

Indian Health Service Tuberculosis Grand Rounds



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The Case

□ 08/25/2015

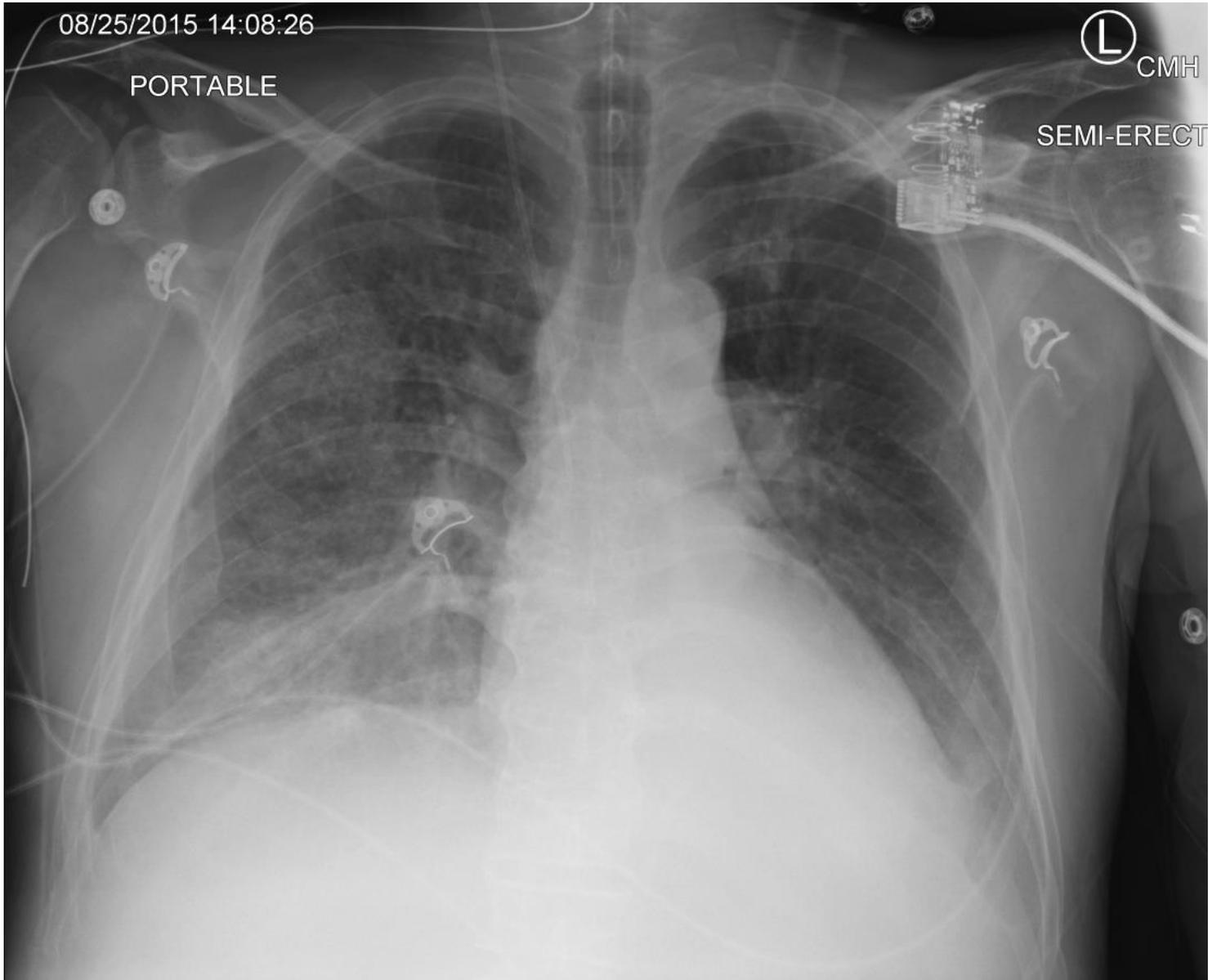
- 47 yo American Indian male presents to an ER off-reservation
- Significant respiratory distress with complaints of
 - Cough, dyspnea, fever
 - Alcohol use, but little other additional history
- Rapidly intubated

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PORTABLE

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SEMI-ERECT



The Case

□ ER and Hospital Care

- ER physician (ex-IHS) concerned about atypical nature of pneumonia
- Insisted on AFB smears, cultures, and isolation
- Hospitalists admitted patient to ICU on ventilator and broad spectrum antibiotics
- Progressive respiratory distress

□ Death from respiratory failure two days later

The Case

□ September 2015

- Reference lab identifies AFB+ organisms on smears
- State TB lab confirms: *Mycobacterium tuberculosis*
- Sample sent on to national reference lab for genotyping

□ November 2015

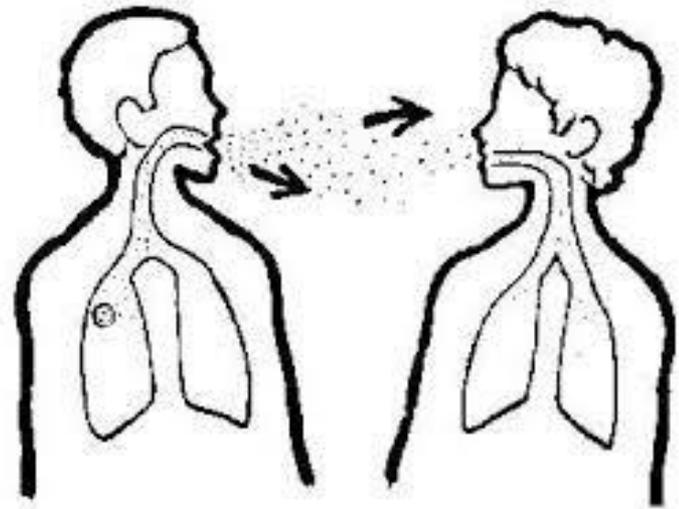
- One other case with same genotype in the state: Non-Native person on same reservation community as deceased
- Resulting contact investigation – multiple TST+ patients

A Quick Review

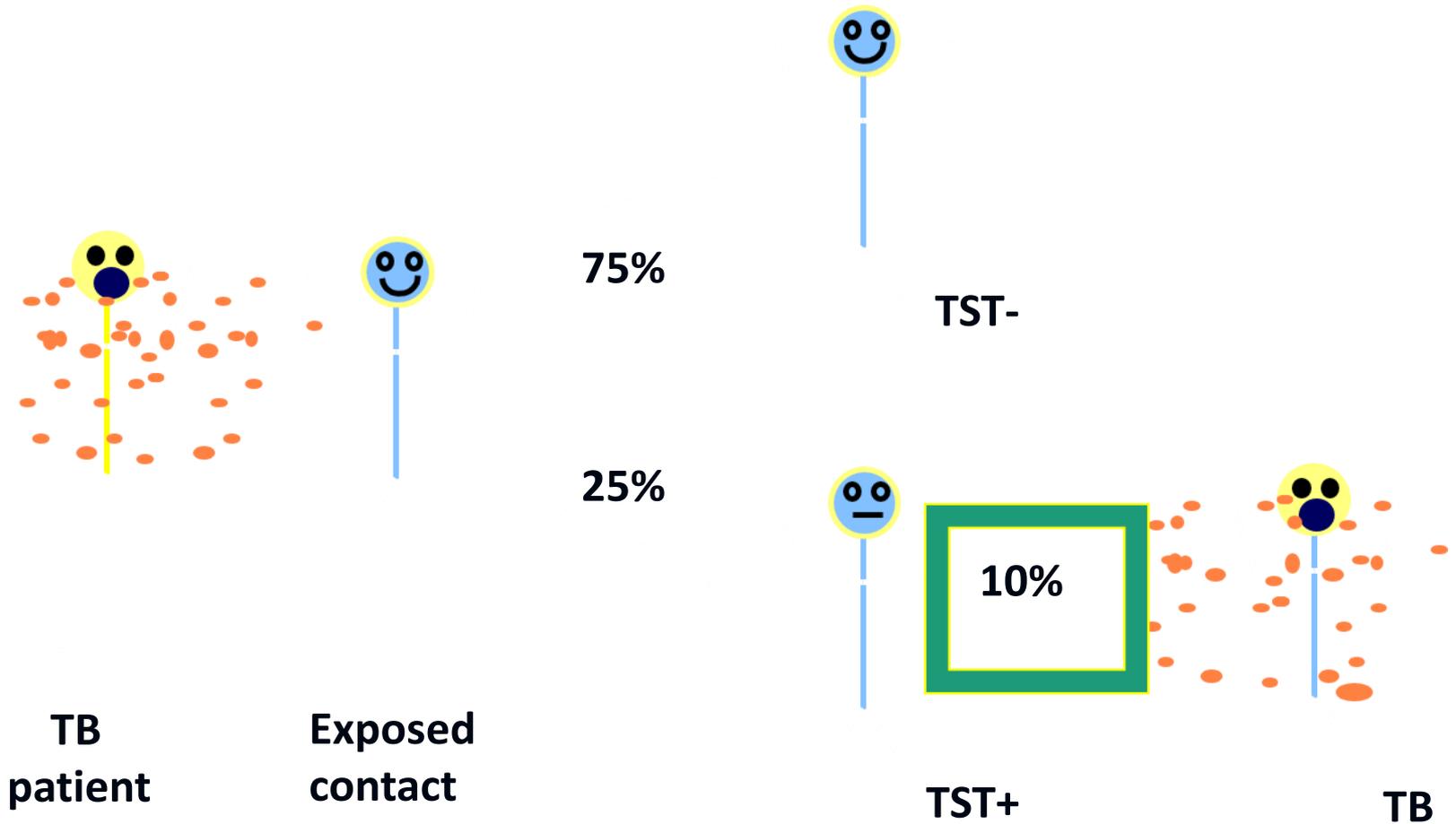
□ Caused by *Mycobacterium tuberculosis* (MTB)

□ Spread by respiratory droplets

- Coughing
- Sneezing
- Speaking
- Singing



Natural History of TB



How many people have TB in the world?

- ❑ **1/3 of the world's population is estimated to be infected with TB**

- ❑ **Worldwide estimates in 2014:***
 - **8.6 million new cases of active TB (12.6% in persons with HIV)**

 - **1.4 million deaths from TB (30.7% in persons with HIV)**

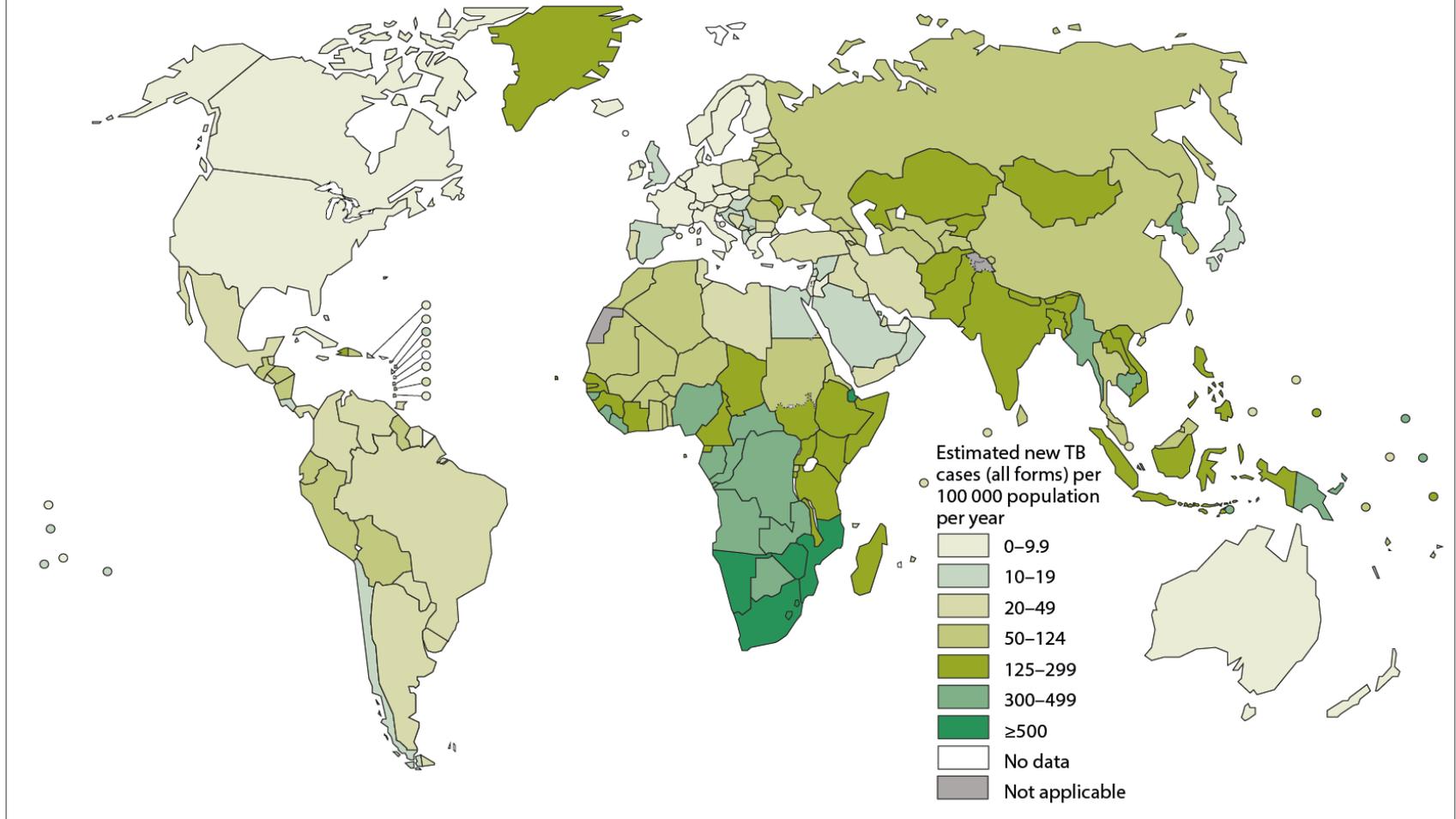
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Estimated TB incidence rates, 2013



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2014*. WHO, 2014.

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TAKE
ON **TB**

Too many people in our country
still suffer from tuberculosis (TB).



9,563 TB CASES*
reported in the U.S. in 2015

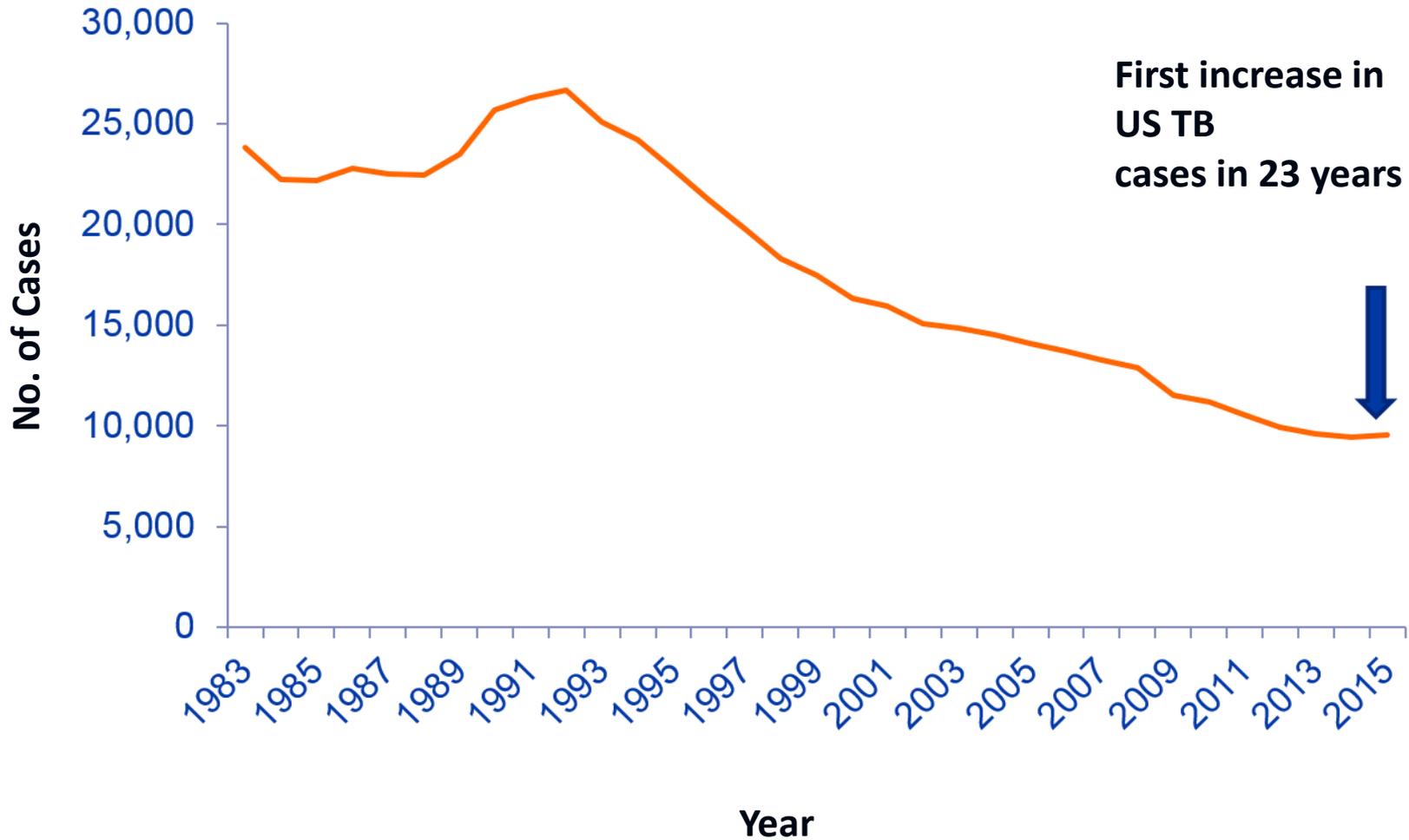
**Provisional Data*

www.cdc.gov/tb



**Centers for Disease
Control and Prevention**
National Center for HIV/AIDS,
Viral Hepatitis, STD, and
TB Prevention

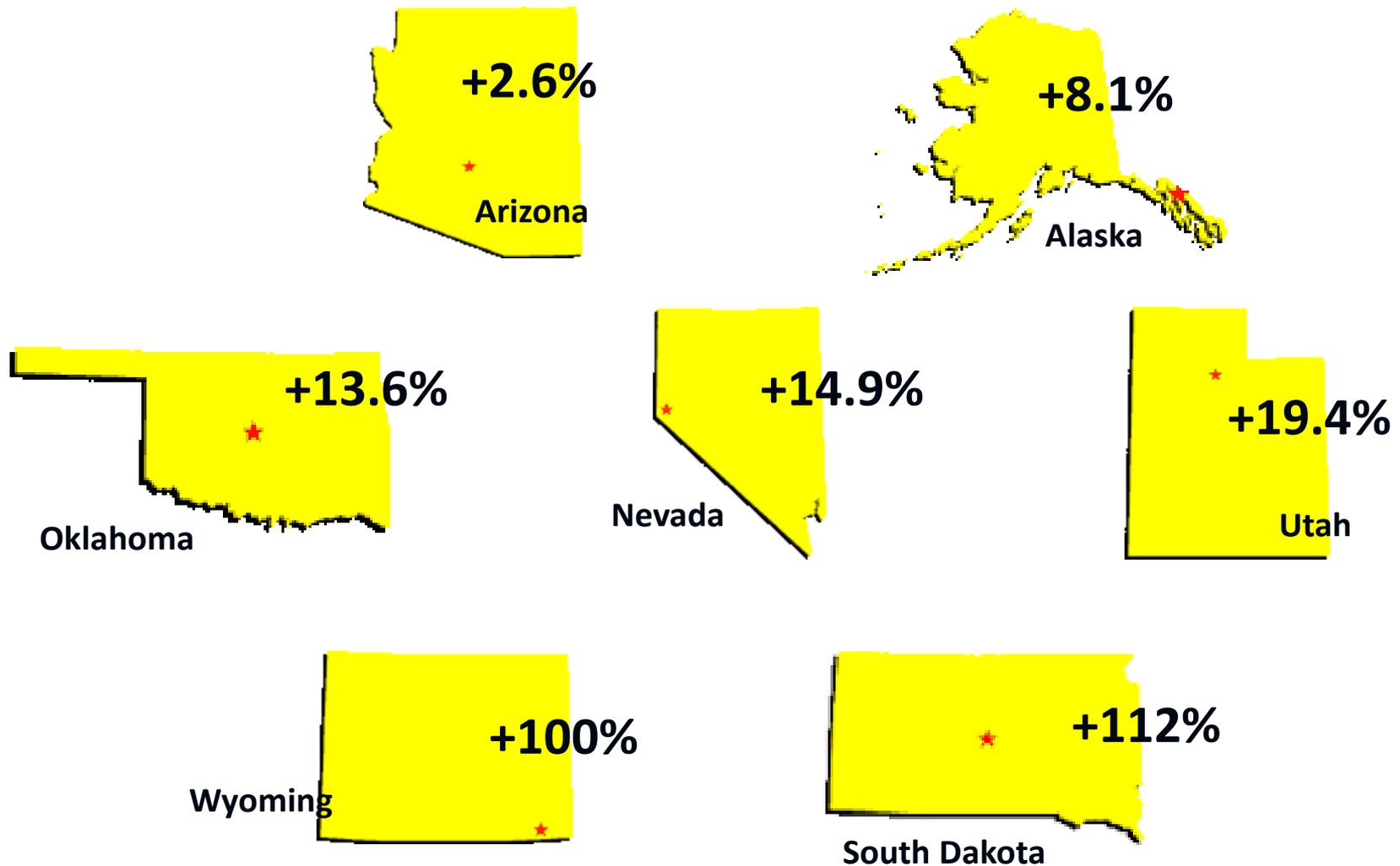
Reported TB Cases, United States 1982–2015*



*Updated as of March 2016

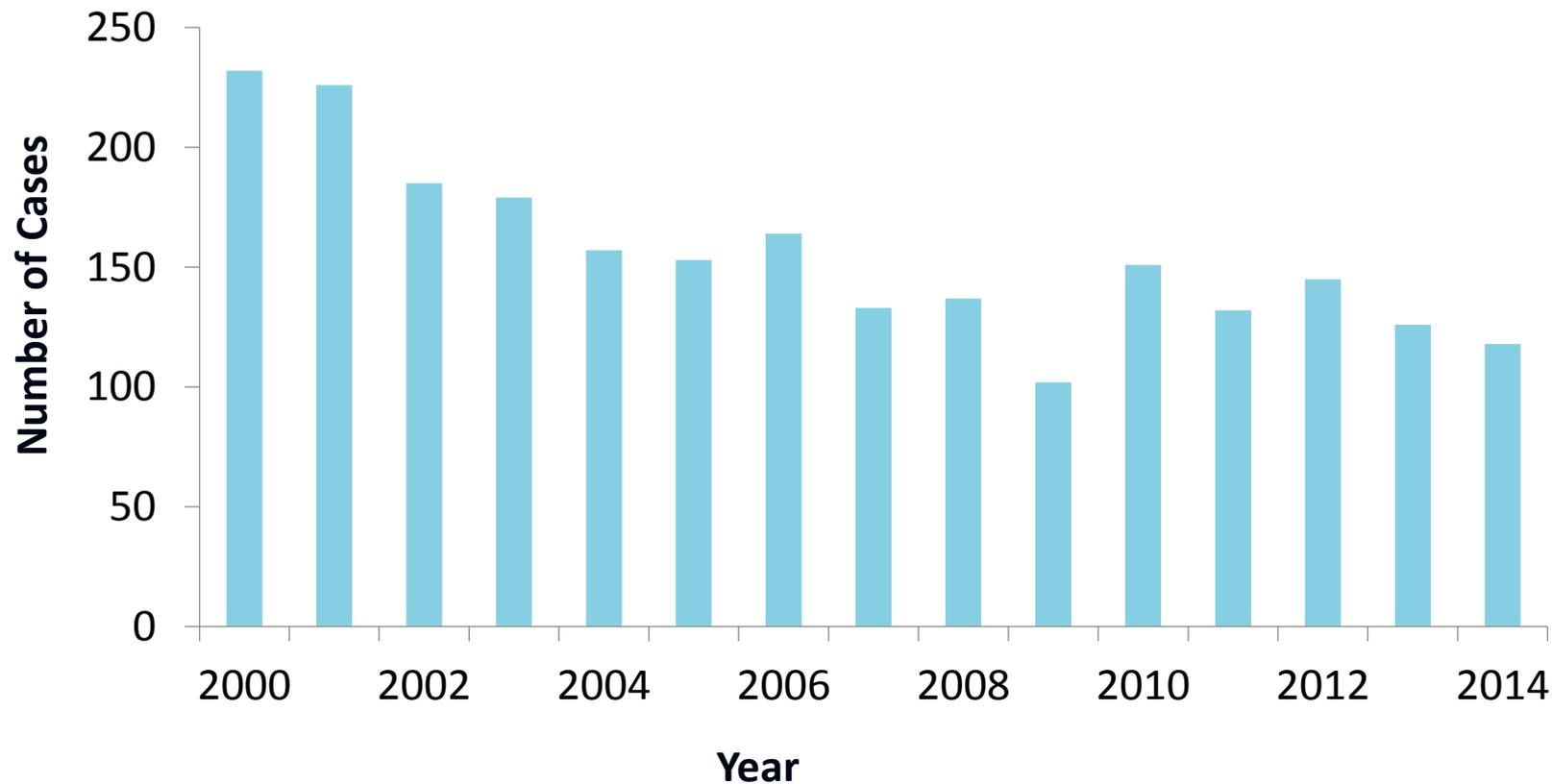
Source: Centers for Disease Control and Prevention

TB Case Number Increases in States with Large American Indian / Alaska Native Populations (2014 to 2015)

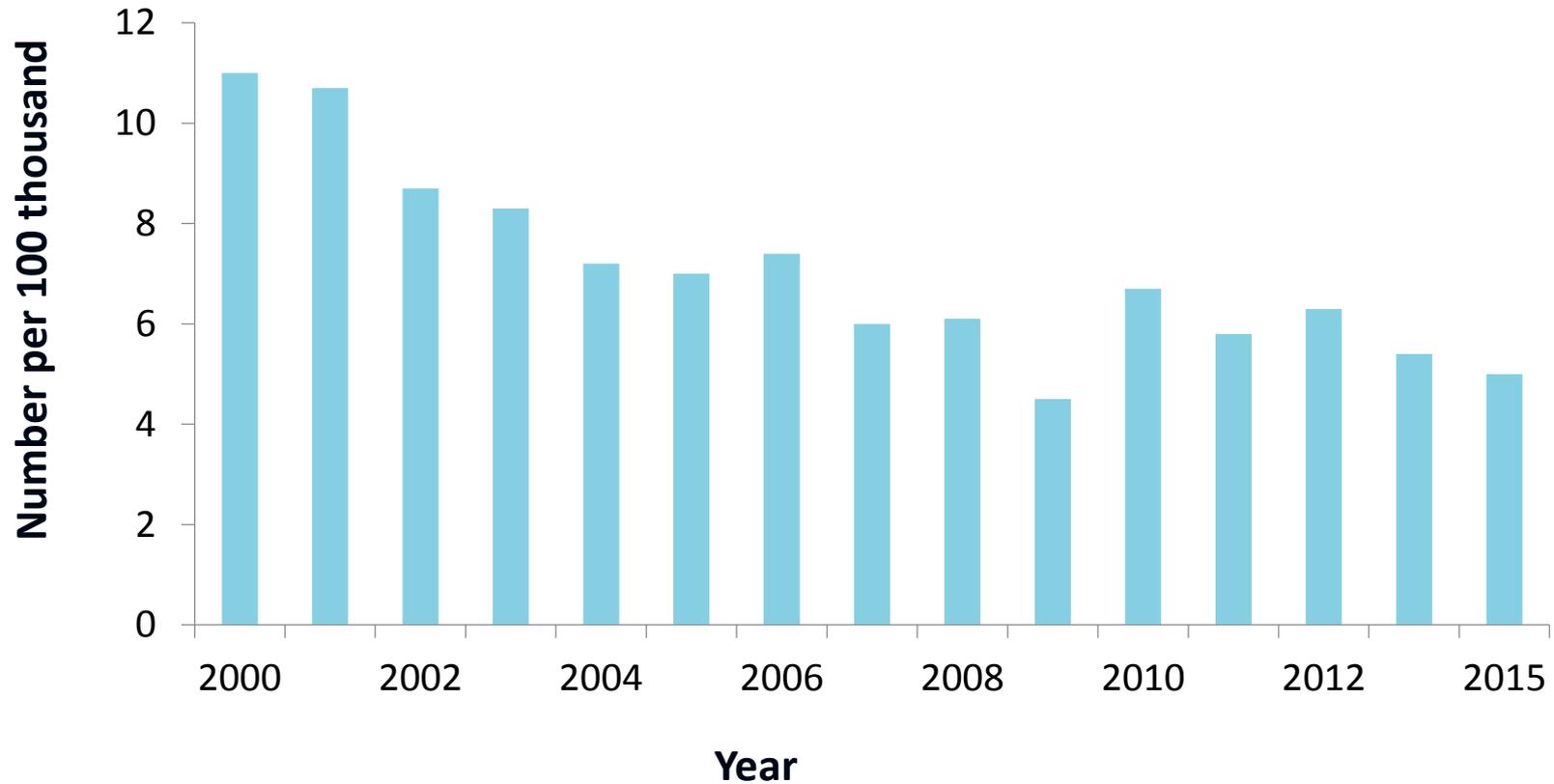


Source: MMWR 2016

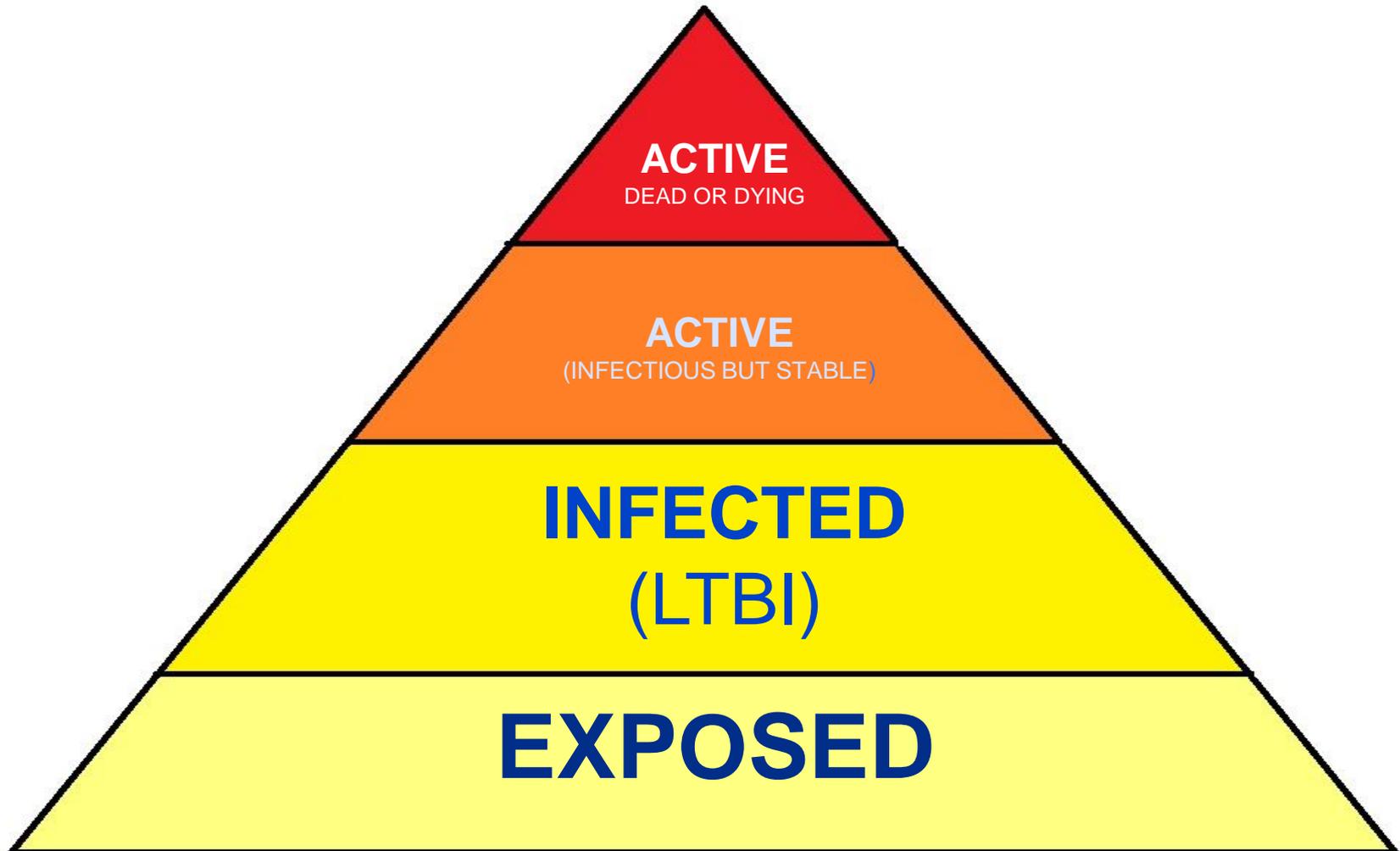
Cases of Active TB Nationally in American Indians/Alaska Natives 2000 - 2014



Rate of Active TB Nationally in American Indians/Alaska Natives 2000-2014



Tuberculosis Pyramid



An illustration of an iceberg floating in the ocean. The tip of the iceberg is above the water line, while the much larger, submerged part is below. The sky is light blue with a few birds flying. The water is a darker blue. The text is overlaid on the right side of the image.

Millions of people in the U.S. have
latent TB infection. Without
treatment, they are at risk for
developing **TB disease.**



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

Learn more:
www.cdc.gov/tb

KEY POINTS

- ❑ **Progress toward TB elimination in the U.S. has stopped**
- ❑ **American Indians / Alaska Natives are at historically high risk for TB and still have rates approximately 2x U.S. average**
- ❑ **TB cannot be eliminated in the U.S. without increased efforts to test and treat latent TB infection among high-risk groups.**

Tuberculosis Diagnosis and Treatment

Jonathan V Iralu, MD, FACP

Indian Health Service

Chief Clinical Consultant for

Infectious Diseases

Objectives

1. Differentiate between Latent Tuberculosis Infection and Active Tuberculosis Disease
2. Grasp the special importance of treating Latent TB in IHS diabetic patients
3. Be prepared to diagnose and treat active TB disease

Case Presentation

- A 36 year old man is diagnosed with new onset diabetes mellitus type II in the urgent care clinic. He is started on metformin by his new PCP and a PPD comes back positive at 11 mm.

- What should the PCP do next?

Latent Tuberculosis Infection

- Positive Tuberculosis Skin Test (TST) or Interferon Gamma Release Assay (IGRA)
- Asymptomatic
- Normal CXR

Why do a TST or IGRA on a healthy person in the first place???

- Screen Contacts of active cases for latent infection
- Screen Health Care workers for acquisition of TB
- Screen high risk patients with comorbid illness that might lead to activation of TB
 - HIV
 - Immunosuppressive therapy
 - Diabetes

IHS Diabetes Audit 2014

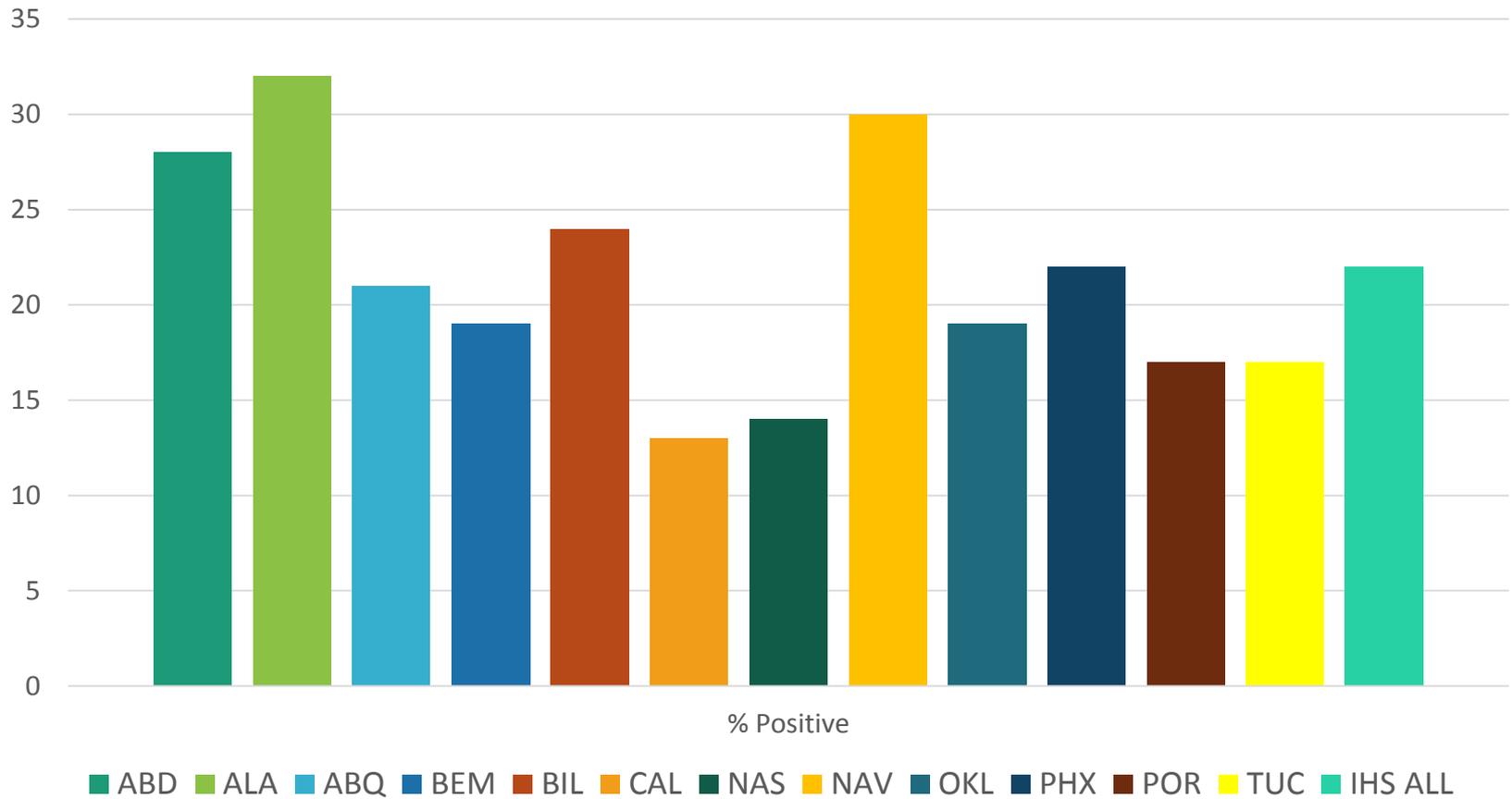
- Audit
 - January-December 2013
 - 331 facilities
 - ~116,000 AI/AN people with DM in database
 - Represents ~145,000 AI/AN with DM in registries

Latent TB in IHS Diabetics: IHS Diabetic Audit 2014

- 52% of IHS diabetics have had a TB test (99% of tests are PPD; 1% are blood tests)
 - 22% of those TB tests were positive
 - Only 20% were known to have completed treatment
 - 62% of the negative tests were performed after DM diagnosis

2014 IHS DM Audit

Percent positive PPD test by Area



DM Audit 2014 – TB Positive Tests by Age Group (National)

Age Group	# Patients	% Tested	% Positive
<40	14,639	46	6
40-44	9,204	48	8
45-49	11,876	49	10
50-54	15,270	51	13
55-59	16,154	52	17
60-64	15,535	53	22
65-69	12,579	55	28
70-74	9,274	57	43
75+	11,193	59	51

Impact of TB in diabetics

- 10% of TB cases worldwide are linked to DM
- The risk for active TB in diabetics is 2-3 x higher than nondiabetics
- Diabetics at a higher risk of death if they get TB

TB Mortality Risk in AI/AN

- TB Death Rate 1999-2009
 - AI/AN 1.5 TB deaths/ 100,000/year
 - Non Hispanic Whites 0.1 TB deaths/ 100,000/year

- Relative risk of death is 11.5!

Latent TB Infection

- ***Who to treat*** --do not treat every positive PPD.
- Only treat those with these risk factors:
 - Patients at risk for spreading TB
 - Patients at personal risk for reactivating **TB**

Latent TB Infection

- **Patients at risk for spreading TB**
 - ***Health Care Workers with direct patient contact*** (doctors, nurses, radiology and lab techs, custodians, food services, clinic secretaries, etc.)
 - ***School Employees*** with student contact (teachers, cafeteria workers, school bus drivers, etc)
 - ***Residential facility employees and residents*** (nursing homes, group homes, jails, detox centers, shelters, etc)

Latent TB Infection

- **Patients at personal risk for reactivating TB**
 - 5 mm PPD cutoff:
 - HIV positive
 - Contact of active TB case
 - Fibrosis on CXR consistent with healed TB
 - Immunosuppressed (>15 mg prednisone/d for >1 month, transplant, infliximab, etc)
 - 10 mm PPD cutoff:
 - Recent immigrant
 - IDU
 - Resident or HCW at jail, nursing home, hospital, shelter
 - **DM**, CKD, lymphoma/leukemia, weight loss, silicosis, gastrectomy, age < 4years old, ALD

Latent TB Infection

- **Important Reminders:**

- Don't test and don't offer treatment for people with no risk factors.
- Symptomatic patients or those with abnormal CXR suggesting TB need 3 negative sputum cultures before treatment for latent TB.
- Ignore the old age cut-off of 35 years.

IGRAs

- **Interferon Gamma Release Assays**

- Measure release of IFN- γ in response to Tb Ags
 - T-Spot (ESAT-6 and CFP-10)
 - Sensitivity 96%
 - Specificity 99%
 - Quantiferon Gold IT(ESAT-6, CFP 10)
 - Sensitivity: 87%
 - Specificity: 99%
- Not affected by BCG, M avium, M kansasii

IGRA's

- Uses:
 - Contact investigation
 - Evaluating Immigrants who had BCG
 - Screening HCW's and Residential facility residents annually
 - All other settings where PPD is used for screening
- Limitations:
 - Recent exposure, immunocompromised, age <17

How to treat Latent TB Infection

- Preferred Adult Regimens for routine cases:
 - INH 300 mg po daily for 9 months
 - Rifampin 600 mg po daily for 4 months
 - INH 900 mg po weekly plus Rifapentine 900 mg po weekly for 12 weeks, directly observed therapy

How to treat Latent TB

Important Reminders:

- Supplement INH with pyridoxine 50 mg po daily
- Rifampin *cannot* be given intermittently like INH
- INH historically was preferred over Rifampin for most patients. Rifampin was reserved for the patient with pre-existing hepatitis or history of nonadherence.
- INH-Rifapentine is becoming the new “go-to” regimen for patients with no contraindication due to drug interactions or allergy

How to treat Latent TB

Monitoring for toxicity

- Monitor the patient for symptoms of toxicity and physical exam monthly
 - INH: rash, neuropathy, N/V, anorexia, jaundice, lupus-like illness
 - Rifampin: rash, , flu-like illness, jaundice, bleeding
- Monitor the LFT's monthly on INH and the LFT's and CBC monthly on Rifampin
 - INH: transaminitis
 - Rifampin: cholestasis, thrombocytopenia, leukopenia

Case Presentation

- A 29 year-old man from a remote rural reservation site has a 3 month history of cough and night sweats. His CXR shows a right upper lobe cavitary infiltrate. He lives in a hogan with his wife and 3 pre-school children.
- How should you proceed?

Diagnosing TB with a CXR

- Upper lobe disease predominates
- Cavitation often present
- The hilum is pulled upward
- Lymph node enlargement or calcification present
- Pleural cap or pleural effusion



Extrapulmonary TB

- Sites of involvement
 - Meningeal
 - Pleural
 - Pericardial
 - Bone/Joint
 - Renal/Testicular
 - Skin
 - Ophthalmic
 - Miliary



Reconstituted DICOM Image

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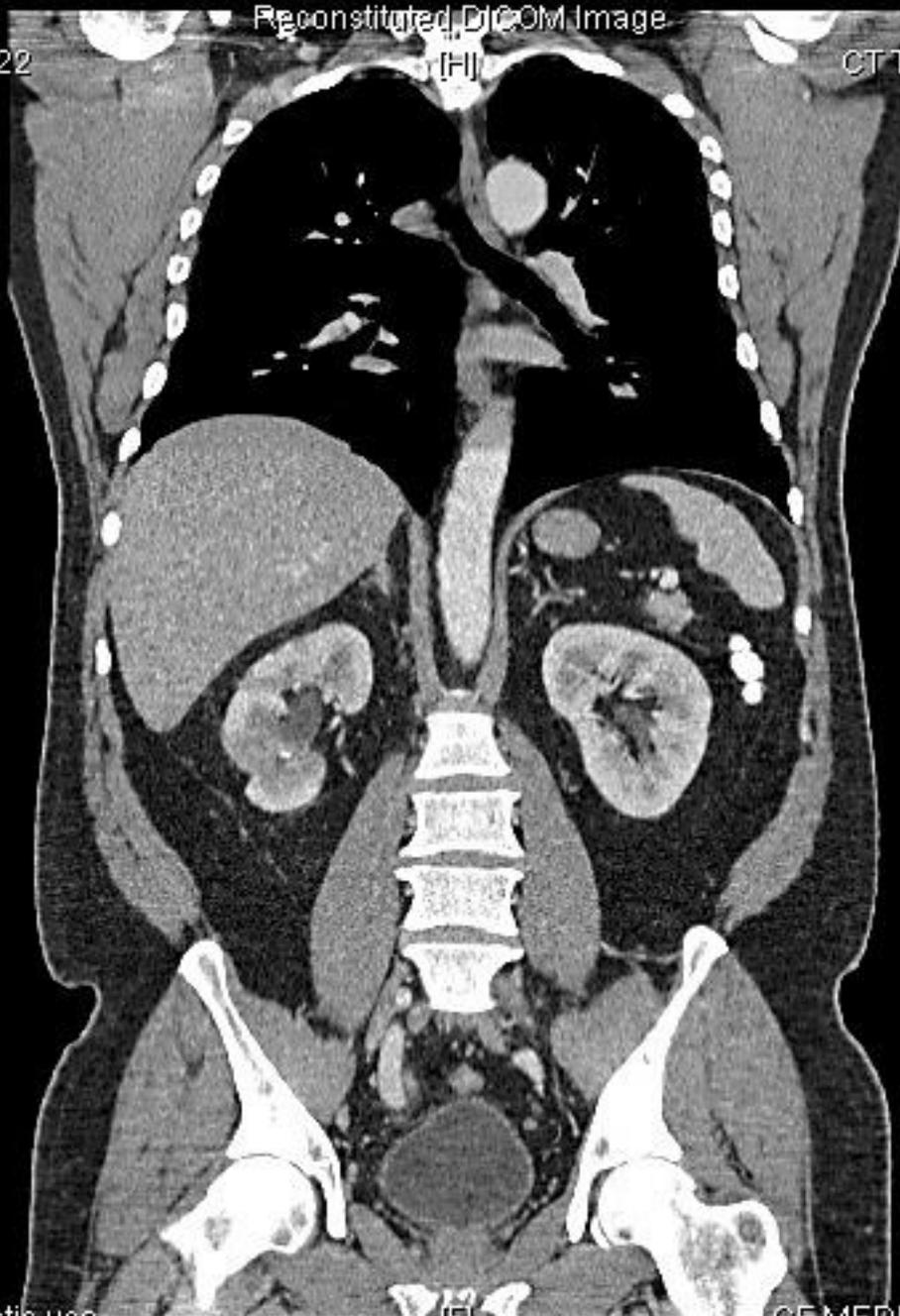
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Not for diagnostic use

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GE MEDICAL SYSTEMS



Active TB

Initial Evaluation

- Admit to the hospital
- Place on Airborne Isolation
- Collect 3 sputa for AFB in the first 24 hours including one early morning sputum.
- Start anti-TB therapy within 24 hours if TB is strongly suspected
- Obtain an HIV serology and viral hepatitis panel on every case

Nucleic Acid amplification tests

- Two tests:
 - E-MTD: isothermal amplification 16S ribosomal gene
 - Amplicor: PCR of 16S ribosomal gene
 - > 95% sensitive if smear positive
 - 60-90% if smear negative
- Interpretation:
 - If NAA test positive: treat for TB and contact investigate
 - If NAA test is negative: TB is not definitively ruled out

Nucleic Acid drug resistance testing

- CDC utilizes PCR and DNA sequencing
- Rifampin resistance:
 - detect mutations in *rpoB* gene of MTb
 - Sensitivity 0.96, specificity 0.97
- INH resistance
 - Detect mutations in *inhA* and *katG* genes of MTb
 - Sensitivity 0.89, specificity 0.98

NAATs continued

- CDC recommend NAAT for 1 of the 3 sputum specimens collected to evaluate for TB
- **Xpert MTB/RIF: New NAAT allows for evaluation of sputum for TB and Rifampin resistance simultaneously.**
- Genotyping is useful for contact investigation

Active TB

Initiation of treatment

- ***Treat all IHS Patients with 4 drugs***: INH, Rifampin, EMB, PZA
- ***Treat 2 weeks in the hospital*** with daily therapy to monitor response and labs
- ***Continue for 6 weeks with 4 drugs***
always with home based DOT



© : AVERT

Active TB

- When to simplify the regimen:
 - Stop EMB as soon as the culture results show sensitivity to the other 3 drugs
 - Stop PZA when 8 weeks of therapy are completed

Active TB- Continuation Phase

- 6 months total with INH and Rifampin if:
 - cultures collected at 8 weeks are subsequently negative
 - there were no cavities on the CXR
- 9 months of INH & Rifampin if:
 - there were cavities on the first CXR and
 - the week 8 culture is positive
- ***Always*** use DOT for the duration!

Active TB- Monitoring Response

- Monitor for treatment success by
 - checking a monthly sputum for AFB smear and culture for the duration of therapy and at completion
 - Obtain a follow-up chest x-ray at 2 months and at the completion of therapy.

Active TB- Monitoring for Toxicity

- Monitor for **INH and Rifampin** toxicity as we did for the LTBI patient
- Monitor for **EMB** toxicity with a baseline color vision test and repeat as needed
- Monitor for **PZA** toxicity by following for hepatotoxicity, rash and gout

Conclusions

- Treatment of latent TB is easy and simple now
 - INH plus Rifapentine for 12 weeks
- Treatment of active TB is very manageable at IHS sites with assistance from a TB specialist
 - Please consider joining the monthly IHS TB ECHO teleconference by contacting me or Dr. Yost.