ICD-9-CM codes have also been used to evaluate mortality of NTM lung disease in the U.S.,[26] hospital-based antibiotic use,[27] and healthcare costs associated with NTM disease.[28] Thus, the majority of our current understanding of the epidemiology of NTM disease is based on results from studies using ICD-9-CM claims-based algorithms for identifying NTM disease.

The accuracy of diagnosis codes used to estimate pulmonary NTM disease occurrence has been evaluated in limited fashion.[23] Although cases identified based on microbiological (≥1 positive NTM culture) definitions showed a positive predictive value (PPV) of 74% in identifying true cases based on the ATS/IDSA diagnostic criteria in this study, the accuracy of ICD-9-CM diagnosis codes is still poorly understood. Knowledge of the validity of case definitions of pulmonary NTM is key to understanding the magnitude of potential misclassification bias in the current literature and to planning future studies. As such, it is critical to validate case definitions against a gold standard, where the true disease status is known, in order to evaluate their performance in case identification.[29]

In 2015, conversion to ICD-10-CM codes was mandated, and ICD-10 codes are beginning to be incorporated into NTM case finding algorithms in research. However, the majority of the currently available data on NTM disease are based on ICD-9-CM codes, which map directly onto ICD-10-CM codes (**Table 2.2**). Understanding the validity of

the ICD-9-CM codes used to identify and enumerate NTM cases will aid in the planning and interpretation of studies using ICD-10-CM codes.

Table 2.2. Conversion between ICD-9-CM and ICD-10-CM codes

ICD-9-CM codes		**ICD-10-CM codes**	
031.0	Pulmonary disease due to other mycobacteria	A31.0	Pulmonary mycobacterial infection
031.8	Other specified mycobacterial diseases	A31.8	Other mycobacterial infections
031.9	Unspecified disease due to mycobacteria	A31.9	Mycobacterial infection, unspecified

2.3. Current recommendations for the treatment of pulmonary MAC disease and treatment burden

NTM disease often requires aggressive, long-term, species-specific multi-drug antibiotic therapy, and can be extremely difficult to manage. The recommended standard regimen targeted for pulmonary MAC disease is an 18–24-month period of treatment with a minimum of 3 antibiotics, including a macrolide (azithromycin or clarithromycin), rifamycin (rifampin or rifabutin) and ethambutol until being negative on culture for one year while on therapy (**Table 3**).[5 7] For advanced disease or for patients who fail standard multi-drug regimens, a parenteral (i.e. intravenous) agent, most often amikacin, is added. Despite this, treatment outcomes remain poor. Among patients with pulmonary MAC disease, 50–88% achieve sputum conversion (12 months of negative sputum cultures), but 4-12% experience a relapse (true relapse with the same species as opposed to reinfection with a different species),[30-32] and many experience reinfection requiring additional treatment. In addition, *in-vitro* susceptibility for antibiotic drugs targeted for pulmonary NTM disease may not be predictive of treatment outcomes *in-vivo*,[30 32 33] further complicating treatment decisions. Furthermore, the prolonged treatment for

pulmonary NTM disease not only induces severe adverse events in patients but also creates a high burden to society; it has been estimated that a total of $815 million was spent in relation to pulmonary NTM disease in the U.S. in 2010.[28]

Table 2.3. Recommended therapy for MAC lung disease by disease status and/or severity

	Initial therapy for nodular/ bronchiectatic disease	Initial therapy for cavitary disease	Advanced (severe) or previously treated disease
Macrolide	Clarithromycin or azithromycin	Clarithromycin or azithromycin	Clarithromycin or azithromycin
Ethambutol	Yes	Yes	Yes
Rifamycin	Rifampin or rifabutin	Rifampin or rifabutin	Rifampin or rifabutin
Intravenous aminoglycoside	None	Streptomycin or amikacin	Streptomycin or amikacin

2.4. Prescribing patterns of multi-drug antibiotic therapy used to treat pulmonary NTM disease due to MAC

Few non-U.S. studies have reported on the prescribing patterns of antibiotic treatment for pulmonary MAC disease. Studies have suggested that clinicians frequently diverge from guideline-based recommendations, and regimen switches are common.[34] Using linked laboratory and healthcare administrative databases, a cohort study of adults 66 years or older in Ontario showed that treatment was prescribed for 24% of MAC patients.[35] In this study, although the most commonly prescribed regimen was the guideline-recommended 3-drug combination, many MAC patients received regimens associated with macrolide resistance. According to physician survey studies, 68% of NTM patients from 5 countries in the European Union, and 43% of NTM patients in Japan initiated therapy.[34] Studies from South Korea[36] and Germany[37] reported treatment rates within 3 years of diagnosis of 65% for pulmonary MAC disease. The surveys indicated that 16.9% of 746 treated

pulmonary MAC patients received >6 months of the guideline-recommended macrolide-rifamycin-ethambutol regimen (41.9% in Japan and 9.2% in European countries).[34] A German study based on healthcare administrative data from healthcare insurances reported that 45.2% of 93 patients with pulmonary NTM disease were prescribed a guideline-recommended 3-drug regimen.[37] A Japanese study using claims data reported that the guideline recommended 3-drug regimen was used in 25.1% of the patients, while monotherapy was used in as high as 30.6%.[38]

Less is known about pulmonary MAC therapy use in the U.S., and prescribing patterns are poorly understood. A recent population-based study in Oregon reported that 54% of 102 pulmonary NTM cases initiated treatment within 2 years of diagnosis.[39] The proportion of pulmonary NTM patients who received treatment was lower (18%) in another study involving 4 integrated U.S. healthcare delivery systems.[4] According to a physician survey study, antimicrobial drug treatment was prescribed to 55% of pulmonary MAC patients in the U.S.[40] This study reported that among regimens prescribed to patients with pulmonary MAC infection, only 13% were guideline-recommended triple-drug therapy, and 30% were associated with macrolide resistance.

It is important to note that the case definition of pulmonary NTM disease differed across these studies. These studies involved patients being treated with antibiotics specific for MAC infection, and misclassification of NTM cases was likely minimal. Yet, case identification by microbiological criteria only[41] could have misclassified a small number of patients from whom NTM were repeatedly isolated as having disease (e.g., a case of airway colonization or contamination in absence of radiologic or clinical findings). In

contrast, the Oregon study reviewed the full diagnostic criteria,[39] and the Germany study used diagnosis codes.[37] Also, some studies included the full spectrum of disease severity and physician expertise.[41] Additionally, some studies may differ from those conducted at specialty clinic-based studies,[39 42] which likely included patients with more severe disease and physicians who may be more likely to prescribe treatment because of greater experience.

2.5. Adverse events and drug toxicity associated with pulmonary MAC therapy

Therapy for pulmonary MAC is often prolonged, leads to drug interactions and causes drug-related toxicities and tolerability issues resulting in treatment interruptions or discontinuation. Common adverse events include allergic reactions and drug toxicity, especially in older individuals, patients with existing liver or renal disease, those using other medical therapies, and those with lower body mass index.[5 43] Azithromycin is often associated with reversible hearing loss, diarrhea, gastrointestinal disturbance, nausea and vomiting.[44] Similar adverse events are common with clarithromycin, an alternative macrolide. Irreversible ototoxicity and vestibular toxicity are often associated with aminoglycosides such as amikacin. Ototoxicity is of great concern because many patients with NTM are elderly and frequently have baseline hearing loss or tinnitus. Rifamycin-induced side effects include hepatotoxicity, gastrointestinal disturbance and immunological reactions including acute renal failure and thrombocytopenia.[5] Rifabutin-associated side effects include uveitis, gastrointestinal disturbance, flu-like symptoms, polyarthralgia and leukocytopenia.[5 45] Optic neuritis, vision changes, numbness/tingling in hands and feet, and ocular toxicity are among well-documented adverse events associated with ethambutol.[6 46]

Given the long duration of treatment, adherence often can be problematic.[40] Furthermore, drug–drug interaction is an important issue in the elderly, which is the population primarily affected by NTM disease. Macrolides, rifamycins and fluoroquinolones, which are used for macrolide resistant MAC (e.g., ciprofloxacin), are vastly used to target slowly growing mycobacteria such as MAC and usually cause interaction with metabolism of other drugs.[21] For example, leukopenia and uveitis are complications associated with rifabutin and clarithromycin together.[21] Macrolide resistance is also of serious concern if a macrolide is used as a monotherapy or when used in combination with concurrent antibiotics.[47]

2.6. Need for a better understanding of pulmonary MAC therapy

Understanding of the treatment used for pulmonary NTM infection is severely limited, and treatment decisions are often made based on limited evidence. Many of the current antibiotic drugs used to treat NTM infection were not designed specifically for NTM. Instead, antibiotics developed for tuberculosis have often been extrapolated to treat NTM infection. Further, many prospective treatment studies for NTM were conducted in the setting of disseminated MAC in patients positive for human immunodeficiency virus (HIV) before the advent of highly active antiretroviral therapy.[6] Population-based studies for NTM infection outside of HIV settings are rare, and it is not known whether results from such studies can be applied to typical manifestations of pulmonary NTM infection. Although treatment trials have been conducted for pulmonary MAC disease, they were often single-centered with a small sample size.[30 48-50] Importantly, among the consequences of inadequate MAC therapy is the emergence of macrolide-resistant MAC,

which is associated with high rates of treatment failure and increased mortality.[51] Furthermore, as pulmonary NTM infections are steadily increasing for older individuals,[4] age-related changes in drug absorption, metabolism and excretion, which may lead to decreased efficacy and increased toxicity, are of concern.[52]

The macrolide-based multi-drug regimen recommended by the guidelines is currently recognized as the most effective regimen.[40 53] Other studies have also suggested that success of treatment is likely maximized during the initial treatment episode, and subsequently declines at later attempts,[54 55] which underscores the importance of choosing an appropriate regimen at the initial attempt. While the recommended regimen is standard, it is relatively unknown what proportion of patients who initiate MAC therapy, start with the guideline-recommended regimen or adhere to it during therapy. More importantly, the proportion of U.S. patients who complete therapy for 12 months or longer (guidelines recommend therapy to continue for at least 12 months post-culture conversion) is also unknown. Similarly, very little is known about factors associated with treatment initiation as well as patterns in treatment interruptions and restart.

U.S. population-based data on NTM disease, particularly on therapy used for pulmonary NTM are scarce,[5 8] and access to evidence-based therapy is limited among U.S. patients with MAC pulmonary disease. Even after the most recently published treatment guidelines, we still lack valid estimates of the patterns in the use of antibiotic therapy for pulmonary NTM disease and adverse outcomes associated with the currently recommended therapy. Finally, given the difficulty of treating MAC disease, poor treatment outcomes, lengthy treatment duration, and frequent drug-related toxicities,

there is an urgent public health need for a better understanding of patterns in NTM therapy use as well as safety and tolerability associated with such therapy.

CHATER 3. RESEARCH PAPER #1

The Validity of Diagnosis Code–based Medicare Claims to Identify Pulmonary Nontuberculous Mycobacterial Infection in U.S. Patients with Bronchiectasis

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Running head: pulmonary NTM case-finding using Medicare claims

Key words: bronchiectasis; nontuberculous mycobacterial infection; validation; Medicare claims

3.1. Abstract

Nontuberculous mycobacteria (NTM) is an infection of increasing incidence caused by environmental organisms that can lead to chronic, debilitating pulmonary disease. With data from 457 participants matched between the U.S. Bronchiectasis and NTM Research Registry (BRR) and Medicare, I validated the accuracy of ICD diagnosis code-based claims in Medicare using the BRR as a gold standard. I observed that diagnosis code-based claims (ICD-9 031.0 pulmonary mycobacterial infection) had moderate validity for identifying NTM infection. Positive predictive value was improved when requiring a second claim, and when restricted to those assigned by an infectious disease specialist. Our results indicate that a definition with ≥2 claims 30 days apart but within 12 months of each other is useful in identifying cases with pulmonary NTM infection in the setting of bronchiectasis. However, given low sensitivity, incidence may be severely underestimated in claims-based epidemiologic research on pulmonary NTM infection.

3.2. Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that can cause chronic, debilitating pulmonary disease.[5 9] NTM disease primarily affects older individuals, and disproportionally affect post-menopausal women. NTM disease commonly occurs in the setting of chronic underlying lung disease such as chronic obstructive pulmonary disease (COPD) and bronchiectasis where the abnormal lung architecture increases the risk of collecting pathogens from the environment.[4 10] The prevalence of NTM pulmonary disease has been estimated as 12.6 - 17.3 cases per 100,000 in 2000-2006.[2 3] The burden of NTM pulmonary disease has increased significantly in the last few decades with both prevalence and incidence rising, especially in the elderly.[1-4] Patients typically suffer from symptoms including chronic cough, wheezing, difficulty breathing, fatigue, night sweats, weight loss, depression, social anxiety and hemoptysis. Though not communicable, NTM infection may cause extensive destruction and progressive inflammatory damage of lung tissues as well as airway dilation, leading to respiratory failure in rare cases. Diagnosis of NTM disease involves clinical, radiological and microbiologic assessments (i.e. acid-fast bacilli cultures) and is often difficult due to non-specific symptoms, frequent coinfections, and the need for collection of acid-fast bacilli cultures, which are not routinely collected.

Administrative healthcare data such as Medicare claims containing International Classification of Diseases (ICD) diagnosis codes can provide a readily available, inexpensive, efficient and powerful tool for case identification in research studies. Such data sources may also provide advantages such as minimal referral bias, minimal missing

data and lower costs. With large population coverage and the ability to link between databases using a unique identification number, administrative healthcare data have been used extensively for epidemiologic and health services research.[15-18] Healthcare reimbursement claims data containing ICD Clinical Modification (CM) diagnosis codes have provided valuable tools to identify NTM cases in epidemiologic studies to estimate prevalence and incidence measures, disease trends and geographic distribution in the U.S.[19-24] and in other parts of the world.[25] ICD-9-CM codes have also been used to evaluate mortality of NTM lung disease in the U.S.,[26] hospital-based antibiotic use,[27] and healthcare costs associated with NTM disease.[28] Thus, the majority of our current understanding of the epidemiology of NTM disease is based on results from studies using ICD-9 code-based case definitions for identifying NTM pulmonary disease.

The accuracy of ICD diagnosis codes used to estimate pulmonary NTM disease occurrence has only been validated in one small study of patients with rheumatoid arthritis.[23] Although cases identified based on microbiological (≥1 positive NTM culture) algorithms demonstrated a positive predictive value (PPV) of 74% in identifying true cases based on the American Thoracic Society (ATS) / Infectious Disease Society of America (IDSA) diagnostic criteria[5] in this study, the accuracy of ICD diagnosis codes is still poorly understood. Knowledge of the validity of case definitions is key to understanding the magnitude of potential misclassification bias in the current literature and to planning future studies. It is critical to validate ICD-9-CM code-based definitions used to identify patients against a gold standard, where the true disease status is known,[29] in order to evaluate their performance in case identification. Accordingly, I sought to

validate the accuracy of ICD diagnosis codes for NTM in Medicare data using the U.S. Bronchiectasis and NTM Research Registry (BRR) as a gold standard.

3.3. Methods

3.3.1. Gold standard

I used the BRR as a gold standard, against which I validated ICD-9-CM code-based case definitions for NTM pulmonary infection. The BRR is a national prospective cohort of patients with a physician-established diagnosis of bronchiectasis and/or NTM infection enrolled from 13 clinical sites throughout the U.S.[56] The BRR has enrolled >1,800 patients to date in the U.S., and has collected extensive patient data including demographic characteristics, medical history, respiratory symptoms and clinical procedures relevant to bronchiectasis and NTM, such as radiography, microbiology and treatment data. At enrollment, data within 2 years prior to the enrollment date are collected (baseline data) on consented participants, and follow-up data are collected annually. Annual follow-up data include updated contact information and clinical endpoints (e.g. hospitalizations and deaths), respiratory symptoms, therapies, clinical procedures (e.g. pulmonary function tests), laboratory results and microbiology. The BRR observation time began at the beginning of the baseline period and ended at the date lost to follow-up or death. "True" cases of NTM pulmonary infection were identified in the BRR based on: 1) a documented diagnosis for NTM; 2) culture positivity on ≥1 respiratory specimen (sputum, bronchial wash or lavage, or lung biopsy) (**Appendix A**); or 2) a history of macrolide-based multi-drug antibiotic treatment for NTM (a macrolide plus one or more of the following antibiotics: amikacin, rifamycin, and fluoroquinolone)

during the observation period. A macrolide-based multidrug regimen has been recommended as the first-line therapy for patients with pulmonary disease due to Mycobacterium avium complex,[7 56] which accounts for up to 90% of pulmonary NTM disease.[5 6] A macrolide-based multidrug regimen is specific to for the use to treat pulmonary MAC disease. Further, antibiotic treatment for pulmonary NTM infection recorded in the BRR are those determined to have been used for pulmonary NTM infection by the investigators.

3.3.2. Validation cohort

I obtained claims records for Medicare beneficiaries with an ICD-9-CM claim for bronchiectasis (ICD-9-CM 494.0 or 494.1 bronchiectasis with or without acute exacerbation) from the national 2006 – 2014 Medicare database Parts A and B plus D, but not Part C.[57 58] I restricted to beneficiaries aged 65 years and older at Medicare enrollment. I also excluded those with a diagnosis of cystic fibrosis (ICD-9-CM codes 277.00-277.09), human immunodeficiency virus infection (042), or a history of organ transplant (V42.0, V42.1, V42.6, V42.7, V42.8).

3.3.3. Linkage

I linked enrolled in the BRR at 7 geographically varied sites (Columbia University Medical Center, Georgetown University Hospital, National Jewish Health, University of North Carolina at Chapel Hill, Oregon Health & Science University [OHSU], University of Texas Health Science Center, and Mayo Clinic) to Medicare data.[57] Participants enrolled at OHSU and National Jewish Health were linked by the Research Data

Assistance Center using a finder file including date of birth, sex, and social security number. For the remaining five sites, social security numbers were unavailable, and I performed probabilistic linkage by date of birth, sex, and treating physician associated with an outpatient visit up to 3 visits. Medicare observation time began on the later date of Medicare enrollment or data start date (01/01/2006) and ended on the earliest date of: 1) coverage end; 2) death; 3) or end of data (12/31/2014). Participant were required to have an overlap in the BRR observation time and Medicare enrollment to be included in the final analytic cohort; I only considered claims (**Figure 3.1**) and cultures (**Figure 3.2**) that occurred within this overlapping observation period.

Figure 3.1: Inclusion and exclusion of Medicare claims

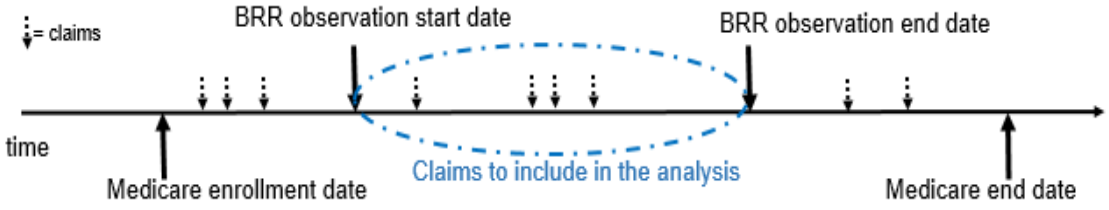
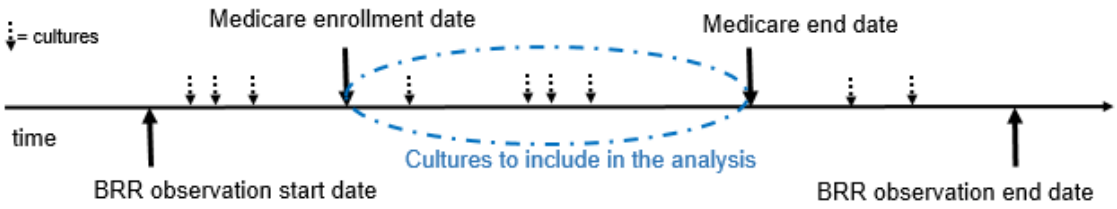


Figure 3.2: Inclusion and exclusion of BRR culture results



3.3.4. Statistical analysis

I examined the validity of ICD-9-CM-based case definitions for NTM pulmonary disease in the Medicare data using cases identified in the BRR as the gold standard. I explored our primary case definition for pulmonary NTM as ≥1 inpatient discharge or outpatient visit code ICD-9 031.0 (pulmonary mycobacterial infection) given by a clinician. Claims given by a clinician included those given by physicians (e.g. M.D. and D.O.), physician assistants and nurse practitioners, excluding radiology or laboratory-associated claims. I also explored codes given by an infectious disease specialist and pulmonologists. I explored the secondary definition, defining NTM infection as ≥1 inpatient discharge or outpatient visit code ICD-9 031.0, requiring a second claim >30 days apart from but within 12 months of the first code, given by a clinician, infectious disease specialist or pulmonologist. Only ICD-9-CM 031.0 code was considered; other codes for NTM (031.8 other specified mycobacterial diseases and 031.9 Unspecified disease due to mycobacteria) were not considered.

For each case definition, I calculated positive predictive values (PPV) as the proportion of claims-based pulmonary NTM cases meeting the case definition in the BRR ±12 months of the first Medicare claim for pulmonary NTM infection. Sensitivity was calculated as the proportion of those meeting a case definition in BRR, who had a Medicare claim for NTM within ±12 months of meeting the definition in the BRR. All analyses were performed using the Statistical Analysis System statistical software package,

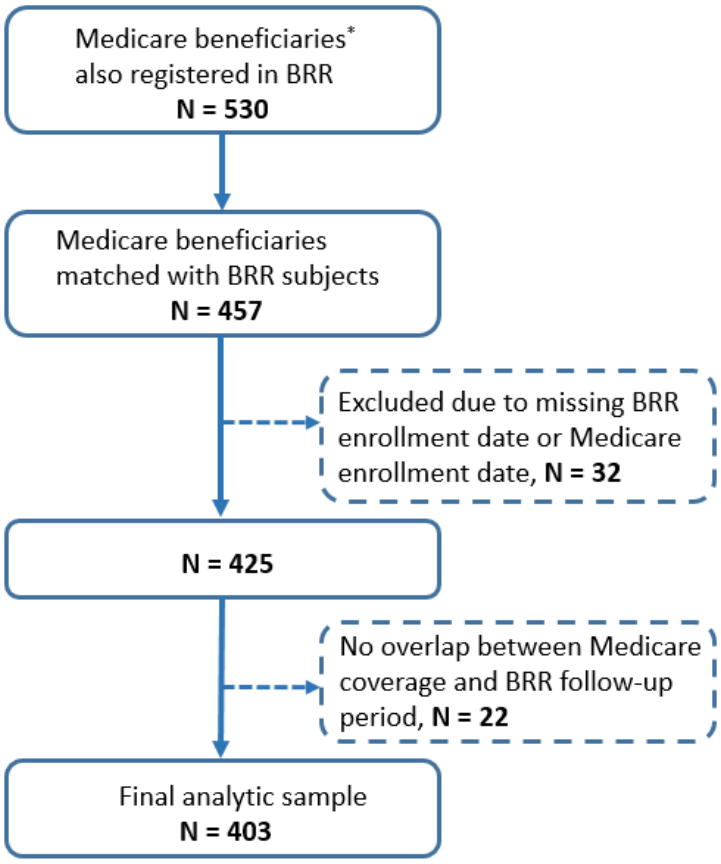
version 9.4. SAS Institute Inc., Cary, NC, USA. This study was approved by the Institutional Review Board at OHSU.

3.4. Results

Among 530 Medicare beneficiaries also enrolled in the BRR at the 7 sites, 457 (86.2%) were linked (**Figure 3.3**). After excluding 32 subjects missing the BRR enrollment date or Medicare enrollment date, and an additional 22 without overlap between Medicare coverage and BRR observation period, our final analytic cohort included 403 participants. The participants averaged 73.5 years in age (s.d. 6.2), were mostly female (80.4%), and white (95.8%). Of the 403 participants, 205 (50.9%) carried ≥1 NTM diagnosis code-based claim given by a clinician. I observed that diagnosis code-based claims have moderate validity for identifying NTM pulmonary infection. Our primary case definition of a single ICD-9-CM 031.0 code given by a clinician had a PPV of 63.2% (95% CI: 57.1, 69.4) (**Table 3.1.**), and was 69.9% (95% CI: 63.9, 75.9) sensitive in detecting NTM pulmonary infection within ±12 months of the first Medicare claim date. The PPV improved slightly when restricting to infectious disease specialist and pulmonologist-given codes combined (65.4%; 95% CI 58.9, 71.9), but not when restricting to codes given by a pulmonologist only (PPV 60.9%; 95% CI 52.6, 69.2). Results were similar when requiring a second ICD-9-CM 031.0 code (at least 30 days apart from, but within 12 months of, the first code), but with improved PPV (72.1%; 95% CI 63.3, 79.9) and decreased sensitivity (41.6%; 95% CI 35.2, 48.0). Similar to the primary case definition, when requiring a second claim, PPV improved when restricted to pulmonologist and infectious disease specialist assigned codes (74.0%; 95% CI 64.3,

82.3). This definition, when restricted to codes assigned by infectious disease specialists, yielded the best PPV overall (82.2%; 95% CI 57.0, 83.9).

Figure 3.3. Flow diagram of the analytic sample of patients matched between 2006-2014 Medicare enrollees and national U.S. Bronchiectasis and NTM Research Registry (BRR) participants



* From parts A, B, and D but not C, excludes those with cystic fibrosis and a history of human immunodeficiency virus or organ transplant

Table 3.1. Positive predictive value and sensitivity of ICD-9-CM diagnosis code-based case definitions for nontuberculous mycobacterial pulmonary infection in 2006-2014 U.S. Medicare data using the U.S. Bronchiectasis and NTM Research Registry as a gold standard

NTM case definition	Number of participants with a diagnosis-based Medicare claim for NTM infection	PPV (95% CI)	Number of participants meeting the BRR case definition for NTM infection	Sensitivity (95% CI)
Primary definition: ICD-9-CM 031.0				
All clinician assigned codes	234	63.2 (57.1, 69.4)	226	69.9 (63.9, 75.9)
ID specialist and pulmonologist assigned codes only	205	65.4 (58.9, 71.9)	226	61.5 (55.2, 67.9)
ID specialist assigned codes only	127	70.1 (62.1, 78.0)	226	39.8 (33.4, 46.2)
Pulmonologist assigned codes only	133	60.9 (52.6, 69.2)	226	36.7 (30.4, 43.0)
Secondary definition: ICD-9-CM 031.0 (requiring a second 031.0 claim >30 days apart from, but within 12 months of the first claim)				
All clinician assigned codes	122	72.1 (63.3, 79.9)	226	41.6 (35.2, 48.0)
ID specialist and pulmonologist assigned codes only	100	74.0 (64.3, 82.3)	226	33.2 (27.1, 39.7)
ID specialist assigned codes only	45	82.2 (71.1, 93.4)	226	16.4 (11.6, 21.2)
Pulmonologist assigned codes only	44	70.5 (57.0, 83.9)	226	13.3 (30.4, 43.0)

Abbreviations: BRR = Bronchiectasis & NTM Research Registry; NTM = nontuberculous mycobacterial infection; ICD-9-CM = International classification of diseases, 9th version, clinical modification; PPV = positive predictive value; ID = infectious disease; CI = confidence interval

3.5. Discussion

Using Medicare claims data linked to the BRR, the case definition requiring at least 2 diagnosis codes (031.0) given by infectious disease specialists was 82.2% (95% CI: 71.1, 93.4) accurate in identifying pulmonary NTM infection among patients with bronchiectasis. This case definition can be useful in identifying a cohort of patients with NTM pulmonary infection using large administrative claims data. Other less restrictive case definitions (e.g. not restricted to codes assigned by specialists) with a lower PPV may still be useful for finding possible cases of NTM but may need more detailed review.

In a previous study evaluating laboratory data, the use of the microbiologic aspect of the NTM case definition[5] had a high PPV (77%), and yielded maximized sensitivity and PPV when combined with ICD-9 codes.[23] Our results were similar, in that NTM codes had fairly high PPVs but lower sensitivities overall. There are several explanations for false positive diagnosis codes. First, the Medicare population includes patients with chronic infections who may carry codes from prior NTM disease episodes. For example, for a patient who has been previously treated for NTM disease and no longer has active disease, the treating physician may assign an NTM diagnosis code to all subsequent follow-up visits, even in the absence of active disease. This possibility could not be evaluated because we had very limited claims data prior to the beginning of the observation time for BRR. More than half of participants carrying a claim associated with an NTM diagnosis code, but not identified as true cases, had at least one negative culture recorded in BRR during the observation period. This indicates that the code was likely given for evaluation of NTM during the initial consultation in clinic, or for follow-up

monitoring for historical diagnoses in the absence of active disease. PPVs improved when case definitions were based on specialist-assigned codes. This suggests that general clinicians in community settings may assign the disease code when disease criteria are not necessarily met. I was not surprised by the observed poor sensitivity of the claims; NTM is frequently under-diagnosed and miscoded as non-pulmonary NTM or even other mycobacteria such as tuberculosis. In addition, my case definition only required one positive culture while the current diagnostic guidelines require two if from sputum. Thirty-five percent of those meeting our case definition had a second positive culture within 12 months; this indicates that my case definition may have included those who had not met the microbiologic criteria for the diagnosis of NTM pulmonary infection.

In summary, I systematically validated diagnosis code-based claims for identification of pulmonary NTM infection. Population-based data for NTM research are scarce, and administrative healthcare data such as Medicare codes can provide a powerful tool for case identification in NTM research. The application of claims data to research is predicated on the use of billing codes as a proxy for clinical events. Validation of case definitions based on codes, which represent actual clinical events, is a step critical in producing reliable research findings. This work provides important data on the validity of NTM case-finding definition to better understand the current data as well as to facilitate utilization of readily available, large population-based administrative healthcare data.

This study also has some limitations. Generalizability of the findings is limited because I only included Medicare beneficiaries aged 65 and older with bronchiectasis. Also, the

BRR collects data from specialized NTM centers, and the level of expertise and clinical practice may be different than general clinic settings. Patients who are referred to specialized NTM centers may have more advanced disease, and be more likely to receive a diagnosis for NTM than those who are evaluated in community clinic settings. The Medicare data ended in December 2014, limiting the sample size and overlap with the BRR observation time. Lastly, I only evaluated ICD-9-CM codes. In 2015, conversion to ICD-10-CM codes was mandated,[59] and ICD-10 codes are beginning to be incorporated into NTM case definitions in research. However, the majority of the currently available data on NTM disease is based on ICD-9-CM codes. Thus, understanding the validity of ICD-9-CM codes is essential for interpretation of the existing literature and to inform future research using ICD-10-CM codes. Further, ICD-9-CM codes for NTM directly map on to ICD-10-CM codes (ICD-9-CM 031.0 equates to ICD-10-CM A31.0 pulmonary mycobacterial infection), helping facilitate future comparisons.

Overall, the results indicate that a case definition with ≥2 claims assigned at least 30 days apart within 12 months of each other may accurately identify patients with pulmonary NTM infection in the setting of bronchiectasis. However, given low sensitivity, incidence may be severely underestimated in studies using diagnosis code-based definitions for case identification. A validated, well-performing claims-based case-definition will enable future studies to generate clinically important and relevant real-world data to study the epidemiology of pulmonary NTM infection. Additional validation of case definitions in a non-Medicare population and with ICD-10 codes may further strengthen the utility of

claims-based case definitions as a valuable tool in studying the epidemiology of pulmonary NTM infection and improve the validity of future studies using claims data.

CHATER 4. RESEARCH PAPER #2

Prescribing patterns of multi-drug antibiotic therapy for pulmonary *Mycobacterium avium* complex infection in a U.S. Medicare population with bronchiectasis

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Running title: Multi-drug antibiotic therapy for pulmonary MAC

Key words: bronchiectasis; nontuberculous mycobacterial infection; Medicare claims; treatment patterns; *mycobacterium avium* complex

4.1 Abstract

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that can cause chronic, debilitating pulmonary disease, among which *Mycobacterium avium* complex (MAC) is the most common species. Guideline-recommended treatment of pulmonary MAC comprises long-term multi-drug antibiotic therapy, and population-data on patterns of antibiotic treatment for MAC are scarce. In this work, I sought to describe patterns of multi-drug antibiotic regimens used to treat pulmonary MAC among U.S. Medicare beneficiaries with non-cystic fibrosis bronchiectasis. The source population was Medicare beneficiaries with an ICD-9-CM-based claim for bronchiectasis (494.0 or 494.1) from U.S. Medicare data (2006-2014, Parts A, B and D). My cohort included beneficiaries aged ≥65 years at Medicare enrollment, excluding those with a diagnosis of cystic fibrosis, HIV infection, or a history of organ transplant. MAC therapy was defined as a multi-drug regimen containing a macrolide plus ≥1 other drug targeted for pulmonary MAC (rifamycin, ethambutol, fluoroquinolone, or amikacin) prescribed concomitantly for >28 days, with no evidence of MAC therapy for ≥12 months since Medicare enrollment. In this cohort of new MAC therapy users, I described patterns of multi-drug regimens used to treat pulmonary NTM. Among 618,303 Medicare beneficiaries in the source population, I identified 9,189 (1.5%) new NTM therapy users, who were mean 74 years of age (s.d. 6) at therapy start, 75% female and 87% non-Hispanic white. These beneficiaries were treated for a mean of 141 days (s.d. 161) prior to any change in their initial drug regimen. At treatment initiation, standard regimens were most common; 4,691 (51%) received a three-drug combination containing macrolide, rifamycin and ethambutol, and 1,153 (13%) received a macrolide in

combination with ethambutol (Table). Regimens associated with an increased risk of acquired macrolide-resistance[35 4735 4735 4735 4735 471,2] were also reported (macrolide + rifamycin 8%, macrolide + fluoroquinolone 23%). My study adds important data to the current literature on treatment patterns for pulmonary NTM infection in the U.S. The results indicated that half of new NTM therapy users in Medicare started on a guideline-recommended regimen, but regimens associated with macrolide-resistance were common. Further research is needed to understand barriers and facilitators of guideline-adherent prescribing for NTM.

4.2. Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that can cause chronic, debilitating pulmonary disease.[5 9] NTM disease primarily affects older individuals, and post-menopausal women are disproportionally affected. Among NTM species, *Mycobacterium avium* complex (MAC) is the most frequently encountered pathogen, accounting for up to 90% of pulmonary NTM disease.[5 6 60] Incidence and prevalence of pulmonary NTM have been increasing in the last few decades. In 1981–1983, the prevalence of pulmonary NTM in the U.S. was estimated as 2.4 cases per 100,000.[1] More recent studies reported prevalence estimates for pulmonary NTM ranging from 12.6 to 17.3 cases per 100,000.[2 3] Among persons aged 60 years and older, annual prevalence increased from 19.6 per 100,000 during 1994–1996 to 26.7 per 100,000 during 2004–2006.[4] Pulmonary NTM disease commonly occurs in the setting of chronic underlying lung disease such as chronic obstructive pulmonary disease (COPD) and bronchiectasis, where the abnormal lung architecture increases the risk of retaining environmental microorganisms.[4 10] Patients typically suffer from chronic cough, wheezing, difficulty breathing, fatigue, night sweats, weight loss, depression, social anxiety, hemoptysis, and other symptoms. Though not communicable, NTM infection may cause extensive destruction and progressive inflammatory damage of lung tissues as well as airway dilation, leading to respiratory failure in rare cases.

MAC disease often requires aggressive, long-term, species-specific multi-drug antibiotic therapy, and can be extremely difficult to manage. The recommended standard regimen targeted for pulmonary MAC disease is an 18–24-month period of treatment with a

minimum of 3 antibiotics, including a macrolide, rifamycin and ethambutol ("guideline-based therapy").[5 7] For more severe disease or for patients who fail standard multi-drug regimens, a parenteral agent, most commonly amikacin, is often added. While the recommended regimen is fairly standard, it is relatively unknown what proportion of patients actually start this regimen or adhere to it during therapy. The proportion of U.S. patients who complete therapy for 12 months or longer (guidelines recommend therapy to continue for ≥12 months post-culture conversion) is also unknown. Some non-U.S. studies have reported poor adherence to guideline recommendations.[41 61] U.S. population-based data on NTM disease, particularly on therapy used for pulmonary NTM, are scarce,[5 8] and the use of evidence-based therapy is limited among U.S. patients with MAC pulmonary disease. Population-based data on treatment practices are needed in light of recent clinical practice guidelines. Therefore, we sought to describe prescribing patterns of macrolide-based multi-drug antibiotic therapy of first-time MAC therapy users among a U.S. Medicare bronchiectasis cohort between January 2006 and December 2014.

4.3 Methods

I used U.S. Medicare data from the Centers for Medicare and Medicaid Services (Parts A and B plus D, but not Part C) from January 1st, 2006 – December 31st, 2014. I leveraged an existing source population from my team's prior work,[57 58] in which we obtained records for Medicare beneficiaries with bronchiectasis identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 494.0 or 494.1 (bronchiectasis with or without acute exacerbation). I restricted my study

population to those aged 65 years or older at Medicare enrollment, and excluded those with a diagnosis of cystic fibrosis (ICD-9-CM 277.00-277.09), human immunodeficiency virus infection (042), or a history of organ transplant (V42.0, V42.1, V42.6, V42.7, V42.8) during the baseline period, as patients with these conditions typically represent an entirely different spectrum of NTM disease than those without (**Figure 4.1**). The baseline period was defined as the time between individuals' Medicare enrollment and their MAC therapy start date.

I identified a cohort of first-time MAC therapy users for inclusion in the study cohort. I defined a MAC treatment regimen as a prescription of ≥28 day-supply of antibiotic drug regimen containing a macrolide (azithromycin or clarithromycin) plus an overlapping ≥28 day-supply of ≥1 of the following: rifamycin (rifampin or rifabutin), ethambutol, fluoroquinolone, or intravenous/ inhaled amikacin. This regimen is highly specific to MAC pulmonary infection, as this combination is not used for any other infections other than few much rarer NTM species. I required a minimum of 12 months of enrollment in Medicare without evidence of MAC therapy to be eligible to enter our cohort of first-time MAC therapy users. National Drug Codes were obtained from First Databank by the University of Alabama at Birmingham,[57] which houses Medicare data, and were used to identify antibiotic drugs of interest. The pharmacy variable 'days-supply' was used to estimate the duration of each prescription. Treatment start date was defined as the first date of meeting the treatment criteria (i.e. the first date of overlapping prescriptions). Treatment end date was estimated by adding the number of days of supply to the treatment start date. A macrolide-based multi-drug antibiotic treatment episode was

considered ‘ended’ when the beneficiary no longer met the MAC therapy definition, and the beneficiary did not refill the prescription within 30 days of the end of the drug supply. This 30-day timeframe allowed for those who refilled their prescriptions late to not be considered to have a lapse in treatment. If the beneficiary started a new MAC treatment regimen after an episode ended, the subsequent treatment was considered a separate episode. A regimen change during a treatment episode was defined as any drug change while still meeting the MAC therapy definition without a 30-day lapse. I excluded those with an erroneous concurrent prescription for both macrolides (azithromycin and clarithromycin) or both rifamycins (rifabutin and rifampin) as part of their initial regimen.

Using descriptive statistics, I examined beneficiaries’ demographic characteristics such as age at treatment start, sex and race as a proxy for disparities due to racism in prescribing practice, Charlson’s comorbidities scores as an index for comorbities,[62] and clinical characteristics such as underlying conditions during the baseline period (**Appendix C**). I examined MAC therapy regimens prescribed at treatment start by individual drugs and drug combinations, as well as by treatment duration. To describe prescribing patterns over time, I illustrated treatment regimens at treatment initiation, 6, 12, and 18 months after treatment start. To examine the possibility that those on a short-term therapy (<31 days) may have been treated for a different condition other than pulmonary MAC, I examined the demographic factors, proportion with a diagnosis code for NTM (ICD-9-CM 031.0: pulmonary mycobacteria), and proportion with a diagnosis code for pseudomonas infection (482.1: pseudomonas pneumonia, or 41.7: pseudomonas,

unspecified site) during the baseline period. All analyses were performed using SAS statistical software 9.4 (SAS Institute Inc., https://www.sas.com). This study was reviewed and approved by the Institutional Review Board at Oregon Health & Science University.

4.4 Results

Of the 618,303 Medicare beneficiaries with a bronchiectasis claim, 20,531 (3.3%) used macrolide-based multi-drug antibiotic therapy for pulmonary MAC infection for ≥28 days (**Figure 4.1**). Of the 20,531, we excluded 7,574 (36.9%) with Medicare coverage <12 months between Medicare enrollment and MAC therapy initiation, 1,469 (7.2%) with a diagnosis of cystic fibrosis, HIV or history of organ transplant, and 2,273 (22.1%) who were aged <65 years at Medicare enrollment. We excluded an additional 26 (0.1%) beneficiaries with a concurrent prescription for more than one macrolide or more than one rifamycin in their first treatment regimen, leaving an analytic population of 9,189 Medicare beneficiaries. Our analytic population had a mean age of 78.1 years (s.d. = 6.2) at treatment start, was mostly female (74.9%) and non-Hispanic white (87.0%), and had been enrolled in Medicare for a mean of 7 years (s.d. = 2.2) prior to treatment initiation (**Table 4.1**). COPD/emphysema (78.4%) and gastroesophageal reflux (58.3%) were among the most common comorbidities present during the baseline period.

The 9,198 beneficiaries in our cohort were treated for a mean of 140.5 days (s.d. = 160.9) on their initial treatment regimen prior to changing or stopping the regimen. Of the 9,189, 2,086 (22.7%) continued on a second regimen for mean 171.6 days (s.d. = 166.1), and

511 (5.6%) went onto a third regimen (mean duration = 166.4 days; s.d. = 156.3) during the initial treatment episode; only 111 (1.2%) used a fourth regimen (1.2%; mean duration = 164.1 days; s.d. = 194.1), and 24 (0.3%) used a fifth regimen (mean duration = 187.4 days; s.d. = 248.6). The most commonly prescribed drug in the first treatment regimen was azithromycin (68.0%), followed by ethambutol (66.7%) and rifampin (52.2%) (**Table 4.2**). The most common regimen (n=4,690, 51.1%) was the guideline-based regimen (macrolide + rifamycin + ethambutol with or without amikacin), used for a mean duration of 175.6 days (s.d. = 172.5). Among the guideline-based regimens, a regimen containing azithromycin, ethambutol, and rifampin was most common (n=2,637, 28.7%) and was used for a mean of 188.7 days (s.d. = 177.7). Use of non-guideline-recommended therapy regimens were also common. A 2-drug regimen containing a macrolide and ethambutol was prescribed to 1,153 individuals (12.5%) for a mean of 159.5 days (s.d. = 179.9) while a 2-drug therapy with a macrolide plus fluoroquinolone was prescribed to 2,103 individuals (22.9%) for a mean of 72.0 days (s.d. = 100.2). Those who did not continue treatment after the initial prescription (duration ≤31 days; n=2,362, 25.8%) were similar to those who continued beyond the first 31 days (6,827, 74.2%), with respect to the proportion with a diagnosis code for pulmonary NTM (47.0% versus 46.0% respectively), and a diagnosis code for pseudomonas (10.3% versus 9.6% respectively) during the baseline period. The groups were also similar in demographic characteristics.

Figure 4.2 shows the flow of antimicrobial drug treatment regimens at treatment start, 6 months, 12 months and 18 months of therapy, among the 9,104 first-time MAC therapy

users after excluding an additional 85 beneficiaries with a concurrent prescription for more than one macrolide or rifamycin during any treatment episodes. The mean number of regimen changes while enrolled in Medicare per beneficiary was 1.8 (s.d. = 1.4). At treatment start, 4,630 (50.9%) started with the guideline-based therapy, of which 1,877 (40.5%) were continuing on the standard therapy at 6 months, 762 (7.5%) at 12 months and 235 (5.1%) at 18 months. Those who were still on the guideline-based therapy at 6 months were on average 1 year younger (s.d. = 6.0) than those who were not ($p<0.01$), had 1.2 (s.d. = 4.6) less clinic visits ($p<0.01$) and 0.3 (s.d. 1.5) less hospitalizations annually during the baseline period, and had a higher mean Charlson comorbidities index score (0.3 points higher, s.d. 1.6). We observed a large number of beneficiaries discontinuing treatment before reaching 18 months; by 6 months, 4,278 (47.0%) were off macrolide-based treatment, by 12 months, 4,758 (52.3%) were off treatment and by 18 months, 5,840 (64.2%) had discontinued macrolide-based treatment. Of the 4,278 who were off treatment at 6 months, only 287 (6.7%) had restarted therapy by 12 months. Of the 4,758 who were off treatment at 12 months, 201 (4.2%) had restarted therapy by 18 months. Overall, of the 9,104 who initiated treatment, 982 (10.8%) were still on macrolide-based multi-drug antibiotic therapy at 18 months; 3,083 (33.9%) were censored: 1) because Medicare coverage ended due to death before reaching 18 months after therapy initiation [n = 397] or; 2) due to administrative censoring where the observation end date (12/31/2014) occurred prior to reaching 18 months after therapy initiation. For all episodes combined, the 9,104 beneficiaries were on an average 1.5 treatment episodes (s.d. = 0.9) for a mean time of 257.9 days (s.d. = 268.7).

4.5 Discussion

I examined patterns of macrolide-based multi-drug antibiotic therapies for the presumptive treatment of pulmonary MAC infection in Medicare beneficiaries between January 2006 and December 2014. I found that the guideline-based therapy with or without amikacin was prescribed in 51% of new MAC therapy users at treatment start, of which only 41% were continuing on the guideline-based therapy at 6 months, and 17% at 12 months. Overall, by 18 months, of the 9,104 who initiated treatment, only 11% were still on MAC treatment, 55% had discontinued therapy, and the remaining 34% were censored.

The current treatment guidelines for pulmonary MAC recommend a daily or three-times-weekly drug regimen with a macrolide, ethambutol and a rifamycin until the patient has remained culture negative for one year,[5 7] which is currently recognized as the most effective regimen.[40 53] Other studies have also suggested that success of treatment is likely maximized during the initial treatment episode, and subsequently declines at later attempts;[54 55] this underscores the importance of choosing an appropriate regimen at the initial attempt. Few non-U.S. studies have reported on the prescribing patterns of antibiotic treatment for pulmonary MAC disease. Recently, using linked laboratory and healthcare administrative databases, a cohort study of adults 66 years or older in Ontario described patterns of MAC therapy.[35] In this study, although the most commonly prescribed regimen was the guideline-based therapy; many MAC patients received regimens associated with macrolide resistance. Another study based on physician surveys

reported that 16.9% of 746 treated MAC patients received >6 months of the guideline-based therapy (41.9% in Japan and 9.2% in European countries).[34] A German study based on healthcare administrative data from healthcare insurances reported that 45.2% of 93 patients with pulmonary NTM disease were prescribed the guideline-based therapy.[37] A Japanese study using claims data reported that the guideline-based therapy was used in 25.1% of the patients, while monotherapy was used in as high as 30.6%.[38] Less is known about prescribing patterns of pulmonary MAC therapy used in the U.S. According to U.S. physician survey studies, among regimens prescribed to patients with MAC infection, only 13% were guideline-based therapy, and 30% were associated with macrolide resistance.[40]A recent U.S. multicenter retrospective study observed guidelines' adherence in 33% of patients, though specific regimens were not described.[61]

I observed an unexpectedly low percentage of beneficiaries still on MAC therapy at months 6, 12 and 18, particularly those on guideline-based therapy, although 33% were censored. Reasons for the majority with early treatment interruption and discontinuation are unclear, but many likely discontinue treatment prematurely due to drug-associated adverse events. MAC therapy-associated adverse events, including allergic reactions and drug toxicity, are common especially in older individuals, patients with existing liver or renal disease, those using other medical therapies, and those with lower body mass index.[5 43] Macrolides are often associated with reversible hearing loss, tinnitus, QT prolongation (measure of delayed ventricular repolarization), gastrointestinal disturbance, nausea and vomiting.[44] Hepatotoxicity, gastrointestinal disturbance and immunological reactions including acute renal failure and thrombocytopenia are among rifamycin-

induced side effects.[5] Optic neuritis, vision changes, numbness/tingling in hands and feet, and ocular toxicity are among well-documented adverse events associated with ethambutol.[6 46] Irreversible ototoxicity and vestibular toxicity are often associated with aminoglycosides such as amikacin. Furthermore, drug–drug interaction is an important issue in the elderly, which is the population primarily affected by MAC disease. Last, because of the long duration of treatment required for pulmonary MAC infection, patient compliance can often be an issue, especially for older patients.

I also observed that regimens associated with macrolide resistance were often prescribed; 2,103 (22.9%) were prescribed a macrolide plus fluoroquinolone, and 735 (8.0%) were prescribed a macrolide plus rifamycin at treatment initiation. Previous studies have also reported the use of such regimens associated with macrolide resistance, including one report describing a regimen with a macrolide and fluoroquinolone alone used in as many as 30% of MAC therapy users.[34 40 41] Further, although we do not have data on macrolide monotherapy at treatment start because our inclusion criteria required a macrolide-based multi-drug regimen, I observed that of the 9,104 who started with a multi-drug regimen, 35 (0.4%) were on macrolide monotherapy at 6 months, 22 (0.2%) at 12 months and 12 (0.1%) at 18 months. According to the current treatment guidelines, macrolides should never be used as monotherapy for the treatment of pulmonary MAC disease.[5 7] These observations are concerning because macrolide resistant MAC is extremely difficult to treat and is associated with higher mortality rates and poor disease outcomes.[5 7 8] Also, macrolides are among the limited choice of antibiotics used for pulmonary MAC infection, for which *in vitro* susceptibility correlates with clinical response.[5 7 54] It follows

that treatment options are extremely limited for patients with macrolide-resistant infections. Patients with macrolide-resistant infections no longer respond adequately to standard macrolide-based regimens, leading to poor disease outcomes.[5 7 8] However, it is encouraging that only few of those who started on a macrolide-based multi-drug therapy later began macrolide-monotherapy. Those who switched to macrolide-monotherapy after starting on multi-drug antibiotic therapy may have been empirically started on MAC therapy in the absence of microbiologic data; they could have switched to macrolide monotherapy, after obtaining negative culture results, for the prevention of bronchiectasis exacerbations.

Our work identified a higher proportion of adherence to guidelines as compared to prior studies, which is encouraging given that this study reflects a large U.S. population covered by Medicare. However, as observed in previous studies, a large proportion of beneficiaries in this study was treated with non-guideline-recommended regimens. The reason for poor adherence to the guideline-based therapy is unclear. Because the current guidelines are largely based on data from small observational studies as opposed to randomized control trials, prescribing practitioners may have low confidence in strictly adhering to the guidelines. Additionally, given the small number of treatment centers specialized in treating pulmonary NTM infections throughout the U.S., some practitioners in community settings may not have the extent of expertise in NTM treatment as those at specialized treatment centers do.

This work has several notable strengths. My results add important data to the current literature on prescribing practices for antibiotic therapy used to treat pulmonary MAC infection among U.S. Medicare beneficiaries. Medicare claims data provide a readily available, inexpensive, efficient and powerful tool to conduct epidemiologic studies. Pulmonary MAC disease primarily affects older individuals and recent increases in incidence and prevalence have been most evident among persons aged 60 years or older. Given the age distribution of MAC disease, and that 96% of Americans aged 65 and older have Medicare coverage,[63] these data provide an ideal source of healthcare administrative data to conduct epidemiologic studies that are representative of the older U.S. population with access to healthcare. Additionally, missing data constitute a very minor problem in the Medicare data system as Medicare data likely capture the entirety of beneficiaries' healthcare encounters; this includes pharmacy prescriptions in those with Part D coverage although only 75% of total Medicare enrollees are also covered by Part D.[64]

This work has some limitations. First, diagnostic criteria for pulmonary NTM include microbiological data. However, because clinical data are not available in Medicare data, my case definition was based on prescriptions for a macrolide-based multi-drug regimen without microbiologic data. Misclassification of non-cases as pulmonary MAC cases is possible (e.g. those treated for another condition such as pseudomonas exacerbation, or for species other than MAC). I examined the possibility that those on a short-term therapy (<31 days) may have been treated for another condition other than pulmonary MAC. The proportion of those with a claim for pseudomonas was similar in those on a short-term therapy (≤31 days) and those who were on therapy for a longer period (>31

days) (10.3 versus 9.6%). Similarly, the proportion of those with a claim for pulmonary NTM also was similar in the two groups (47.0% versus 46.0%). I did not use a diagnosis code-based definition; because diagnosis-based claims codes in Medicare have shown poor sensitivity in previous studies,[23 65] a code-based case definition would likely have led to substantial undercount of true cases (i.e., true cases misclassified as non-cases). Second, I did not have access to beneficiaries' full treatment history prior to Medicare enrollment to ensure all included beneficiaries were treatment naïve at Medicare enrollment at the age of 65 years. I required ≥12 months of no evidence of MAC therapy since Medicare enrollment and prior to treatment start to be included in the cohort. This should have reduced the potential for non-treatment naïve individuals in the dataset The fact that NTM primarily affects older individuals, and multiple years of Medicare coverage to treatment start should strengthen this likelihood. Yet, it is possible that my cohort still included some beneficiaries who received treatment prior to Medicare enrollment, and clinical response to prior therapy may have had an impact on the choice of subsequent therapy. Lastly, because my cohort consisted of Medicare beneficiaries aged 65 years and older with bronchiectasis, it is unclear if the results of this work are generalizable to younger patients with pulmonary MAC disease or those without bronchiectasis.

In summary, my findings indicate that the most commonly prescribed regimen for pulmonary MAC infection was the guideline-based therapy in Medicare beneficiaries with bronchiectasis, although a large number of beneficiaries received a non-guideline-based therapy and in some cases, even regimens associated with macrolide resistance.

Treatment discontinuation was common, and once discontinued, few beneficiaries resumed therapy at a later time. Our study adds important data to the current literature on treatment patterns for pulmonary NTM infection among older U.S. populations. Future research should examine treatment patterns using more contemporary data sources, as new drugs become available. Additionally, further research is needed to better understand factors associated with therapy discontinuation, barriers and facilitators of guideline-adherent prescribing for NTM, and associations between treatment and clinical outcomes.

Table 4.1. Baseline* demographic and clinical characteristics+ of 9,198 Medicare beneficiaries receiving macrolide-based multi-drug antibiotic therapy for presumptive *Mycobacterium avium* complex pulmonary infection between January 2006 and December 2014

	N (%) or mean (s.d.)
Demographic characteristics	
Age at treatment start (years)	78.1 (s.d. 6.2)
Female	6,881 (74.9%)
Race/Ethnicity	
White	7,998 (87.0%)
Asian	500 (5.4%)
Hispanic	388 (4.2%)
Black	202 (2.2%)
North American Native	23 (0.3%)
Unknown	<10 (<0.1%)
Number of years in Medicare since age 65	7.0 (s.d. 2.2)
Clinical characteristics+	
Chronic obstructive pulmonary disease/emphysema	7,140 (78.4%)
Oral corticosteroid use	5,652 (61.5%)
Gastroesophageal reflux	5,355 (58.3%)
Asthma	2,941 (32.0%)
Pulmonary nontuberculous mycobacteria infection	4,252 (46.3%)
Diabetes mellitus	2,817 (30.7%)
Rheumatologic disease	2,342 (25.5%)
Pseudomonas infection	897 (9.8%)
Lung cancer	823 (9.0%)
Primary immune deficiency	606 (6.6%)
Allergic bronchopulmonary aspergillosis	92 (1.0%)
Alpha-1 antitrypsin deficiency	44 (0.5%)
Primary ciliary dyskinesia	11 (0.1%)
Silicosis	<10 (<0.1%)
Chronic kidney disease	<10 (<0.1%)
Charlson modified index score[62]	2.3 (s.d. 1.7)
Healthcare utilization	
Number of clinician office visits per year	5.8 (s.d. 5.4)
Number of visits to pulmonologist per year	1.6 (s.d. 2.0)
Number of any hospitalizations per year	1.3 (s.d. 1.3)
Number of hospitalizations due to respiratory illness per year	0.7 (s.d. 1.0)
Number of visits to infectious disease specialists per year	0.7 (s.d. 1.2)
Number of acute exacerbations per year	0.7 (s.d. 1.0)

[*] time between Medicare enrollment and treatment start date

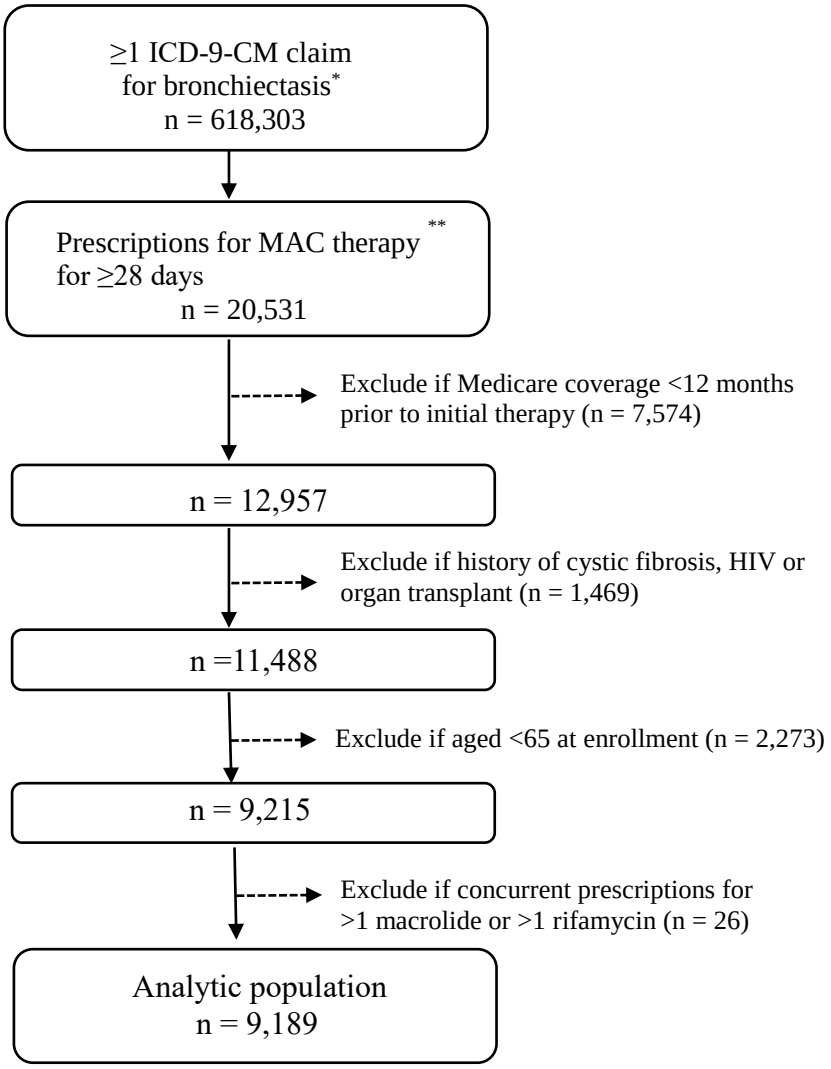
[+]identified by International Classification of Diseases, Ninth Revision, Clinical Modification codes-based Medicare claims made during the baseline period

Table 4.2. Individual drugs and drug regimens prescribed to treat presumptive *Mycobacterium avium* complex pulmonary infection among 9,198 Medicare beneficiaries (initial treatment regimen prescribed between January 2006 and December 2014)

	N (%)	Mean duration (SD); Median (25^{th} and 75^{th} percentile) in days
Individual drugs		
Macrolide	9,189 (100%)	140.5 (s.d. 159.9); 66.0 (31.0, 186.0)
Azithromycin	6,245 (68.0%)	139.7 (s.d. 161.6); 64.0 (32.0, 182.0)
Clarithromycin	2,945 (32.0%)	142.4 (s.d. 156.2); 73.0 (31.0, 193.0)
Ethambutol	6,128 (66.7%)	169.9 (s.d. 171.1); 96.0 (34.5, 254.0)
Rifamycin	5,627 (61.2%)	163.5 (s.d. 169.8); 81.0 (31.0, 240.0)
Rifampin	4,800 (52.2%)	171.5 (s.d. 173.6); 97.5 (35.0, 260.0)
Rifabutin	827 (9.0%)	117.4 (s.d. 137.3); 59.0 (31.0, 151.0)
Amikacin (inhaled or intravenous)	125 (1.4%)	89.7 (s.d. 88.7); 59.0 (37.0, 99.0)
Fluoroquinolone	2475 (26.9%)	79.2 (s.d. 109.5); 42.0 (31.0, 71.0)
Drug regimens		
Macrolide + rifamycin + ethambutol with/without amikacin	4,690 (51.1%)	175.6 (s.d. 172.5); 105.0 (38.0, 269.0)
Azithromycin + ethambutol + rifampin	2,637 (28.7%)	188.7 (s.d. 177.7); 121.0 (51.0, 291.0)
Clarithromycin + ethambutol + rifampin	1,420 (15.5%)	173.4 (s.d. 170.3); 101.0 (37.0, 262.0)
Azithromycin + ethambutol + rifabutin	382 (4.2%)	131.2 (s.d. 150.7); 62.0 (31.0, 172.0)
Clarithromycin + ethambutol + rifabutin	246 (2.7%)	117.2 (s.d. 134.2); 62.0 (31.0, 142.0)
Azithromycin + ethambutol + rifabutin + amikacin	<10 (<0.1%)	167.3 (s.d. 95.1); 206.0 (59.0, 237.0)
Clarithromycin + ethambutol + rifampin + amikacin	<10 (<0.1%)	63.0 (s.d. 48.1); 63.0 (29.0, 97.0)
Macrolide + ethambutol	1,153 (12.5%)	159.5 (s.d. 179.9); 86.0 (31.0, 221.0)
Azithromycin + ethambutol	729 (7.9%)	164.2 (s.d. 173.6); 87.0 (31.0, 87,0)
Clarithromycin + ethambutol	424 (4.6%)	151.6 (s.d. 166.2); 83.5 (31.0, 200.0)
Other regimens	3,346 (36.4%)	84.9 (s.d. 116.2); 42.0 (31.0, 83.0)
Azithromycin + fluoroquinolone	1,723 (18.8%)	69.0 (s.d. 97.2); 41.0 (32.0, 60.0)
Clarithromycin + fluoroquinolone	380 (4.1%)	86.6 (s.d. 111.9); 45.0 (31.0, 86.0)
Azithromycin + rifampin	363 (4.0%)	110.6 (s.d. 157.6); 55.0 (31.0, 130.0)
Clarithromycin + rifampin	225 (2.5%)	99.9 (s.d. 122.6); 42.0 (31.0, 106.0)
Azithromycin + ethambutol + fluoroquinolone	119 (1.3%)	137.6 (s.d. 138.2); 91.0 (31.0, 175.0)
Azithromycin + rifabutin	85 (0.9%)	103.8 (s.d. 128.6); 34.0 (31.0, 116.0)
Clarithromycin + rifabutin	62 (0.7%)	80.0 (s.d. 87.3); 54.0 (31.0, 128.0)
Clarithromycin + ethambutol + fluoroquinolone	56 (0.6%)	156 (s.d. 141.3); 90.50 (33.0, 238.0)
Azithromycin + amikacin	54 (0.6%)	105.1 (s.d. 107.0); 63.0 (37.0, 109.0)
Azithromycin + rifampin + fluoroquinolone	41 (0.5%)	152.8 (s.d. 225.8); 85.0 (40.0, 189.0)
Azithromycin + ethambutol +rifampin +fluoroquinolone	35 (0.4%)	101.6 (s.d. 178.3); 39.0 (31.0, 75.0)
Clarithromycin + rifampin +fluoroquinolone	33 (0.4%)	95.7 (s.d. 104.6); 47.0 (31.0, 98.0)
Clarithromycin + ethambutol +rifampin +fluoroquinolone	28 (0.3%)	60.5 (s.d. 56.0); 32.0 (31.0, 60.5)
Clarithromycin + amikacin	24 (0.3%)	73.9 (s.d. 49.5); 58.5 (37.5, 90.0)

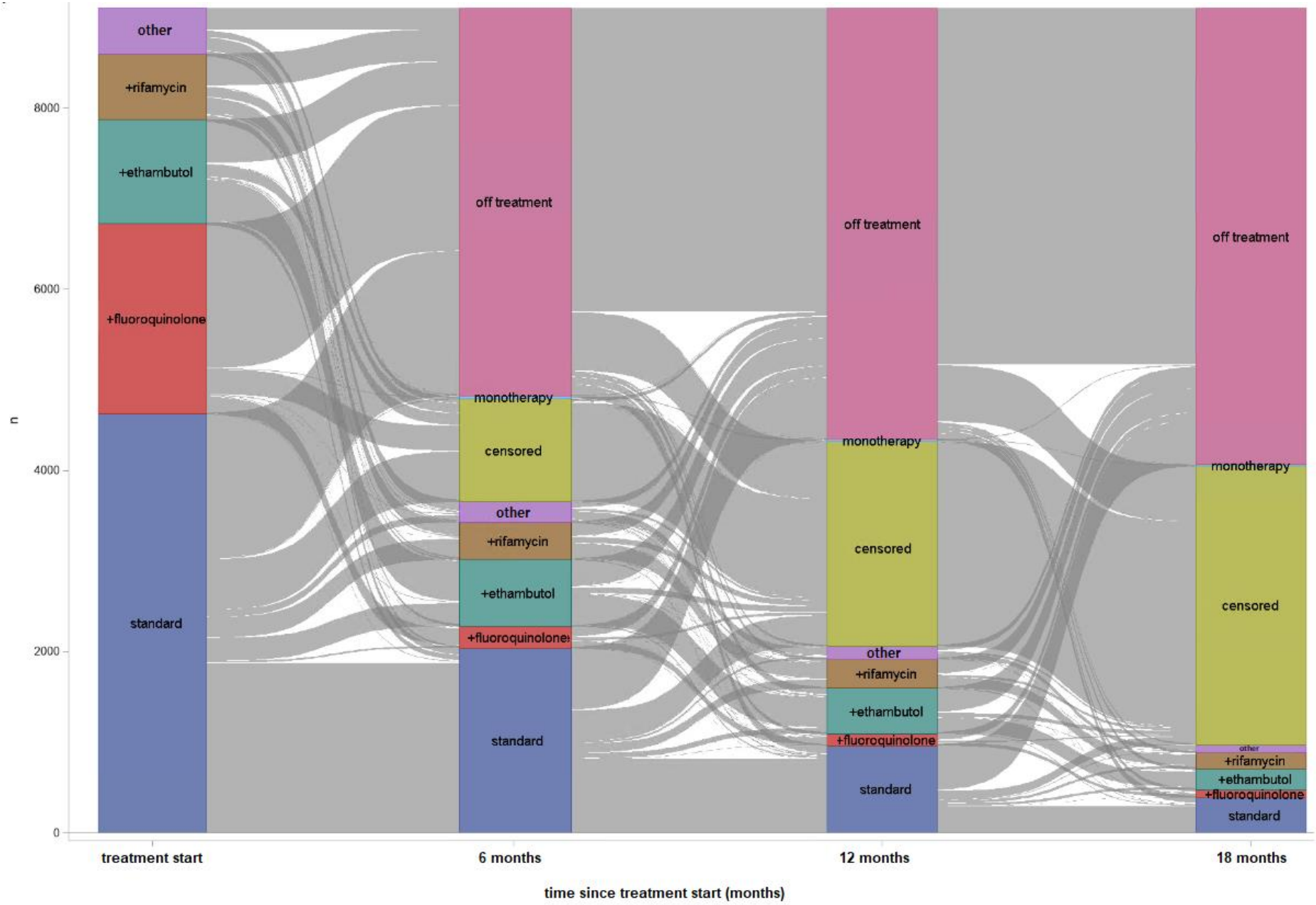
Azithromycin + rifabutin + fluoroquinolone	15 (0.2%)	66.6 (s.d. 80.2); 31.0 (29.0, 94.0)
Azithromycin + linezolid	13 (0.1%)	48.0 (s.d. 24.9); 41.0 (31.0, 55.0)
Other	89 (1.0%)	72.2 (s.d. 84.9); 43.0 (31.0, 71.0)

Figure 4.1. Flow diagram for the analytic population: 9,189 Medicare beneficiaries receiving macrolide-based multi-drug presumptive pulmonary *Mycobacterium avium* complex (MAC) treatment (2006 - 2014)



*ICD-9-CM code for bronchiectasis (494.0 or 494.1 bronchiectasis with or without acute exacerbation)
** Macrolide + ≥1 other antibiotic drug targeted for MAC infection: rifamycin (rifampin or rifabutin), ethambutol, fluoroquinolone, and amikacin

Figure 4.2. Macrolide-based multi-drug antimicrobial presumptive therapy for pulmonary *Mycobacterium avium* complex infection prescribed for 9,104 Medicare beneficiaries between January 2006 and December 2015 (at treatment start, 6, 12 and 18 months)



Blocks represent treatment regimen groups and gray stream fields between the blocks represent changes in the treatment regimens. The height of a block represents the number of beneficiaries in the regimen group, and the height of a stream field represents beneficiaries contained in both blocks connected by the stream field.

n = number of beneficiaries

“standard” = Guideline recommended 3-drug regimen (macrolide + ethambutol + rifamycin, with or without amikacin)
“+ethambutol” = macrolide + ethambutol
“+fluoroquinolone” = macrolide + fluoroquinolone
“+rifamycin” = macrolide + rifamycin
“+monotherapy” = macrolide monotherapy
“other” = all other macrolide-based multi-drug regimens not listed above
“censored” = 1) Medicare coverage ended (e.g. death) before reaching 18 months after therapy initiation or; 2) administratively censored because data end date (12/31/2014) was before reaching 18 months after therapy initiation.

CHAPTER 5. RESEARCH PAPER #3

Tolerability outcomes of multi-drug antibiotic treatment for pulmonary nontuberculous mycobacterial disease due to *Mycobacterium avium* complex in U.S. Medicare beneficiaries with bronchiectasis

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Running head: tolerability of MAC therapy

Key words: bronchiectasis; nontuberculous mycobacterial infection; *mycobacterium avium* complex; Medicare claims; antibiotic therapy

5.1. Abstract

Nontuberculous mycobacteria (NTM) is an infection of increasing incidence caused by environmental organisms that can lead to chronic, debilitating pulmonary disease, of which *Mycobacterium Avium* complex (MAC) is the most common species. Pulmonary MAC disease often is difficult to treat, and requires aggressive, long-term, multi-drug antibiotic therapy. Adverse events associated with therapy for pulmonary MAC are common, especially in older individuals. The current treatment guidelines are based on expert opinions and findings from small case-series, and population-based data on treatment outcomes are severely lacking. Therefore, we examined the tolerability outcomes of guideline-based 3-drug regimens targeted for pulmonary MAC in U.S. Medicare beneficiaries with bronchiectasis.

5.2 Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that can cause chronic, debilitating pulmonary disease,[5 9] among which species within *Mycobacterium avium* complex (MAC) are the most frequently encountered pathogens.[5 6 60] NTM disease primarily affects older individuals, especially post-menopausal women. Incidence and prevalence of pulmonary NTM have been increasing in the last few decades,[1 2 3] especially among persons aged 60 and older.[4]

Pulmonary MAC disease often requires aggressive, long-term, multi-drug antibiotic therapy, and can be extremely difficult to manage. Treatment of pulmonary MAC with drugs originally developed to treat tuberculosis was initially unsatisfactory, but treatment outcomes improved with the introduction of new drugs such as macrolides.[66] The current guidelines recommend an 18–24-month period of treatment with a minimum of 3 antibiotics, including a macrolide, rifamycin and ethambutol for pulmonary MAC disease.[5 7] Despite this, treatment outcomes remain poor, and many patients experience relapse or reinfection with a different species even after treatment completion, necessitating treatment restart.[30-32] In addition, *in-vitro* susceptibility for antibiotic drugs targeted for pulmonary NTM may not be predictive of treatment outcomes *in-vivo,*[30 32 33] further complicating treatment decisions. Prolonged treatment duration, side effects, and reinfection are among important factors responsible for the suboptimal treatment outcomes of pulmonary MAC,[67] resulting in frequent treatment interruptions or discontinuation. Adherence also may be problematic given the long treatment duration.[40]

Adverse events associated with therapy for pulmonary MAC are common, especially in older individuals.[5 43] Macrolides can be associated with reversible hearing loss, diarrhea, gastrointestinal disturbance, nausea and vomiting.[44] Along with hepatotoxicity, gastrointestinal disturbance and immunological reactions, cytopenias are among important rifamycin-induced side effects.[5] Rifabutin-associated adverse events also include uveitis, gastrointestinal disturbance, flu-like symptoms, polyarthralgia and leukocytopenia.[5 45] Furthermore, drug–drug interaction is an important issue in the elderly, which is the population primarily affected by NTM disease. Macrolides, rifamycins and fluoroquinolones, which are used for macrolide resistant MAC (i.e. ciprofloxacin), are widely used to target slowly growing mycobacteria and usually interact with the metabolism of other drugs.[21] For example, leukopenia and uveitis are complications associated with rifabutin and clarithromycin alone or together.

Despite recent advances in the understanding of MAC therapy, treatment outcomes remain inadequate.[67] Most studies of the treatment of pulmonary MAC have been small case series treated in a single institution.[7 30 44 48 54 68 69] In this study, we examined the association between guideline-based 3-drug regimens targeted for pulmonary MAC and tolerability outcomes in U.S. Medicare beneficiaries with bronchiectasis. We hypothesized that the rate of drug-associated adverse event occurrence and regimen change/discontinuation will be greater in those prescribed clarithromycin-based regimens as compared to those using azithromycin-based regimens, and in those using rifabutin-containing regimens as compared to those using rifampin-based regimens.

5.3. Methods

5.3.1. Study population

I used U.S. Medicare data from the Centers for Medicare and Medicaid Services (Parts A, B and D, but not C, January 1st, 2006 – December 31st, 2014). I leveraged an existing source population from our prior work,[57 58] in which we obtained records for Medicare beneficiaries with bronchiectasis identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) claim (494.0 or 494.1 bronchiectasis with or without acute exacerbation). In Aim 2,[70] I identified a cohort of first-time MAC therapy users, aged 65 years and older, excluding those with cystic fibrosis, human immunodeficiency virus infection, or a history of organ transplant. MAC therapy was defined as a prescription of ≥28 day-supply of antibiotic drug regimen containing a macrolide plus ≥1 of the following: rifamycin, ethambutol, fluoroquinolone, or intravenous/inhaled amikacin. The baseline period was defined as the time between the date of Medicare enrollment and the MAC therapy start date. To ensure that only first-time MAC therapy users were included in the cohort, I required a minimum of 12 months of enrollment in Medicare without evidence of MAC therapy (baseline period). A more detailed description of this cohort can be found in Aim 2.[70] For the current analysis, I further restricted this cohort to those who were prescribed a guideline recommended 3-drug regimen (macrolide, ethambutol and rifamycin) as their initial treatment (**Figure 5.1**). Those with a concurrent prescription for both macrolides (azithromycin and clarithromycin) or both rifamycins (rifabutin and rifampin) during any treatment episode were excluded as these were likely due to administrative error.

5.3.2. Exposure of interest

My comparison groups of interest were: (1) azithromycin-ethambutol-rifamycin versus clarithromycin-ethambutol-rifamycin (macrolide comparison); (2) macrolide-ethambutol-rifampin versus macrolide-ethambutol-rifabutin (rifamycin comparison); and (3) azithromycin-ethambutol-rifampin versus clarithromycin-ethambutol-rifabutin.

5.3.3. Outcomes of interest

I examined the following time-to-event tolerability outcomes of the MAC therapy regimens described above: (1) pre-specified adverse events typical of the drugs under study; and (2) regimen change or discontinuation within 12 months of therapy start. For outcome 1, typical macrolide or rifamycin-associated adverse events were identified by ICD-9-CM code-based Medicare claims. For the macrolide comparison, adverse events that commonly occur with azithromycin or clarithromycin were included (QT prolongation [ICD-9-CM 426.82], hearing loss [ICD-9-CM 389.9], tinnitus [ICD-9-CM 388.3X] and gastrointestinal disturbance [ICD-9-CM 536.9]). For the rifamycin comparison, cytopenias were examined as adverse events that commonly occur with rifampin or rifabutin (pancytopenia [ICD-9-CM 284.19], thrombocytonia [ICD-9-CM 2878.5]). An adverse event was considered attributed to the regimen of interest if the claim for the adverse event was made during the exposure time, requiring no claim for that event during the baseline period. The event date was determined by the claim date.

For the second outcome (regimen change or discontinuation), the event date was defined as the date of regimen change or treatment discontinuation. Time-to-event was estimated

by the treatment end date (last prescription start date plus number of days of supply). Treatment start date was defined as the first date of meeting the treatment criteria of being prescribed a guideline-based 3-drug regimen consisting of a macrolide, ethambutol and a rifamycin for a minimum overlapping period of 28 days. The treatment regimen was considered discontinued when the beneficiary no longer met the therapy definition (i.e., no refilling the companion drug(s) for which prescription ended, within 30 days of the end of the drug supply). If the lapse in the prescription for one or more prescription drugs was >30 days, the treatment regimen was considered discontinued. We defined a regimen change as changing one or more of the companion drugs within the initial regimen. Treatment duration was defined as the number of days between regimen start date and treatment end date (prescription date plus number of days of supply). For example, if a beneficiary started a macrolide on 01/01/2013, ethambutol on 01/07/2013, and rifamycin on 01/14/2013, the therapy start date would be 01/14/2013 (the first date of the 3-drug prescription overlap). If the rifamycin prescription ended on 06/01/2013, but macrolide and ethambutol continued on, this would be considered a regimen change occurring on 06/01/2013. If the prescription for ethambutol also ended on 06/01/2013, and only the macrolide was continued, this would be considered a treatment end (no longer meeting the multi-drug therapy definition). All prescriptions ending was also considered treatment discontinuation.

5.3.4. Exposure time

For outcome 1, exposure time began at the time of therapy start, and ended: (1) after a 30-day grace period following the prescription end date; (2) at outcome occurrence; (3) at

Medicare coverage end (i.e. death); (4) end of follow-up (365 days since therapy start date); (5) or at data end date (12/31/2014), which ever came first. For outcomes 2 and 3, exposure time began at the time of therapy start, and ended: (1) at the time of regimen change or discontinuation (outcome occurrence); (2) end of Medicare coverage (i.e. death); (3) end of follow-up (365 days since therapy start date), or at data end date (12/31/2014), whichever came first.

5.3.5. Statistical analysis

I described the cohort's demographic characteristics such as age at treatment start, sex and race, and clinical characteristics such as underlying conditions during the baseline period. To test the hypotheses, I examined the associations between MAC treatment regimens and therapy-associated adverse events occurring within 12 months of treatment start (hearing loss, tinnitus, gastrointestinal disturbance, or QT prolongation for macrolide comparisons, and cytopenias for the rifamycin comparisons). We also examined the association between each specific MAC treatment regimen and the regimen change or discontinuation within 12 months of the MAC therapy start date. Cox proportional hazards models were used to examine these associations. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated to compare the occurrence of the outcomes in the MAC therapy regimens of interest. Due to the low frequency, macrolide-associated adverse events (QT prolongation, hearing loss, tinnitus, or gastrointestinal disturbance) were collapsed into a composite measure. Multivariable Cox models were used to examine potential confounding effects of select baseline characteristics and concomitant medications on the association between MAC treatment

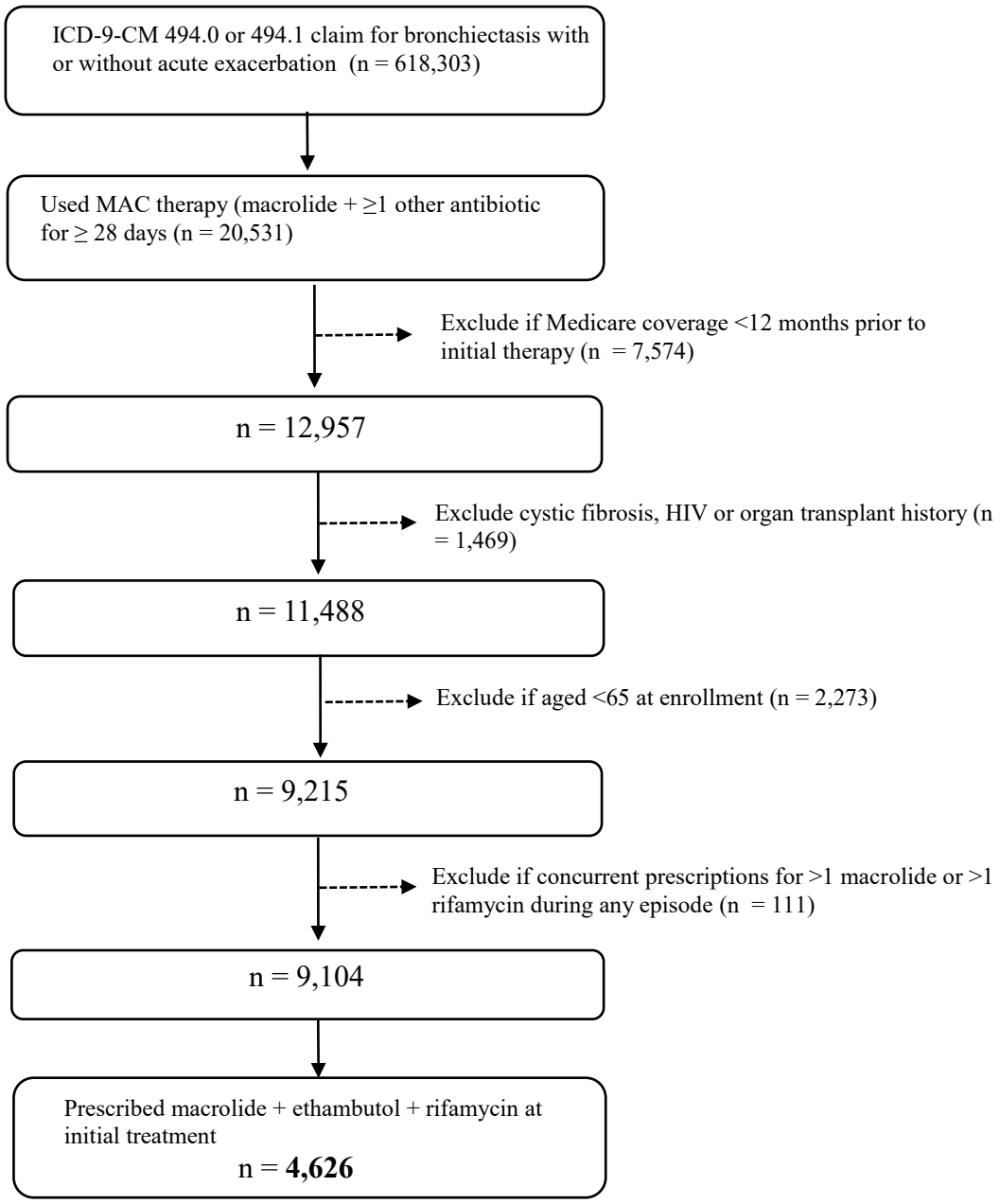
regimen and the tolerability outcomes. Adjusted models controlled for covariates selected *a priori* based on a causal model and associated directed acyclic graphs.[71] Selected covariates were: demographics (sex, region of residence, age at treatment start, and race/ethnicity as a proxy for disparities due to racism in prescribing practices[72]); baseline Charlson comorbidities scores[62] as an index for comorbidities; and concomitant medications used during the baseline period (digoxin, anticoagulants, antihypertensive/beta-blockers, narcotics, and oral steroids). Covariate-adjusted Kaplan-Meier curves were estimated to illustrate the time-without-adverse event or time-without-regimen change/discontinuation during the first 12-month period on MAC therapy. I checked for the model assumptions by: visual inspection of the survival functions; Schoenfeld residuals and proportionality to check for the proportional hazards assumption; and Martingale residuals to check for non-linearity. Because my cohort included older individuals, I performed a sensitivity analysis after excluding those who died within the first 12 months of MAC therapy start date. All analyses were performed using SAS statistical software 9.4 (SAS Institute Inc., https://www.sas.com). This study was reviewed and approved by the Institutional Review Board at Oregon Health & Science University.

5.4. Results

There were 4,626 beneficiaries who were prescribed a guideline-recommended 3-drug regimen (macrolide, ethambutol and rifamycin) at initial treatment for pulmonary MAC (**Figure 5.1**). The cohort had a mean age of 77.9 years (s.d. = 6.1) at treatment start, was mostly female (77.7%), non-Hispanic white (87.2%), and had been enrolled in Medicare

for a mean duration of 7.0 years (s.d. = 2.2) prior to treatment initiation (**Table 5.1**). Chronic obstructive pulmonary disease/emphysema (74.5%) and gastroesophageal reflux (55.9%) were among the most common comorbidities present during the baseline period. We did not observe substantial differences in the baseline demographic or clinical characteristics across the macrolide or rifamycin comparison groups.

Figure 5.1. Flow diagram of the analytic population: 4,626 Medicare beneficiaries prescribed a guideline-based 3-drug regimen (macrolide, ethambutol and a rifamycin) at initial treatment for pulmonary *Mycobacterium avium* complex (MAC) between 2006 and 2014



A total of 138 (3.0%) beneficiaries experienced a macrolide-associated adverse event (QT prolongation, hearing loss, tinnitus, or gastrointestinal disturbance) within the first 12 months of treatment start date (**Table 5.2**). Of these, 93 (3.1%) were among those prescribed an azithromycin-ethambutol-rifamycin regimen, and 45 (2.7%) were among those receiving a clarithromycin-ethambutol-rifamycin regimen. A total of 110 (2.4%) beneficiaries developed cytopenia within the first 12 months of treatment start. Ninety-three (2.3%) were among those receiving a macrolide-ethambutol-rifampin regimen, while 17 (2.8%) were among those receiving a macrolide-ethambutol-rifamycin regimen. Regimen changes and discontinuations were more frequently observed than drug-associated adverse events. Within the first 12 month of MAC therapy start, 3,928 (84.9%) either changed or discontinued their first regimen. In the macrolide comparison groups, regimen change/discontinuation was slightly more common for those prescribed a clarithromycin-based regimen (n = 1,421; 86.3%), compared to those prescribed an azithromycin-based regimen (n = 2,507; 84.1%).

Cox proportional hazard regression models did not demonstrate a significant association between the macrolide-comparison groups and the time to macrolide-associated adverse event within 12 months of therapy start (**Table 5.3**). Similarly, no statistically significant association between the time-to-cytopenia and rifamycin-comparison groups was observed. As such, the covariate-adjusted Kaplan Meier curves (**Figures 5.2A** and **5.2B**) for these associations did not illustrate divergence of the two lines, indicating that survival functions of the outcome (% without adverse events) were similar between the regimen groups for either the macrolide or rifamycin comparison. However, the rate of

regimen change/discontinuation within 12 months of therapy start was 12% higher for those who were prescribed a clarithromycin-ethambutol-rifampin regimen compared to an azithromycin-ethambutol-rifampin regimen at therapy start (adjusted HR: 1.12, 95% CI: 1.04, 1.29). Similarly, the rate of regimen change/discontinuation in those prescribed a rifabutin-containing regimen was significantly higher compared to a rifampin-containing regimen (adjusted HRs: 1.49, 95% CI: 1.33, 1.68 for azithromycin-ethambutol-rifabutin versus azithromycin-ethambutol-rifampin, and 1.47, 95% CI: 1.27, 1.70 for clarithromycin-ethambutol-rifabutin versus clarithromycin-ethambutol-rifampin). These observations were consistent with covariate-adjusted Kaplan Meier curves (**Figures 5.3 – 5.5**), which illustrated divergence of the lines indicating a statistically significant difference in the survival functions for regimen change or discontinuation in each of the macrolide and rifamycin comparison groups. The increase in the rate of drug regimen change or discontinuation was as high as 65% greater in those prescribed a clarithromycin-ethambutol-rifabutin regimen compared to an azithromycin-ethambutol-rifampin regimen (adjusted HR: 1.64, 95% CI: 1.43, 1.64)

In a sensitivity analysis, I repeated the proportional cox regression analyses after excluding beneficiaries who died within the first 12 months of therapy start date (**Appendix D.1**); results of the sensitivity analysis were consistent with our primary analyses. I observed a consistently greater hazard rate for regimen change or discontinuation in the clarithromycin-based regimen compared to the azithromycin-based regimen. Similarly, I observed a consistent and statistically significant increase in the

hazard rate of change/discontinuation in those prescribed a rifabutin-containing regimen compared to a rifampin-containing regimen.

Table 5.1. Baseline demographic and clinical characteristics of 4,626 U.S. Medicare beneficiaries prescribed guideline-based 3-drug antibiotic therapy for pulmonary *Mycobacterium avium* complex infection between January 2006 and December 2014

Characteristics	Azithromycin + ethambutol + rifamycin (n=2,980)	Clarithromycin + ethambutol + rifamycin (n=1,646)	Macrolide + ethambutol + rifampin (n=4,011)	Macrolide + ethambutol+ rifabutin (n=615)
Demographic characteristics				
Age at enrollment (years)	78.1 (s.d. 6.0)	77.6 (s.d. 6.1)	77.9 (s.d. 6.1)	78.1 (s.d. 6.1)
Female	2,360 (79.2%)	1,236 (75.1%)	3,119 (77.7%)	477 (77.6%)
Hispanic	129 (4.3%)	64 (4.8%)	165 (4.1%)	27 (4.4%)
Race				
White	2,603 (87.4%)	1,432 (87.0%)	3,499 (87.2%)	536 (87.2%)
Asian	159 (5.3%)	95 (5.8%)	226 (5.6%)	28 (4.6%)
Hispanic	129 (4.3%)	63 (3.8%)	165 (4.1%)	27 (4.4%)
Black	57 (1.9%)	34 (2.1%)	73 (1.8%)	18 (2.9%)
North American Native	<10 (< 0.3%)	<10 (<1.5%)	<10 (<0.2%)	<10 (<1.5%)
Unknown	<10 (< 0.3%)	<10 (<1.5%)	<10 (<0.2%)	<10 (<1.5%)
Other	24 (0.8%)	17 (1.0%)	36 (0.9%)	<10 (<1.5%)
Number of years in Medicare since age 65	7.0 (s.d. 2.2)	7.0 (s.d. 2.2)	7.0 (s.d. 2.2)	6.9 (s.d. 2.3)
U.S. Regions				
South	1,226 (41.3%)	729 (44.3%)	1,711 (42.8%)	244 (39.7%)
West	604 (20.3%)	350 (21.3%)	832 (20.8%)	122 (19.9%)
Northeast	573 (19.3%)	235 (14.3%)	684 (17.1%)	124 (20.2%)
Midwest	567 (19.1%)	330 (20.1%)	773 (19.3%)	124 (20.2%)
Clinical characteristics				
Chronic obstructive pulmonary disease / emphysema	2,184 (73.3%)	1,263 (76.7%)	2,996 (74.7%)	451 (73.3%)
Gastroesophageal reflux	1,695 (56.9%)	893 (54.3%)	2,250 (56.1%)	338 (55.0%)
Asthma	871 (29.2%)	472 (28.7%)	1,171 (29.2%)	172 (28.0%)
Diabetes mellitus	823 (27.6%)	443 (26.9%)	1,092 (27.2%)	174 (28.3%)
Rheumatologic disease	707 (23.7%)	370 (22.5%)	930 (23.2%)	147 (23.9%)
Pseudomonas infection	204 (6.9%)	114 (6.9%)	270 (6.7%)	48 (7.8%)
Lung cancer	259 (8.7%)	173 (10.5%)	370 (9.2%)	62 (10.1%)
Primary immune deficiency	151 (5.1%)	75 (4.6%)	193 (4.8%)	33 (5.4%)
Allergic bronchopulmonary aspergillosis	27 (0.9%)	16 (1.0%)	37 (0.9%)	<10 (<1.5%)
Alpha-1-antitrypsin deficiency	11 (0.4%)	<10 (<1.5%)	16 (0.4%)	<10 (<1.5%)

Primary ciliary dyskinesia	<10 (< 0.3%)	<10 (<1.5%)	<10 (<0.2%)	<10 (<1.5%)
Silicosis	<10 (< 0.3%)	<10 (<1.5%)	<10 (<0.2%)	<10 (<1.5%)
Charlson modified comorbidities index score	2.1 (s.d. 1.6)	2.2 (s.d. 1.6)	2.1 (s.d. 1.6)	2.2 (s.d. 1.8)
Concomitant drugs				
Oral corticosteroid	1,679 (56.3%)	910 (55.3%)	2,260 (56.4%)	329 (53.5%)
Antihypertensive / beta-blocker	2,288 (49.5%)	1,277 (27.6%)	3,093 (66.9%)	472 (10.2%)
Narcotics	1,905 (41.2%)	1,013 (21.9%)	2,533 (54.8%)	385 (8.3%)
Digoxin	243 (5.3%)	125 (2.7%)	324 (6.0%)	44 (1.0%)
Anticoagulants	65 (2.2%)	43 (0.9%)	87 (1.9%)	21 (0.5%)
Healthcare Utilization				
Number of clinician office visits per year	5.4 (s.d. 4.6)	4.9 (s.d. 4.6)	5.2 (s.d. 4.6)	5.5 (s.d. 5.0)
Number of visits to pulmonologist per year	1.4 (s.d. 1.7)	1.4 (s.d. 2.2)	1.4 (s.d. 2.0)	1.4 (s.d. 1.5)
Number of any hospitalization per year	1.0 (s.d. 1.4)	1.1 (s.d. 1.7)	1.0 (s.d. 1.5)	1.1 (s.d. 1.5)
Number of hospitalization due to respiratory illness per year	1.0 (s.d. 1.4)	1.1 (s.d. 1.7)	1.0 (s.d. 1.5)	1.1 (s.d. 1.5)
Number of visits to infectious disease specialist per year	0.6 (s.d. 0.9)	0.6 (s.d. 0.9)	0.6 (s.d. 0.9)	0.6 (s.d. 1.0)
Number of acute exacerbations per year	0.6 (s.d. 0.7)	0.7 (s.d. 0.7)	0.6 (s.d. 0.7)	0.6 (s.d. 0.7)

Table 5.2. MAC therapy-associated adverse events or regimen change/discontinuation occurring within 12 months of pulmonary MAC therapy in 4,626 U.S. Medicare beneficiaries prescribed guideline-based 3-drug antibiotic therapy for pulmonary *Mycobacterium avium* complex (MAC) infection between January 2006 and December 2015

MAC therapy-associated adverse events occurring within 12 months of MAC therapy start				
	n (%)	Time to adverse event (days) Mean (s.d.); median (25^{th}, 75^{th} percentile)	n (%)	Time to adverse event (days) Mean (s.d.); median (25^{th}, 75^{th} percentile)
Outcomes	Azithromycin + ethambutol + rifamycin (n=2,980)		Clarithromycin + ethambutol + rifamycin (n=1,646)	
QT prolongation (ICD-9-CM 426.82)	<10 (0.1%)	151.6 (s.d. 181.7); 151.5 (IQR: 23.0, 280.0)	<10 (0.1%)	139.5 (s.d. 111.0); 139.5 (IQR: 61.0, 218.0)
hearing loss (ICD-9-CM 389.9)	56 (1.9%)	173.0 (s.d. 176.4); 100.0 (IQR: 22.0, 384.0)	25 (1.5%)	116.5 (s.d. 194.5); 100.0 (IQR: 36.0, 175.0)
tinnitus ICD-9-CM (388.3X)	33 (1.1%)	164.3 (s.d. 126.4); 146.0 (IQR: 49.0, 280.5)	18 (1.1%)	99.2 (s.d. 92.1); 83.0 (IQR: 22.0, 142.0)
gastrointestinal disturbance (ICD-9-CM 536.9)	<10 (0.1%)	219.8 (s.d. 146.7); 255.0 (IQR: 130.0, 309.5)	<10 (0.1%)	25.0 (s.d. 18.4); 25.0 (IQR: 12.0, 38.0)
all adverse events combined	93 (3.1%)	150.5 (s.d. 154.4); 87.0 (IQR: 23.0, 252.0)	45 (2.7%)	129.2 (s.d. 113.4); 112.0 (IQR: 36.0, 112.0)
	Macrolide + ethambutol + rifampin (n=4,011)		Macrolide + ethambutol + rifamycin (n=615)	
Cytopenia (pancytopenia ICD-9-CM 284.19, thrombocytopenia ICD-9-CM 287.5)	93 (2.3%)	99.7 (s.d. 120.6); 59.0 (IQR: 21.0, 131.0)	17 (2.8%)	108.4 (s.d. 141.5); 24.0 (IQR: 14.0, 148.0)
Regimen change or discontinuation occurring within 12 months of MAC therapy start				
Outcomes	n (%)	Time to regimen change/discontinuation (days) Mean (s.d.); median (25^{th}, 75^{th} percentile)	n (%)	Time to regimen change/discontinuation (days) Mean (s.d.); median (25^{th}, 75^{th} percentile)
	Azithromycin + ethambutol + rifamycin (n=2,980)		Clarithromycin + ethambutol + rifamycin (n=1,646)	

Drug regimen change/ discontinuation	2,507 (84.1%)	282.7 (s.d. 175.6); 113.0 (IQR: 42.0, 282.0)	1,421 (86.3%)	154.5 (s.d. 166.8); 91.5 (IQR: 31.0, 244.0)
	Macrolide + ethambutol + rifampin (n=4,011)		Macrolide + ethambutol + rifamycin (n=615)	
Drug regimen change/ discontinuation	3,371 (84.0%)	184.7 (s.d. 175.6); 117.0 (IQR: 46.0, 283.0)	557 (90.6%)	123.7 (s.d. 141.5); 61.0 (IQR: 31.0, 158.0)
	Azithromycin + ethambutol + rifampin (n = 2,607)		Clarithromycin + ethambutol + rifamycin (n = 242)	
Drug regimen change/ discontinuation	2,607 (83.3%)	189.3 (s.d. 178.2); 122.0 (IQR: 51.0, 293.0)	242 (8.5%)	115.9 (s.d. 134.3); 62.0 (IQR: 31.0, 134.0)

Table 5.3. Drug-associated adverse events or regimen change/discontinuation occurring within 12 months of therapy start in 4,626 U.S. Medicare beneficiaries prescribed guideline-based 3-drug antibiotic therapy for pulmonary *Mycobacterium avium* complex (MAC) between January 2006 and December 2015

Drug-associated adverse events occurring within 12 months of MAC therapy start				
Exposure groups	n	outcome n (%)	Unadjusted model Hazard ratio (95% CI)	Adjusted model[+] Hazard ratio (95% CI)
Macrolide (with ethambutol and rifamycin) comparison[*]				
Azithromycin, ethambutol, rifamycin (Reference)	2,980	93 (3.1%)	-	-
Clarithromycin, ethambutol, rifamycin	1,646	45 (2.7%)	0.95 (95% CI: 0.66, 1.38)	0.97 (95% CI: 0.67, 1.40)
Rifamycin (with macrolide and ethambutol) comparison[**]				
Macrolide, ethambutol, rifampin (Reference)	4,011	93 (2.3%)	-	-
Macrolide, ethambutol, rifabutin	615	17 (2.8%)	1.32 (95%CI: 0.76, 2.29)	1.32 (95% CI: 0.76, 2.28)
Regimen change or discontinuation occurring within 12 months of MAC therapy start				
Exposure groups	n	outcome n (%)	Unadjusted model Hazard ratio (95% CI)	Adjusted model[+] Hazard ratio (95% CI)
Macrolide (with ethambutol and rifampin) comparison				
Azithromycin, ethambutol, rifampin (Reference)	2,607	2,171 (83.3%)	-	-
Clarithromycin, ethambutol, rifampin	1,404	1,200 (85.5%)	1.10 (95% CI: 1.02, 1.18)	1.12 (95% CI: 1.04, 1.20)
Macrolide (with ethambutol and rifabutin) comparison				
Azithromycin, ethambutol, rifabutin (Reference)	373	336 (90.1%)	-	-
Clarithromycin, ethambutol, rifabutin	242	221 (91.3%)	1.08 (95% CI: 0.91, 1.28)	1.11 (95% CI: 0.93, 1.32)
Rifamycin (with azithromycin and ethambutol) comparison				
Azithromycin, ethambutol, rifampin (Reference)	2,607	2,171 (83.3%)	-	-
Azithromycin, ethambutol, rifabutin	373	336 (90.1%)	1.50 (95% CI: 1.34, 1.69)	1.49 (95% CI: 1.33, 1.68)
Rifamycin (with clarithromycin and ethambutol) comparison				
Clarithromycin, ethambutol, rifampin (Reference)	1,404	1,200 (85.5%)	-	-
Clarithromycin, ethambutol, rifabutin	242	221 (91.3%)	1.49 (95% CI: 1.24, 1.72)	1.47 (95% CI: 1.27, 1.70)
Azithromycin/Clarithromycin, ethambutol, rifampin/rifabutin				
Azithromycin, ethambutol, rifampin (Reference)	2,607	2,171 (83.3%)	-	-
Clarithromycin, ethambutol, rifabutin	242	221 (91.3%)	1.65 (95% CI: 1.44, 1.90)	1.64 (95% CI: 1.43, 1.64)

[*]Model for the outcome of macrolide-associated adverse events occurring within 12 months of MAC therapy start (gastrointestinal disturbance, QT prolongation, hearing loss and tinnitus).

[**]Model for the outcome of rifamycin-associated adverse events occurring within 12 months of MAC therapy start (cytopenias to include pancytopenia and thrombocytopenia).

[+]Model included sex, region of residence, race/ethnicity, Charlson comorbidities index, age at treatment start and concomitant medications used during the baseline period (digoxin, anticoagulants, antihypertensive/beta-blockers, narcotics, and oral steroids).

Abbreviations: 95% CI = 95% confidence interval

Figure 5.2A. Covariate adjusted Kaplan-Meier curves comparing time-to-macrolide-associated adverse event among U.S. Medicare beneficiaries prescribed **azithromycin vs. clarithromycin plus ethambutol and rifamycin** for pulmonary MAC infection (January 2006 – December 2014)

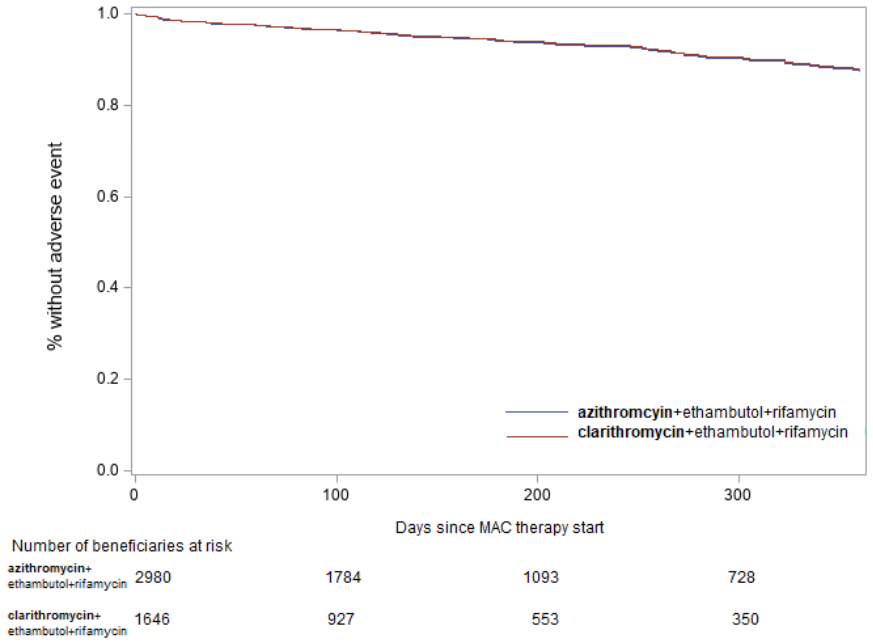


Figure 5.2B. Covariate adjusted Kaplan-Meier curves comparing time-to-macrolide-associated adverse event among U.S. Medicare beneficiaries prescribed **macrolide and ethambutol plus rifampin vs. rifabutin** for pulmonary MAC infection (January 2006 – December 2014)

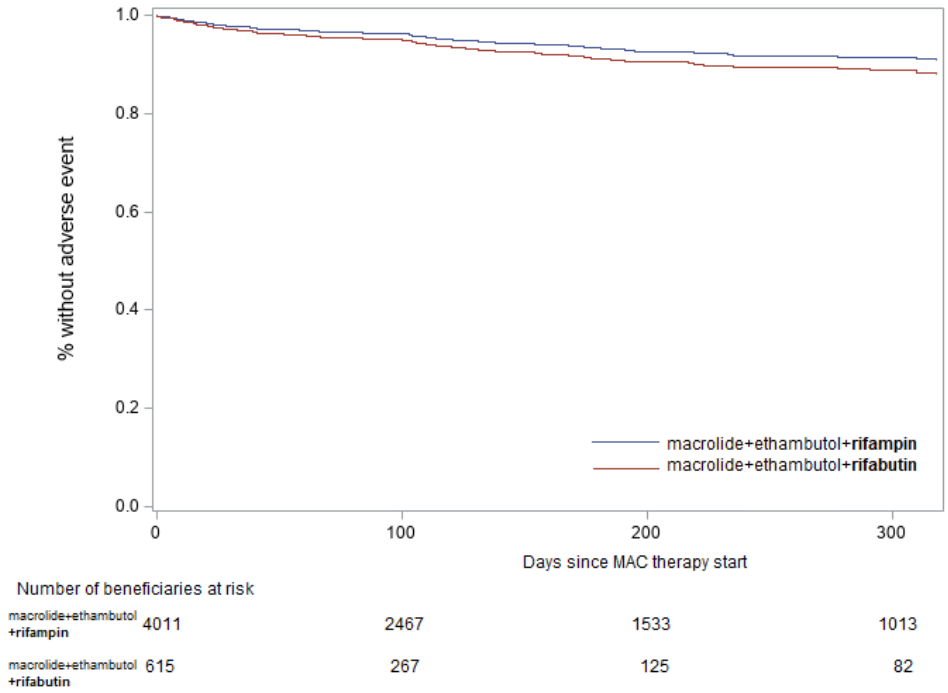
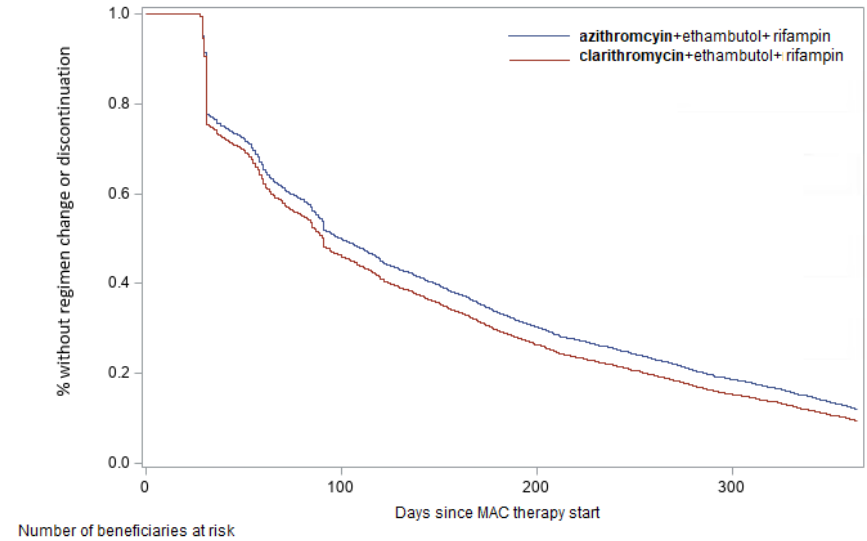


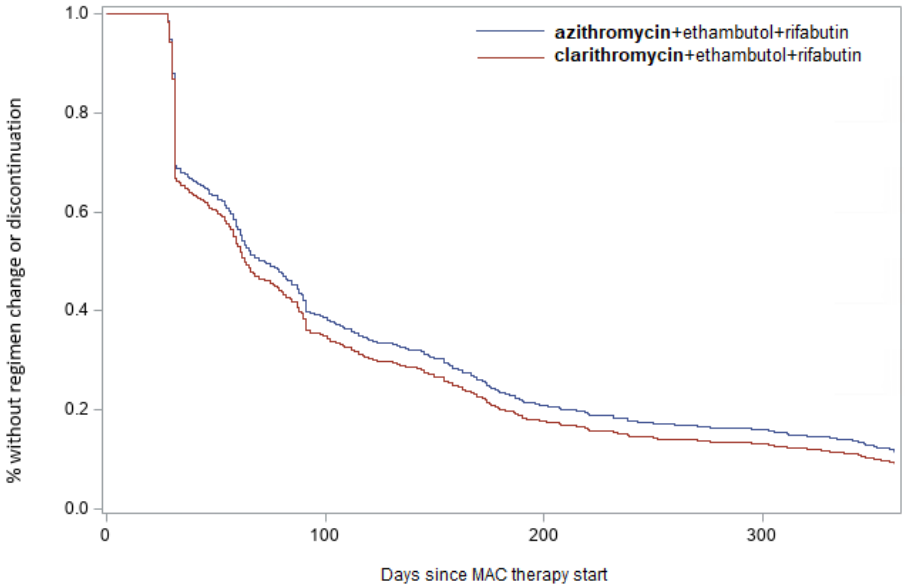
Figure 5.3A. Covariate adjusted Kaplan-Meier curves comparing time to regimen change or discontinuation among U.S. Medicare beneficiaries prescribed **azithromycin vs. clarithromycin plus ethambutol and rifampin** for pulmonary MAC infection (January 2006 – December 2014)



Number of beneficiaries at risk

azithromycin+ ethambutol+rifampin	2607	1441	943	634
clarithromycin+ ethambutol+rifampin	1404	715	458	296

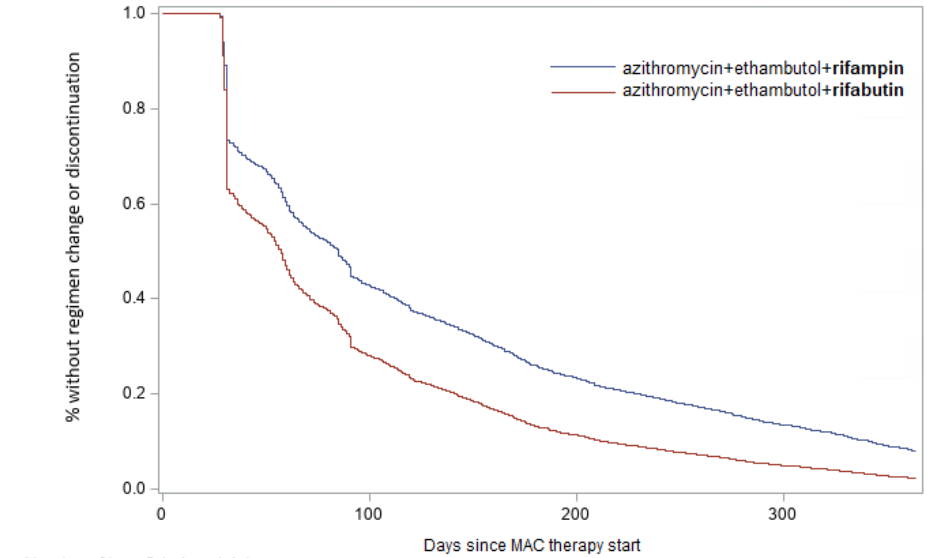
Figure 5.3B. Covariate adjusted Kaplan-Meier curves comparing time to regimen change or discontinuation among U.S. Medicare beneficiaries prescribed **azithromycin vs. clarithromycin plus ethambutol and rifabutin** for pulmonary MAC infection (January 2006 – December 2014)



Number of beneficiaries at risk

azithromycin+ ethambutol+rifabutin	373	132	73	54
clarithromycin+ ethambutol+rifabutin	242	77	36	29

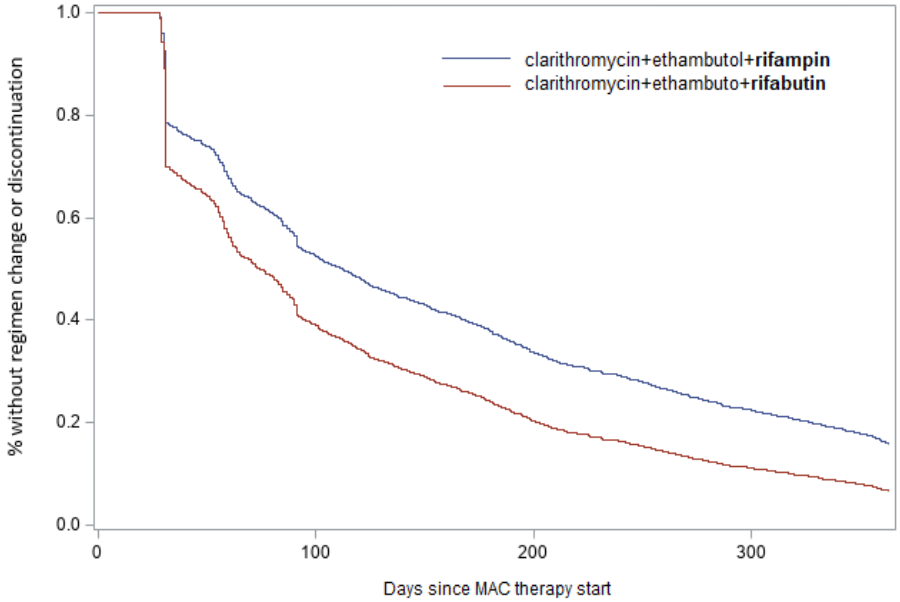
Figure 5.4A. Covariate adjusted Kaplan-Meier curves comparing time to regimen change or discontinuation among U.S. Medicare beneficiaries prescribed **azithromycin, ethambutol plus rifampin vs. rifabutin** for pulmonary MAC infection (January 2006 – December 2014)



Number of beneficiaries at risk

azithromycin+ethambutol+rifampin	2607	1441	943	634
azithromycin+ethambutol+rifabutin	373	132	73	54

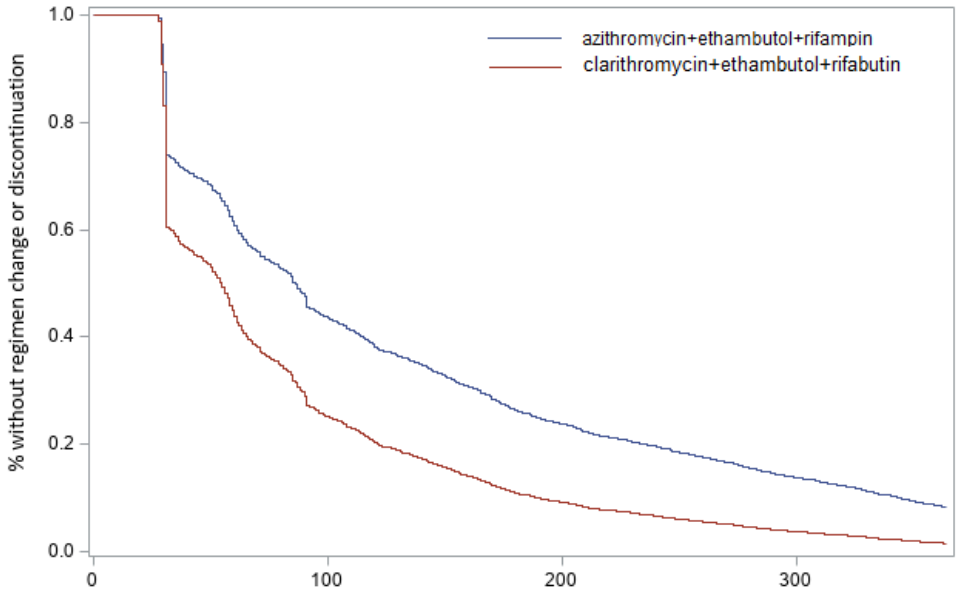
Figure 5.4B. Covariate adjusted Kaplan-Meier curves comparing time to regimen change or discontinuation among U.S. Medicare beneficiaries prescribed **clarithromycin, ethambutol plus rifampin vs. rifabutin** for pulmonary MAC infection (January 2006 – December 2014)



Number of beneficiaries at risk

clarithromycin+ethambutol+rifampin	1404	715	458	296
clarithromycin+ethambutol+rifabutin	242	77	36	29

Figure 5.5. Covariate adjusted Kaplan-Meier curves comparing time to regimen change or discontinuation among U.S. Medicare beneficiaries prescribed **azithromycin-ethambutol-rifampin regimen versus clarithromycin-ethambutol-rifabutin regimen** for pulmonary MAC infection (January 2006 – December 2014)



Number of beneficiaries at risk

azithromycin+ ethambutol-rifampin	2607	1441	943	634
clarithromycin+ ethambutol+rifabutin	242	77	36	29

5.5. Discussion

In this aim, I used U.S. Medicare claims data, a large population-based data source representative of the older U.S. population with access to care, to examine the association between guideline-based 3-drug regimens for pulmonary MAC, and tolerability outcomes. As hypothesized, the results showed that a clarithromycin-based regimen as initial pulmonary MAC therapy was associated with a substantially higher rate of regimen change or discontinuation within 12 months of therapy start, compared to an azithromycin-based regimen. The rate of regimen change or discontinuation was further elevated in those prescribed a rifabutin-containing regimen, compared to a rifampin-containing regimen. The results demonstrated a striking 64% increase in the hazard rate of regimen change/discontinuation in the clarithromycin-ethambutol-rifabutin regimen compared to the azithromycin-ethambutol-rifampin regimen. I did not observe a statistically significant difference in the time-to-adverse event outcomes.

In previous studies, the rate of therapy discontinuation due to drug-associated side effects has been estimated as 10 - 30%, and treatment success rates based on microbiologic and clinical outcomes have been estimated as only 40 - 60%.[48 66] In most of the published clinical trials of treatment with macrolides, a large proportion of patients required a change from the planned treatment because of side effects. In a French study of 45 patients treated with a clarithromycin-based therapy, adverse events were common (mild hearing loss [n = 4], elevated liver enzyme levels [n = 5], and gastrointestinal pain [n = 10]).[68] Of the 45, 41 (91%) patients stopped treatment after a mean period of 300 days due to side effects (n = 3), patient's decision (n = 5) or physician's decision (n = 33); the

remaining 4 died. A U.S. study reported on 50 patients treated with a clarithromycin, ethambutol and a rifampin or rifabutin, of which 41% discontinued one or more companion drugs due to adverse events within the first 3 months.[54] In another U.S. study, 59 patients on clarithromycin, ethambutol and rifabutin were prospectively followed. Of the 59, 10% developed clarithromycin intolerance, and 41% prematurely discontinued therapy or decreased dose due to rifabutin-associated adverse reactions within 6 months.[73] In another U.S. study, in which 30 patients received either clarithromycin or azithromycin, ethambutol, and clofazimine, 22 (73%) reported adverse effects from clarithromycin or azithromycin within 12 months of treatment start (16/19 on clarithromycin and 6/11 on azithromycin [p = 0.08]);[48] these adverse events necessitated a change from the planned treatment protocol, or led to premature discontinuation. Results from previously published studies are difficult to compare directly because of the heterogeneity in patient inclusion criteria, definition of treatment outcomes, and because some studies included patients who had been previously treated for MAC; gender proportions, and pattern and extent of lung disease, also varied in different studies.

In this work, among the 4,626 who started treatment with a guideline-recommended 3-drug regimen for pulmonary MAC, 84% changed or discontinued their regimen within 12 months of therapy start. As hypothesized, the rate of regimen change/discontinuation was higher in those on a clarithromycin-based regimen compared to those on an azithromycin-based regimen, and higher in the rifabutin-containing regimen compared to rifampin-containing regimen. The current guidelines recommend azithromycin over clarithromycin because of better tolerance, less drug-interactions, less pills, single daily

dosing and equal efficacy.[7] The guidelines recommend clarithromycin as an acceptable alternative in case azithromycin is not available or not tolerated. Because no correlation between in vitro susceptibility results for MAC and clinical response for agents other than macrolides has been established, macrolides and amikacin are the only drugs for which susceptibility testing for MAC isolates is recommended.[5] Although clarithromycin appears more potent in laboratory testing than azithromycin (i.e., typically lower minimum inhibitory concentration), drug levels of clarithromycin decreases when given in combination with a rifamycin. Thus, effects of clarithromycin *in vivo* are less clear. Macrolides are the only antimicrobial agents for which there is a demonstrated correlation between *in vitro* susceptibility and *in vivo* response for pulmonary MAC. Macrolides therefore are considered cornerstones of MAC therapy, with the addition of ethambutol and a rifamycin. Less is known about the comparative safety and tolerability of rifampin and rifabutin. Rifampin is known to cause more drug-to-drug interactions than rifabutin. However, rifampin is inexpensive and easily available thus most often chosen over rifabutin. Known adverse events of rifamycins include cytopenias (thrombocytopenia and pancytopenia), and less frequent adverse events include hepatotoxicity, nausea with vomiting, dizziness, muscle weakness. Of the two rifamycins, rifampin is thought to be better tolerated than rifabutin.[5 7] Our results showed that the rate of regimen change/discontinuation was significantly higher in those prescribed a rifabutin-containing-3-drug-regimen compared to a rifampin-containing regimen.

The rate of macrolide-associated adverse events was not significantly different between those on an azithromycin-based regimen and a clarithromycin-based regimen. The hazard

rate of cytopenias was mildly elevated in those prescribed a rifabutin-containing regimen compared to rifampin-containing regimen, but this difference was not statistically significant. I think that these null findings may be largely due to under-reporting of adverse events in Medicare data. Mild cases that did not require a clinical evaluation or intervention were likely missed because I used diagnosis-based claims data. In fact, auditory outcomes such as tinnitus and hearing loss that do not meet the clinical threshold, and thus do not lead to a documented clinical diagnosis are often under-reported in observational studies.[74] Common, but relatively tolerable adverse events such as gastrointestinal disturbance are often missed in claims data unless they become severe enough to require medical intervention.

This work has several notable strengths. U.S. population-based data on NTM disease are generally scarce, and data on treatment outcomes of pulmonary NTM are severely lacking. This work adds important data to the current literature on tolerability outcomes of guideline-recommended 3-drug regimens prescribed for pulmonary MAC infection among U.S. Medicare beneficiaries. Pulmonary NTM disease primarily affects older individuals and recent increases in incidence and prevalence in the U.S. have been most evident among persons aged 60 years or older. Given the age distribution of NTM disease, Medicare claims data, representative of the older U.S. population, provide a readily available, inexpensive, and efficient tool to conduct epidemiologic studies on NTM. Additionally, Medicare data are nearly complete with minimal missing data as they theoretically capture the entirety of beneficiaries' healthcare encounters, including pharmacy prescriptions in those with Part D coverage.

Our study also has some limitations. First, I did not have access to beneficiaries' full treatment history prior to Medicare enrollment to ensure all adverse events were truly incident events. I required at least 12 months of a baseline period prior to treatment start to be included in the cohort. If there was a claim made for an adverse event during this baseline period, that adverse event was not counted as an outcome. I still may have counted some adverse events as new events if they existed prior to Medicare enrollment, potentially making the association appear stronger than truly is. Despite this, I still observed null associations between adverse events and drug regimens. Second, if an adverse event of interest occurred while on therapy, and within 12 months of therapy start, the adverse event was considered "associated" with the drug of interest. This is an important assumption made based on *a prior* knowledge of adverse events typically described as common side effects of that drug, when in fact the adverse events could be due to any of the companion drugs given in a 3-drug combination, or other factors such as viral disease-causing diarrhea. This work is limited in understanding whether these events are truly associated with the drug of interest. Third, dosage information was not included in my analyses. However, because dosage and dosing frequency of macrolides, ethambutol and rifamycins used for treatment of pulmonary MAC are fairly standard, I do not anticipate that adding data on dosage would change our results. Fourth, because I used prescription start date and day of supply to determine treatment start and end dates, I could have captured some beneficiaries who were given prescriptions meeting the MAC therapy definition, but never filled the prescriptions. I required an overlap in all three drugs (macrolide, ethambutol and rifamycin) for at least 28 days to minimize this

misclassification. Confounding by indication could be of concern if beneficiaries prescribed one regimen were inherently different from those prescribed another (e.g., indication or reasons for taking that drug). However, based on *a priori* knowledge, those prescribed azithromycin are not inherently different from those prescribed clarithromycin, and those prescribed rifampin are not inherently different from those prescribed rifabutin. Immortal time bias could also be of concern because beneficiaries were not classified as 'exposed' until filling prescriptions for MAC therapy sometime after entering the cohort (i.e., beneficiaries must have 'survived' the time between entering the cohort and the first prescription for MAC therapy). However, in this study, as opposed to comparing 'treated' versus 'untreated', those exposed to one regimen were compared to those exposed to another. Therefore, if immortal time bias existed, the bias would be non-differential across the comparison groups. Lastly, because the study cohort consisted of Medicare beneficiaries aged 65 years and older with bronchiectasis, generalizability of our findings to younger patient populations and those without bronchiectasis may be limited.

In summary, I evaluated tolerability outcomes of guideline-based 3-drug regimens for pulmonary MAC infection among Medicare beneficiaries with bronchiectasis. Findings indicated that an azithromycin-based regimen is less likely to be changed or discontinued than a clarithromycin-based regimen, and that a rifampin-containing regimen is less likely to be changed or discontinued than a rifabutin-containing regimen within 12 months of therapy start. Further, a clarithromycin-ethambutol-rifabutin regimen had a far worse tolerability outcome than an azithromycin-ethambutol-rifampin regimen. Data on

tolerability outcomes are critical to guide clinicians in their treatment decision-making, and to better council patients about the potential risks of therapy to guide them make informed treatment decisions. My work provides a population-based assessment on the tolerability of multi-drug antibiotic regimens used for treatment of pulmonary MAC, using large data representative of the older U.S. population. More research is needed to better understand the safety and tolerability outcomes of NTM therapy in prospective studies using large, population-based data.

CHAPTER 6. SYNTHESIS OF RESEARCH

6.1. Summary

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that can cause chronic, debilitating pulmonary disease, among which *Mycobacterium avium* complex (MAC) is the most commonly encountered species. Pulmonary NTM disease often requires aggressive, long-term, multi-drug antibiotic therapy, which is frequently associated with substantial side effects leading to treatment interruptions and discontinuation. U.S. population-based epidemiologic data on NTM disease, particularly on therapy used for pulmonary MAC disease are scarce, and access to evidence-based therapy is limited among U.S. patients with MAC pulmonary disease. In this dissertation work, I presented a series of epidemiologic studies on pulmonary NTM. The aims of this dissertation were: 1) examine the validity of diagnosis code-based case definitions for pulmonary NTM infection in Medicare data using the U.S. Bronchiectasis & NTM Research Registry as a gold standard; 2) describe treatment patterns among first time MAC therapy users in U.S. Medicare beneficiaries with bronchiectasis; and 3) evaluate tolerability outcomes of MAC therapy in Medicare beneficiaries with pulmonary MAC disease.

In Chapter 3 (Aim 1), I validated NTM case definitions based on International Classification of Diseases (ICD) diagnosis codes in U.S. Medicare claims data, using the U.S. Bronchiectasis and NTM Research Registry (BRR) as a gold standard. I explored a

primary case definition defining pulmonary NTM infection as ≥1 inpatient discharge or outpatient visit code 031.0 (pulmonary mycobacterial infection) assigned by a clinician, and alternative definitions. For each case definition, I calculated positive predictive values (PPV) as the proportion of claim-based pulmonary NTM cases meeting the case definition in the BRR (gold standard) within ±12 months of the first Medicare claim. I calculated sensitivity as the proportion of those meeting a case definition in the BRR, who had a claim for pulmonary NTM in Medicare within ±12 months of meeting the BRR case definition (gold standard).

Diagnosis code-based claims had moderate validity for identifying cases of pulmonary NTM infection, but poor sensitivity. PPV was maximized when requiring a second claim at least 30 days apart from, but within 12 months of the first claim. PPV also improved when restricting to claims assigned by pulmonologists and infectious disease specialists. Overall, the results indicated that a case definition with ≥2 claims given 30 days apart within 12 months of each other accurately identifies patients with pulmonary NTM infection in the setting of bronchiectasis, but given low sensitivity, incidence may be severely underestimated in claims-based epidemiologic research. Overall, results from Aim 1 highlight that claims data provide important information about the epidemiology of NTM when clinical data are not readily and systematically available, but findings should be interpreted in light of potential misclassification.

In Chapter 4, (Aim2), I examined prescribing patterns of macrolide-based multi-drug antibiotic therapies for the treatment of pulmonary MAC infection in Medicare

beneficiaries aged 65 and older with bronchiectasis between January 2009 and December 2014. MAC therapy was defined as a prescription of ≥28 day-overlap in supply of a macrolide (azithromycin or clarithromycin) plus ≥1 of the following: rifamycin (rifampin or rifabutin), ethambutol, fluoroquinolone, or intravenous/ inhaled amikacin, requiring a minimum of 12 months of enrollment in Medicare without evidence of MAC therapy.

In the 9,189 first-time MAC therapy users, the guideline-recommended standard 3-drug regimen (macrolide + rifamycin + ethambutol with or without amikacin) was mostly commonly prescribed, of which only about half were continuing on the guideline-based regimen at 6 months. However, use of non-guideline-recommended therapy regimens were also common. Shockingly low percentages of beneficiaries were still on MAC therapy at months 6, 12 and 18. By 18 months. Overall, the most commonly prescribed initial regimen for pulmonary MAC infection was the guideline-based standard therapy in Medicare beneficiaries with bronchiectasis, although a large number of beneficiaries received a non-guideline-based therapy and even regimens associated with macrolide resistance. Treatment discontinuation was common, and once discontinued, only small numbers of beneficiaries resumed therapy at a later time.

Given the findings of common treatment discontinuations observed in Chapter 3 (Aim 2), the next logical research question was to investigate factors contributing to premature treatment discontinuations. Reasons for early treatment interruption and discontinuation are unclear, but many are likely due to tolerability issues such as drug-associated adverse events. Accordingly, in Chapter 4 (Aim 3), I examined the tolerability outcomes of multi-

drug antibiotic therapy prescribed for pulmonary MAC infection in U.S. Medicare beneficiaries with bronchiectasis. From the cohort of first-time MAC therapy users identified in Chapter 3 (Aim 2), those who were prescribed a guideline-recommended 3-drug regimen (macrolide, ethambutol and rifamycin) were identified. The comparison groups of interest were: (1) azithromycin-ethambutol-rifamycin versus clarithromycin-ethambutol-rifamycin (macrolide comparison); (2) macrolide-ethambutol- rifampin versus macrolide-ethambutol-rifabutin (rifamycin comparison); and (3) azithromycin-ethambutol-rifampin versus clarithromycin-ethambutol-rifabutin. I examined pre-specified adverse events typical of the drugs under study occurring while on therapy, and regimen change or discontinuation within 12 months of therapy start.

The results showed that a clarithromycin-based regimen as initial pulmonary MAC therapy was associated with a substantially higher rate of regimen change or discontinuation within 12 months of therapy start, compared to an azithromycin-based regimen. The rate of regimen change or discontinuation was further elevated in those prescribed with a rifabutin-containing regimen, compared to a rifampin-containing regimen. Our results demonstrated a striking, but an expected 64% increase in the rate of regimen change/discontinuation in the clarithromycin-ethambutol-rifabutin regimen compared to the azithromycin-ethambutol-rifampin regimen. This work provided an important population-based assessment on the tolerability of multi-drug antibiotic regimens used for treatment of pulmonary MAC, using large data representative of the older U.S. population.

Collectively, this work reflects a meaningful body of work covering construct validation (Aim 1), rigorous descriptive epidemiology (Aim 2) and examination of epidemiologic associations based on causal framework (Aim 3). This work addressed meaningful gaps identified earlier in the epidemiologic research for pulmonary NTM disease. Validation work from Aim 1 serves as the foundation of future quantitative research on the epidemiology of NTM. Results from Aim 2 and 3 provide critical data to inform more optimal treatment decisions, and ultimately to improve treatment outcomes.

6.2. Strengths

This work has several notable strengths. U.S. population-based data on NTM disease, particularly on therapy used for pulmonary NTM are scarce. Our study adds important data to the current literature on the validity of case definitions for pulmonary NTM used in the current literature. This work also provides noble data on prescribing practices for antibiotic therapy used to treat pulmonary MAC infection, and tolerability outcomes of guideline-recommended 3-drug regimens among U.S. Medicare beneficiaries. Medicare claims data provide a readily available, inexpensive, efficient and powerful tool to conduct epidemiologic studies. U.S. Pulmonary NTM disease primarily affects older individuals and recent increases in incidence and prevalence have been most evident among persons aged 60 years or older. Given the age distribution of NTM disease, and that >95% of U.S. seniors have Medicare coverage, these data provide an ideal source of healthcare administrative data to conduct epidemiologic studies that are representative of the older U.S. population with access to healthcare. Additionally, missing data are a very minor problem in the Medicare data system as Medicare data likely capture the entirety

of beneficiaries' healthcare encounters, including pharmacy prescriptions in those with Part D coverage.

6.3. Limitations

This work is not without limitations. Limitations specific to each aim were detailed in the Discussion section of each chapter (Chapters 3 – 5). For Aim 1, I validated NTM case definitions finding algorithms based on ICD-9-CM code-based definitions using the U.S. 2006-2014 Medicare data. ICD-9-CM codes may seem to have less utility than evaluating ICD-10 CM codes, because the current coding system is based on ICD-10-CM codes. However, the majority of the current studies on the epidemiology of NTM disease are based case definitions using ICD-9-CM codes. Moreover, ICD-9-CM codes map directly onto ICD-10-CM codes. Understanding the validity of the ICD-9-CM codes is essential to better understand and interpret results from the current literature and to inform planning and interpretation of our future work using ICD-10-CM codes.

Medicare claims data were utilized for all 3 aims. An important limitation inherent in using such healthcare administrative data for research is that these data are not collected for research purposes. The level of clinical detail encoded by the ICD coding system and problems related to coding accuracy (i.e. incorrect coding of diagnosis) may reduce the suitability of claim databases for use in epidemiology research. Although the magnitude and direction of such bias is not testable, the bias likely is minimal in magnitude as claims data are based on billing codes, which are assigned only when clinical services truly occur.

Further, because clinical data are not available in Medicare data, our case definition was based on prescriptions for a macrolide-based multi-drug regimen without microbiologic data. Because case identification could not be based on microbiologic data, misclassification of non-cases as pulmonary MAC cases was possible (e.g. those treated for another condition such as pseudomonas exacerbation, or for species other than MAC). Also, because data start date is Medicare enrollment date, beneficiaries' full treatment history prior to Medicare enrollment was not available to ensure all included beneficiaries were treatment naïve at Medicare enrollment at the age of 65 years. To minimize this misclassification bias, a minimum of 12 months of a non-treatment period prior to treatment start was required for inclusion into the cohort. Yet, it remains possible that some beneficiaries who received treatment prior to Medicare enrollment were included, and clinical response to prior therapy may have had an impact on the choice of subsequent therapy.

Medicare claims data are collected for billing purposes, and thus provide information on whether clinical procedures were performed. Some beneficiaries who were given prescriptions meeting our MAC therapy definition, but never filled the prescriptions could have still been included as MAC therapy users. The magnitude of this misclassification bias is not testable because Medicare data are de-identified. However, because treatment regimens are distinctively species-specific for MAC, the assumption that MAC therapy users will have MAC infection is reasonable, and misclassification is likely minimal. Similarly, claims dates, which were used to determine the date of adverse

event occurrence, may not necessarily be the date the adverse event actually occurred. Lastly, because the study cohort consisted of Medicare beneficiaries aged 65 years and older with bronchiectasis, it is unclear if the findings are generalizable to younger patients with pulmonary MAC disease or those without bronchiectasis.

6.4. Conclusions and public health impact

The results from this dissertation have clear and important public health implications for epidemiologic research on treatment for pulmonary MAC. We established that prevalence and incidence estimates reported in the previously literature need to be interpreted with the understanding that the estimates may be severely underestimated given the low sensitivity of ICD-9-CM code-based case definitions. We also found that adherence to the guideline-recommended therapy is generally poor, and premature treatment discontinuations are shockingly common. We observed that the use of clarithromycin-based regimen was associated with an increased rate of regimen change or discontinuation compared to a clarithromycin-based regimen. Similarly, the use of rifabutin-containing regimen was associated with an increase rate of regimen change or discontinuation compared to a rifampin-based regimen. Tolerability issues such as development of drug-associated adverse events could provide a reason.

In conclusion, this dissertation work presented important observations from a large U.S. population data source, which are critical in guiding clinicians and patients to make more informed and optimal treatment decisions. This dissertation helped fill the previously identified gaps in the epidemiologic research on pulmonary NTM, and to meet the unmet

need for U.S. population-based epidemiologic evidence for treatment decision making for pulmonary NTM. This dissertation generated critical evidence using Medicare data representative of the older U.S. population to help improve adverse event monitoring, inform the timing of therapy, and ultimately, increase therapy completion for better disease management and improved disease outcomes

6.5. Directions for future research

The body of research addressed in this dissertation work informs meaningful scientific questions and methodological areas for future epidemiologic research for pulmonary NTM. The Medicare data utilized in this work ended in December 2014, limiting the sample size and observation time. Using more contemporary data sources representative of the U.S. population would naturally be the next step. While healthcare administrative data such as Medicare data confer advantages such as low-cost and minimal missing data, administrative healthcare data have inherent limitations such as lack of clinical data (i.e., microbiological data) as detailed earlier. As such, the next logical step is to use primary clinical data sources in observational studies, and ultimately advance to prospective designs to include randomized control trials. Lastly, the data presented in this work point to the need for future research to better understand factors associated with therapy discontinuation, barriers and facilitators of guideline-adherent prescribing for NTM, and their associations with treatment and clinical outcomes.

References

1. O'Brien RJ, Geiter LJ, Snider DE, Jr. The epidemiology of nontuberculous mycobacterial diseases in the United States. Results from a national survey. *Am Rev Respir Dis* 1987;135(5):1007-14. doi: 10.1164/arrd.1987.135.5.1007 [published Online First: 1987/05/01]

2. Bodle EE, Cunningham JA, Della-Latta P, et al. Epidemiology of nontuberculous mycobacteria in patients without HIV infection, New York City. *Emerg Infect Dis* 2008;14(3):390-6. doi: 10.3201/eid1403.061143 [published Online First: 2008/03/08]

3. Cassidy PM, Hedberg K, Saulson A, et al. Nontuberculous mycobacterial disease prevalence and risk factors: a changing epidemiology. *Clin Infect Dis* 2009;49(12):e124-9. doi: 10.1086/648443 [published Online First: 2009/11/17]

4. Prevots DR, Shaw PA, Strickland D, et al. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. *Am J Respir Crit Care Med* 2010;182(7):970-6. doi: 10.1164/rccm.201002-0310OC [published Online First: 2010/06/12]

5. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;175(4):367-416. doi: 10.1164/rccm.200604-571ST [published Online First: 2007/02/06]

6. Egelund EF, Fennelly KP, Peloquin CA. Medications and monitoring in nontuberculous mycobacteria infections. *Clin Chest Med* 2015;36(1):55-66. doi: 10.1016/j.ccm.2014.11.001 [published Online First: 2015/02/14]

7. Daley CL, Iaccarino JM, Lange C, et al. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. *Clin Infect Dis* 2020;71(4):905-13. doi: 10.1093/cid/ciaa1125 [published Online First: 2020/08/17]

8. Haworth CS, Banks J, Capstick T, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). *Thorax* 2017;72(Suppl 2):ii1-ii64. doi: 10.1136/thoraxjnl-2017-210927 [published Online First: 2017/10/22]

9. Falkinham JO, 3rd. Surrounded by mycobacteria: nontuberculous mycobacteria in the human environment. *J Appl Microbiol* 2009;107(2):356-67. doi: 10.1111/j.1365-2672.2009.04161.x [published Online First: 2009/02/21]

10. Winthrop KL, McNelley E, Kendall B, et al. Pulmonary nontuberculous mycobacterial disease prevalence and clinical features: an emerging public health

disease. *Am J Respir Crit Care Med* 2010;182(7):977-82. doi: 10.1164/rccm.201003-0503OC [published Online First: 2010/05/29]

11. Lee G, Lee KS, Moon JW, et al. Nodular bronchiectatic Mycobacterium avium complex pulmonary disease. Natural course on serial computed tomographic scans. *Ann Am Thorac Soc* 2013;10(4):299-306. doi: 10.1513/AnnalsATS.201303-062OC [published Online First: 2013/08/21]

12. Ku JH, Ranches G, Siegel SAR, et al. 'Lady Windermere's counterpart? Pulmonary nontuberculous mycobacteria in men with bronchiectasis. *Diagn Microbiol Infect Dis* 2020;96(2):114916. doi: 10.1016/j.diagmicrobio.2019.114916 [published Online First: 2019/11/20]

13. Contreras MA, Cheung OT, Sanders DE, et al. Pulmonary infection with nontuberculous mycobacteria. *Am Rev Respir Dis* 1988;137(1):149-52. doi: 10.1164/ajrccm/137.1.149 [published Online First: 1988/01/01]

14. Adjemian J, Olivier KN, Seitz AE, et al. Prevalence of nontuberculous mycobacterial lung disease in U.S. Medicare beneficiaries. *Am J Respir Crit Care Med* 2012;185(8):881-6. doi: 10.1164/rccm.201111-2016OC [published Online First: 2012/02/09]

15. Benchimol EI, Guttmann A, Mack DR, et al. Validation of international algorithms to identify adults with inflammatory bowel disease in health administrative data from Ontario, Canada. *J Clin Epidemiol* 2014;67(8):887-96. doi: 10.1016/j.jclinepi.2014.02.019 [published Online First: 2014/04/30]

16. Ducharme R, Benchimol EI, Deeks SL, et al. Validation of diagnostic codes for intussusception and quantification of childhood intussusception incidence in Ontario, Canada: a population-based study. *J Pediatr* 2013;163(4):1073-9.e3. doi: 10.1016/j.jpeds.2013.05.034 [published Online First: 2013/07/03]

17. Hux JE, Ivis F, Flintoft V, et al. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care* 2002;25(3):512-6. doi: 10.2337/diacare.25.3.512 [published Online First: 2002/03/05]

18. Mullen KA, Coyle D, Manuel D, et al. Economic evaluation of a hospital-initiated intervention for smokers with chronic disease, in Ontario, Canada. *Tob Control* 2015;24(5):489-96. doi: 10.1136/tobaccocontrol-2013-051483 [published Online First: 2014/06/18]

19. Spaulding AB, Lai YL, Zelazny AM, et al. Geographic Distribution of Nontuberculous Mycobacterial Species Identified among Clinical Isolates in the United States, 2009-2013. *Ann Am Thorac Soc* 2017;14(11):1655-61. doi: 10.1513/AnnalsATS.201611-860OC [published Online First: 2017/08/18]

20. Vinnard C, Longworth S, Mezochow A, et al. Deaths Related to Nontuberculous Mycobacterial Infections in the United States, 1999-2014. *Ann Am Thorac Soc* 2016;13(11):1951-55. doi: 10.1513/AnnalsATS.201606-474BC [published Online First: 2016/09/09]

21. Mirsaeidi M, Farshidpour M, Ebrahimi G, et al. Management of nontuberculous mycobacterial infection in the elderly. *Eur J Intern Med* 2014;25(4):356-63. doi: 10.1016/j.ejim.2014.03.008 [published Online First: 2014/04/02]

22. Billinger ME, Olivier KN, Viboud C, et al. Nontuberculous mycobacteria-associated lung disease in hospitalized persons, United States, 1998-2005. *Emerg Infect Dis* 2009;15(10):1562-9. doi: 10.3201/eid1510.090196 [published Online First: 2009/10/29]

23. Winthrop KL, Baxter R, Liu L, et al. The reliability of diagnostic coding and laboratory data to identify tuberculosis and nontuberculous mycobacterial disease among rheumatoid arthritis patients using anti-tumor necrosis factor therapy. *Pharmacoepidemiol Drug Saf* 2011;20(3):229-35. doi: 10.1002/pds.2049 [published Online First: 2011/02/26]

24. Jones MM, Winthrop KL, Nelson SD, et al. Epidemiology of nontuberculous mycobacterial infections in the U.S. Veterans Health Administration. *PLoS One* 2018;13(6):e0197976. doi: 10.1371/journal.pone.0197976 [published Online First: 2018/06/14]

25. Ringshausen FC, Wagner D, de Roux A, et al. Prevalence of Nontuberculous Mycobacterial Pulmonary Disease, Germany, 2009-2014. *Emerg Infect Dis* 2016;22(6):1102-5. doi: 10.3201/eid2206.151642 [published Online First: 2016/05/19]

26. Marras TK, Vinnard C, Zhang Q, et al. Relative risk of all-cause mortality in patients with nontuberculous mycobacterial lung disease in a US managed care population. *Respir Med* 2018;145:80-88. doi: 10.1016/j.rmed.2018.10.022 [published Online First: 2018/12/05]

27. Ricotta EE, Olivier KN, Lai YL, et al. Hospital-based antibiotic use in patients with Mycobacterium avium complex. *ERJ Open Res* 2018;4(4) doi: 10.1183/23120541.00109-2018 [published Online First: 2018/11/08]

28. Strollo SE, Adjemian J, Adjemian MK, et al. The Burden of Pulmonary Nontuberculous Mycobacterial Disease in the United States. *Ann Am Thorac Soc* 2015;12(10):1458-64. doi: 10.1513/AnnalsATS.201503-173OC [published Online First: 2015/07/28]

29. Benchimol EI, Manuel DG, To T, et al. Development and use of reporting guidelines for assessing the quality of validation studies of health administrative data. *J Clin Epidemiol* 2011;64(8):821-9. doi: 10.1016/j.jclinepi.2010.10.006 [published Online First: 2011/01/05]

30. Wallace RJ, Jr., Brown-Elliott BA, McNulty S, et al. Macrolide/Azalide therapy for nodular/bronchiectatic mycobacterium avium complex lung disease. *Chest* 2014;146(2):276-82. doi: 10.1378/chest.13-2538 [published Online First: 2014/01/25]

31. Zweijpfenning S, Kops S, Magis-Escurra C, et al. Treatment and outcome of non-tuberculous mycobacterial pulmonary disease in a predominantly fibro-cavitary disease cohort. *Respir Med* 2017;131:220-24. doi: 10.1016/j.rmed.2017.08.031 [published Online First: 2017/09/28]

32. Koh WJ, Moon SM, Kim SY, et al. Outcomes of Mycobacterium avium complex lung disease based on clinical phenotype. *Eur Respir J* 2017;50(3) doi: 10.1183/13993003.02503-2016 [published Online First: 2017/09/29]

33. Brown-Elliott BA, Nash KA, Wallace RJ, Jr. Antimicrobial susceptibility testing, drug resistance mechanisms, and therapy of infections with nontuberculous mycobacteria. *Clin Microbiol Rev* 2012;25(3):545-82. doi: 10.1128/cmr.05030-11 [published Online First: 2012/07/06]

34. van Ingen J, Wagner D, Gallagher J, et al. Poor adherence to management guidelines in nontuberculous mycobacterial pulmonary diseases. *Eur Respir J* 2017;49(2) doi: 10.1183/13993003.01855-2016 [published Online First: 2017/02/10]

35. Brode SK, Chung H, Campitelli MA, et al. Prescribing Patterns for Treatment of Mycobacterium avium Complex and M. xenopi Pulmonary Disease in Ontario, Canada, 2001-2013. *Emerg Infect Dis* 2019;25(7) doi: 10.3201/eid2507.181817 [published Online First: 2019/06/20]

36. Hwang JA, Kim S, Jo KW, et al. Natural history of Mycobacterium avium complex lung disease in untreated patients with stable course. *Eur Respir J* 2017;49(3) doi: 10.1183/13993003.00537-2016 [published Online First: 2017/03/10]

37. Diel R, Jacob J, Lampenius N, et al. Burden of non-tuberculous mycobacterial pulmonary disease in Germany. *Eur Respir J* 2017;49(4) doi: 10.1183/13993003.02109-2016 [published Online First: 2017/04/28]

38. Igari H, Yamagishi K, Yamazaki S, et al. A retrospective observational study of antimicrobial treatment for non-tuberculous mycobacteria disease using a nationwide claims database in Japan. *J Infect Chemother* 2020;26(4):349-52. doi: 10.1016/j.jiac.2019.10.009 [published Online First: 2019/11/16]

39. Henkle E, Novosad SA, Shafer S, et al. Long-Term Outcomes in a Population-based Cohort with Respiratory Nontuberculous Mycobacteria Isolation. *Ann Am Thorac Soc* 2017;14(7):1120-28. doi: 10.1513/AnnalsATS.201610-801OC [published Online First: 2017/04/14]

40. Adjemian J, Prevots DR, Gallagher J, et al. Lack of adherence to evidence-based treatment guidelines for nontuberculous mycobacterial lung disease. *Ann Am Thorac Soc* 2014;11(1):9-16. doi: 10.1513/AnnalsATS.201304-085OC [published Online First: 2013/11/19]

41. Brode SK, Chung H, Campitelli MA, et al. Prescribing Patterns for Treatment of Mycobacterium avium Complex and M. xenopi Pulmonary Disease in Ontario, Canada, 2001-2013. *Emerg Infect Dis* 2019;25(7):1271-80. doi: 10.3201/eid2507.181817 [published Online First: 2019/06/20]

42. Huang JH, Kao PN, Adi V, et al. Mycobacterium avium-intracellulare pulmonary infection in HIV-negative patients without preexisting lung disease: diagnostic and management limitations. *Chest* 1999;115(4):1033-40. doi: 10.1378/chest.115.4.1033 [published Online First: 1999/04/20]

43. McGrath EE, Anderson PB. The therapeutic approach to non-tuberculous mycobacterial infection of the lung. *Pulm Pharmacol Ther* 2010;23(5):389-96. doi: 10.1016/j.pupt.2010.06.002 [published Online First: 2010/06/15]

44. Brown BA, Griffith DE, Girard W, et al. Relationship of adverse events to serum drug levels in patients receiving high-dose azithromycin for mycobacterial lung disease. *Clin Infect Dis* 1997;24(5):958-64. doi: 10.1093/clinids/24.5.958 [published Online First: 1997/05/01]

45. Griffith DE, Brown BA, Wallace RJ, Jr. Varying dosages of rifabutin affect white blood cell and platelet counts in human immunodeficiency virus--negative patients who are receiving multidrug regimens for pulmonary Mycobacterium avium complex disease. *Clin Infect Dis* 1996;23(6):1321-2. doi: 10.1093/clinids/23.6.1321 [published Online First: 1996/12/01]

46. Kamii Y, Nagai H, Kawashima M, et al. Adverse reactions associated with long-term drug administration in Mycobacterium avium complex lung disease. *Int J Tuberc Lung Dis* 2018;22(12):1505-10. doi: 10.5588/ijtld.18.0171 [published Online First: 2019/01/05]

47. Griffith DE, Brown-Elliott BA, Langsjoen B, et al. Clinical and molecular analysis of macrolide resistance in Mycobacterium avium complex lung disease. *Am J Respir Crit Care Med* 2006;174(8):928-34. doi: 10.1164/rccm.200603-450OC [published Online First: 2006/07/22]

48. Field SK, Cowie RL. Treatment of Mycobacterium avium-intracellulare complex lung disease with a macrolide, ethambutol, and clofazimine. *Chest* 2003;124(4):1482-6. doi: 10.1378/chest.124.4.1482 [published Online First: 2003/10/14]

49. Jenkins PA, Campbell IA, Banks J, et al. Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of Mycobacterium vaccae immunotherapy. *Thorax* 2008;63(7):627-34. doi: 10.1136/thx.2007.087999 [published Online First: 2008/02/06]

50. Kobashi Y, Matsushima T, Oka M. A double-blind randomized study of aminoglycoside infusion with combined therapy for pulmonary Mycobacterium avium complex disease. *Respir Med* 2007;101(1):130-8. doi: 10.1016/j.rmed.2006.04.002 [published Online First: 2006/06/06]

51. Philley JV, Griffith DE. Treatment of slowly growing mycobacteria. *Clin Chest Med* 2015;36(1):79-90. doi: 10.1016/j.ccm.2014.10.005 [published Online First: 2015/02/14]

52. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;57(1):6-14. doi: 10.1046/j.1365-2125.2003.02007.x [published Online First: 2003/12/18]

53. Daley CL, Griffith DE. Pulmonary non-tuberculous mycobacterial infections. *Int J Tuberc Lung Dis* 2010;14(6):665-71. [published Online First: 2010/05/22]

54. Wallace RJ, Jr., Brown BA, Griffith DE, et al. Clarithromycin regimens for pulmonary Mycobacterium avium complex. The first 50 patients. *Am J Respir Crit Care Med* 1996;153(6 Pt 1):1766-72. doi: 10.1164/ajrccm.153.6.8665032 [published Online First: 1996/06/01]

55. Kobashi Y, Matsushima T. The microbiological and clinical effects of combined therapy according to guidelines on the treatment of pulmonary Mycobacterium avium complex disease in Japan - including a follow-up study. *Respiration* 2007;74(4):394-400. doi: 10.1159/000095674 [published Online First: 2006/09/07]

56. Aksamit TR, O'Donnell AE, Barker A, et al. Adult Patients With Bronchiectasis: A First Look at the US Bronchiectasis Research Registry. *Chest* 2017;151(5):982-92. doi: 10.1016/j.chest.2016.10.055 [published Online First: 2016/11/28]

57. Henkle E, Curtis JR, Chen L, et al. Comparative risks of chronic inhaled corticosteroids and macrolides for bronchiectasis. *Eur Respir J* 2019;54(1) doi: 10.1183/13993003.01896-2018 [published Online First: 2019/04/20]

58. Henkle E, Chan B, Curtis JR, et al. Characteristics and Health-care Utilization History of Patients With Bronchiectasis in US Medicare Enrollees With Prescription Drug Plans, 2006 to 2014. *Chest* 2018;154(6):1311-20. doi: 10.1016/j.chest.2018.07.014 [published Online First: 2018/07/29]

59. Center for Medicare and Medicaid Services. ICD-10 2020 [updated 03/06/2020. Available from: https://www.cms.gov/Medicare/Coding/ICD10 accessed 04/19 2020.

60. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. *Clin Chest Med* 2015;36(1):13-34. doi: 10.1016/j.ccm.2014.10.002 [published Online First: 2015/02/14]

61. Abate G, Stapleton JT, Rouphael N, et al. Variability in the Management of Adults With Pulmonary Nontuberculous Mycobacterial Disease. *Clin Infect Dis* 2021;72(7):1127-37. doi: 10.1093/cid/ciaa252 [published Online First: 2020/03/22]

62. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40(5):373-83. doi: 10.1016/0021-9681(87)90171-8 [published Online First: 1987/01/01]

63. Institute of Medicine Committee to Design a Strategy for Quality R, Assurance in M. In: Lohr KN, ed. Medicare: A Strategy for Quality Assurance: Volume 1. Washington (DC): National Academies Press (US) Copyright © 1990 by the National Academy of Sciences. 1990.

64. Medicare Part D Enrollment: Part D Enrollees by Type of Plan, Low Income Subsidy (LIS), and Retiree Drug Subsidy

by Area of Residence, Calendar Year 2019 Centers for Medicare & Medicaid Services Jan 19, 2021.

65. Ku JH, Henkle EM, Carlson KF, et al. Validity of Diagnosis Code-Based Claims to Identify Pulmonary NTM Disease in Bronchiectasis Patients. *Emerg Infect Dis* 2021;27(3):982-85. doi: 10.3201/eid2703.203124 [published Online First: 2021/02/25]

66. Xu HB, Jiang RH, Li L. Treatment outcomes for Mycobacterium avium complex: a systematic review and meta-analysis. *Eur J Clin Microbiol Infect Dis* 2014;33(3):347-58. doi: 10.1007/s10096-013-1962-1 [published Online First: 2013/08/28]

67. Kwon YS, Koh WJ. Diagnosis and Treatment of Nontuberculous Mycobacterial Lung Disease. *J Korean Med Sci* 2016;31(5):649-59. doi: 10.3346/jkms.2016.31.5.649 [published Online First: 2016/05/03]

68. Dautzenberg B, Piperno D, Diot P, et al. Clarithromycin in the treatment of Mycobacterium avium lung infections in patients without AIDS. Clarithromycin Study Group of France. *Chest* 1995;107(4):1035-40. doi: 10.1378/chest.107.4.1035 [published Online First: 1995/04/01]

69. Fukushima K, Kitada S, Abe Y, et al. Long-Term Treatment Outcome of Progressive Mycobacterium Avium Complex Pulmonary Disease. *J Clin Med* 2020;9(5) doi: 10.3390/jcm9051315 [published Online First: 2020/05/07]

70. Ku JH HE, Carlson KF, Marino M, Brode SK, Marras TK, Winthrop KL. Multi-drug antibiotic therapy for pulmonary Mycobacterium avium complex infection in a U.S. Medicare population [unpublished manuscript], 2021.

71. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;10(1):37-48. [published Online First: 1999/01/15]

72. Hardeman RR, Karbeah J. Examining racism in health services research: A disciplinary self-critique. *Health Serv Res* 2020;55 Suppl 2(Suppl 2):777-80. doi: 10.1111/1475-6773.13558 [published Online First: 2020/09/26]

73. Griffith DE, Brown BA, Cegielski P, et al. Early results (at 6 months) with intermittent clarithromycin-including regimens for lung disease due to Mycobacterium avium complex. *Clin Infect Dis* 2000;30(2):288-92. doi: 10.1086/313644 [published Online First: 2000/02/15]

74. Turton L, Smith P. Prevalence & characteristics of severe and profound hearing loss in adults in a UK National Health Service clinic. *Int J Audiol* 2013;52(2):92-7. doi: 10.3109/14992027.2012.735376 [published Online First: 2012/12/05]

75. Cooke CR, Joo MJ, Anderson SM, et al. The validity of using ICD-9 codes and pharmacy records to identify patients with chronic obstructive pulmonary disease. *BMC Health Serv Res* 2011;11:37. doi: 10.1186/1472-6963-11-37 [published Online First: 2011/02/18]

76. Gershon AS, Wang C, Guan J, et al. Identifying patients with physician-diagnosed asthma in health administrative databases. *Can Respir J* 2009;16(6):183-8. doi: 10.1155/2009/963098 [published Online First: 2009/12/17]

77. Ramsey SD, Scoggins JF, Blough DK, et al. Sensitivity of administrative claims to identify incident cases of lung cancer: a comparison of 3 health plans. *J Manag Care Pharm* 2009;15(8):659-68. doi: 10.18553/jmcp.2009.15.8.659 [published Online First: 2009/10/07]

78. Herrinton LJ, Harrold LR, Liu L, et al. Association between anti-TNF-alpha therapy and interstitial lung disease. *Pharmacoepidemiol Drug Saf* 2013;22(4):394-402. doi: 10.1002/pds.3409 [published Online First: 2013/01/30]

79. Resnick ES, Bhatt P, Sidi P, et al. Examining the use of ICD-9 diagnosis codes for primary immune deficiency diseases in New York State. *J Clin Immunol* 2013;33(1):40-8. doi: 10.1007/s10875-012-9773-1 [published Online First: 2012/09/04]

80. Dang GT, Barros N, Higgins SA, et al. Descriptive review of asbestosis and silicosis hospitalization trends in North Carolina, 2002-2011. *N C Med J* 2013;74(5):368-75. [published Online First: 2013/10/30]

81. Bili A, Sartorius JA, Kirchner HL, et al. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. *J Clin Rheumatol* 2011;17(3):115-20. doi: 10.1097/RHU.0b013e318214b6b5 [published Online First: 2011/03/29]

82. Chang CM, Chu HT, Wei YH, et al. The Core Pattern Analysis on Chinese Herbal Medicine for Sjögren's syndrome: A Nationwide Population-Based Study. *Sci Rep* 2015;5:9541. doi: 10.1038/srep09541 [published Online First: 2015/04/30]

83. Di Domenicantonio R, Cappai G, Agabiti N, et al. A Systematic Review of Case-Identification Algorithms Based on Italian Healthcare Administrative Databases for Three Relevant Diseases of the Digestive and Genitourinary System: Inflammatory Bowel Diseases, Celiac Disease, and Chronic Kidney Disease. *Epidemiol Prev* 2019;43(4 Suppl 2):88-98. doi: 10.19191/ep19.4.S2.P088.095 [published Online First: 2019/10/28]

84. Jorge A, Castro VM, Barnado A, et al. Identifying lupus patients in electronic health records: Development and validation of machine learning algorithms and application of rule-based algorithms. *Semin Arthritis Rheum* 2019;49(1):84-90. doi: 10.1016/j.semarthrit.2019.01.002 [published Online First: 2019/01/23]

85. Lindström U, Exarchou S, Sigurdardottir V, et al. Validity of ankylosing spondylitis and undifferentiated spondyloarthritis diagnoses in the Swedish National Patient Register. *Scand J Rheumatol* 2015;44(5):369-76. doi: 10.3109/03009742.2015.1010572 [published Online First: 2015/03/24]

86. Dalla Zuanna T, Pitter G, Canova C, et al. A Systematic Review of Case-Identification Algorithms Based on Italian Healthcare Administrative Databases for Two Relevant Diseases of the Endocrine System: Diabetes Mellitus and Thyroid Disorders. *Epidemiol Prev* 2019;43(4 Suppl 2):17-36. doi: 10.19191/ep19.4.S2.P008.089 [published Online First: 2019/10/28]

87. Brook RA, Wahlqvist P, Kleinman NL, et al. Cost of gastro-oesophageal reflux disease to the employer: a perspective from the United States. *Aliment Pharmacol Ther* 2007;26(6):889-98. doi: 10.1111/j.1365-2036.2007.03428.x [published Online First: 2007/09/05]

Appendix A. Institutional Review Board Documentation

IRB MEMO

Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, OR 97239-3098
(503)494-7887 irb@ohsu.edu

APPROVAL OF SUBMISSION

December 16, 2015

Dear Kevin Winthrop:

On 12/16/2015, the IRB reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	Comparative effectiveness and safety of inhaled corticosteroids and antimicrobial compounds for non-CF bronchiectasis
Principal Investigator:	Kevin Winthrop
IRB ID:	STUDY00015347
Funding:	Name: Patient-Centered Outcomes Research Institute (PCORI), PPQ #: 1007751
IND, IDE, or HDE:	None

The IRB granted final approval on 12/16/2015. The study is approved until **12/15/2016**.

Review Category: Expedited Category #5

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB signature (e.g. IIAs, IAAs, DUAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

Ongoing IRB submission requirements:

- Six to ten weeks before the expiration date, you are to submit a continuing review to request continuing approval.
- Any changes to the project must be submitted for IRB approval prior to implementation.

- Reportable New Information must be submitted per OHSU policy.
- You must submit a continuing review to close the study when your research is completed.

Guidelines for Study Conduct

In conducting this study, you are required to follow the guidelines in the document entitled, "Roles and Responsibilities in the Conduct of Research and Administration of Sponsored Projects," as well as all other applicable OHSU IRB Policies and Procedures.

Requirements under HIPAA

If your study involves the collection, use, or disclosure of Protected Health Information (PHI), you must comply with all applicable requirements under HIPAA. See the HIPAA and Research website and the Information Privacy and Security website for more information.

IRB Compliance

The OHSU IRB (FWA00000161; IRB00000471) complies with 45 CFR Part 46, 21 CFR Parts 50 and 56, and other federal and Oregon laws and regulations, as applicable, as well as ICH-GCP codes 3.1-3.4, which outline Responsibilities, Composition, Functions, and Operations, Procedures, and Records of the IRB.

Sincerely,

The OHSU IRB Office

OREGON HEALTH & SCIENCE UNIVERSITY

IRB MEMO

Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, OR 97239-3098
(503)494-7887 irb@ohsu.edu

APPROVAL OF SUBMISSION

November 29, 2016

Dear Investigator:

On 11-29-2016 the IRB reviewed the following submission:

IRB ID:	STUDY00015347	MOD or CR ID:	MODCR00001977
Type of Review:	Modification and Continuing Review		
Title of Study:	Comparative effectiveness and safety of inhaled corticosteroids and antimicrobial compounds for non-CF bronchiectasis		
Title of modification	Protocol modification for data analysis updates		
Principal Investigator:	Kevin Winthrop		
Funding:	Name: Patient-Centered Outcomes Research Institute (PCORI), PPQ #: 1007751		
IND, IDE, or HDE:	None		
Documents Reviewed:	• EMAIL_PII files deleted_OHSUconfirmation • Protocol_v1.3 • ResearchPlan_Winthrop.pdf • HIPAA-WoA_PCORI • EMAIL_PII files deleted_COPDFconfirmation		

The IRB granted final approval on 11/29/2016. The study is approved until **11/28/2017**.

Review Category: Expedited Category # 5

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB signature (e.g. IIAs and IAAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

Ongoing IRB submission requirements:

- Six to ten weeks before the expiration date, you are to submit a continuing review to request continuing approval.
- Any changes to the project must be submitted for IRB approval prior to implementation.
- Reportable New Information must be submitted per OHSU policy.
- You must submit a continuing review to close the study when your research is completed.

Guidelines for Study Conduct

In conducting this study, you are required to follow the guidelines in the document entitled, "Roles and Responsibilities in the Conduct of Research and Administration of Sponsored Projects," as well as all other applicable OHSU IRB Policies and Procedures.

Requirements under HIPAA

If your study involves the collection, use, or disclosure of Protected Health Information (PHI), you must comply with all applicable requirements under HIPAA. See the HIPAA and Research website and the Information Privacy and Security website for more information.

IRB Compliance

The OHSU IRB (FWA00000161; IRB00000471) complies with 45 CFR Part 46, 21 CFR Parts 50 and 56, and other federal and Oregon laws and regulations, as applicable, as well as ICH-GCP codes 3.1-3.4, which outline Responsibilities, Composition, Functions, and Operations, Procedures, and Records of the IRB.

Sincerely,

The OHSU

OREGON HEALTH & SCIENCE UNIVERSITY

IRB MEMO

Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, OR 97239-3098
(503)494-7887 irb@ohsu.edu

APPROVAL OF SUBMISSION

October 24, 2017

Dear Investigator:

On 10/24/2017, the IRB reviewed the following submission:

IRB ID:	STUDY00015347	MOD or CR ID:	MODCR00004079
Type of Review:	Modification and Continuing Review		
Title of Study:	Comparative effectiveness and safety of inhaled corticosteroids and antimicrobial compounds for non-CF bronchiectasis		
Title of modification	2017 Continuing Review for PCORI CE study		
Principal Investigator:	Kevin Winthrop		
Funding:	Name: Patient-Centered Outcomes Research Institute (PCORI), PPQ #: 1007751		
IND, IDE, or HDE:	None		
Documents Reviewed:	• EMAIL_PII files deleted_OHSUconfirmation • Protocol_v1.3 • ResearchPlan_Winthrop.pdf • HIPAA-WoA_PCORI • EMAIL_PII files deleted_COPDFconfirmation		

The IRB granted final approval on 10/24/2017. The study is approved until 10/23/2018.

Review Category: Expedited Category # 5

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB signature (e.g. IIAs and IAAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

Ongoing IRB submission requirements:

- Six to ten weeks before the expiration date, you are to submit a continuing review to request continuing approval.

- Any changes to the project must be submitted for IRB approval prior to implementation.
- Reportable New Information must be submitted per OHSU policy.
- You must submit a continuing review to close the study when your research is completed.

Guidelines for Study Conduct

In conducting this study, you are required to follow the guidelines in the document entitled, "Roles and Responsibilities in the Conduct of Research and Administration of Sponsored Projects," as well as all other applicable OHSU IRB Policies and Procedures.

Requirements under HIPAA

If your study involves the collection, use, or disclosure of Protected Health Information (PHI), you must comply with all applicable requirements under HIPAA. See the HIPAA and Research website and the Information Privacy and Security website for more information.

IRB Compliance

The OHSU IRB (FWA00000161; IRB00000471) complies with 45 CFR Part 46, 21 CFR Parts 50 and 56, and other federal and Oregon laws and regulations, as applicable, as well as ICH-GCP codes 3.1-3.4, which outline Responsibilities, Composition, Functions, and Operations, Procedures, and Records of the IRB.

Sincerely,

The OHSU IRB Office

OREGON HEALTH & SCIENCE UNIVERSITY

IRB MEMO

Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, OR 97239-3098
(503)494-7887 irb@ohsu.edu

APPROVAL OF SUBMISSION

October 5, 2018

Dear Investigator:

On 10/5/2018, the IRB reviewed the following submission:

IRB ID:	STUDY00015347	MOD or CR ID:	MODCR00007702
Type of Review:	Modification and Continuing Review		
Title of Study:	Comparative effectiveness and safety of inhaled corticosteroids and antimicrobial compounds for non-CF bronchiectasis		
Title of modification	2018 CRQ only (no modification)		
Principal Investigator:	Kevin Winthrop		
Funding:	Name: Patient-Centered Outcomes Research Institute (PCORI), PPQ #: 1007751		
IND, IDE, or HDE:	None		
Documents Reviewed:	• EMAIL_PII files deleted_OHSUconfirmation • HIPAA-WoA_PCORI • ResearchPlan_Winthrop.pdf • Protocol_v1.4 • EMAIL_PII files deleted_COPDFconfirmation		

The IRB granted final approval on 10/5/2018. The study is approved until **10/4/2019**.

Review Category: Expedited Category # 5

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB

signature (e.g. IIAs and IAAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

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- You must submit a continuing review to close the study when your research is completed.

Guidelines for Study Conduct

In conducting this study, you are required to follow the guidelines in the document entitled, "Roles and Responsibilities in the Conduct of Research and Administration of Sponsored Projects," as well as all other applicable OHSU IRB Policies and Procedures.

Requirements under HIPAA

If your study involves the collection, use, or disclosure of Protected Health Information (PHI), you must comply with all applicable requirements under HIPAA. See the HIPAA and Research website and the Information Privacy and Security website for more information.

IRB Compliance

The OHSU IRB (FWA00000161; IRB00000471) complies with 45 CFR Part 46, 21 CFR Parts 50 and 56, and other federal and Oregon laws and regulations, as applicable, as well as ICH-GCP codes 3.1-3.4, which outline Responsibilities, Composition, Functions, and Operations, Procedures, and Records of the IRB.

Sincerely,

The OHSU IRB Office

OREGON HEALTH & SCIENCE UNIVERSITY

IRB MEMO

Research Integrity Office
3181 SW Sam Jackson Park Road - L106RI
Portland, OR 97239-3098
(503)494-7887 irb@ohsu.edu

APPROVAL OF SUBMISSION

September 10, 2019

Dear Investigator:

On 9/10/2019, the IRB reviewed the following submission:

IRB ID:	STUDY00015347	MODCR ID:	MODCR00010935
Type of Review:	Modification and Continuing Review		
Title of Study:	Comparative effectiveness and safety of inhaled corticosteroids and antimicrobial compounds for non-CF bronchiectasis		
Title of modification	Comparative effectiveness and safety of inhaled corticosteroids and antimicrobial compounds for non-CF bronchiectasis		
Principal Investigator:	Kevin Winthrop		
Funding:	Name: Insmed Inc, PPQ #: n/a; Name: Patient-Centered Outcomes Research Institute (PCORI), PPQ #: 1007751; Name: OHSU-PSU School of Public Health, PPQ #: n/a, Funding Source: please see attachment		
IND, IDE, or HDE:	None		
Documents Reviewed:	• IRB MOD Submission Memo_21Nov2018.docx • EMAIL_PII files deleted_OHSUconfirmation • HIPAA-WoA_PCORI • ResearchPlan_Winthrop.pdf • OHSU-PSU SPH funding_Karen Camp.pdf • 2018 SPH Catalyst Proposal Henkle aims.pdf • SPECIFIC AIMS 01Jun2018 Medicare.pdf • Protocol_v2.0 • EMAIL_PII files deleted_COPDFconfirmation		

The IRB granted final approval on 9/10/2019. The study is approved until **9/9/2020**.

Review Category: Expedited Category # 5

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB.

Ongoing IRB submission requirements:

- Six to ten weeks before the expiration date, you are to submit a continuing review to request continuing approval.
- Any changes to the project must be submitted for IRB approval prior to implementation.
- Reportable New Information must be submitted per OHSU policy.
- You must submit a continuing review to close the study when your research is completed.

Guidelines for Study Conduct

In conducting this study, you are required to follow the guidelines in the document entitled, "Roles and Responsibilities in the Conduct of Research and Administration of Sponsored Projects," as well as all other applicable OHSU IRB Policies and Procedures.

Requirements under HIPAA

If your study involves the collection, use, or disclosure of Protected Health Information (PHI), you must comply with all applicable requirements under HIPAA. See the HIPAA and Research website and the Information Privacy and Security website for more information.

IRB Compliance

The OHSU IRB (FWA00000161; IRB00000471) complies with 45 CFR Part 46, 21 CFR Parts 50 and 56, and other federal and Oregon laws and regulations, as applicable, as well as ICH-GCP codes 3.1-3.4, which outline Responsibilities, Composition, Functions, and Operations, Procedures, and Records of the IRB.

Sincerely,

The OHSU IRB Office

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Research Integrity Office
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APPROVAL OF SUBMISSION

July 31, 2020

Dear Investigator:

On 7-31-2020, the IRB reviewed the following submission:

IRB ID:	STUDY00015347	MOD or CR ID:	MODCR00014427
Type of Review:	Modification and Continuing Review, Study Closure or Check-in		
Title of Study:	Comparative effectiveness and safety of inhaled corticosteroids and antimicrobial compounds for non-CF bronchiectasis		
Title of modification	Comparative effectiveness and safety of inhaled corticosteroids and antimicrobial compounds for non-CF bronchiectasis		
Principal Investigator:	Kevin Winthrop		
Funding:	Name: Insmed Inc, PPQ #: n/a; Name: Patient-Centered Outcomes Research Institute (PCORI), PPQ #: 1007751; Name: OHSU-PSU School of Public Health, PPQ #: n/a, Funding Source: please see attachment		
IND, IDE, or HDE:	None		
Documents Reviewed:	• IRB MOD Submission Memo_21Nov2018.docx • EMAIL_PII files deleted_OHSUconfirmation • HIPAA-WoA_PCORI • ResearchPlan_Winthrop.pdf • OHSU-PSU SPH funding_Karen Camp.pdf • 2018 SPH Catalyst Proposal Henkle aims.pdf • SPECIFIC AIMS 01Jun2018 Medicare.pdf • Protocol_v2.0 • EMAIL_PII files deleted_COPDFconfirmation		

The IRB granted final approval on 7/31/2020. The study is approved until **7/30/2021**.
Review Category: Expedited Category # 5

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB signature (e.g. IIAs and IAAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

Ongoing IRB submission requirements:

- Six to ten weeks before the expiration date, you are to submit a continuing review to request continuing approval.
- Any changes to the project must be submitted for IRB approval prior to implementation.
- Reportable New Information must be submitted per OHSU policy.
- You must submit a continuing review to close the study when your research is completed.

Guidelines for Study Conduct

In conducting this study, you are required to follow the guidelines in the document entitled, "Roles and Responsibilities in the Conduct of Research and Administration of Sponsored Projects," as well as all other applicable OHSU IRB Policies and Procedures.

Requirements under HIPAA

If your study involves the collection, use, or disclosure of Protected Health Information (PHI), you must comply with all applicable requirements under HIPAA. See the HIPAA and Research website and the Information Privacy and Security website for more information.

IRB Compliance

The OHSU IRB (FWA00000161; IRB00000471) complies with 45 CFR Part 46, 21 CFR Parts 50 and 56, and other federal and Oregon laws and regulations, as applicable, as well as ICH-GCP codes 3.1-3.4, which outline Responsibilities, Composition, Functions, and Operations, Procedures, and Records of the IRB.

Sincerely,

The OHSU IRB Office

Appendix B. Supplemental materials for Chapter 3

Appendix B. 1. List of variables in the U.S. Bronchiectasis & NTM Research Registry used to identify pulmonary NTM infection

Variable name	Question / Note
MHXB11	Has the patient ever been diagnosed with pulmonary NTM infection? (Yes/No)
NTMA1	Has the participant been diagnosed with NTM? (Yes/No)
NTMA2	Has the participant ever received treatment for NTM? (Yes/No)
NTMA2A	Date of first treatment of NTM (Date)
NTMA2B	Number of treatment episodes for NTM (Count)
TDFA1	Is the patient currently taking or has the patient recently taken any antibiotics in the previous 12 months for the treatment of NTM disease? (Yes/No)
TDFA3	Is the patient currently taking or has the patient recently taken any oral antibiotics for the treatment of the mycobacteria? (Yes/No)
TDFA38	Did the patient experience a recurrence of NTM disease in the last 12 months (recurrence of culture confirmed disease at least 6 months after being cured)? (Yes/No)
DIAGNOSIS	Categorical (none, NTM, bronchiectasis, or NTM/bronchiectasis)

Appendix B. 2. List of microbiologic variables in the U.S. Bronchiectasis & NTM Research Registry used to identify pulmonary NTM infection

BRR Variable name	Question / Note
MRBC7A MRBC8A MRBC9A	Culture dates (Date)
MRBC7E MRBC8E MRBC9E	Culture results: Mycobacterium Avium Complex (Yes/No)
MRBC7F MRBC8F MRBC9F	Culture results: Mycobacterium Abscessus (Yes/No)
MRBC7G MRBC8G MRBC9G	Culture results: Mycobacterium Kansasii (Yes/No)
MRBC7H MRBC8H MRBC9H	Culture results: Mycobacterium- other (Yes/No)
MRBC7H1 MRBC8H1 MRBC9H1	Culture results: Mycobacterium- other specify (Free text)

Appendix C. Supplemental materials for Chapter 4

Appendix C. 1. List of demographic and clinical baseline characteristics

Demographic characteristics	**Note / ICD-9 code**
Age	Continuous
Sex	Binary: male / female
Race	Category
Ethnicity	Category
Median household income	Continuous
Rural / urban	Binary: rural / urban
Region of residence	Midwest, Northeast, South or West
Clinical characteristics	**Note / ICD-9 code**
Number of clinician office visits	Count: outpatient, non-emergency room visits
Number of visits to pulmonologist	Count: outpatient, non-emergency room visits
Number of visits to infectious disease specialist	Count: outpatient, non-emergency room visits
Number of any hospitalization	Count: hospital stay >24 hours
Number of hospitalization due to respiratory illness	Count: hospital stay >24 hours Respiratory illness 480 viral pneumonia (480.0 – 480.9) 481 pneumococcal pneumonia 482 other bacterial pneumonia (482.0 – 482.9) 483 pneumonia due to other specified organism (483.0, 483.1, 483.8) 484 pneumonia in infectious disease classified elsewhere (484.1, 484.3, 484.5, 484.6, 484.7, 484.8) 485 bronchopneumonia, organism unspecified 486 pneumonia, organism unspecified 487 influenza (487.0, 487.1, 487.8)
Oral corticosteroid use	Binary: yes / no
Total number of acute exacerbations	Count: prescriptions of antibiotics typically used for acute respiratory exacerbation (erythromycin, azithromycin, clarithromycin, inhaled tobramycin, levofloxacin, moxifloxacin, ciprofloxacin, amoxicilin, amoxicilin/clavulanate, or doxycycline) for ≥7 days but < 28 days

COPD/ emphysema	Categorical: chronic bronchitis (491.xx), emphysema (492.xx), chronic obstructive asthma (493.2), chronic airway obstruction, not elsewhere classified (496.xx)[75]
Pseudomonas infection	Binary: yes / no, (041.7, 482.1, 008.42)
Asthma	Binary: yea / no, (493.90)[76]
Lung cancer	Binary: yes / no, (162.x but not 162.0, 231.2)[77]
Alpha-1 antitrypsin deficiency	Binary: yes / no, (273.4)
Interstitial lung disease	Binary: yes / no, 515, 516.3, 516.8, and 518.89[78]
Primary immune deficiency	Binary: yes / no, (279.x, excluding lymphoma/leukemia, HIV)[79]
Primary ciliary dyskinesia	Binary: yes / no, (759.3)
Allergic bronchopulmonary aspergillosis	Binary: yes / no, (518.6)
Silicosis	Binary: yes / no, (502)[80]
Rheumatologic disease	Binary: Rheumatoid arthritis (714.0) at 2 outpatient encounters[81]; Sjogren's syndrome (710.2)[82]; inflammatory bowel disease (555.x)[83]; osteoarthritis (715.96); lupus (710.0)[84]; spondyloarthropathies (ankylosing spondylitis 720.A[85] and psoriatic arthritis 696.0); gout (274.9)
Chronic kidney disease	Binary: yes / no, (584 acute renal failure, 585 chronic kidney disease, 7531 polycystic kidney disease)[83]
Diabetes mellitus	Binary: yes / no, (250.x)[86]
Gastroesophageal reflux	Binary: yes / no, (530.1 esophagitis, unspecified; 530.81 (esophageal reflux, 781.1x heartburn, 787.2x dysphagia, complete; 251.5x hyperscretory condition)[87]
Charlson modified index score[62]	Index for comorbidities

Appendix D. Supplemental materials for Chapter 5

Appendix D. 1. Drug-associated adverse events or regimen change/discontinuation occurring within 12 months of pulmonary MAC therapy in 4,626 U.S. Medicare beneficiaries prescribed guideline-based 3-drug antibiotic therapy for pulmonary *Mycobacterium avium* complex infection between January 2009 and December 2015, excluding beneficiaries who died within 12 months of MAC therapy start

Drug-associated adverse events occurring within 12 months of MAC therapy start				
Exposure groups	N	outcome N (%)	Unadjusted model	Adjusted model[+]
			Hazard ratio (95% CI)	Hazard ratio (95% CI)
Macrolide (with ethambutol and rifamycin) comparison[*]				
Azithromycin, ethambutol, rifamycin (Reference)	2,778	86 (3.1%)	-	-
Clarithromycin, ethambutol, rifamycin	1,523	41 (2.7%)	0.95 (95% CI: 0.65, 1.39)	0.96 (95% CI: 0.65, 1.40)
Rifamycin (with macrolide and ethambutol) comparison[**]				
Macrolide, ethambutol, rifampin (Reference)	3,743	73 (2.0%)	-	-
Macrolide, ethambutol, rifabutin	558	12 (2.2%)	1.36 (95% CI: 0.74, 2.51)	1.30 (95% CI: 0.70, 2.40)
Regimen change or discontinuation occurring within 12 months of MAC therapy start				
Exposure groups	N	outcome N (%)	Unadjusted model	Adjusted model[+]
			Hazard ratio (95% CI)	Hazard ratio (95% CI)
Macrolide (with ethambutol and rifampin) comparison				
Azithromycin, ethambutol, rifampin (Reference)	2,438	2,005 (82.2%)	-	-
Clarithromycin, ethambutol, rifampin	1,305	1,101 (84.4%)	1.09 (95% CI: 1.02, 1.18)	1.11 (95% CI: 1.03, 1.20)
Macrolide (with ethambutol and rifabutin) comparison				
Azithromycin, ethambutol, rifabutin (Reference)	340	303 (89.1%)	-	-
Clarithromycin, ethambutol, rifabutin	218	197 (90.4%)	1.08 (95% CI: 0.90, 1.29)	1.10 (95% CI: 0.92, 1.33)
Rifamycin (with azithromycin and ethambutol) comparison				
Azithromycin, ethambutol, rifampin (Reference)	2,438	2,005 (82.2%)	-	-
Azithromycin, ethambutol, rifabutin	340	303 (89.1%)	1.51 (95% CI: 1.34, 1.71)	1.50 (95% CI: 1.33, 1.70)
Rifamycin (with clarithromycin and ethambutol) comparison				
Clarithromycin, ethambutol, rifampin (Reference)	1,305	1,101 (84.4%)	-	-

Clarithromycin, ethambutol, rifabutin	218	197 (90.4%)	1.51 (95% CI: 1.30, 1.76)	1.49 (95% CI: 1.28, 1.74)
Azithromycin/Clarithromycin, ethambutol, rifampin/rifabutin				
Azithromycin, ethambutol, rifampin (Reference)	218	197 (90.4%)	-	-
Clarithromycin, ethambutol, rifabutin	2,438	2,005 (82.2%)	1.67 (95% CI: 1.44, 1.93)	1.67 (95% CI: 1.44, 1.94)

[*]Model for the outcome of macrolide-associated adverse events occurring within 12 months of MAC therapy start (gastrointestinal disturbance, QT prolongation, hearing loss and tinnitus).

[**]Model for the outcome of rifamycin-associated adverse events occurring within 12 months of MAC therapy start (cytopenia to include pancytopenia and thrombocytopenia).

[+]Model included sex, region of residence, race/ethnicity, Charlson comorbidities index, age at treatment start and concomitant medications used during the baseline period