A photograph of several bright orange, round pills scattered on a white surface. One pill is in sharp focus in the lower right foreground, while the others are blurred in the background.

Public Meeting on Non-Tuberculous Mycobacterial (NTM) Lung Infections Patient-Focused Drug Development

October 15, 2015



Welcome

Soujanya Giambone, MBA

Office of Strategic Programs

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

October 15, 2015

Agenda

- **Setting the context**
 - Opening Remarks
 - Overview of FDA's Patient-Focused Drug Development Initiative
 - Background on NTM and Therapeutic Options
 - Overview of Discussion Format
- **Discussion Topic 1:** Disease symptoms and daily impacts that matter most to patients
- **Discussion Topic 2:** Patients' perspectives on current approaches to treating NTM
- **Lunch**
- **Scientific Discussion**

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Opening Remarks

John Farley, MD MPH

Deputy Director, Office of Antimicrobial Products (OAP)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 15, 2015



FDA's Patient-Focused Drug Development Initiative

Theresa Mullin, PhD

Director, Office of Strategic Program
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 15, 2015

Patient-Focused Drug Development under PDUFA V

- **FDA is developing a more systematic way of gathering patient perspective on their condition and available treatment options**
 - Patient perspective helps inform our understanding of the context for the assessment of benefit-risk and decision making for new drugs
 - Input can inform FDA's oversight both during drug development and during our review of a marketing application
- **Patient-Focused Drug Development is part of FDA commitments under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V)**
 - FDA will convene at least 20 meetings on specific disease areas over the next five years
 - Meetings will help develop a systematic approach to gathering patient input

Identifying Disease Areas for the Patient-Focused Meetings

- **In September 2012, FDA announced a preliminary set of diseases as potential meeting candidates**
 - Public input on these nominations was collected. FDA carefully considered these public comments and the perspectives of our drug review divisions at FDA
- **FDA identified a set of 16 diseases to be the focus of meetings for fiscal years 2013-2015**
 - Another public process was initiated and 8 diseases were determined as the disease set for fiscal years 2016-2017

Disease Areas to be the focus of meetings for FY 2013-2017

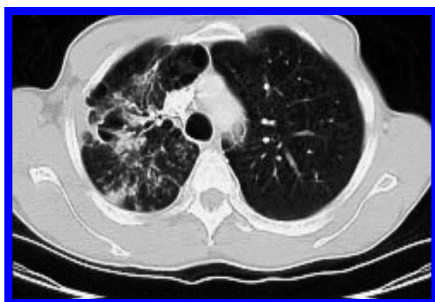
Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Year 2016-2017
<ul style="list-style-type: none"> Chronic fatigue syndrome/myalgic encephalomyelitis HIV Lung cancer Narcolepsy 	<ul style="list-style-type: none"> Sickle cell disease Fibromyalgia Pulmonary arterial hypertension Inborn errors of metabolism Hemophilia A, B, and other heritable bleeding disorders Idiopathic pulmonary fibrosis 	<ul style="list-style-type: none"> Female sexual dysfunction Breast cancer Chagas disease Functional gastrointestinal disorders Huntington’s disease and Parkinson’s disease Alpha-1 antitrypsin deficiency 	<ul style="list-style-type: none"> Non-tuberculous mycobacterial lung infections <p><i>To be announced</i></p> <ul style="list-style-type: none"> Alopecia areata Autism Hereditary angioedema Patients who have received an organ transplant Psoriasis Neuropathic pain associated with peripheral neuropathy Sarcopenia

Tailoring Each Patient-Focused Meeting

- **Each meeting focuses on a set of questions that aim to elicit patients' perspectives on their disease and on treatment approaches**
 - We start with a set of questions that could apply to any disease area; these questions are taken from FDA's benefit-risk framework and represent important considerations in our decision-making
 - We then further tailor the questions to the disease area of the meeting (e.g., current state of drug development, specific interests of the FDA review division, and the needs of the patient population)
- **Focus on relevant current topics in drug development for the disease at each meeting**
 - E.g., focus on HIV patient perspectives on potential “cure research”
- **We've learned that active patient involvement and participation is key to the success of these meetings.**

“Voice of the Patient” Reports

- Following each meeting, FDA publishes a Voice of the Patient report that summarizes the patient testimony at the meeting, perspectives shared in written docket comments, as well as any unique views provided by those who joined the meeting webcast.
- These reports serve an important function in communicating to both FDA review staff and the regulated industry what improvements patients would most like to see in their daily life.
- FDA believes that the long run impact of this program will be a better, more informed understanding of how we might find ways to develop new treatments for these diseases.



NTM Lung Infections

Hala Samsuddin, MD

Division of Antimicrobial Products (DAIP)
Center for Drug Evaluation and Research

FDA



Outline

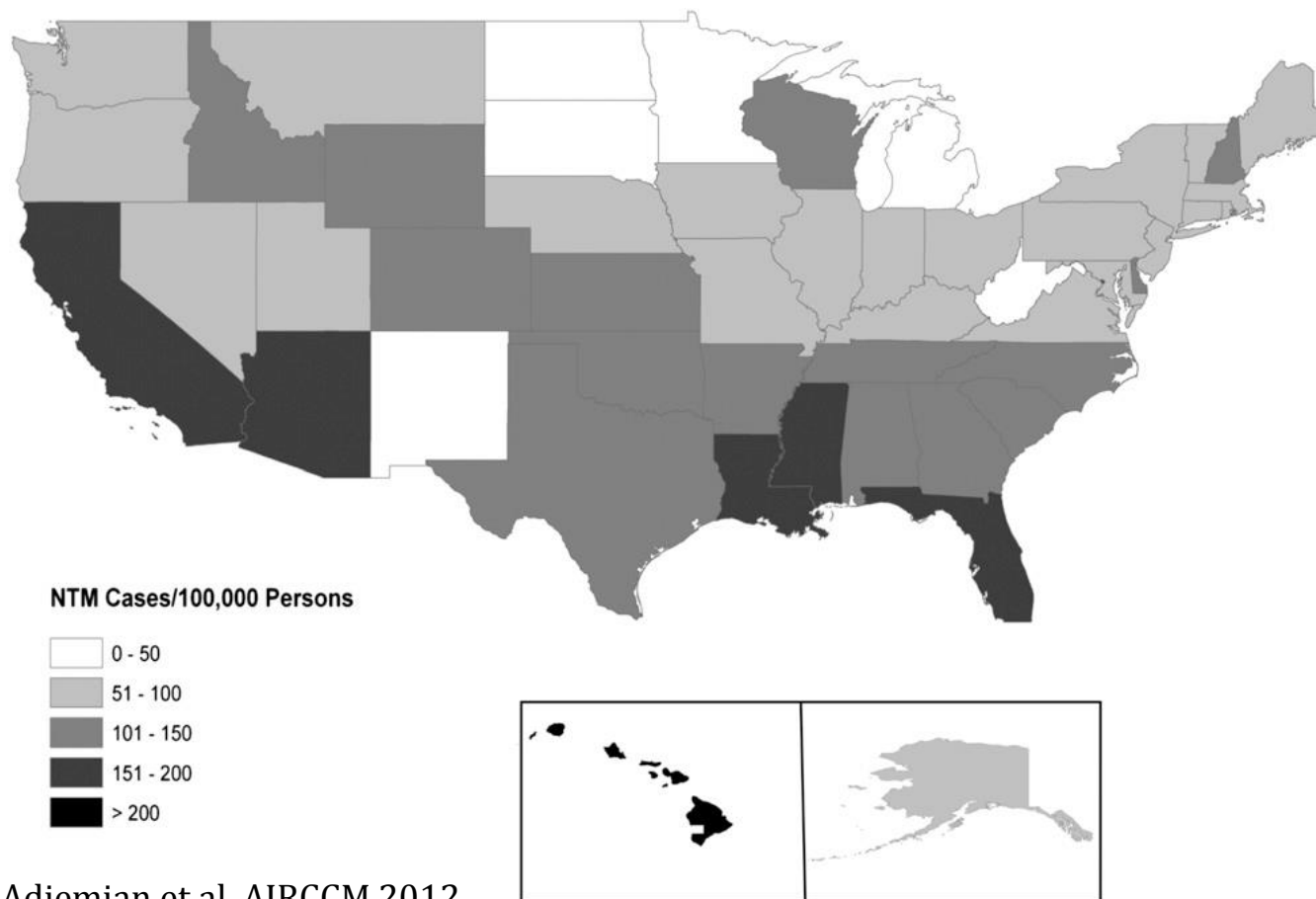
- What are non-tuberculous mycobacteria (NTM)?
- Who is at risk for NTM lung infections?
- What are the clinical manifestations?
- How many people are affected in the US?
- Treatment?
- Challenges in drug development for NTM lung infections

Non-Tuberculous Mycobacteria

- More than 150 species recognized
- Examples: *M. avium* complex (MAC), *M. abscessus*, *M. kansasii*, *M. xenopi*, etc.
- In the US, MAC accounts for approximately 70-80%, *M. abscessus* group for most of the remainder
- Acquired by inhalation from environment
- water thought to be the main source



Lung NTM Distribution and Prevalence in the United States



Adjemian et al. AJRCCM 2012

Who is at Risk?

- Underlying lung disease and/or genetic predisposition
- Bronchiectasis (damage and scarring of airways)
 - Body type: thin, chest cage abnormalities, mainly women
- Cystic Fibrosis
- COPD (chronic obstructive pulmonary disease)
- Prior tuberculosis
- Alpha-one antitrypsin deficiency
- Primary ciliary dyskinesia
- Immunosuppressive therapy

Clinical Manifestations

- Cough
- Shortness of breath
- Sputum production
- Hemoptysis (coughing up blood)
- Chest pain
- Fatigue
- Weight loss
- Fever
- Findings of cavity or lung nodules on X-ray or CT scan of lungs
- Positive sputum cultures

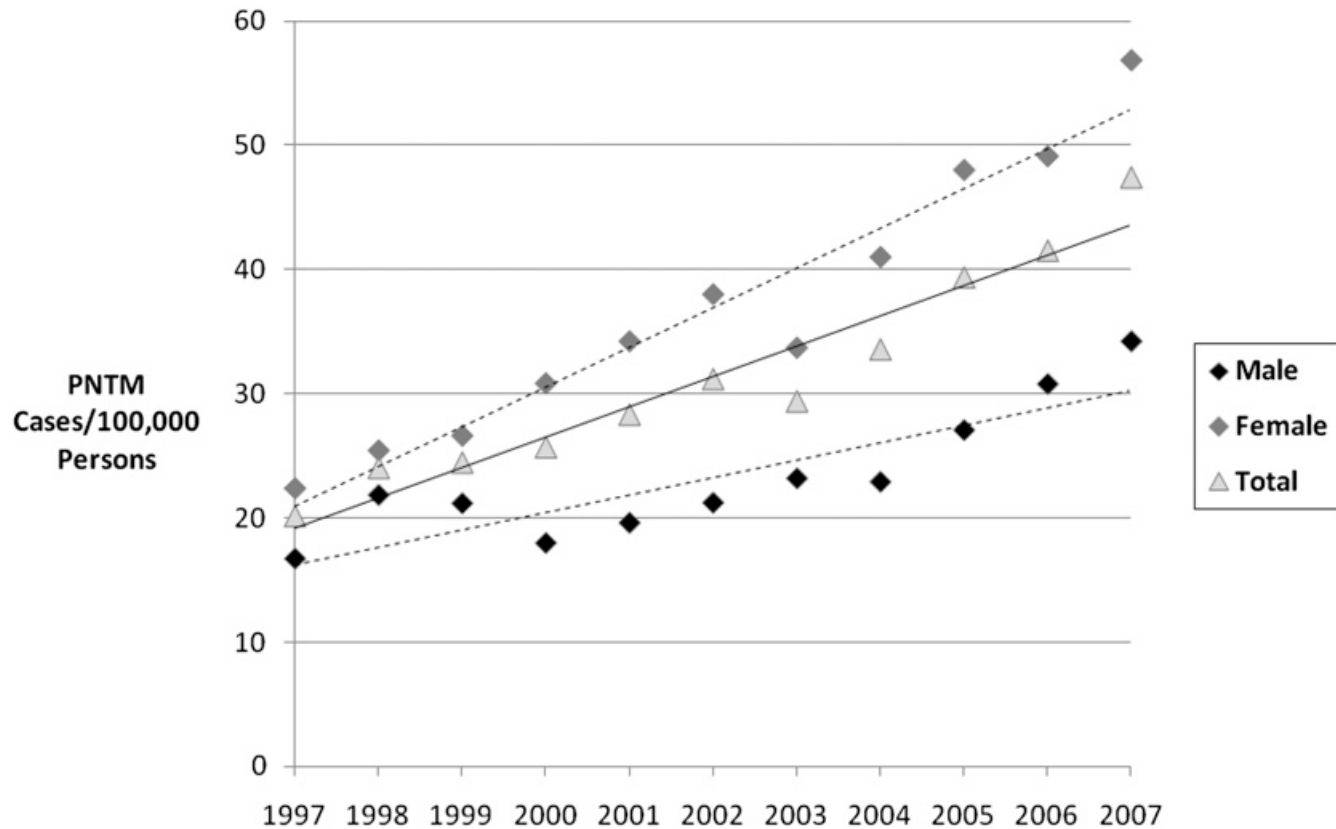
How Common are NTM Lung Infections

- Increasing in the general population and in CF
- In the US, estimated to be present (prevalence) in approximately 8-9 per 100,000 people¹
- Approximately 20 per 100,000 people older than 50 years of age^{1,2}
- Approximately 47 per 100,000 in people older than 70 years of age³
- Approximately 10-15% of CF patients⁴

¹ Winthrop et al. AJRCCM 2010, ² Prevots et al. AJRCCM 2010, ³ Adjemian et al. AJRCCM 2012,

⁴Leung et al. Curr Opin Pulm Med 2013

Increase in NTM Lung Infections - Medicare



Adjemian et al. AJRCCM 2012

Why are NTM Lung Infections Increasing

- Increased awareness
- Increased number of susceptible individuals
 - Older population
 - More chronic lung disease
 - More immunocompromised
 - Improved survival among CF patients
- Possibly increased exposure

Treatment

- No FDA-approved drugs for NTM lung infections
- Physicians use antibiotics that are approved to treat tuberculosis or other bacterial infections
- Antibiotic combinations recommended:
 - 3 or more drugs, may include an injectable
- Optimal combination and duration of injectable and overall therapy are not clearly defined
- Treatment is lengthy
 - goal is culture negative sputum for 12 consecutive months¹

¹ Griffith et al. AJRCCM 2007

Treatment

- Study 2004-2005¹:
 - Median 5 antibiotics (range 1-10)
 - Median treatment 2638 drug days (range 84-7689)
 - Median cost per patient \$19,876 (range 389-70,917)
 - *M. abscessus* associated with higher treatment cost
- Adverse reactions (side effects) are common:
 - 50% for “commonly used” drugs
 - 100% for “less commonly” used drugs

¹ Ballarino et al. Resp. Med. 2009

Challenges to Drug Development

- Disease progression varies by underlying lung disease and appearance on X-rays
- Response to treatment varies by species
- Therefore a drug that may treat one NTM species or one affected patient population may not treat other NTM or other patient populations
- Treatments (and therefore trials) are lengthy
- Need to define early assessments that may lead to faster drug approval (will be discussed further this afternoon)

Conclusions

- NTM lung infections are increasing in the US
- Affected population in the US are mainly patients with bronchiectasis, and individuals with underlying lung disease
- No FDA-approved drugs for lung NTM
- Currently used treatments are multiple drugs for lengthy periods and with significant side effects
- **Unmet** medical need
- Many challenges to drug development



Thank You

A background image showing a cluster of orange, round pills in the upper left corner, with one pill in sharp focus in the lower right corner. The pills are set against a white background with a blue curved border at the top.

Overview of Discussion Format

Soujanya Giambone, MBA

Office of Strategic Programs

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

October 15, 2015

Discussion Overview

Topic 1: The symptoms that matter most to you

- Which symptoms have the most significant impact on your life?
- How do these symptoms affect your ability to do specific activities?
- How have your symptoms changed?

Topic 2: Current approaches to treating NTM lung infections

- What are you doing to treat NTM lung infections?
- How well is/are the treatment(s) treating your significant symptoms?
- What are the biggest downsides to your treatments?
- What would you look for in an “ideal” treatment?

Discussion Format

- **We will first hear from a panel of patients and caregivers**
 - The purpose is to set a good foundation for our discussion
 - They reflect a range of experiences with NTM lung infections

- **We will then broaden the dialogue to include patients and patient representatives in the audience**
 - The purpose is to build on the experiences shared by the panel
 - We will ask questions and invite you to raise your hand to respond
 - Please state your name before answering

Discussion Format, continued

- **You'll have a chance to answer "polling" questions**
 - Their purpose is to aid our discussion
 - In-person participants, use the "clickers" to respond
 - Web participants, answer the questions through the webcast
 - Patients and patient representatives only, please
- **Web participants can add comments through the webcast**
 - Although they may not all be read or summarized today, your comments will be incorporated into our summary report
 - We'll occasionally go to the phones to give you another opportunity to contribute

Send us your comments!

- **You can send us comments through the “public docket”**
 - The docket will be open until December 15, 2015
 - Share your experience, or expand upon something discussed today
 - Comments will be incorporated into our summary report
 - Anyone is welcome to comment

Visit:

<http://www.regulations.gov/#!/documentDetail;D=FDA-2012-N-0967-0748>

Click Comment Now!

The screenshot shows the website www.regulations.gov with a document detail page. The document title is "Patient-Focused Drug Development for Functional Gastrointestinal Disorders; Public Meeting; Request for Comments". The page includes a "Comment Now!" button in the top right corner, which is highlighted by a red arrow. The document information section on the right shows the ID "FDA-2015-N-0244-0001" and the date posted as "Feb 11, 2015". The main content area contains a summary of the public meeting announcement, stating that the FDA is announcing a public meeting and an opportunity for public comment on Patient-Focused Drug Development for functional gastrointestinal (GI) disorders, including irritable bowel syndrome, gastroparesis, chronic persistent symptomatic gastroesophageal reflux despite standard therapeutic interventions, and chronic idiopathic constipation. The public meeting is intended to allow FDA to obtain patient perspectives on the impact of functional GI disorders on daily life and patient views on treatment. The public meeting will be held on May 11, 2015, from 1 p.m. to 5 p.m. Registration to attend the meeting must be received by May 1, 2015 (see SUPPLEMENTARY INFORMATION for instructions). Submit electronic or written comments to the public docket by July 13, 2015.

Resources at FDA

- FDA Office of Health and Constituent Affairs
 - Contact: PatientNetwork@fda.hhs.gov, (301) 796-8460
 - Liaison between FDA and stakeholder organizations
 - Runs the Patient Representative Program
 - Patient Representatives advise FDA at Advisory Committee meetings
- CDER Office of Center Director
 - Professional Affairs and Stakeholder Engagement (PASE)
 - Contact: Francis Kalush, francis.kalush@fda.hhs.gov
 - Facilitates communication and collaboration between CDER and patient and healthcare professional stakeholders and others on issues concerning drug development, drug review and drug safety.

Discussion Ground Rules

- We encourage patients to contribute to the dialogue—caregivers and advocates are welcome too
- FDA is here to listen
- Discussion will focus on symptoms and treatments
 - Open Public Comment Period is available to comment on other topics
- The views expressed today are personal opinions
- Respect for one another is paramount
- Let us know how the meeting went today; evaluation forms at registration desk



Discussion Topic 1

Disease symptoms and daily impacts that matter most to patients

Soujanya Giambone

Facilitator

Topic 1 Panel Participants

- Marilyn Lundy
- Philip Leitman
- Barbara Hudson
- Kathleen Keating

Topic 1 Discussion: Disease symptoms and daily impacts that matter most to patients

- Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life?
- Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition?
- How has your condition and its symptoms changed over time?
- What worries you most about your condition?



BREAK



Discussion Topic 2

Patients' perspectives on current approaches to treating NTM Lung Infections

Soujanya Giambone
Facilitator

Topic 2 Panel Participants

- Jennifer Bogenrief
- Betsy Glaeser
- Gaby Chien
- Mary Fisher
- Patricia Yost

Topic 2 Discussion: Patients' perspectives on current approaches to treating NTM

- What are you currently doing to help treat your condition or its symptoms?
 - What specific symptoms do your treatments address?
 - How has your treatment regimen changed over time, and why?
- How well does your current treatment regimen treat the most significant symptoms of your disease?
- What are the most significant downsides to your current treatments, and how do they affect your daily life?
- Assuming there is no complete cure for your condition, what specific things would you look for in an ideal treatment for your condition?

Scenario

Imagine that...

- You have been invited to participate in a clinical trial to study an experimental antibiotic treatment for NTM lung infections
- The purpose of the study is to better understand how well this treatment works and its safety
- This clinical study lasts 2 years, and clinical visits will occur every month for 2 years, in addition to regular doctor's visits
- Visits will involve monthly sputum collections, lab tests, lung function tests, and other laboratory tests as needed
- Treatments may involve either IV medication (administered via catheter) or inhaled therapy (administered for 1-2 hours)
- Treatment will be given in addition to standard of care

What thoughts and questions come to mind as you hear this scenario?



LUNCH

A photograph of several orange, round pills scattered on a white surface. One pill is in sharp focus in the lower right foreground, while the others are blurred in the background.

Scientific Discussion on Non-tuberculous Mycobacterial (NTM) Lung Infections

October 15, 2015



Welcome

John Farley, MD MPH

Deputy Director, OAP

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

October 15, 2015

FDA Public Meeting on
Nontuberculous Mycobacterial Lung Infection:
Patient-Focused Drug Development

Epidemiology & Natural History of NTM Lung Infections

Kenneth N Olivier, MD, MPH
Cardiovascular & Pulmonary Branch/NHLBI
Oct 15, 2015



NTM Epid...historic

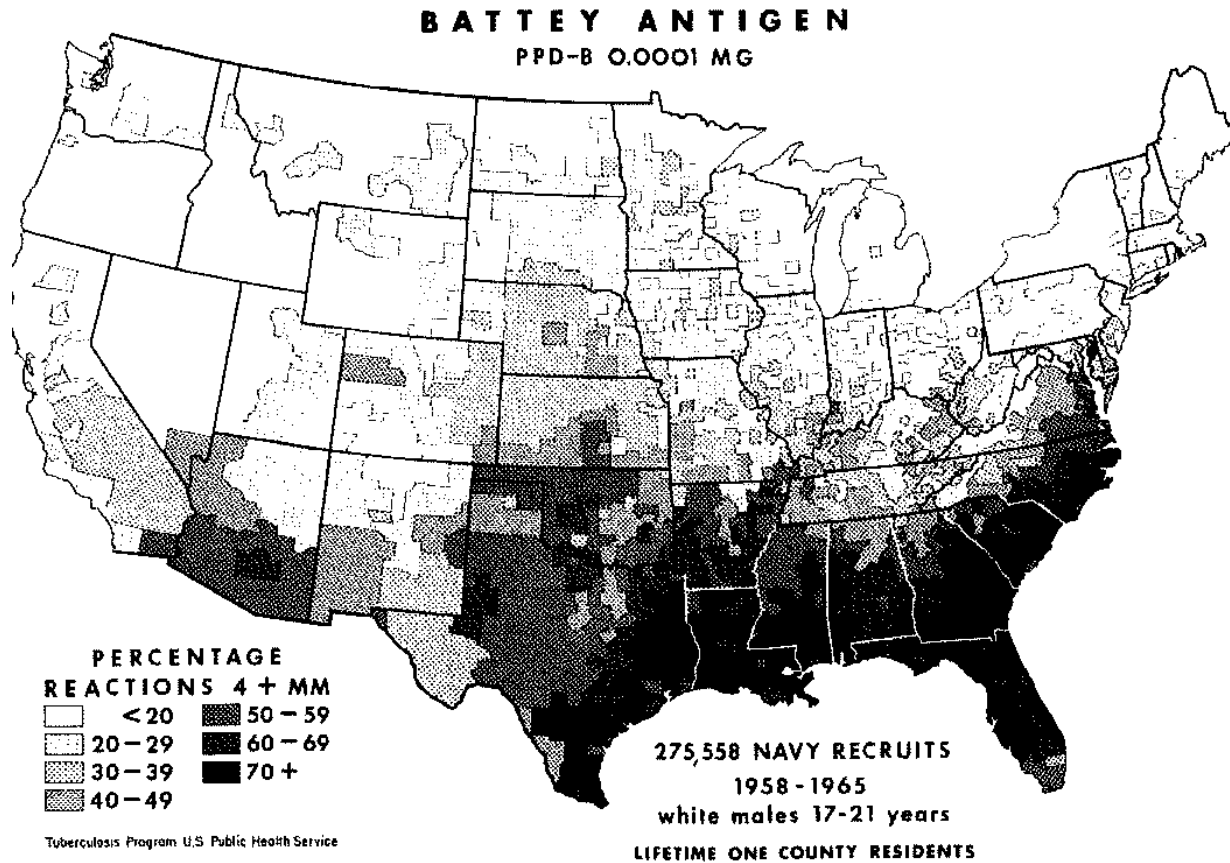
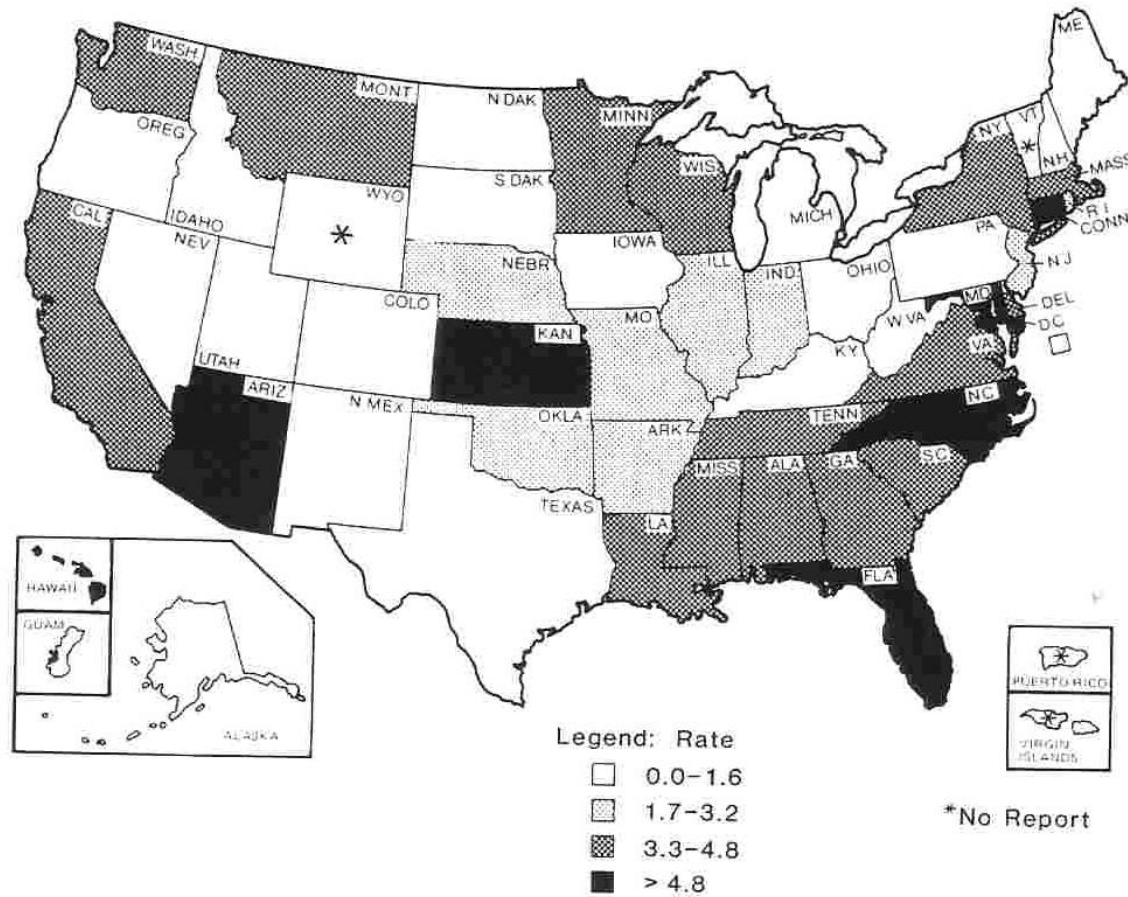


FIG. 11. Geographic variation in the frequency of reactors to 0.0001 mg PPD-B.

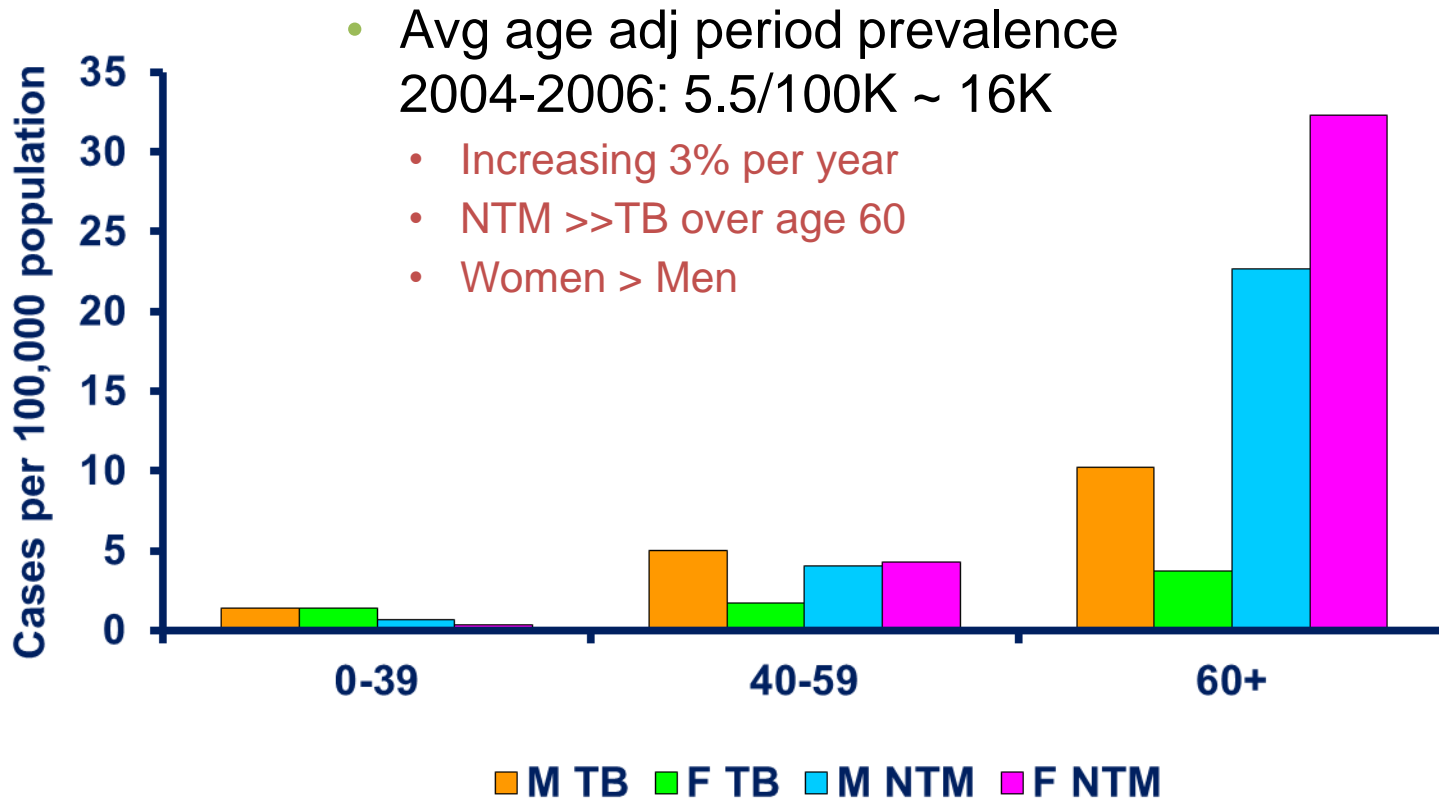
NTM Epid...historic



Prevalence *M. avium* complex/100,000 by state
Good. J Infect Dis 1982; 146:829-833

Nontuberculous Mycobacterial Lung Disease Prevalence at Four Integrated Health Care Delivery Systems

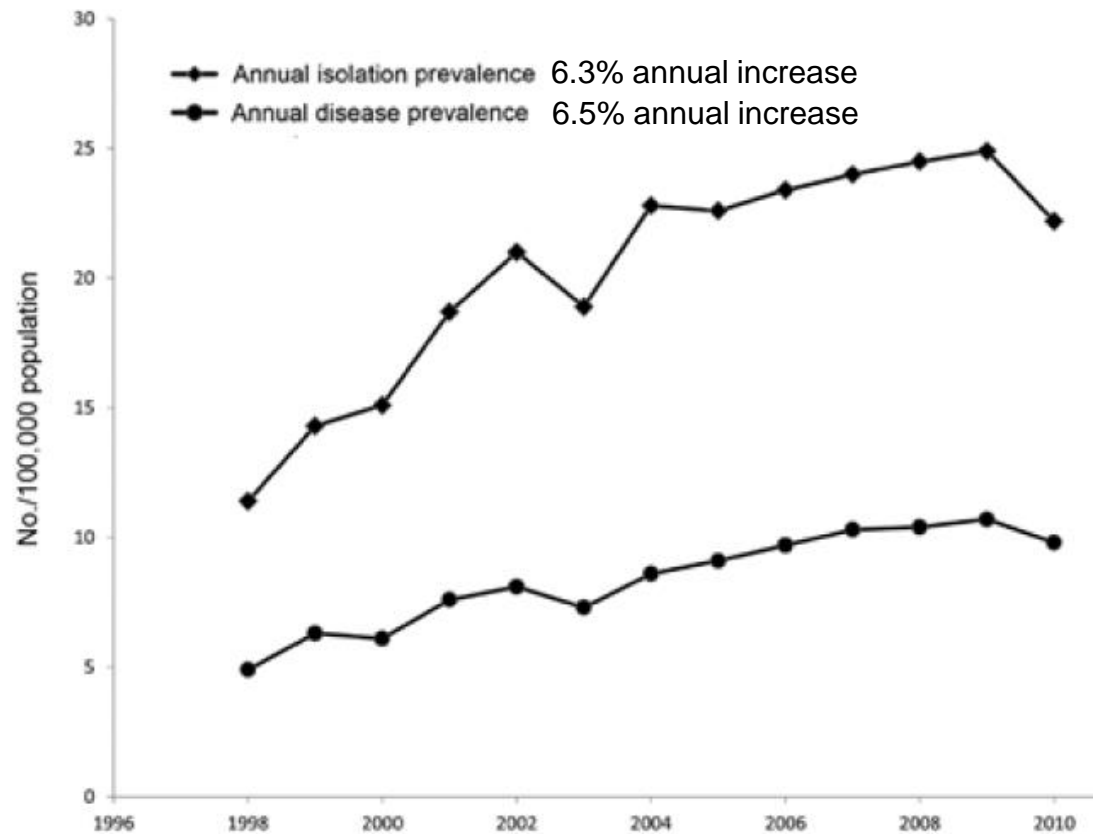
D. Rebecca Prevots¹, Pamela A. Shaw², Daniel Strickland³, Lisa A. Jackson⁴, Marsha A. Raebel⁵, Mary Ann Blosky⁶, Ruben Montes de Oca¹, Yvonne R. Shea⁷, Amy E. Seitz¹, Steven M. Holland¹, and Kenneth N. Olivier¹



Pulmonary Nontuberculous Mycobacterial Disease, Ontario, Canada, 1998–2010

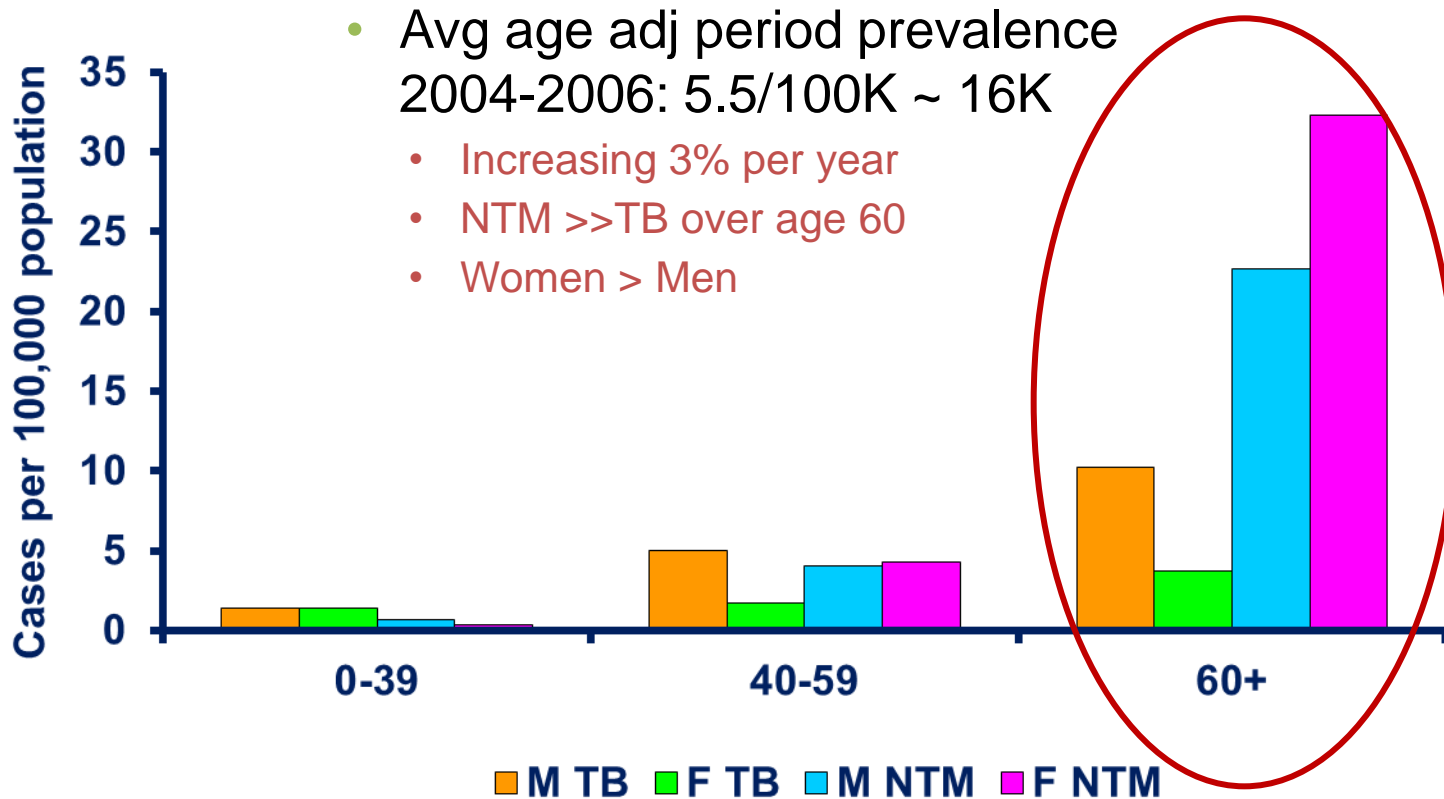
Theodore K. Marras, David Mendelson,
Alex Marchand-Austin, Kevin May,
and Frances B. Jamieson

- Retrospective study Ontario
- Case = ≥ 2 pos sputum or 1 bronch/bx
- Species in 2010
 - Mac 12.2/100K
 - *M. xenopi* 3.9/100K
 - *M. abscessus* 0.6/100K



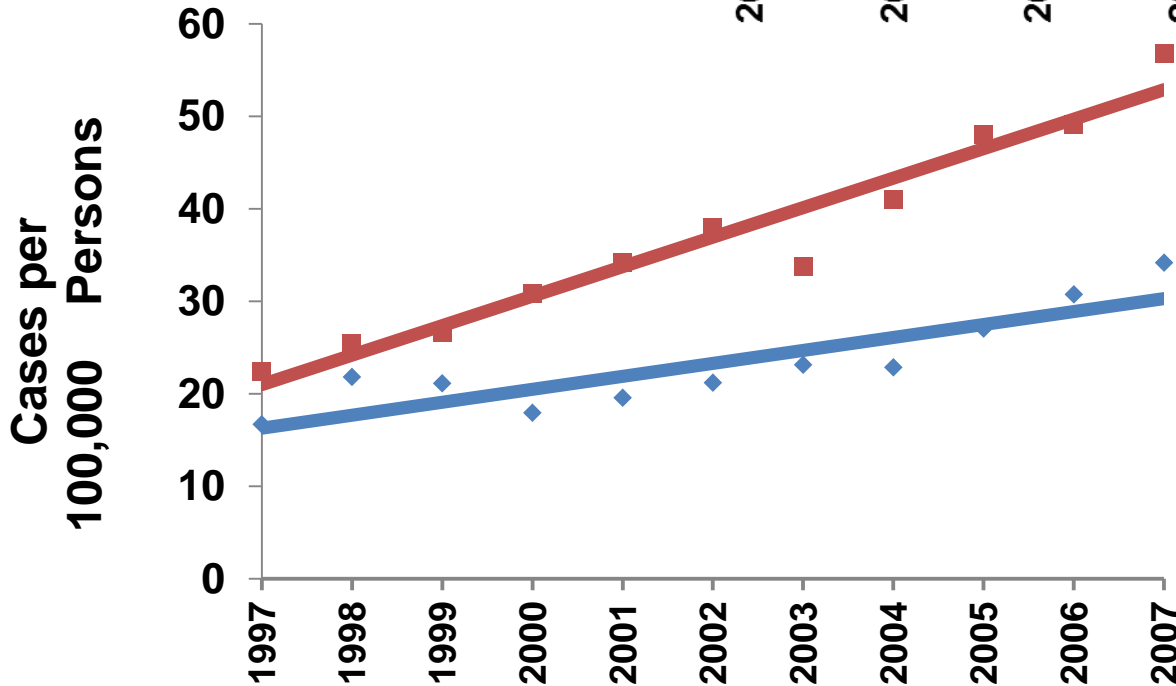
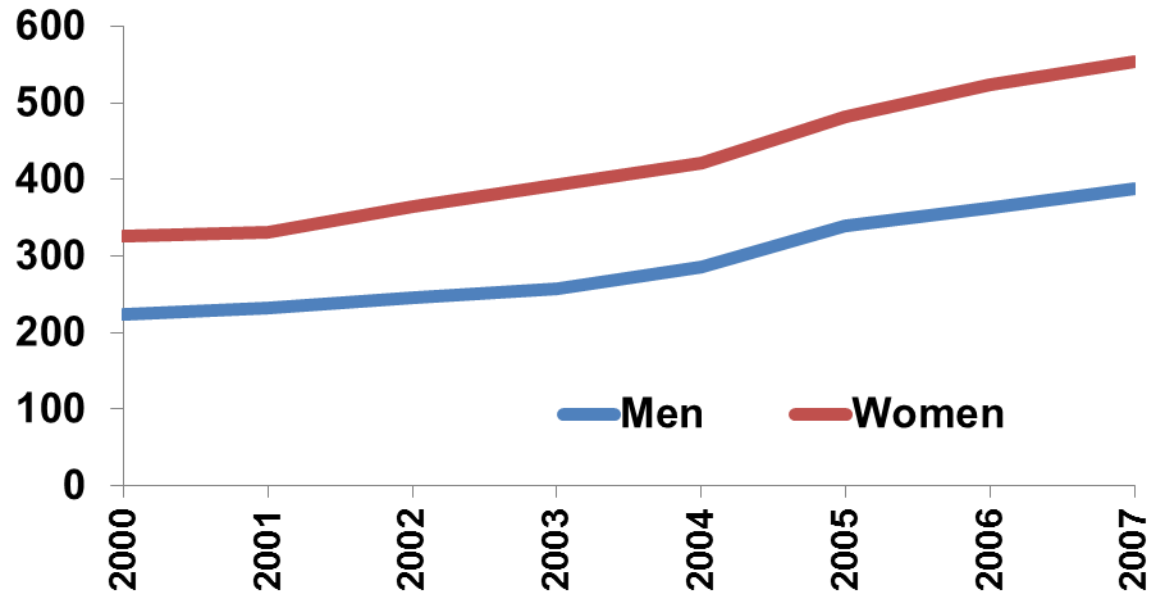
Nontuberculous Mycobacterial Lung Disease Prevalence at Four Integrated Health Care Delivery Systems

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US Medicare: Bronchiectasis Prevalence

Seitz A. Chest 2012



US Medicare: NTM Prevalence

Adjemian J. AJRCCM 2012

The Burden of Pulmonary Nontuberculous Mycobacterial Disease in the United States

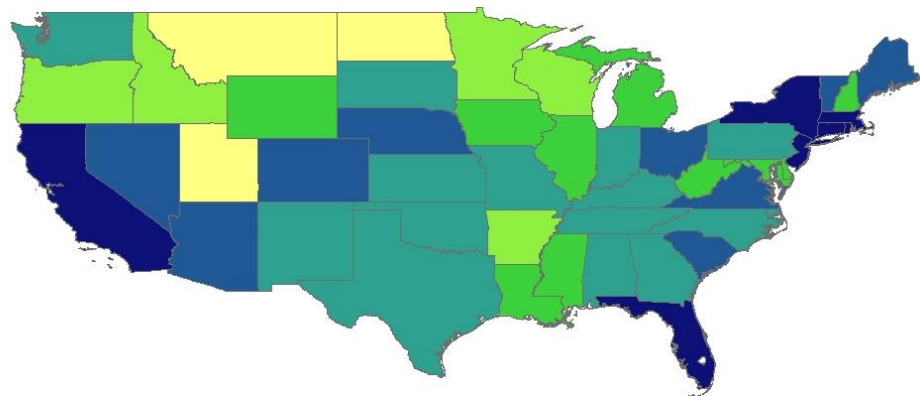
Sara E. Stollo¹, Jennifer Adjemian^{1,2}, Michael K. Adjemian³, and D. Rebecca Prevots¹

¹Epidemiology Unit, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; ²Commissioned Corps, United States Public Health Service, Rockville, Maryland; and ³Market and Trade Economics Division, Economic Research Service, United States Department of Agriculture, Washington, DC

- Estimated annual medical costs
 - Extrapolated data from US Medicare and practice survey studies
 - Assumed
 - 73% cases missed based on ICD9 coding
 - 31% NTM cases are younger than age 65
 - 8.2% annual increase in prevalence
 - 2010 US Census Bureau data

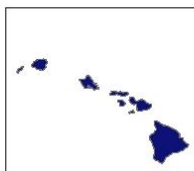
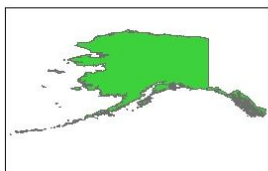
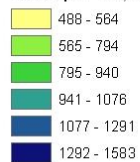
	National Nontuberculous Mycobacterial Disease Estimates	National Nontuberculous Mycobacterial Disease Estimates Assuming 1 Additional Outpatient Visit per Year	National Nontuberculous Mycobacterial Disease Estimates Assuming 2 Additional Outpatient Visits per Year	National Nontuberculous Mycobacterial Disease Estimates Assuming 3 Additional Outpatient Visits per Year
Annual medical encounters*	86,244	172,487	258,731	344,974
Annual cost†	\$815,098,690	\$937,491,959	\$1,059,885,228	\$1,182,278,496

- 80% costs attributed to prescription medication costs



Bronchiectasis Period Prevalence

cases per 100,000 individuals

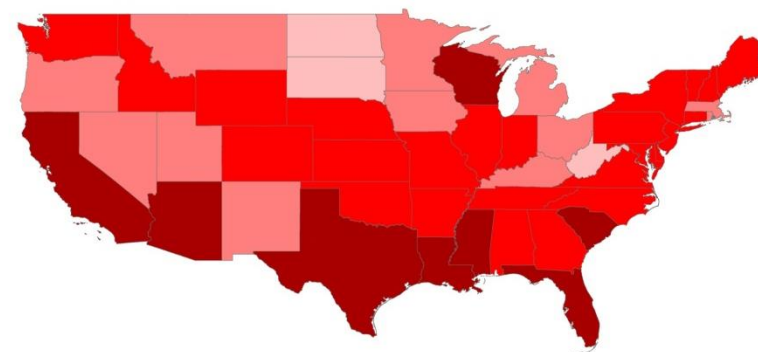


Bronchiectasis

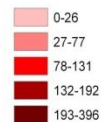
Seitz A. Chest 2012

NTM

Adjemian J. AJRCCM 2012



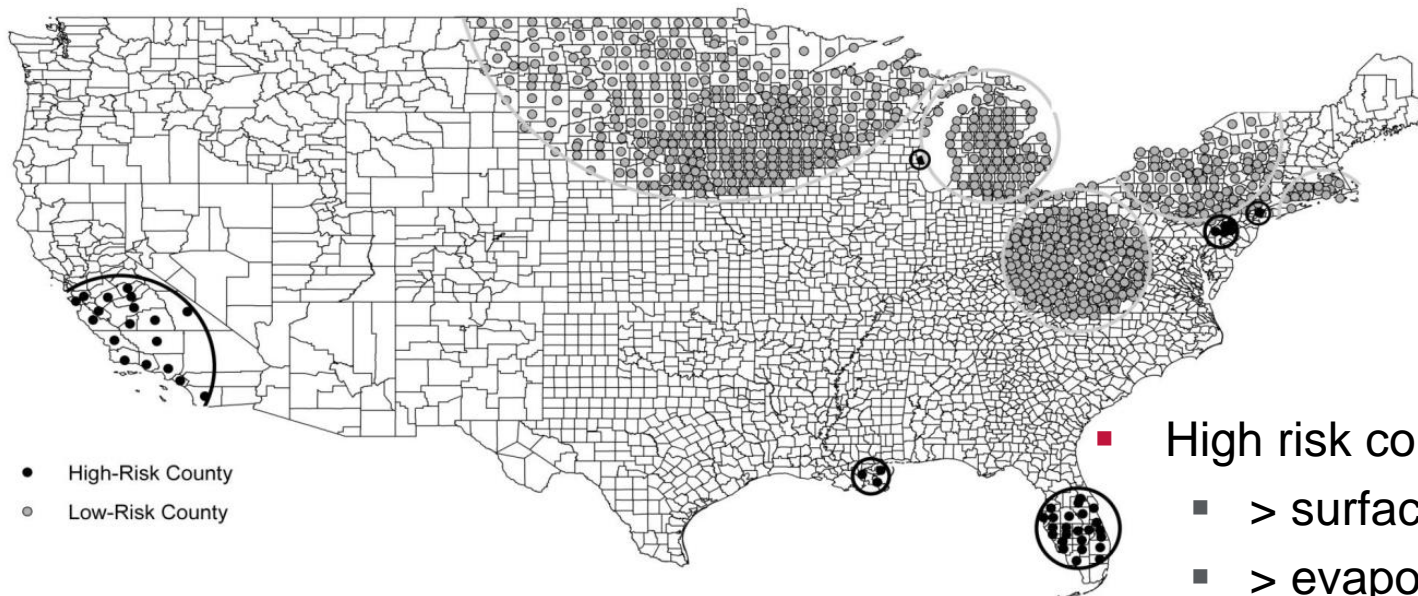
NTM Cases/100,00 Persons



Spatial Clusters of Nontuberculous Mycobacterial Lung Disease in the United States

Jennifer Adjemian^{1,2}, Kenneth N. Olivier², Amy E. Seitz^{1,2}, Joseph O. Falkinham III³, Steven M. Holland², and D. Rebecca Prevots^{1,2}

¹Epidemiology Unit and ²Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and ³Virginia Polytechnic Institute and State University, Blacksburg, Virginia



High risk counties

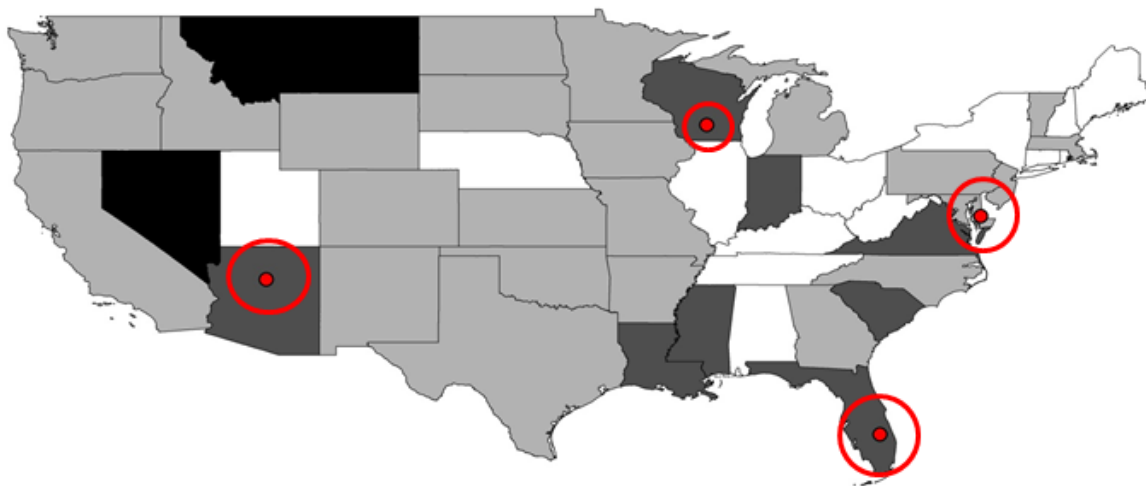
- > surface water (OR 4.6)
- > evapotranspiration (4.0)
- > copper (1.2) & Na⁺ (1.9)
- < manganese (0.7)

Nontuberculous Mycobacteria among Patients with Cystic Fibrosis in the United States

Screening Practices and Environmental Risk

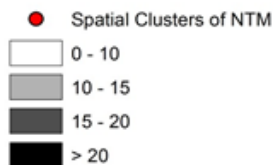
Jennifer Adjemian^{1,2}, Kenneth N. Olivier³, and D. Rebecca Prevots¹

¹Epidemiology Unit and ³Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and ²United States Public Health Service, Rockville, Maryland



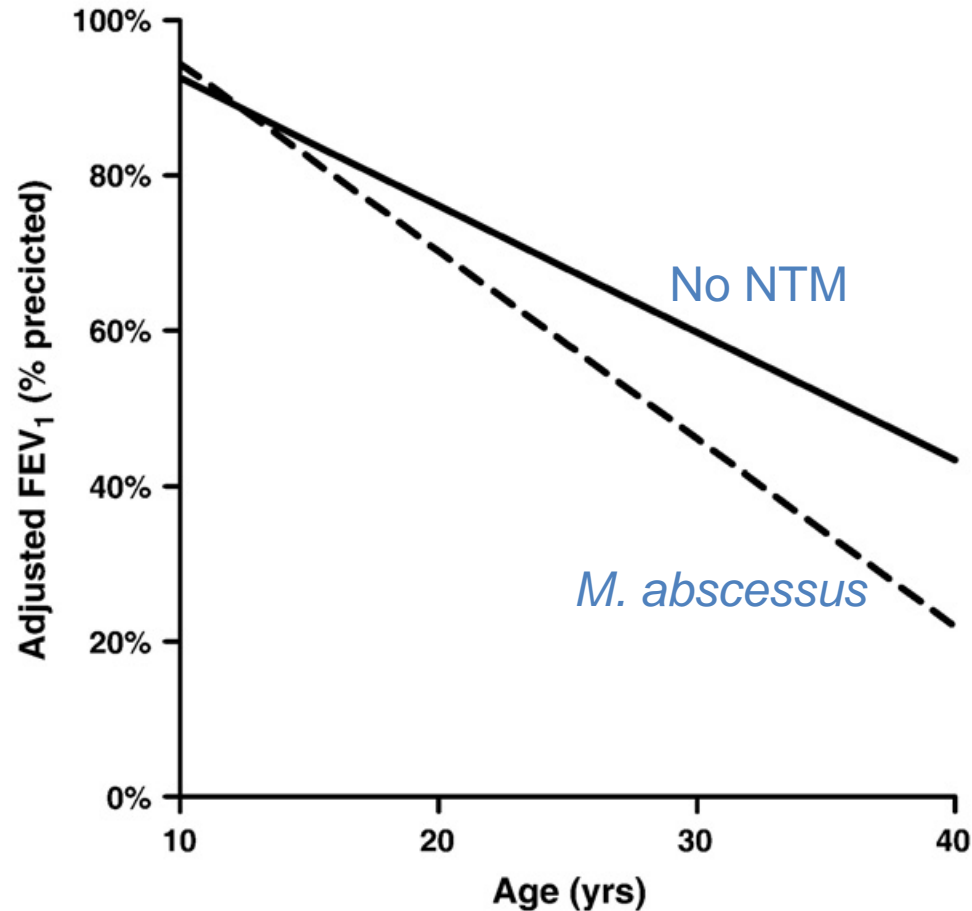
- CF Patient Registry 2010 & 2011
- 18,003 pts >12 yrs
 - 14% pos Mac/Mab
 - 4 significant geospatial clusters
 - **Saturated vapor pressure** specific climatic risk

Prevalence of NTM among CF Patients



Significance of *M. abscessus*

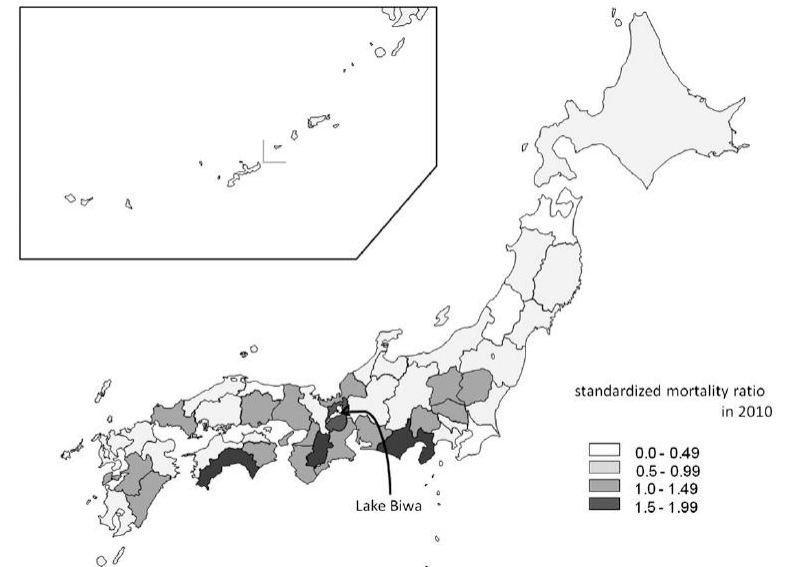
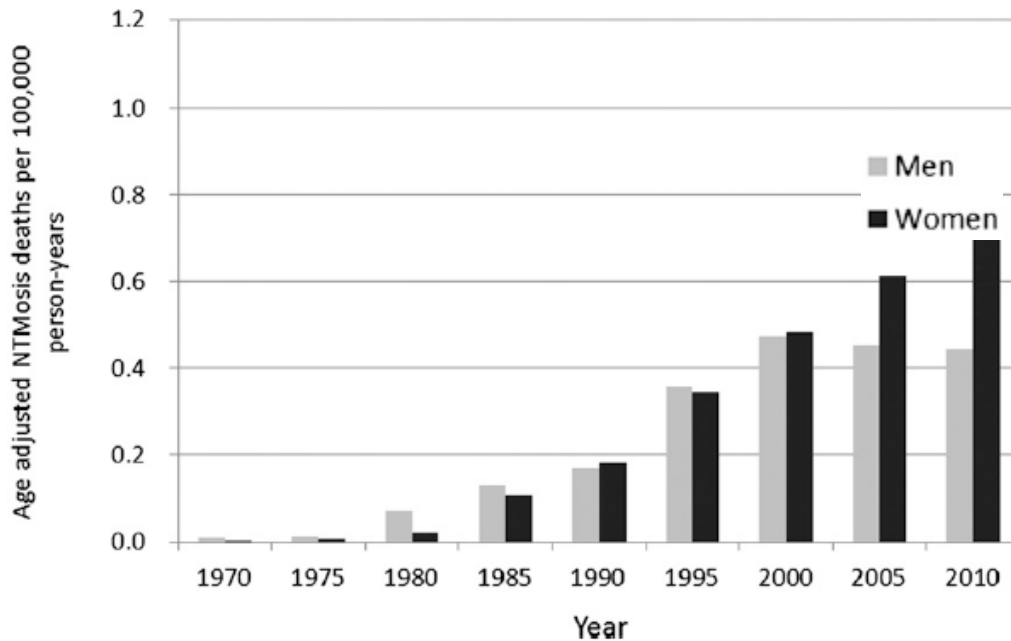
- *M. abscessus* excess decline of -0.78% per year vs no NTM (p=0.02)
- Other NTM were intermediate between *M. abscessus* and no NTM



A Steady Increase in Nontuberculous Mycobacteriosis Mortality and Estimated Prevalence in Japan

Kozo Morimoto¹, Kazuro Iwai², Kazuhiro Uchimura², Masao Okumura¹, Takashi Yoshiyama¹, Kozo Yoshimori¹, Hideo Ogata¹, Atsuyuki Kurashima¹, Akihiko Gemma³, and Shoji Kudoh¹

¹Respiratory Disease Center, Fukuji Hospital, Japan Anti-Tuberculosis Association, ²Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, and ³Division of Pulmonary Medicine, Infectious Diseases, and Oncology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan



- Increasing mortality for both sexes through 2000, then only in women
 - Increased in warm areas, high rainfall

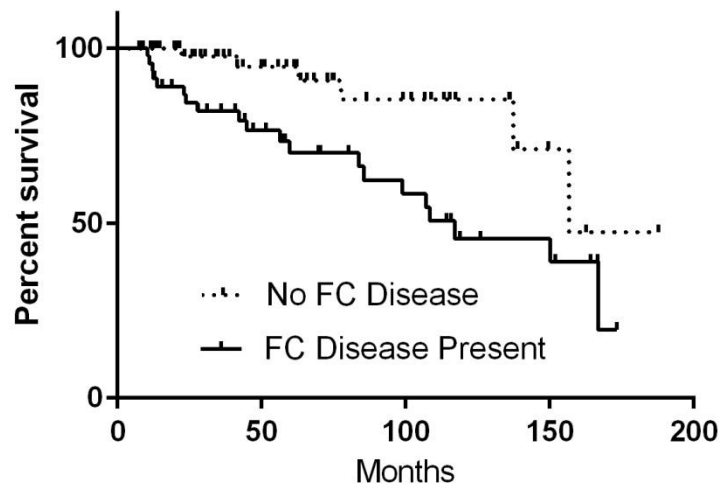
- Estimated prevalence 33-65/100K
 - >50% dx with Mac remained cx pos at 2yr; 36% cx pos at 5 yr

Mortality in NTM

- Several studies have reported 5-year mortality
 - Hayashi AJRCCM 2012 – Japan: 25%
 - Ito IJTLD 2012 – Japan: 28%
 - Andrejak AJRCCM 2010 – Denmark: 40%
 - Kotilainen SJID 2013 – Finland: 28% (4yr)
 - Strollo (unpub 2015) – NIH cohort: 25%

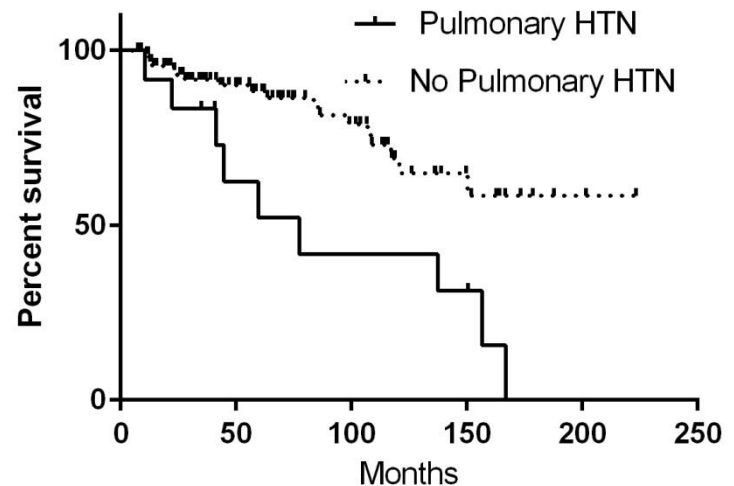
Mortality risk factors

Fibrocavitory Disease



- Median survival
 - FCD = 9.0 years
 - No FCD = 13.1 years
 - $p = 0.006$

Pulmonary Hypertension



- Median survival
 - PH = 6.8 years
 - No PH = >18 years
 - $p = 0.48$

Summary

- US prevalence difficult to assess
 - ~16K – 84K
- Increased in women and age >60
- Considerable geographic variability
 - Likely reflects environmental influences
- Disease burden and costs are substantial
- Adversely effects lung function
- Associated with increased mortality



Review Considerations for New Drugs

Hala Shamsuddin, MD

Patient Focused Drug Development

NTM Lung Infections

October 15, 2015

Outline

- Adequate and Well Controlled Clinical Trials
- Drugs in Combination
- Trial Endpoints

Drug Development

- Non-Clinical
 - Chemistry and Manufacturing
 - Toxicology
 - Pharmacology
 - In vitro activity
 - Animal models of infection (if any)

Clinical Trials

- For market authorization/approval, drug must show substantial evidence of efficacy
 - Section 505(d) of the FD&C act: adequate and well-controlled investigations
- 21 CFR 314.126
 - Adequate and well controlled clinical trials
 - To distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo-effect, or biased observation.

Types of A &WC Clinical Trials

- Placebo concurrent control
 - Randomized trial in which test drug is compared to inactive drug that is similar in appearance
- No treatment concurrent control
 - Randomized trial in which test drug is compared to no treatment
- Dose-comparison concurrent control
 - Randomized trial in which two or more doses of the test drug are compared

Types of A &WC Clinical Trials

- Active treatment concurrent control
 - Randomized trial in which test drug is compared to known effective therapy (active control)
- Historical control
 - Test drug is compared to historical experience
 - Reserved for special circumstances (e.g., disease with high mortality, course of illness predictable, or where drug effect is self-evident such as in general anesthetics)

Types of Clinical Trials

- Superiority Trials: test drug better than comparator
 - Placebo, no treatment, dose-comparison, active control or historical trials
- Advantage: Can assess any outcome of interest regardless of what previous trials had assessed

Clinical Trials

- Non-inferiority trials: test drug no worse than an active comparator by a certain pre-specified degree (non-inferiority margin)
- Disadvantages
 - The effect of the active comparator compared to placebo needs to be estimated in the particular population and for the particular outcome of interest
 - May limit choice of study population and study outcome measures
 - Possible that study cannot support efficacy if no historical evidence of active comparator exists

NTM Lung Infection Trials

- Monotherapy is not recommended
- Complicates trial design for a new regimen; For diseases that require use of drugs in combination, the new drug(s) must be demonstrated to make a contribution to the overall regimen
 - The contribution may be additive treatment effect, prevention of emergence of resistance or mitigation of toxicity
 - Demonstrating the contribution of a drug in a combination regimen may be difficult unless the clinical trial is an add-on trial
- In some instances, drugs in a combination regimen can be co-developed.

Drugs in Combination

- Guidance for Industry – Co-development of two or more new investigational drugs for use in combination
 - Treatment of serious disease (lung NTM is)
 - Compelling reasons why the drugs cannot be developed independently (monotherapy is not recommended)
 - Strong biologic rationale for the combination (e.g., drugs act on different microbial targets)
 - Nonclinical evidence that combination provides significant therapeutic advance over available therapy and is superior to the individual drugs (in vitro synergy or prevention of resistance; effects in animal model)

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf>

NTM Lung Infection Trials

- Superiority trials
 - Add-on trials: Test drug or test drug combination added to background regimen (BR) compared to placebo or no treatment added to BR
 - Test drug plus BR vs. BR used in TB trials
 - New Regimen
 - Test drug combination compared to placebo or no treatment (no BR) in patients in whom delaying treatment may be clinically acceptable
 - Test combination regimen compared to another combination that does not include the same drugs
 - Contribution of each component may be demonstrated in vitro or animal model

NTM Lung Infection Trials

- Non-inferiority trials
 - Test drug substitutes for a drug in the BR (has been used in TB to allow treatment shortening)
 - If feasible, compare new combination regimen to another combination regimen for treatment shortening or mitigation of toxicities
- NI trials are likely to be extremely challenging
 - Treatment effect of single drug substitution for efficacy or to allow shorter treatment duration is not known to allow derivation of NI margin

Trial Endpoints (Outcome Measures)

- Assess a clinically meaningful endpoint that is a direct measure of how a patient feels, functions or survives
 - Federal Register/Vol. 57, No.73/April 15, 1992
- Include:
 - Improved survival
 - Improvement of symptoms or functional capacity
 - Prevention of disease complication (e.g., treatment of latent TB)

Biomarkers and Surrogates

- Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention.
 - Biomarkers Definitions Working Group 2001 & IOM Report 2011
- A surrogate is a laboratory measurement or physical sign that is used as a substitute for a clinically meaningful outcome
 - Reasonably likely to predict clinical benefit [21 CFR 314.500 (subpart H)]
 - Examples: BP, HIV viral load

Surrogate Endpoints

- A surrogate is a biomarker, but not every biomarker is a surrogate
- However, for a biomarker to be established as a surrogate that is predictive of clinical outcome, evidence that changes in the biomarker correlate with changes in the clinical outcome should be established.
- Once established, surrogates allow faster drug development
- If accelerated approval on the basis of surrogate biomarker, a confirmatory trial that assesses the clinical outcome is required
 - Example: TB drugs may receive accelerated approval based on culture conversion to negative but a confirmatory trial showing relapse free survival is required

Endpoints in NTM Lung Infections Trials

- Endpoints under consideration in NTM lung infection trials
 1. Survival
 2. Measures of symptoms or function
 - Clinician reported outcomes: may be difficult for some symptoms
 - Patient reported outcomes (PRO): require validation
 - 6MWT or other functional assessment: degree of change that is meaningful to the patient should be defined

Endpoints in NTM Lung Infections Trials

3. Surrogate biomarkers to consider

- Microbiologic: Sputum culture conversion to negative
 - Similar to TB trials, but
 - Number of consecutive negative cultures not established
 - Timing of determining conversion during therapy not established
 - Correlation with clinical outcomes needs to be established
- Other surrogates? (e.g., radiologic – same considerations as microbiologic endpoints):

Conclusions

- Drugs need to show evidence of *efficacy for a clinically meaningful outcome* evaluated in *adequate and well controlled trials*
- Surrogate markers can be used for approval if the surrogate has been shown to *predict/correlate with* a meaningful clinical outcome
- PROs, if validated, can be used for approval
- Co-development of a new test drug combination may be possible in certain situations



The Road from Patient-Focused Drug Development Public Meetings to Clinical Study Endpoints

Selena R. Daniels, Pharm.D., M.S.

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Office of New Drugs

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

PATIENT-FOCUSED DRUG DEVELOPMENT (PFDD) MEETINGS



WHERE DO WE GO FROM HERE



PATIENTS' VOICE





Two Pathways for FDA Clinical Outcome Assessment Review & Advice

1

Within an individual drug development program

- Investigational New Drug (IND) submissions to FDA
- Potential to result in labeling claims

2

Within the Drug Development Tool (DDT) qualification program; outside of an individual drug development program

- Potential to result in qualification*

Key Takeaways

- PFDD meetings are a “starting point” for developing patient-focused outcome measures and endpoints
- The outcomes of PFDD meetings will support and guide FDA risk-benefit assessments in drug reviews
- Patients’ input ultimately helps determine:
 - WHAT is measured to provide evidence of treatment benefit
 - HOW best to measure concepts in a clinical study
 - WHAT a meaningful improvement is in treatment benefit



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Quality of Life- NTM Module

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ACKNOWLEDGEMENTS: KEN OLIVIER, KEVIN WINTHROP,
MATTHIAS SALATHE

Quittner A, Madan A, Saez-Flores E, Olivier K, Fennelly K, Schmid A, & Salathe M. Development of the quality of life module for nontuberculous mycobacteria (NTM). *European Respiratory Journal*, 2015; 46, Supp. 59, No. 275. (Abstract)

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- **Dr. Ken Olivier, NIH**
- **Dr. Matthias Salathe**
- **Dr. Kevin Withrop**

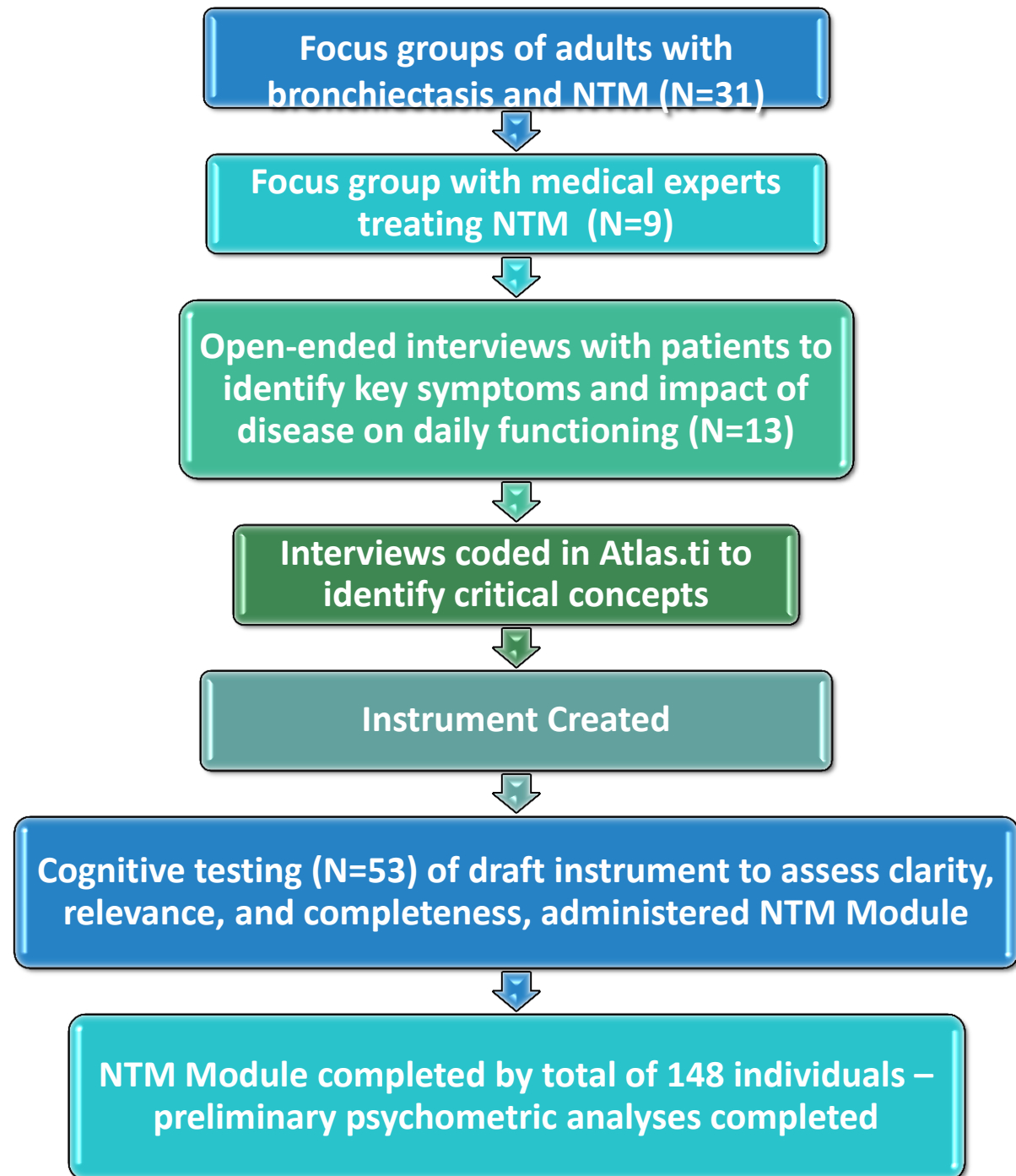
Objectives

- **Nontuberculous mycobacteria (NTM) is a substantial cause of pulmonary infections and can affect those with chronic respiratory diseases, such as cystic fibrosis (CF) and bronchiectasis.**
- **NTM is rare, poorly understood, and difficult to treat, with few clear identified endpoints to evaluate new medications in randomized, controlled trials.**
- **We are developing a patient-reported outcome (PRO) that identifies key symptoms, tracks the progression of disease, and can serve as an important end-point in clinical trials of new therapies (FDA Guidance, 2009)**
- **The aim of this study was to develop an instrument for NTM symptoms; this can be used with existing PROs measures for CF (CFQ-R) and bronchiectasis (QOL-B)**

Methods

- **We followed the FDA Guidance on PROs (2009)**
- **Reviewed published literature on NTM to identify critical symptoms and challenges of living with NTM**
- **Focus groups, moderated by a psychologist, were conducted with adults with NTM + bronchiectasis at 2 sites, N=31**
- **A consensus panel of 9 pulmonologists with expertise in NTM provided input on how NTM and its treatment affects their patients**
- **Open-ended interviews were conducted with 13 patients: asked how NTM affects their daily lives; including frequent and difficult symptoms, effects on physical, emotional, and social functioning. Patients then completed the QOL-B; coded in Atlas.ti**
- **Cognitive testing, using a standard “think aloud” procedure conducted with 53 adults; input on the preliminary items & rating scale options**
- **We completed an initial psychometric validation of the module in 148 patients**

Measurement Development Process



Patient Demographics

	Focus Groups (N=31)	Open-Ended Interviews (N=13)	Cognitive Testing (N=53)
Gender N (%)			
Female	29 (93.5%)	12 (92.3%)	45 (83.3%)
Male	2 (6.5%)	1 (7.7%)	8 (14.8%)
Ethnicity/Race			
Caucasian	31 (100%)	13 (100%)	47 (87%)
Hispanic	0	0	5 (9.3%)
Not reported	0	0	2 (3.8%)
Age			
Mean (Range)	67.8 years (54.9 – 91.1 years)	65.9 years (42 – 82 years)	66.3 years (28 – 86 years)

Key Themes

Main themes from Focus Groups (N=31)

- Frequent pain (dull, aches, pressure in chest)
 - Metal taste in mouth
 - Fever
 - Lack of sleep

Main themes from Open-Ended Interviews (N=13)

- Fatigue
- Sensitivity to smell
- Sensitivity to cold/chills
- Hot flashes/sweats

Main themes from Physician Panel (N=9)

- Memory loss
- Body Image issues
- Side effects from medications: GI problems
- Weight loss with greater disease severity

Results

- **Focus groups and open-ended interviews identified eating issues, sleep quality, fever, and chills; physicians also identified body image as a concern**
- **The new NTM Module consists of eight unique symptoms; administered to 148 patients ($\alpha = .73$); very good reliability**

Sample items from NTM module

“Bothered by cold weather?”

“Have you experienced problems with memory?”

Internal consistency of NTM module (N = 148)

Scale Name	Cronbach's Alpha
NTM Symptoms	0.73
Body Image	0.76
Eating Problems	0.89
Digestive Symptoms	0.75

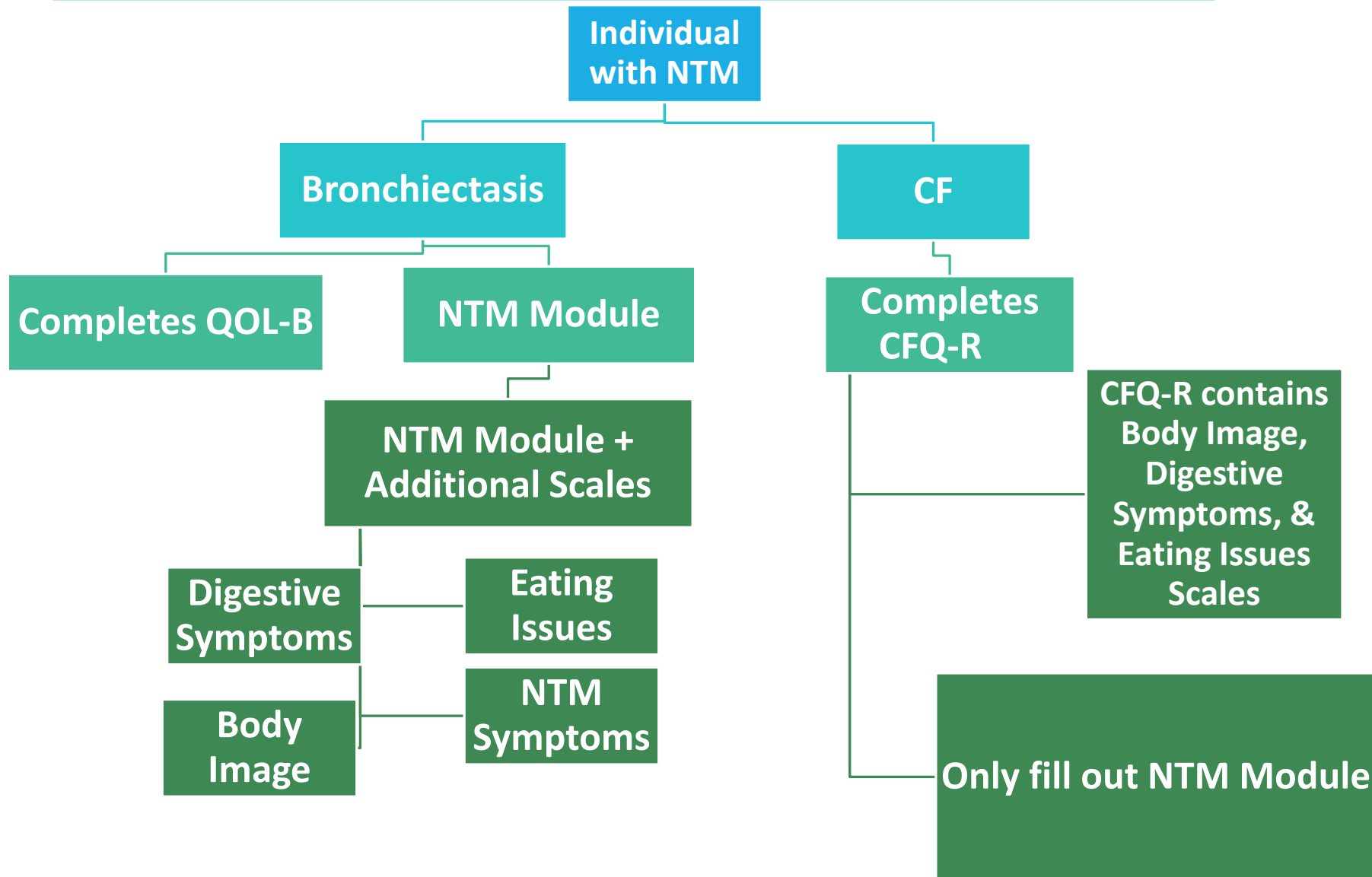
Multitrait analysis of NTM module (N = 148)

Item	Abbreviated Item Content	<i>NTM Symptoms</i>
NTM48	Feverish (chills, sweating)	0.42 ^a
NTM49	Problems sleeping	0.39 ^{a,b}
NTM50	Pain	0.41 ^a
NTM51	Bothered by cold weather	0.51 ^a
NTM52	Sensitivity to smell	0.37 ^{a,b}
NTM53	Sensitivity to taste	0.39 ^a
NTM54	Bad taste in mouth	0.48 ^a
NTM55	Memory problems	0.45 ^a

^aItem-scale correlation adjusted for overlap (item removed from its scale for correlation)

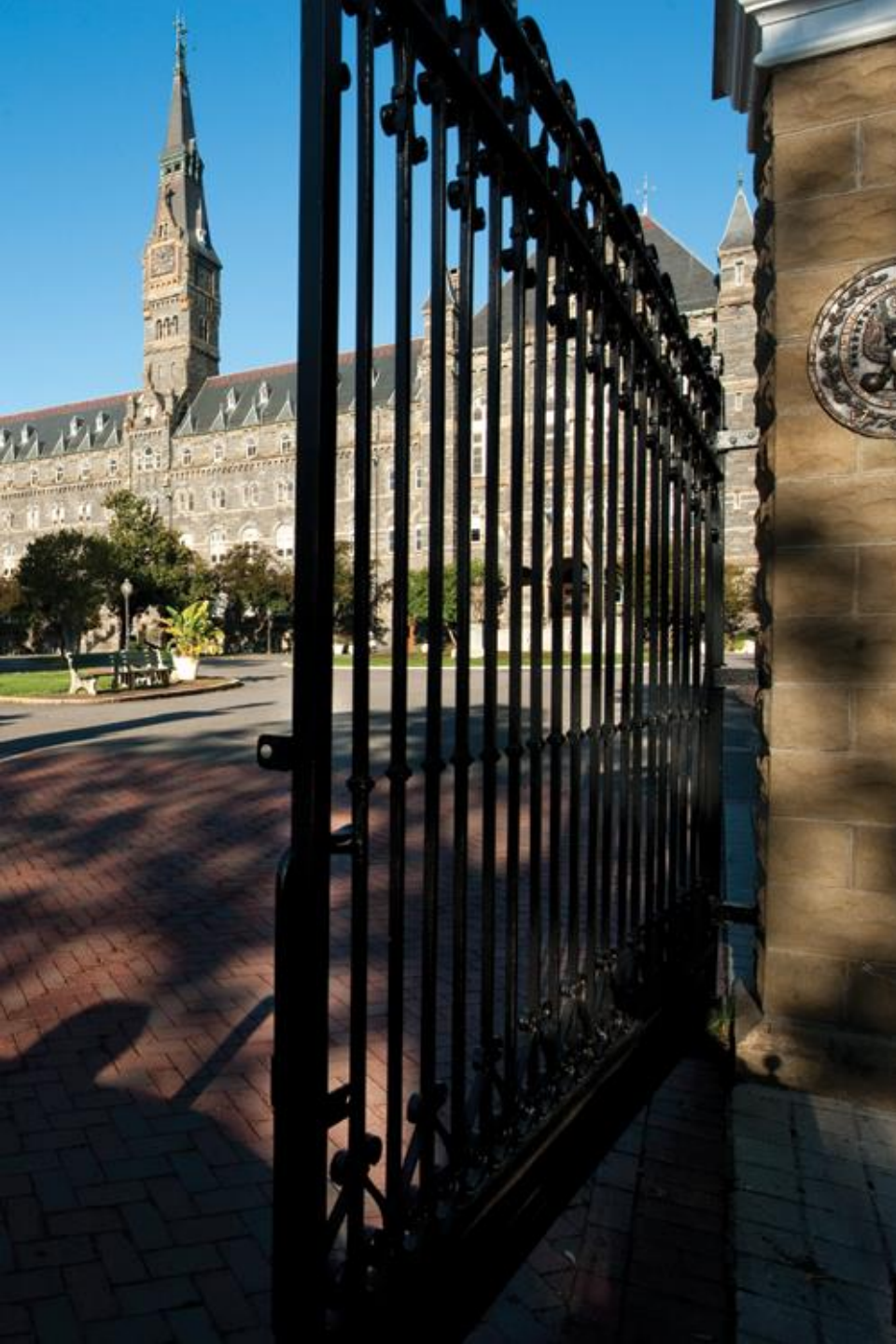
^bItem-scale correlation is <.40

Algorithm for administering NTM module with QOL-B or CFQ-R



Summary & Future Directions

- **Cognitive testing indicated that the draft items were relevant, clear, and easy to understand**
- **Strong reliability**
- **When utilizing NTM module with non-CF bronchiectasis: use module + Body Image, Eating Issues, & Digestive Symptoms scale (elicited from those with bronchiectasis)**
- **Next steps include additional psychometric testing, and identification of the meaningful change on this instrument**



Challenges in design of clinical trials for NTM lung infections

Anne E. O'Donnell MD

October 15, 2015



GEORGETOWN UNIVERSITY

Disclosures

- Principal Investigator/Grant support to GU for clinical trials
 - Insmed (inhaled liposomal amikacin)
- Foundation support to GU for Bronchiectasis Registry
 - COPD Foundation
- Consultant/Advisor
 - Insmed (inhaled liposomal amikacin): in Jan 2014
 - Xellia Pharmaceuticals (manufactures amikacin and colistin)
- No FDA approved therapies

NTM and clinical trials

In a perfect world

- Medications are simple
- Medications are tolerable
- Results are easy to evaluate:
 - Patient feels better
 - Infection is cured
 - Lung damage reversed
- Infection never recurs

Reality

- Regimen is complex
- Side effects are troublesome
- What constitutes response?
 - Microbiology
 - Imaging
 - Lung function
 - Patient's symptoms
- “Cure” is elusive

NTM and clinical trials

- Microbiologic results
 - Reduction in organism counts
 - Eradication of organism
 - Duration of response
 - Presence or development of resistance
- Imaging results
- Lung function results
- Patient reported outcomes
 - Exacerbations are not a clinical feature in NTM

NTM and clinical trials

Microbiology

- Current “gold standard”
 - 12 months of negative cultures while receiving Rx
 - How are cultures processed?
 - Routine practice
 - Haphazard, standard lab evaluation
 - Tyler
 - Monthly
 - Semiquantitative cultures
 - Macrolide susceptibility testing
 - Genotyping
- *Griffith DE et al. Am J Respir Crit Care Med 2015;192:754-760*

NTM and clinical trials

Microbiology

- Tyler results
 - 180 patients with MAC and nodular bronchiectasis
 - Greater than 12 months of three drug therapy
 - 82% had culture conversion to negative
 - Microbiologic recurrences during therapy in 14%
 - 73% reinfection
 - 27% true relapse
 - Microbiologic recurrences after therapy in 48%
 - 75% reinfection
 - 25% true relapse
 - ***Wallace RJ et al. Chest 2014;146:276-282***

NTM and clinical trials

Microbiology

- South Korean results
 - 217 patients with MAC and nodular bronchiectasis
 - Daily or intermittent three drug therapy
 - 71-72% sputum culture conversion to negative
 - Only 4 patients had recurrence while on therapy
 - No post therapy results
 - *Jeong B et al. Am J Respir Crit Care Med 2015;191:96-103*
- Cavitory MAC disease
 - 49 subjects with MAC and cavitory disease
 - Thrice weekly regimen
 - 4.1% culture conversion
 - *Lam PK et al. Am J Respir Crit Care Med 2006;173:1283-1289*

NTM and clinical trials

Microbiology

- MAC and M. abscessus refractory to treatment
 - Salvage with bedaquiline
 - 10 subjects
 - 8 macrolide resistance
 - 6/10 had microbiologic response
 - **Philly JV et al. Chest 2015;148:499-506**
 - Salvage with inhaled liposomal amikacin
 - 90 patients: MAC 64%, m. abscessus 36%
 - 10/44 MAC patients converted at day 56; 11/44 at day 84
 - 0/15 M. abscessus converted at day 56; 1/15 at day 84
 - **Biller JA et al. Am J Respir Crit Care Med 2015;191:A6295**

NTM and clinical trials

Microbiology endpoint

- Advantages
 - Hard end point
 - Reproducible if done in advanced mycobacterial lab
- Problems
 - How to define success?
 - Three negative cultures while on therapy
 - One positive culture “doesn’t count”
 - What about after the conclusion of therapy
 - Defining relapse vs new infection
 - How long to monitor

NTM and clinical trials

Imaging

- Heterogeneous findings
- Nodular vs cavitary disease
 - Waxing and waning bronchiolitis
- Lack of standardized CXR or CT scoring
- Radiation dosing and exposure
 - *McCunney RJ. Chest 2015;147:872*
 - *Doss M. Chest 2015;147:874*
- Two trials that reported serial imaging findings
 - *Jeong B et al. Am J Respir Crit Care Med 2015;191:96-103*
 - *Lam PK et al Am J Respir Crit Care Med 2006;173:1283-89*

NTM and clinical trials

Lung function testing

- Lung function results
 - Pulmonary function tests
 - 6 min walk test
- Paucity of published data
- Heterogeneous patient population
- Probably only helpful for monitoring adverse effects of inhaled medications

NTM and clinical trials

Patient reported outcomes

- Mortality
 - Fortunately, a rare outcome
- Morbidity
 - Fatigue
 - Fever
 - Cough
 - Hemoptysis
 - Weight loss
 - Night sweats
 - Shortness of breath
 - Sputum production
 - *Olivier KN et al. Annals ATS 2014;11:30-35*

NTM and clinical trials

Patient reported outcomes

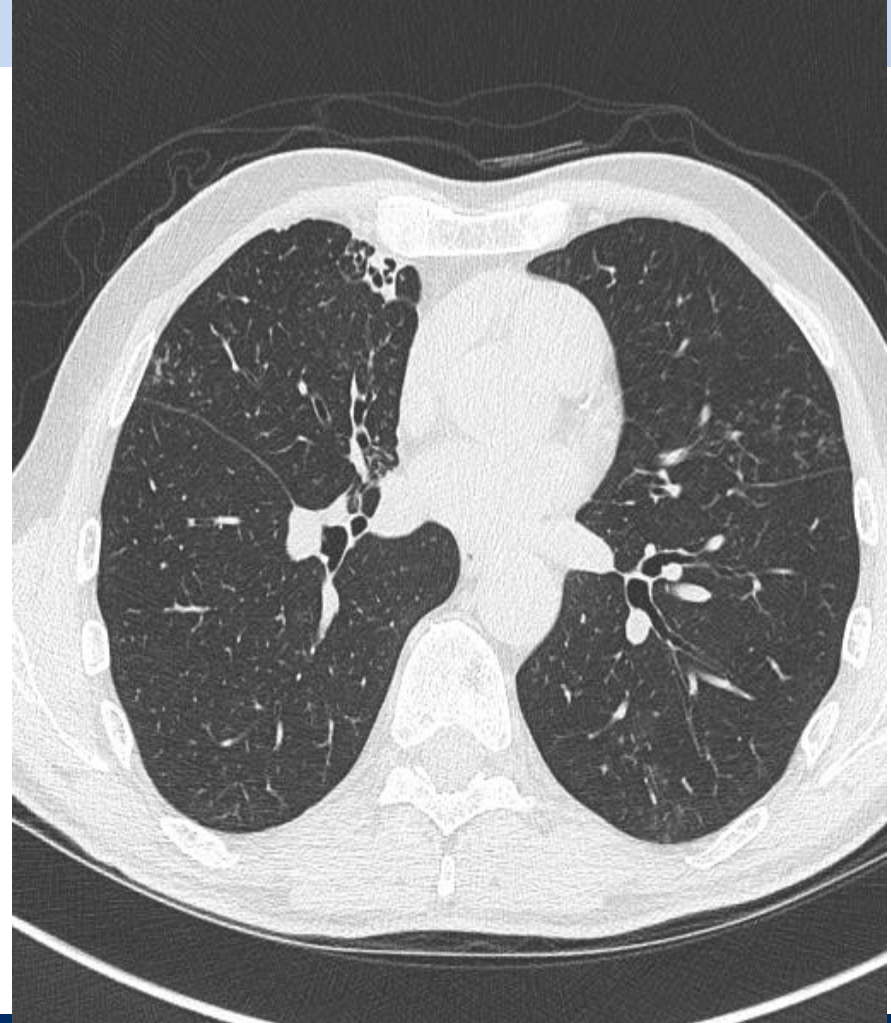
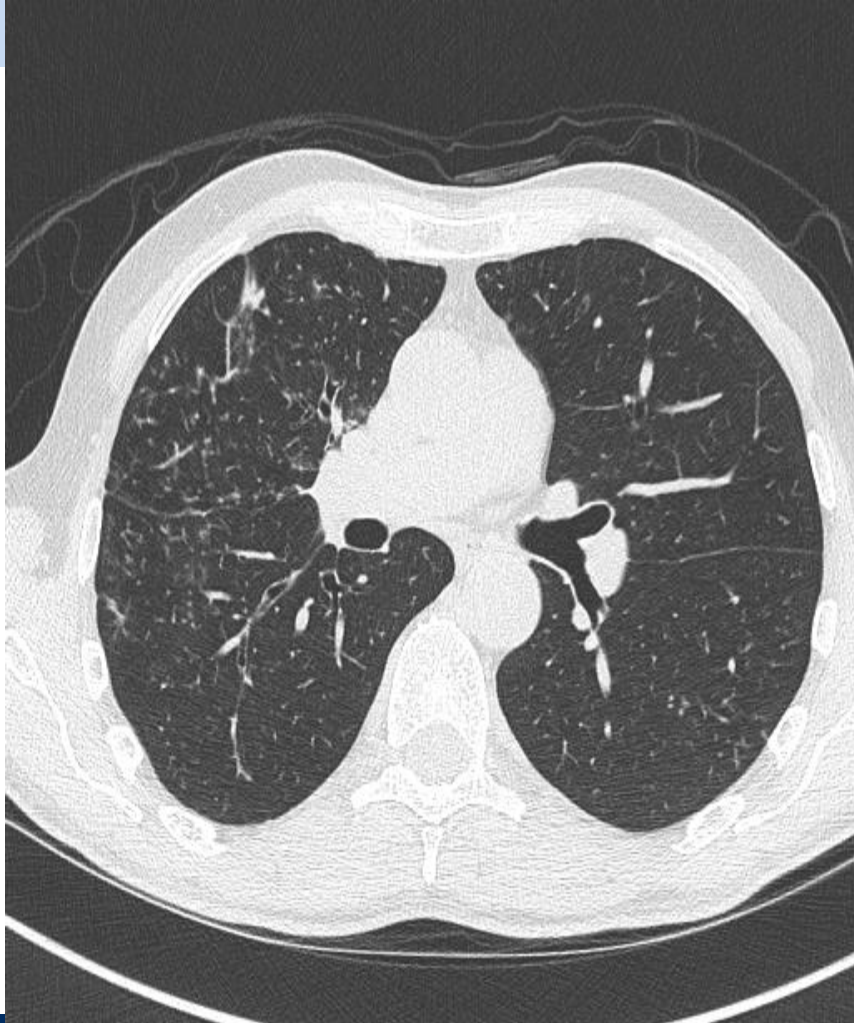
- 20 patients with refractory NTM infection
 - 15 m. abscessus, 5 MAC
 - Inhaled amikacin added to regimen
 - 8/20 had at least one negative culture
 - 5/20 had persistently negative cultures
 - 9/20 had improved symptom scores
 - 7 unchanged, 4 worsened symptom scores
- » *Olivier KN et al. Annals ATS 2015;11:30-35*
- Quality of life bronchiectasis with NTM specific questions
 - » *Quittner A et al. ERJ 2015;46:A2635*

NTM and clinical trials

Confounding factors

- Heterogeneous disease
 - MAC vs *M. abscessus*
 - Nodular bronchiectasis vs cavitory disease
 - NTM causing the structural damage
 - Female predominant
 - NTM superimposed on chronic disease
 - Males and females affected
 - Cystic fibrosis
 - Emphysema
- Co-infections with other bacteria
 - *Pseudomonas*, *staphylococcus*, *nocardia*, *aspergillus*

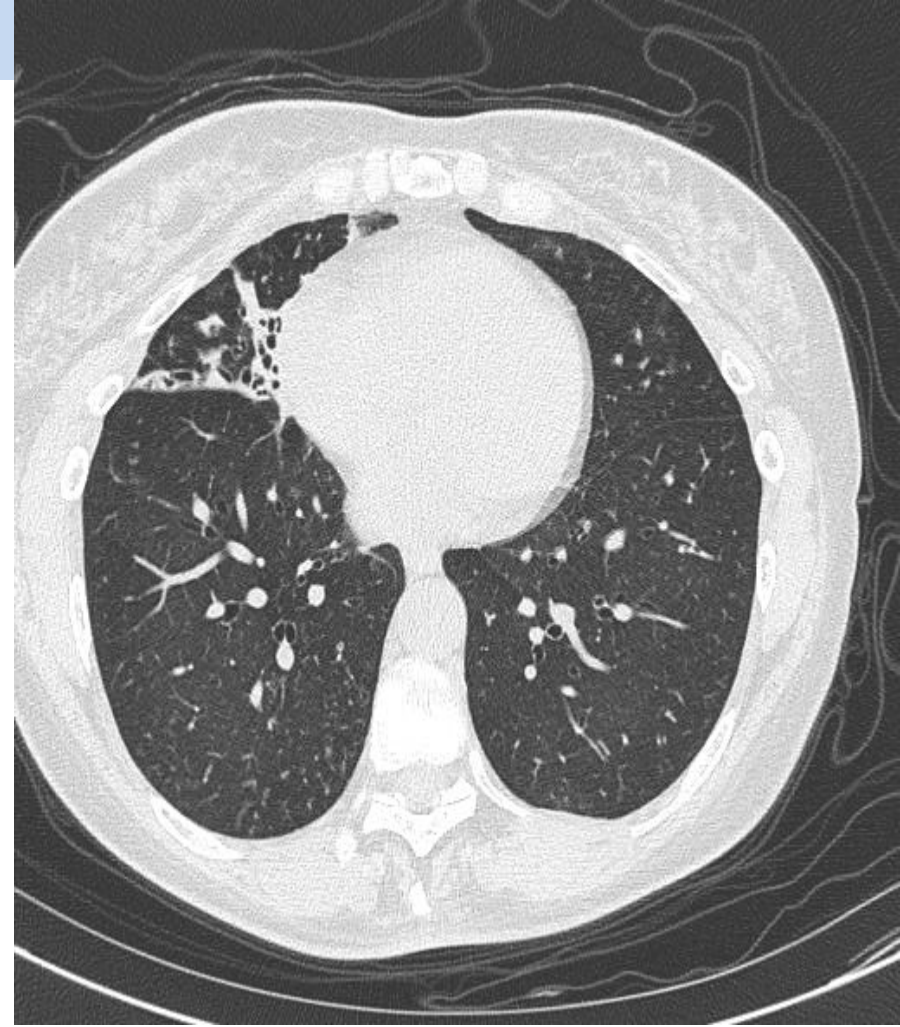
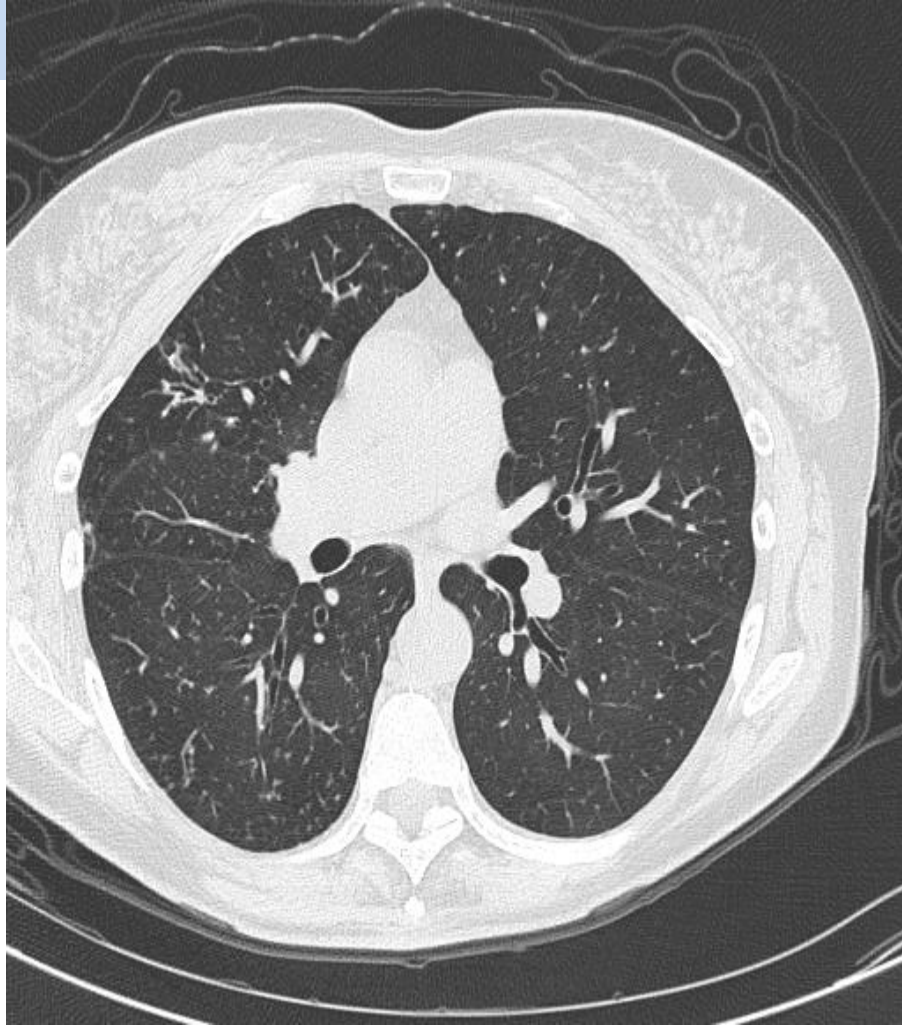
65 year old male with MAC and *pseudomonas aeruginosa*



59 year old female with MAC



56 year old female with MAC



72 year old female with m. abscessus



NTM and clinical trials

Conclusions/Discussion

- Imaging endpoints
 - Not currently feasible
- Pulmonary function endpoints
 - Not predictive of overall outcomes
 - Helpful for monitoring inhaled antibiotic toxicity
- Patient reported outcomes
 - Vital, need to be in all trials
 - Need to continue after conclusion of therapy
 - Assess adverse treatment effects vs disease effects

NTM and clinical trials

Conclusions/Discussion

- Microbiologic endpoint probably best
 - Standardization of culture collection and processing
 - Consider Stratifying trials
 - MAC only: *M. avium* vs *M. intracellulare* vs others
 - Virulence issues
 - ***Koh W et al. Chest 2012;142:1486-1488***
 - ***Boyle DP et al. Am J Respir Crit Care Med 2015;191:1310-1317***
 - *M. abscessus* only: *M. abscessus abscessus* vs others
 - ***Griffith DE et al. Annals ATS 2015;12:436-439***
 - Nodular vs cavitary disease
 - Evaluate impact on co-infecting organisms, if present
 - Prolonged microbiologic follow up after therapy

NTM and clinical trials

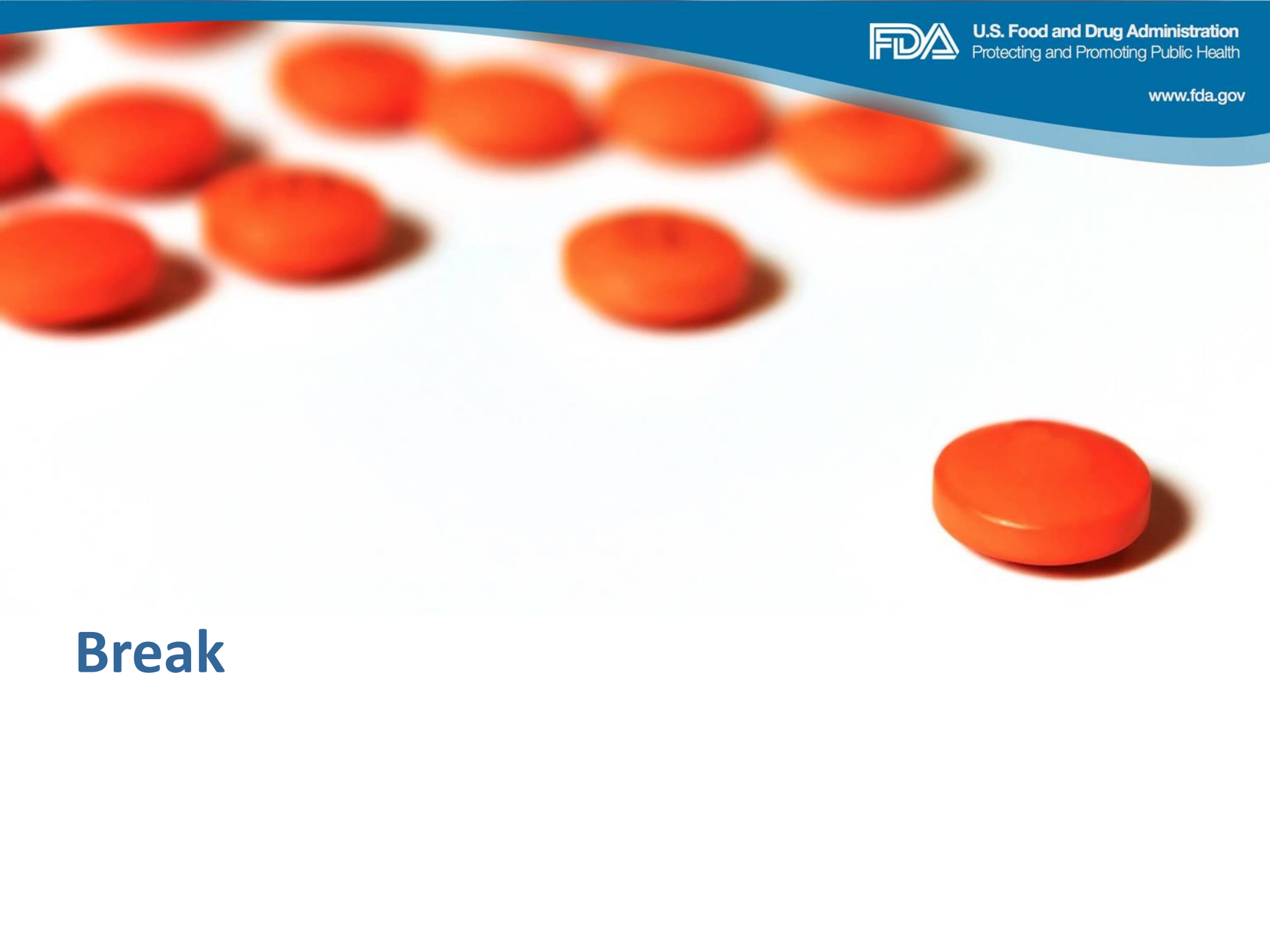
Serological monitoring?

- Serodiagnosis of MAC reported from Japan
 - IgA antibodies against mycobacterial glycopeptidolipid
 - Potentially supportive for confirming diagnosis
 - Possibly helpful for monitoring response to disease
 - Not commercially available in US
 - Not validated as a diagnostic or monitoring tool
 - May be helpful in the future/may warrant further evaluation
 - *Kobayashi K. Jpn J Infect Dis 2014;67:329-332*
 - *Shigeki K et al. Eur Respir J 2015;46:PA2675*

NTM and clinical trials

- Questions for the panel and the FDA
 - Microbiologic endpoint AND clinical outcome
- Acknowledgments:
 - Work done to date
 - FDA and pharma
 - Patients
 - NTM Info and Research
 - US Bronchiectasis Registry





Break



Panel Discussion

Clinical Trial Considerations

- *Eligible population: CF vs. non-CF, Rx naïve vs. Rx experienced, MAC vs. other NTM (especially M. abscessus)*
- *Use of Control: active or placebo: Add-on therapy vs. new regimen, how to choose optimized background regimen if there is no correlation between the results of susceptibility testing and clinical activity*

Clinical Trial Considerations

Trial endpoints

- Microbiologic endpoint:
 - Effect of inhaled therapies?
 - Sputum Conversion and Clearance: definitions, timing and durability – how many consecutive cultures define sputum conversion to negative? Sputum clearance?
 - How many months after sputum clearance is a “cure” declared?
 - Correlation of microbiologic endpoints with clinical outcomes
- Patient Reported Outcome endpoint: which PRO, when to assess, effect of other concomitant interventions for underlying lung disease
- Assessments of exercise tolerance: 6MWT: what change is clinically meaningful, effect of other interventions for underlying lung disease
- Other endpoints

Clinical Trial Considerations

Trial Feasibility

- Trial feasibility: frequency of visits, frequency of labs, available treatment centers, length of study, possible need for equipment (IV or inhaled therapies)



Open Public Comment Period



Closing Remarks