Who Has It?
The Epidemiology of NTM

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Presentation Outline

I. Background on the epidemiology of NTM

II. Recent findings from epidemiologic studies on pulmonary NTM in the United States

III. Summary and future research needs

NTM and Chronic Lung Disease

- Environmental bacteria with >180 species identified
  - Geographic variation in species distribution
  - Ubiquitous in soil and water sources for many exposures
- Can cause pulmonary disease in susceptible persons
  - Severe and chronic infection in affected individuals

NTM Disease: Host versus Environment

Environment

- Individual exposures
  - Local soil
  - Local water sources/distribution
- Environmental conditions
  - Climate
  - Elevation
  - Mycobacterial species present

Host

- Behavioral factors
  - Smoking
  - Activities (gardening, swimming)
- Comorbidities/genetic risk factors
  - Pulmonary defects (CF, COPD)
  - Connective tissue defects
  - Other (race/ethnicity as proxy?)

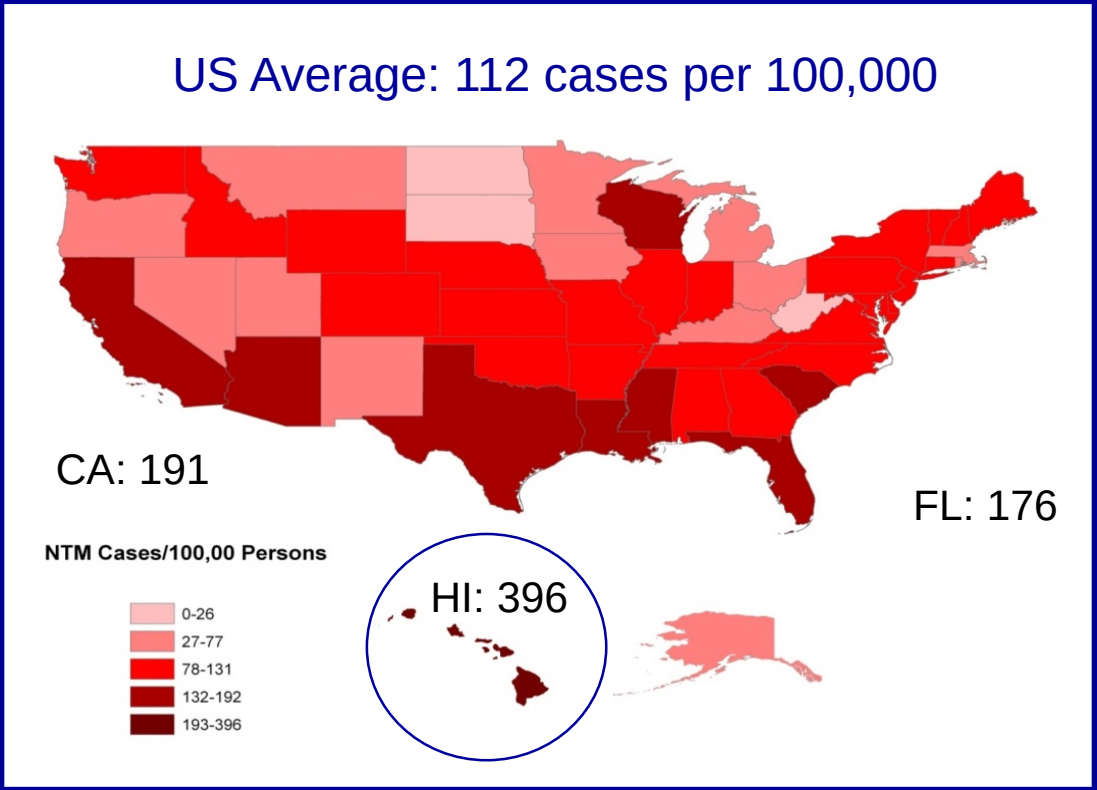
NTM Lung Disease

Epidemiology of NTM Lung Disease

- Only reportable in 11 states and not a nationally notifiable disease to CDC, so other data sources needed
  - Local studies (surveillance, site studies)
  - Large national datasets (lab/claims-based, patient registries)
    - Each targets different questions based on strengths/limitations
- ATS/IDSA-defined PNTM disease requires strict criteria
  - Presents challenges in estimating actual prevalence due to differences in access and use of medical services needed
    - Varies across populations by socioeconomic status

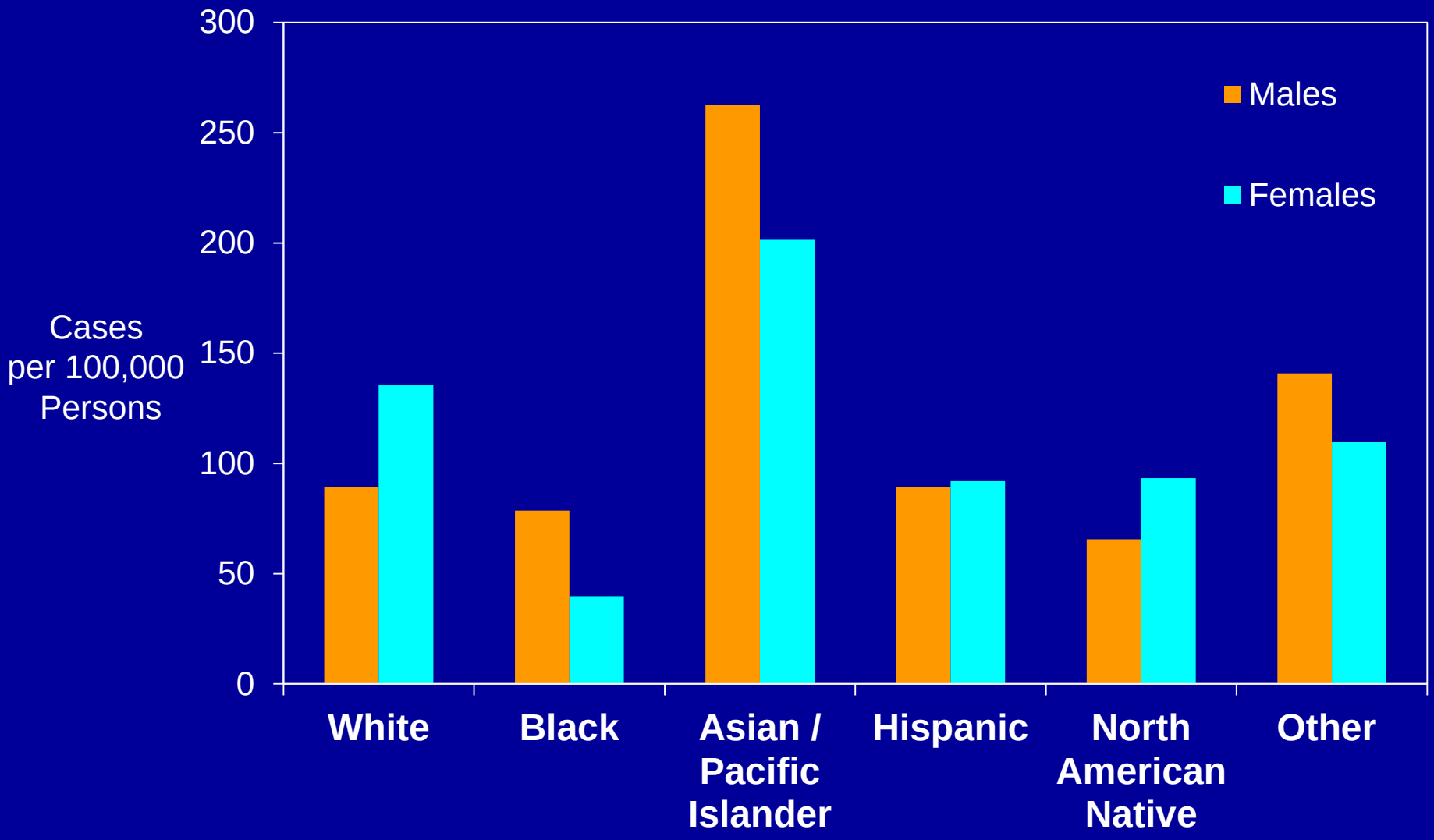
First US Prevalence Estimates for Pulmonary NTM (PNTM) in Medicare Data

- Increasing national prevalence by 8% per year
- Significant geographic differences



Adjemian et al. AJRCCM . 2012; 185(8):881-886.

PNTM Period Prevalence by Sex and Race/Ethnicity, US Medicare Beneficiaries Aged >65 years



Spatial Clusters of Nontuberculous Mycobacterial Lung Disease in the United States

Jennifer Adjemian[1,2], Kenneth N. Olivier[2], Amy E. Seitz[1,2], Joseph O. Falkinham III[3], Steven M. Holland[2], and D. Rebecca Prevots[1,2]

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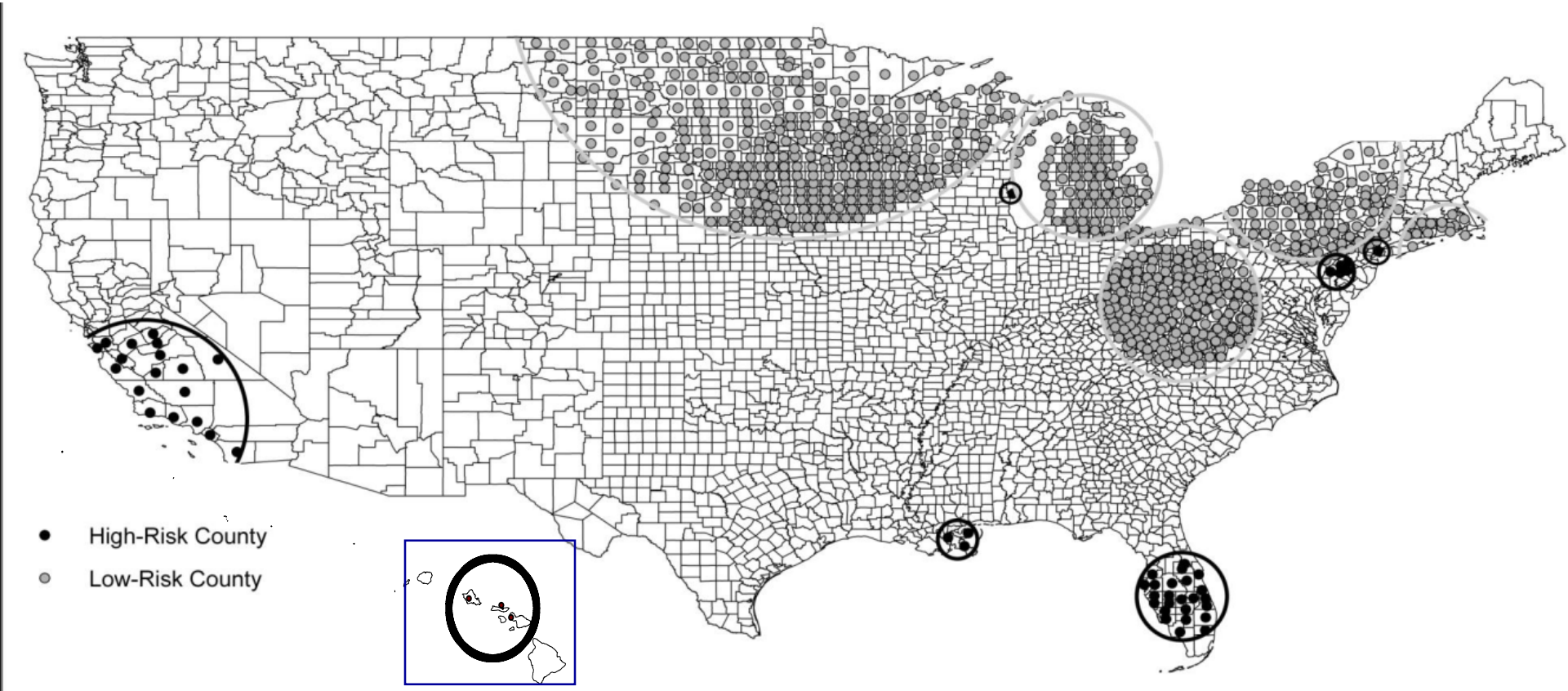
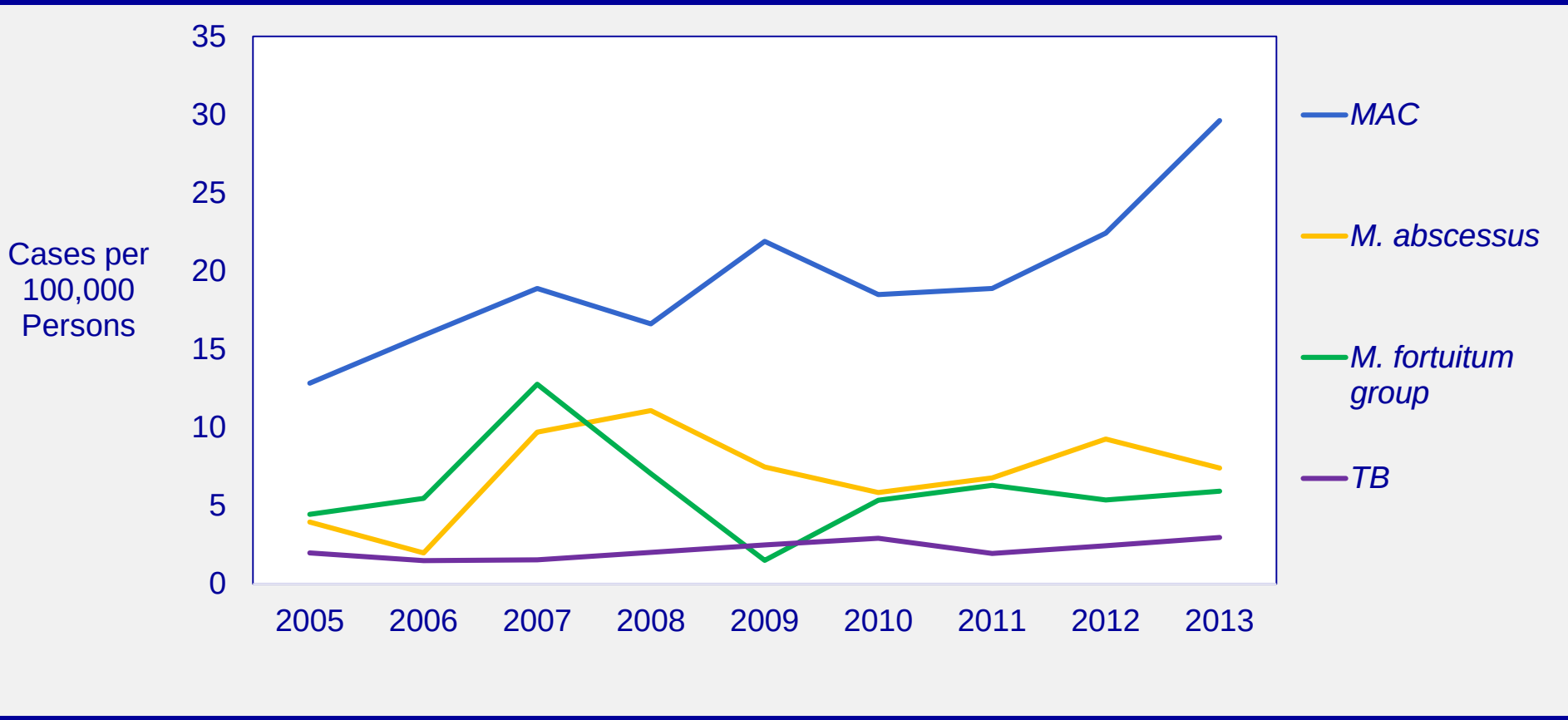


- High risk counties: greater surface water (OR 4.6), evapotranspiration (4.0), Cu (1.2) & Na (1.9) and lower manganese (0.7)

Adjemian et al. AJRCCM . 2012

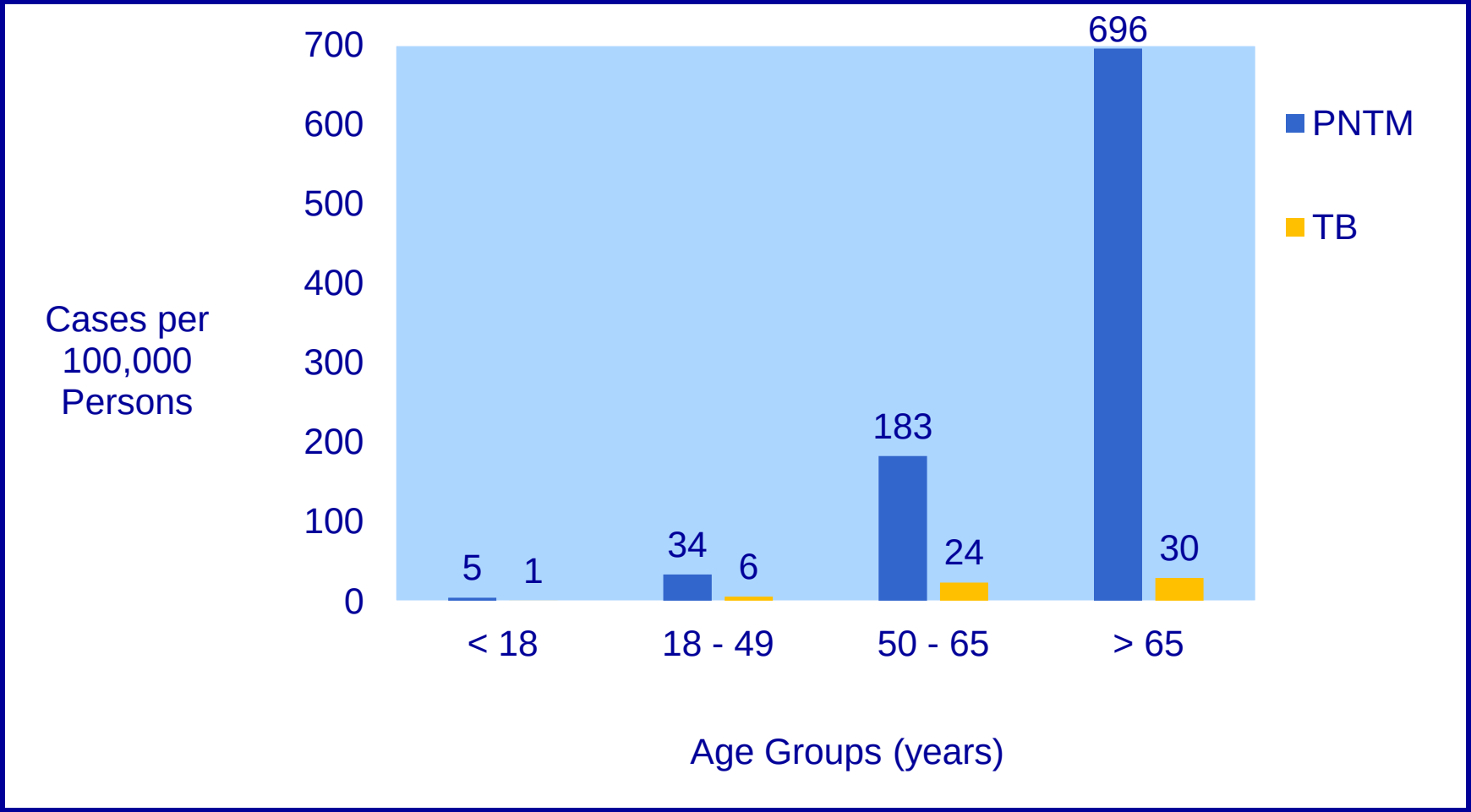
Precise Epidemiology of NTM in a High-Risk State using Kaiser Permanente Data

- NTM prevalence doubled over time but not for all species

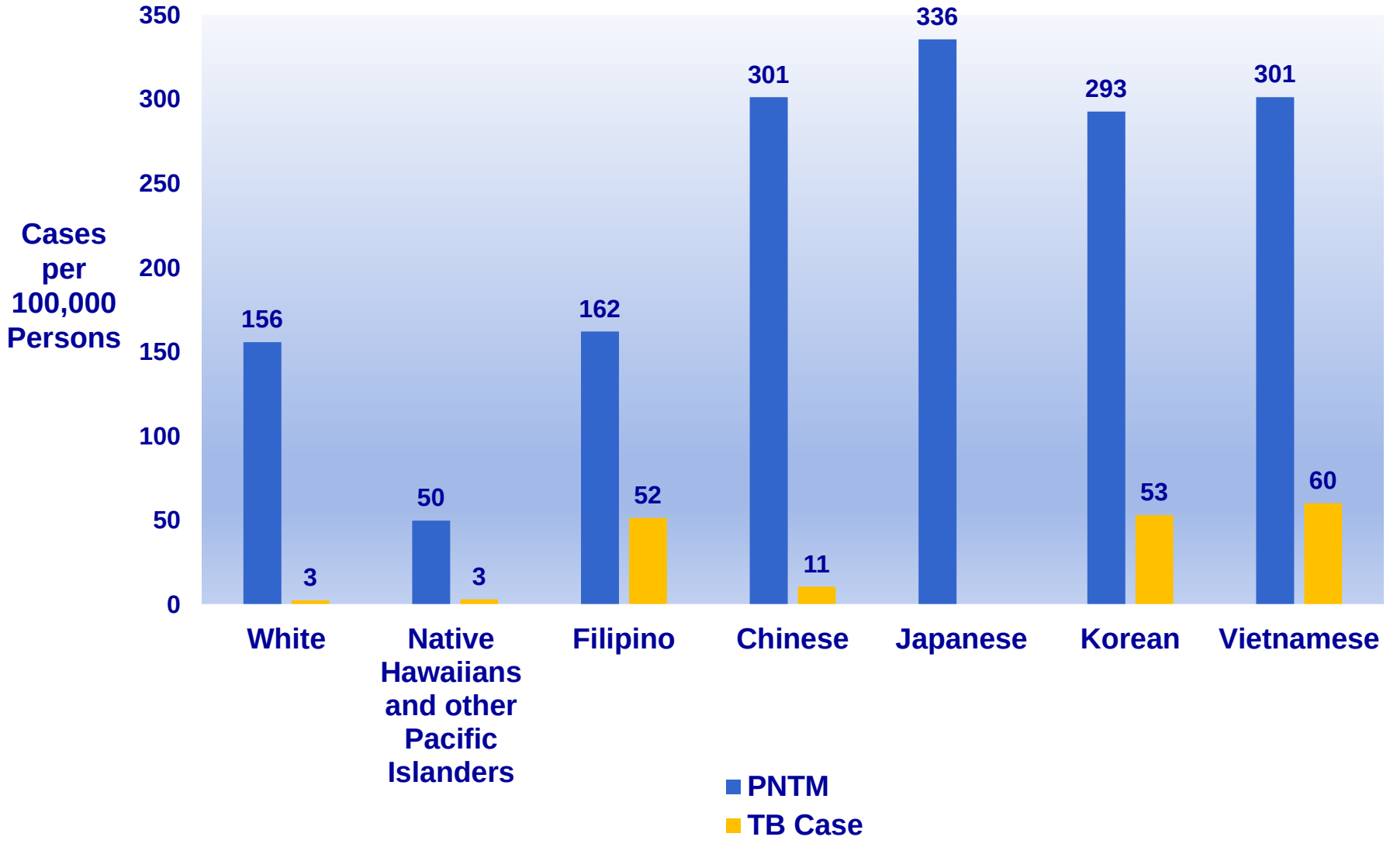


Adjemian et al. EID . 2017

Period Prevalence of PNTM and TB by Age Group

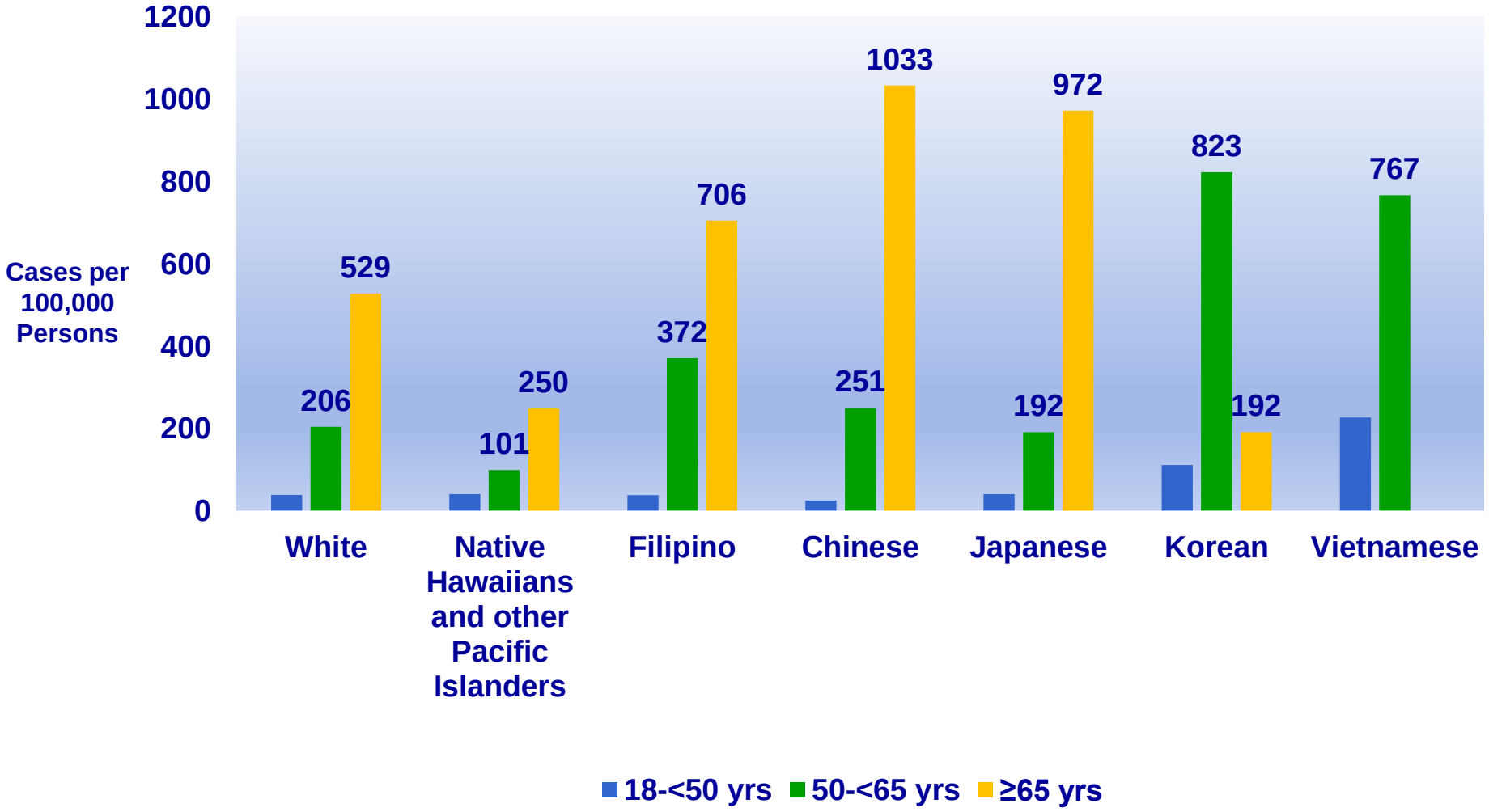


Prevalence by Race/Ethnicity for NTM and TB



Adjemian et al. EID . 2017

Period Prevalence by Race/Ethnicity and Age Group for PNTM



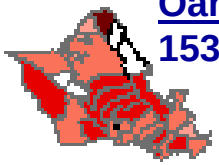
Risk Factors for NTM and TB in a High-Risk State

	NTM		TB	
Variable	aOR	95% CI	aOR	95% CI
Years in KPH				
1 year	Ref	--	Ref	--
2 – 4 years	2.6	1.4-4.7*	1.7	0.5-5.7
≥ 5 years	6.4	3.6-11.2*	2.3	0.8-6.9
Comorbid Condition				
Bronchiectasis	8.3	6.5-10.7*	0.4	0.09-2.2
COPD	1.8	1.4-2.2*	0.4	0.2-1.1

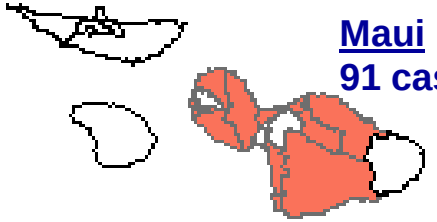
Adjusted Risk Associated with NTM by Species

	M. abscessus		MAC	
Variable	**aOR**	**95% CI**	**aOR**	**95% CI**
Racial/Ethnic Group				
White	0.7	0.4-1.1	1.0	0.7-1.2
NHPI	0.1	0.01-1.4	0.4	0.2-0.9*
Black	1.1	0.7-16.4	1.0	0.2-4.8
Asian	2.5	1.7-3.9*	1.4	1.1-1.8*
Filipino	2.0	1.2-3.3*	1.5	1.1-2.1*
Japanese	2.0	1.2-3.2*	1.0	0.7-1.4
Chinese	1.9	0.9-3.9	1.5	0.95-2.3
Korean	2.0	0.6-7.0	1.4	0.6-3.2
Vietnamese	5.0	1.0-24.6*	3.7	1.3-10.6*
Years in KPH				
1 year	Ref	--	Ref	--
2 – 4 years	1.1	0.4-2.9	2.7	1.1-6.3*
≥ 5 years	2.3	0.96-5.4	7.7	3.5-16.8*
Comorbid Condition				
Bronchiectasis	12.0	7.6-18.8*	7.0	5.2-9.2*
COPD	1.3	0.8-2.0	1.9	1.5-2.5*

PNTM Period Prevalence by Zip Code and Island



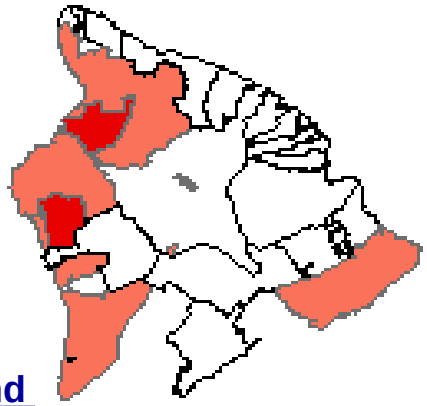
Oahu
153 cases per 100,000 persons



Maui
91 cases per 100,000 persons

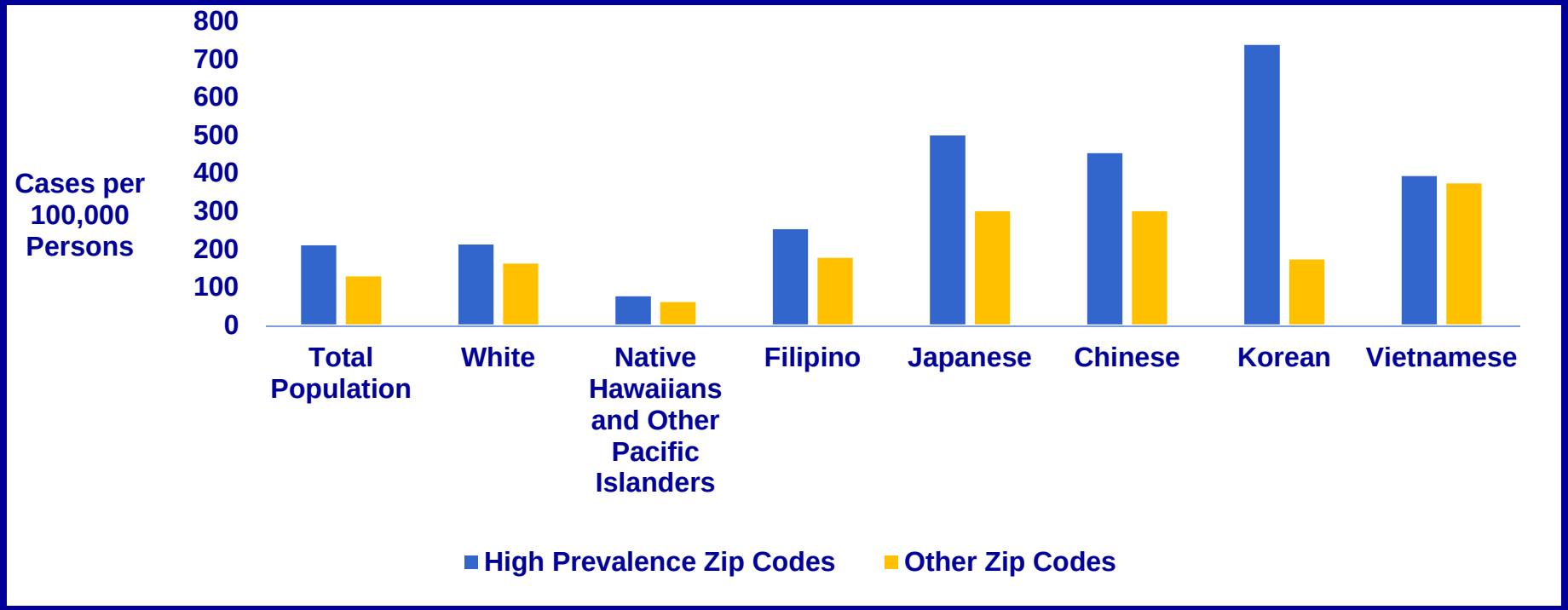
NTM Cases per 100,000 Persons

- 0
- 1 - 50
- 51 - 150
- 151 - 250
- 251 - 465



Big Island
84 cases per 100,000 persons

PNTM Period Prevalence by Race/Ethnicity in High Prevalence Zip Codes in Oahu



- Socioeconomic: Greater % of high-income homes (each 10%: aOR=2.0, p<0.0001)
- Environmental: Greater % of water coverage (each 10%: aOR=1.2, p<0.0001) and larger annual temperature range (each degree: aOR=1.1, p<0.0001)

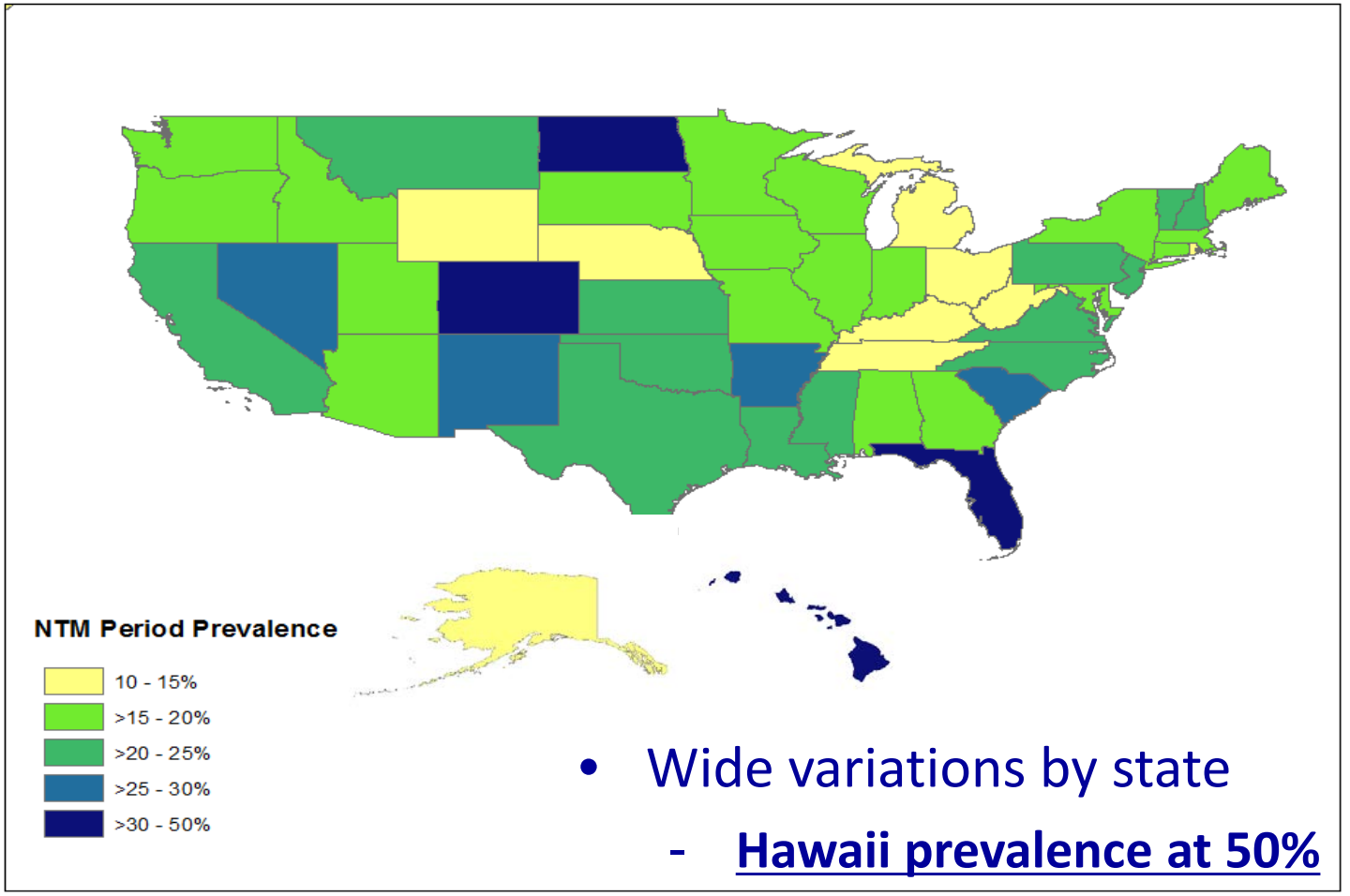
Epidemiology of NTM in Persons with Cystic Fibrosis (CF) using Patient Registry Data

- CF Foundation (CFF) began collecting detailed NTM data starting in 2010

- Conducted several epidemiologic NTM analyses
  - Annual prevalence 90 times > than general population
  - Increase of 5.3% per year
  - Species-specific epidemiologic differences in risk and outcome

Adjemian et al. Annals ATS, 2018
Adjemian et al. AJRCCM. 2014
Binder et al. AJRCCM. 2013

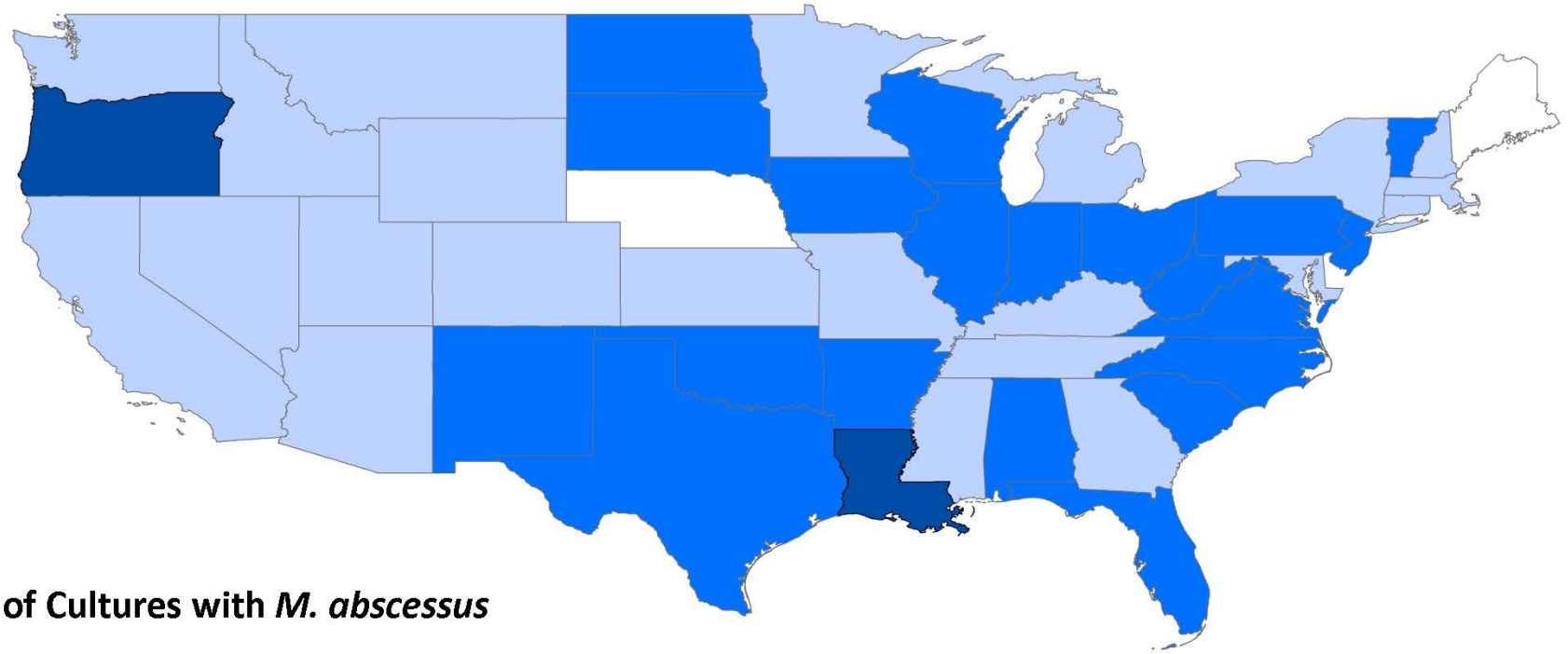
Prevalence of PNTM isolated from persons with CF in the United States, 2010-2014



- Wide variations by state
  - **Hawaii prevalence at 50%**

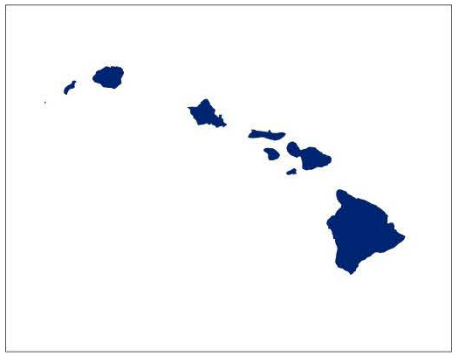
Adjemian et al. Annals ATS, 2018

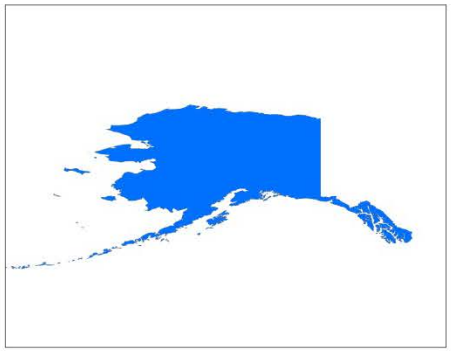
Percentage of Positive Mycobacterial Cultures Attributed to *Mycobacterium abscessus* among U.S. Cystic Fibrosis Patients, 2010-2011



% of Cultures with *M. abscessus*

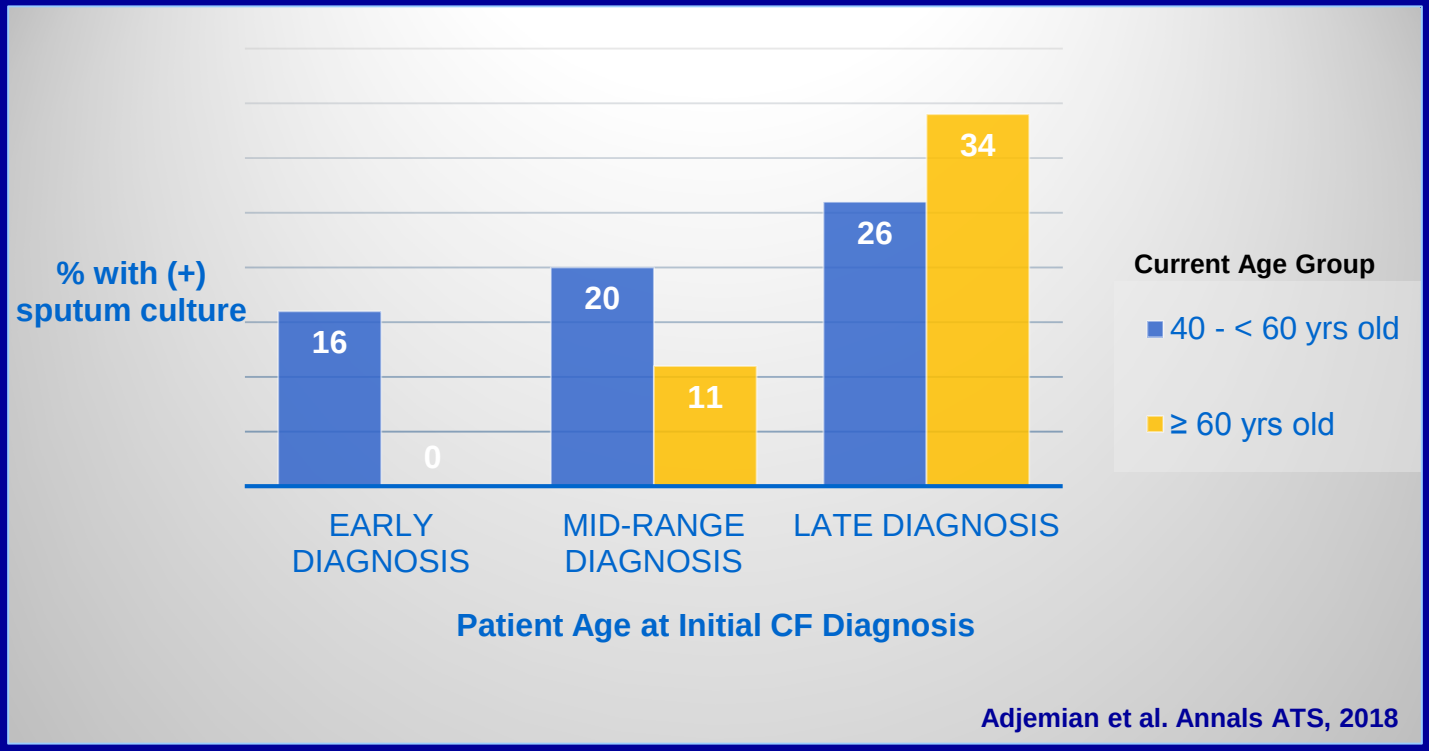
- >80 – 100
- >60 – 80
- >40 – 60
- >20 – 40
- 0 – 20





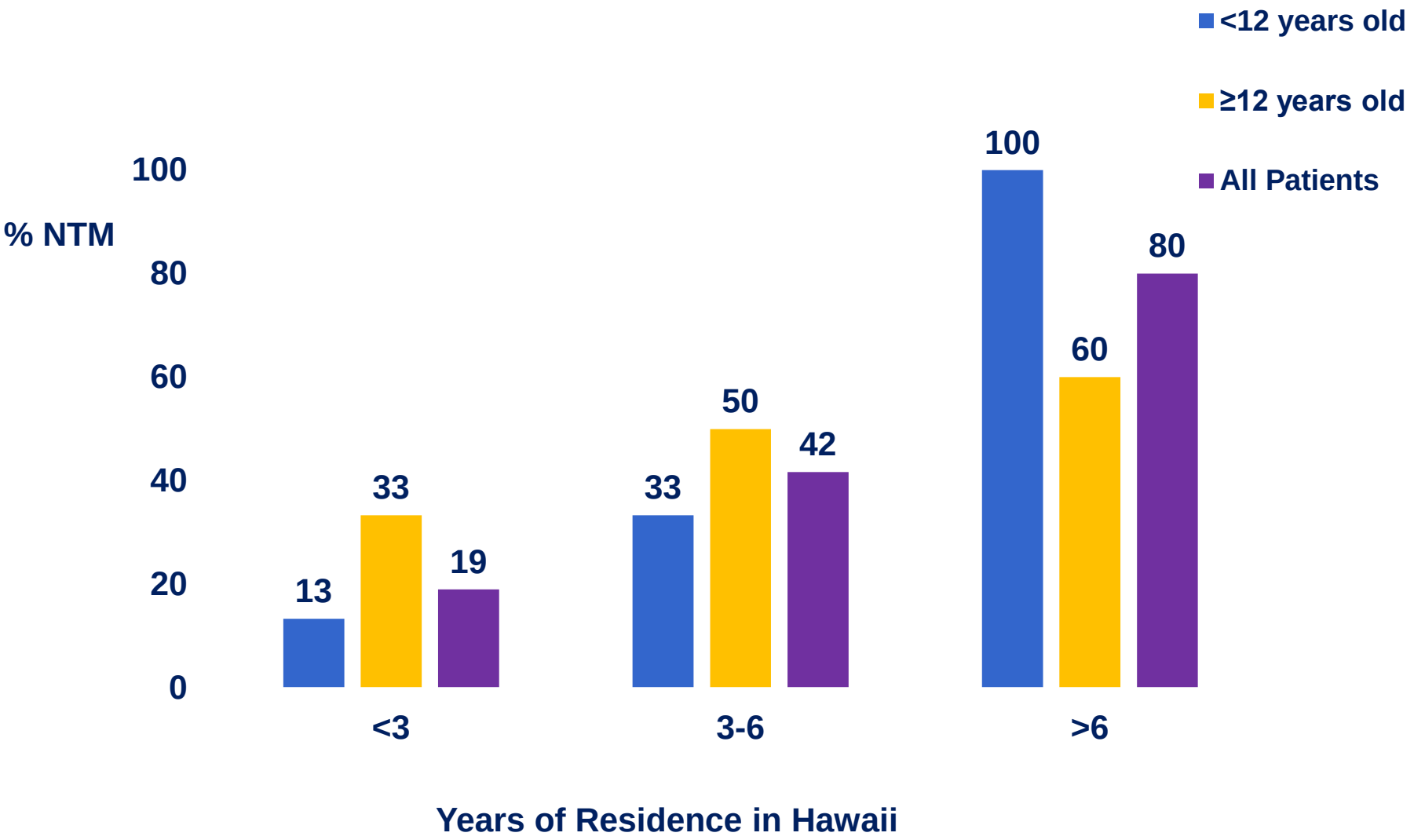
Adjemian et al. AJRCCM. 2014

Period Prevalence of PNTM by Age Group and by Age of Initial CF Diagnosis, 2010-2014

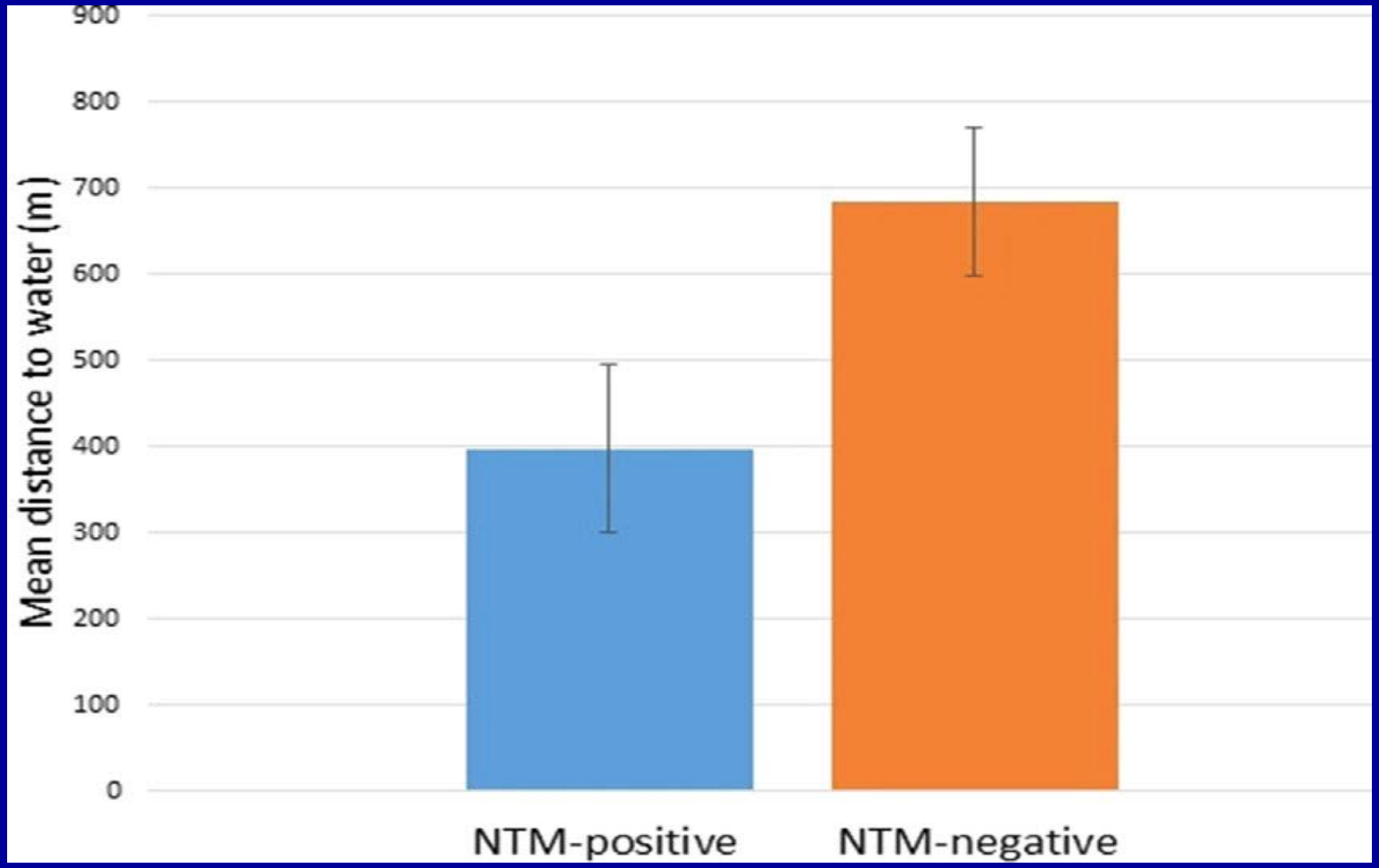


- Early diagnosis=study participants diagnosed ≤3 years old
- Mid-range diagnosis=study participants diagnosed >3 and <30 years old
- Late diagnosis=study participants diagnosed ≥30 years

Prevalence of NTM in Persons with CF by Age Group and Years of Residence in Hawaii among US Military Families



Mean Distance to Water by NTM Positivity in Persons with CF in Central Florida, 2012-2015



Bouso et al. Household Proximity to Water and Nontuberculous Mycobacteria in Children With Cystic Fibrosis; Pediatric Pulmonology 52:324–330 (2017)

Summary of Host Risk Factors

- Host risks include structural, immunologic, and genetic factors
  - Structural defects like COPD identified in 18-38% of patients with NTM
  - Lung cancer also associated with increased prevalence
  - Disorders of mucocilliary clearance like CF and PCD
  - Low ciliary beat frequency in study of patients with no other conditions
  - Correlations in family studies with low BMI, thoracic skeletal abnormalities, mitral valve prolapse, and connective tissue disorders
  - Older age increases risk and differences by race/ethnicity
- Certain treatment for these lung disorders can modify risk
  - TNF-α blockers increase risk by inhibiting immune response to NTM
  - In CF, chronic macrolide use appears to be protective

Summary of Environmental Risk Factors

- Geographic variation in prevalence and species distribution
  - High-risk areas include parts of CA, FL, HI, LA, NY, PA, OK and WI
    - Greater amounts of moisture in air and more surface water present
    - Soil factors like higher copper and sodium and lower manganese levels
  - Hawaii consistently identified as highest risk state in the nation
    - Increased duration of residence seems to increase risk
    - Unique conditions like humic soil is associated with high numbers of NTM
  - "High-risk" states often also associated with more *M. abscessus*
    - In US hospital patients MAC ranged from 61% in West South Central states (AR, LA, OK, TX) to 91% in East South Central states (AL, KY, MS, TN)
    - In CF, MAC also ranged greatly by state, from 29% in LA to 100% in NE

Summary of Household Risk Factors

- Household water source and water pipe biofilms may represent a potentially important source of NTM exposure
  - Studies show genetic matches between variants in samples from patient households and clinical isolates from same patients
  - Watershed affiliated with patient's area of residence may alter risk
- Soil and dust in homes also identified as potential sources
  - Aerosols from potting soils in patient homes with pathogenic species
  - Study in Florida found dose-response relationship with greater amounts of soil exposure and positive *M. avium* skin test reaction

Summary of Behavioral Risk Factors

- Difficult to assess due to 1) rarity of disease, 2) ubiquity of organism, and 3) high frequency of common exposures

- Some case-control studies identified a few potential factors
  - Indoor swimming pool use (in CF)
  - Tap water appearing rusty or unclear (in CF)
  - Spraying plants with spray bottles (in general population in Oregon)
  - Higher levels of soil exposure (in bronchiectasis patients in Japan)

Summary and Future Directions

- Recent epidemiologic studies highlight:
  - Increasing prevalence over time
  - Greater burden on older adults, persons of Asian ancestry, and those with certain structural and/or genetic pulmonary diseases
  - Wide geographic variations in NTM risk and species
- Future epidemiologic studies needed on:
  - Species-specific environmental reservoirs
  - Genetic modifications of risk
  - Risks for initial infection and reinfection
  - Mechanisms for dose-response relationship with greater exposure and risk of NTM

Acknowledgements

- National Institute of Allergy and Infectious Diseases (NIAID)
- National Heart, Lung and Blood Institute (NHLBI)
- Walter Reed National Military Medical Center
- Tripler Army Medical Center
- University of Colorado, Denver
- National Jewish Health
- Cystic Fibrosis Foundation
- Kaiser Permanente
- Premier Perspectives
- US Centers for Medicare and Medicaid Services

Thank you!

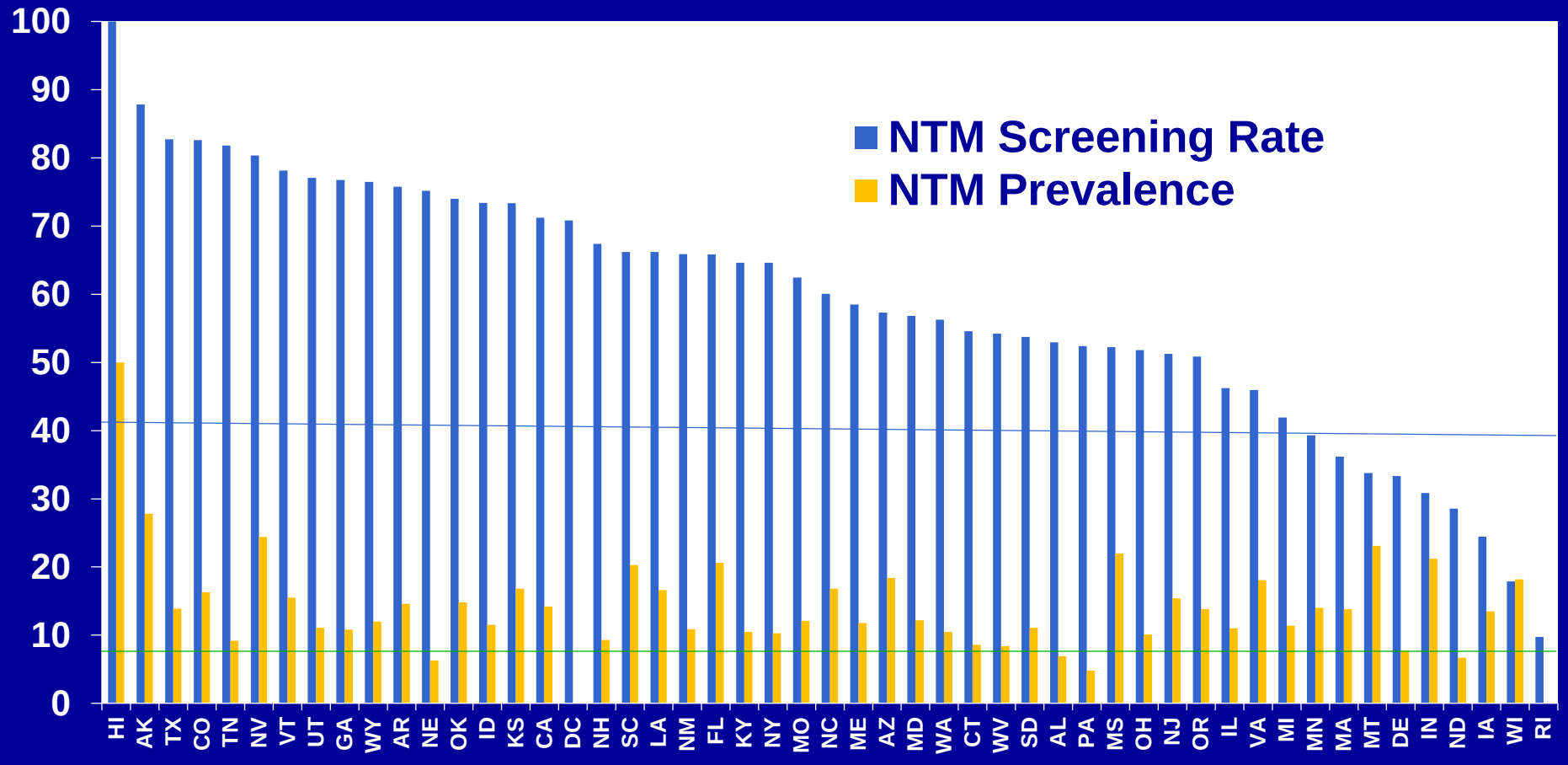
Burden of NTM in the United States

- Results showed higher financial and case burden than TB

State	Total 2010 Cases	Rank of State Population (Largest to Smallest)	Cases per 100,000 Population	Annual Cost (2014 Dollars)
California	12,544	1	44.5	$110,690,528
Florida	11,580	4	53.6	$98,527,193
Texas	6,792	2	39.4	$54,983,825
New York	5,055	3	29.1	$48,600,779
Pennsylvania	3,969	6	30.5	$41,312,486
North Carolina	2,890	10	35.3	$26,071,179
Arizona	2,859	16	48.9	$24,664,441
Illinois	2,643	5	24.8	$26,361,795
Georgia	2,365	9	34.5	$20,847,084
Hawaii	2,131	40	164.6	$21,800,504
U.S. total	**86,244**	**n.a.**	**27.9**	**$815,098,690**

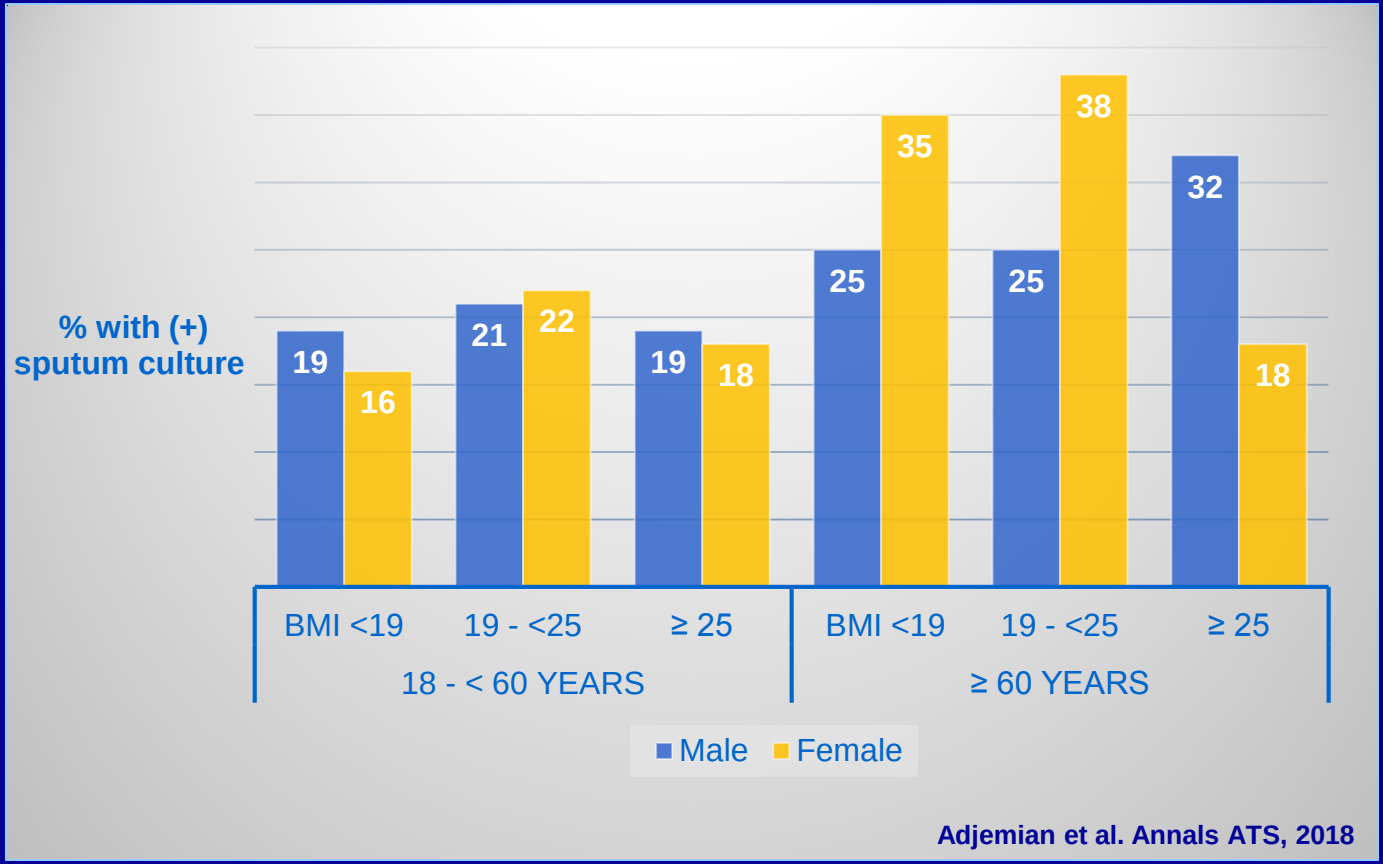
Strollo, Adjemian, Adjemian, Prevots. Annals ATS. 2015.

NTM Screening Rates and Prevalence in CF Patients by State



Adjemian et al AJRCCM. 2014

Period Prevalence of PNTM by Age Group, Gender and BMI in Persons with CF, 2010-2014



Adjemian et al. Annals ATS, 2018

NTM Treatment Guideline Adherence using Clinician Surveys and Patient EMR Data

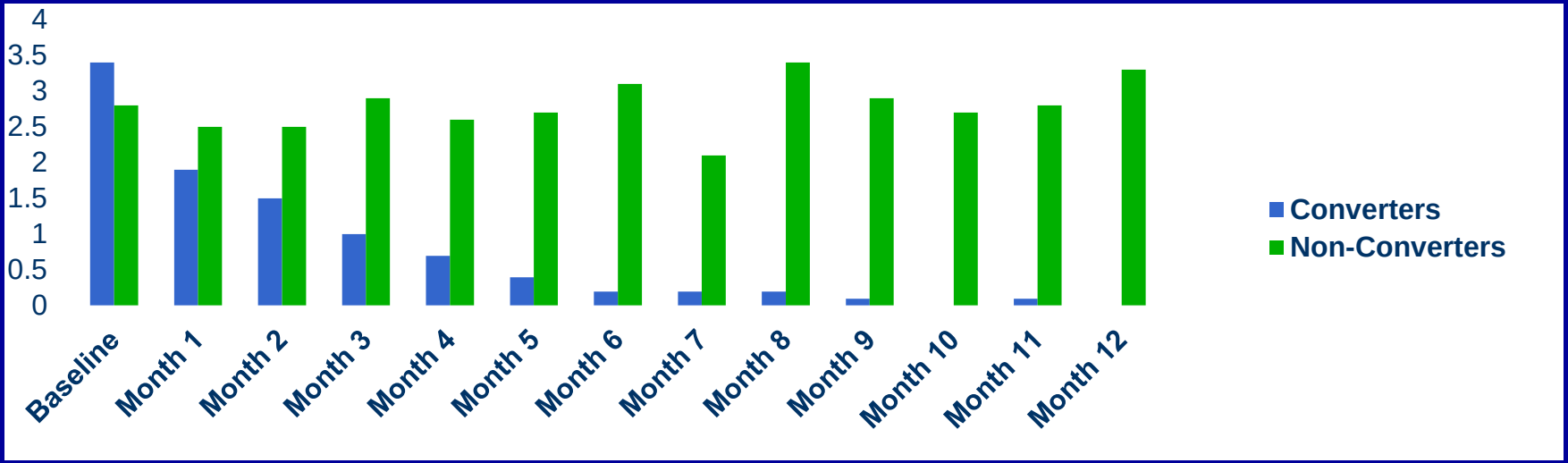
- Surveyed clinicians to evaluate guideline adherence and identified poor compliance and often harmful practices
- Results led to global campaign to improve treatment practices through seminars, trainings, patient groups and websites

Treatment Regimen	Regimens for MAC n (% of All Regimens)
Met ATS/IDSA guidelines for MAC*	77 (13)
Did not meet ATS/IDSA guidelines for MAC*	502 (87)
Regimens that may increase macrolide resistance	174 (30)
Regiments of unknown clinical significance	3 (0.5)
Regimens that do not include macrolides	325 (56)

Adjemian et al. Annals of ATS. 2014

Identify New Potential Clinical Trial Endpoints using Patient EMR Data

- Challenging to get new drugs approved due to lack of robust “hard outcomes” and length of observation time for NTM
- Used patient EMR data to identify earlier measures of treatment success for clinical trials
  - Semi-quantitative culture results
  - Quality of life measures



Griffith, Adjemian et al. AJRCCM . 2015