World TB Day From the Heartland News Desk

Barbara Seaworth, MD
Medical Director
Heartland National TB Center

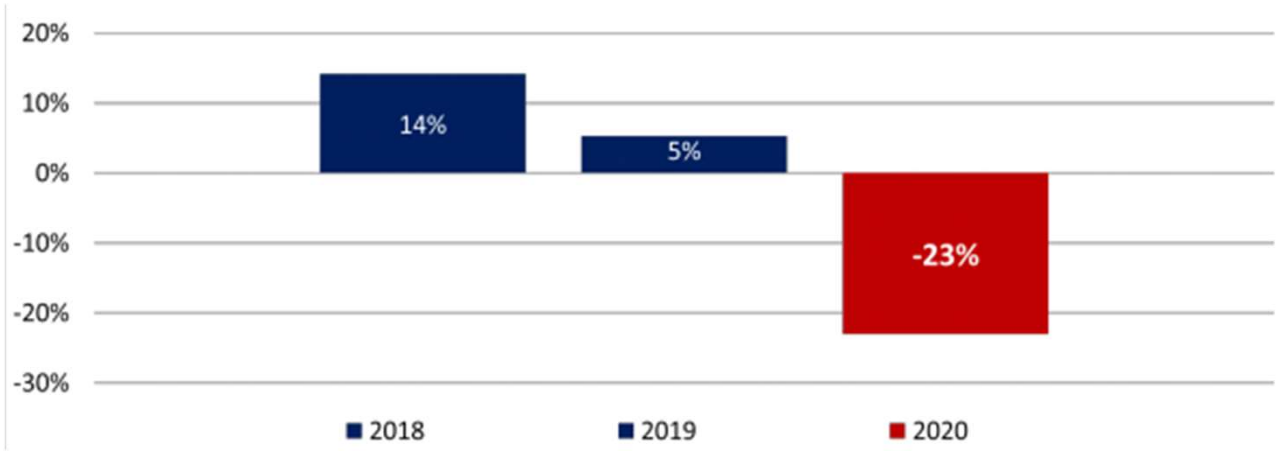
Professor of Medicine
UT Health Science Center at Tyler

Lisa Armitige, MD, PhD
Assistant Medical Director
Heartland National TB Center

Associate Professor of Medicine/Pediatrics
UT Health Science Center at Tyler

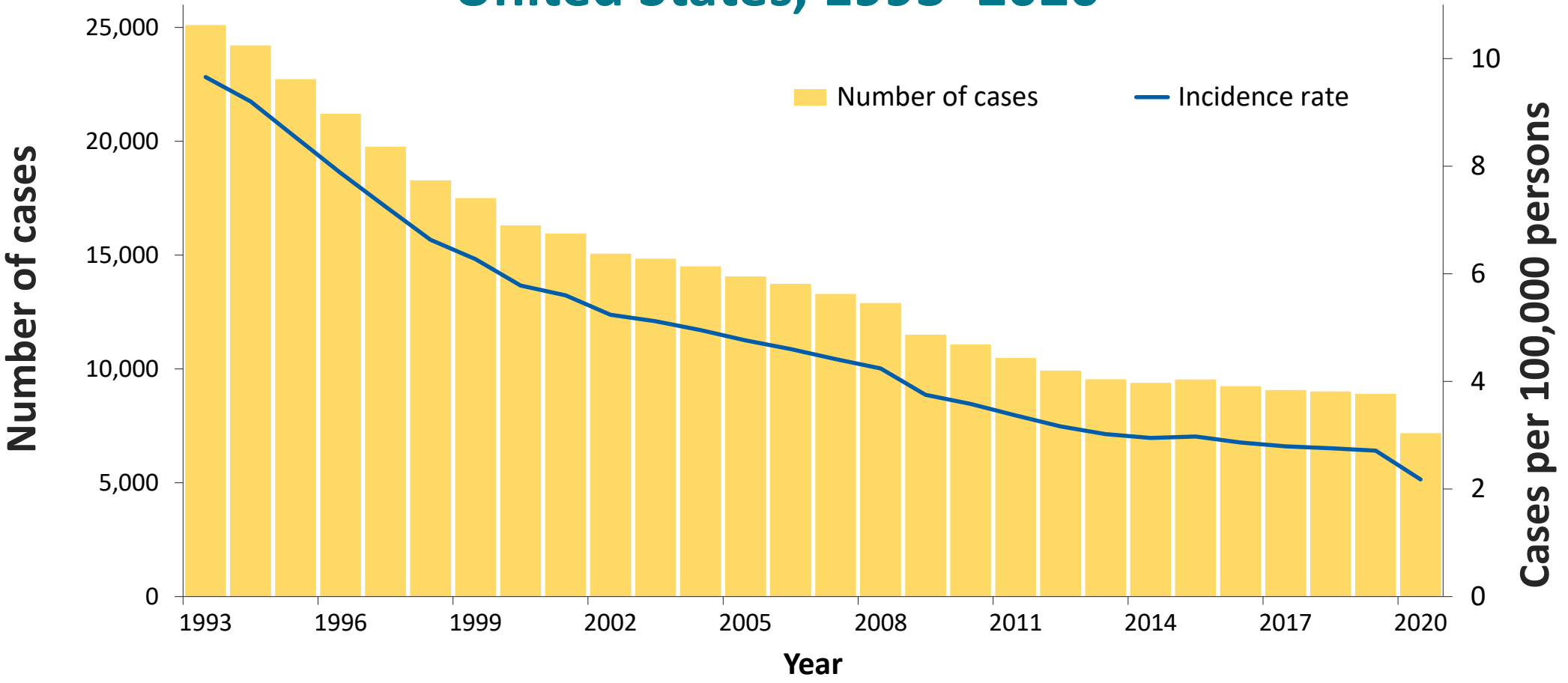
Impact of the COVID-19 Pandemic on TB Numbers and Deaths

Annual percentage change in TB diagnosis and enrollment for nine high-TB burden countries

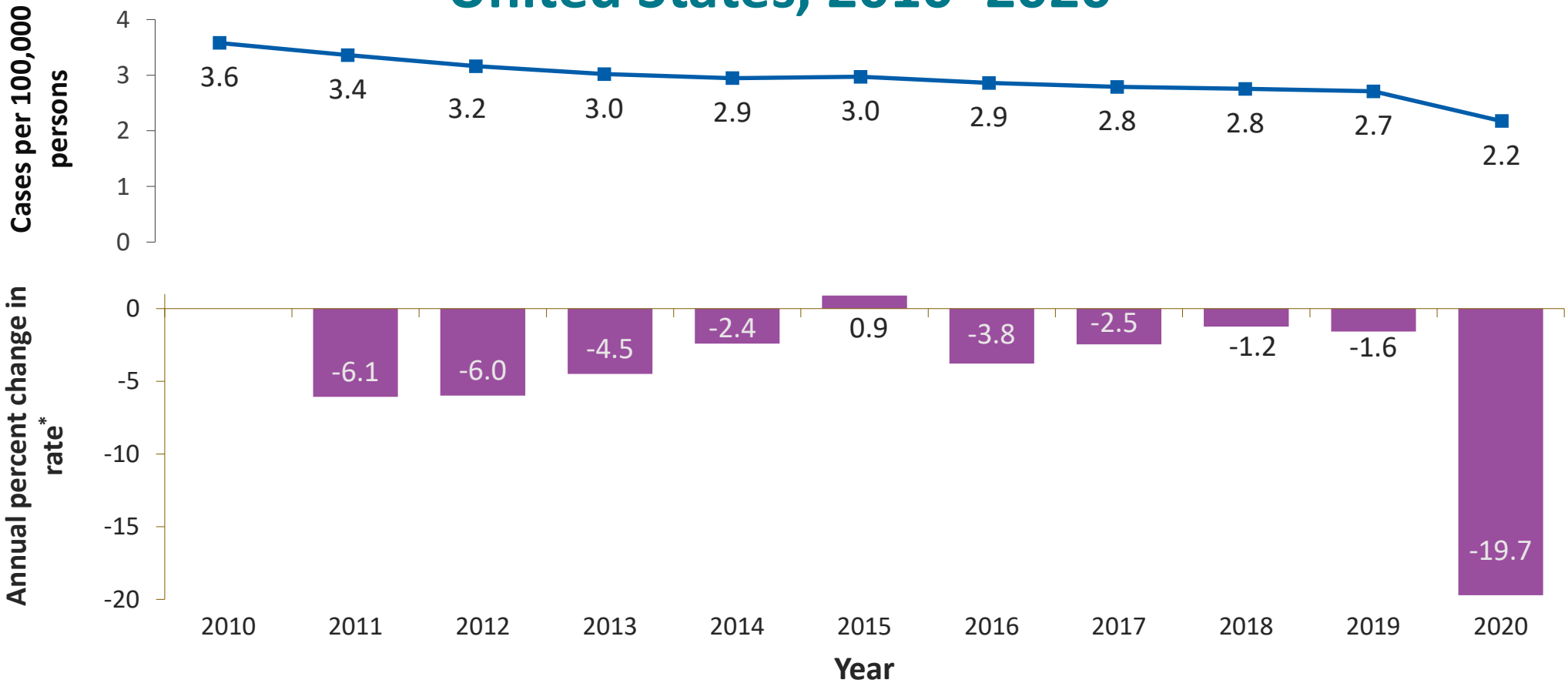


https://healthpolicy-watch.news/covid-19-eliminates-12-years-progress-tb/

TB Cases and Incidence Rates, United States, 1993–2020

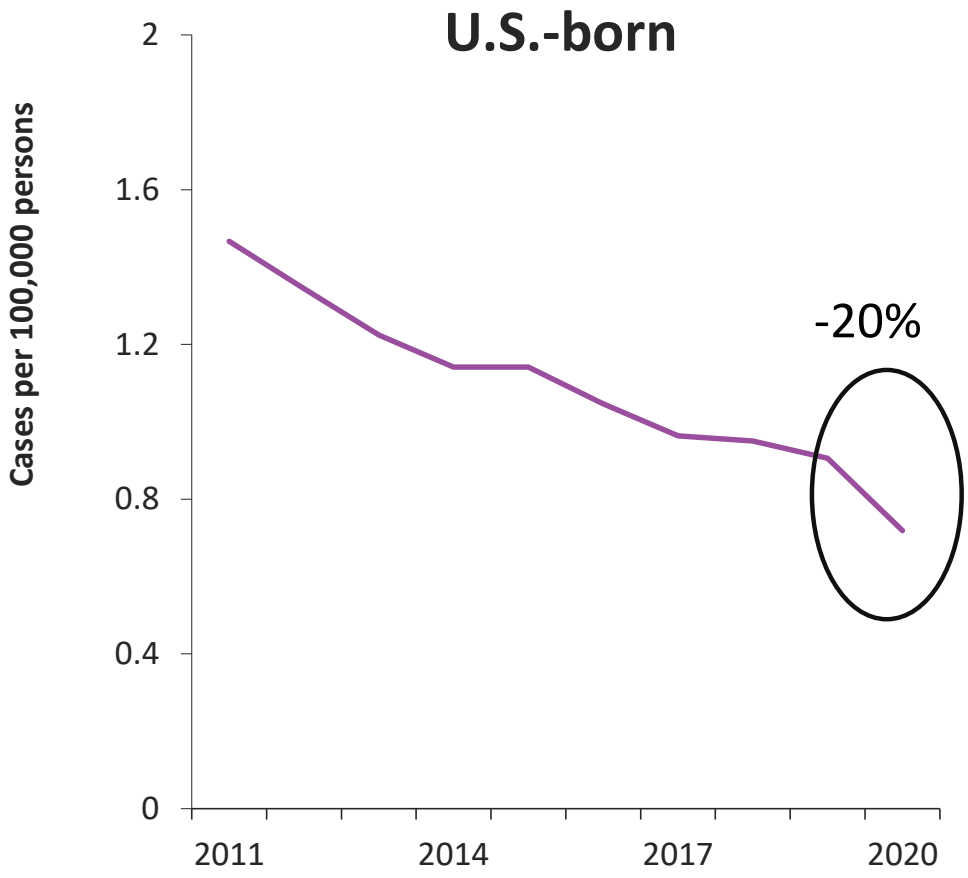


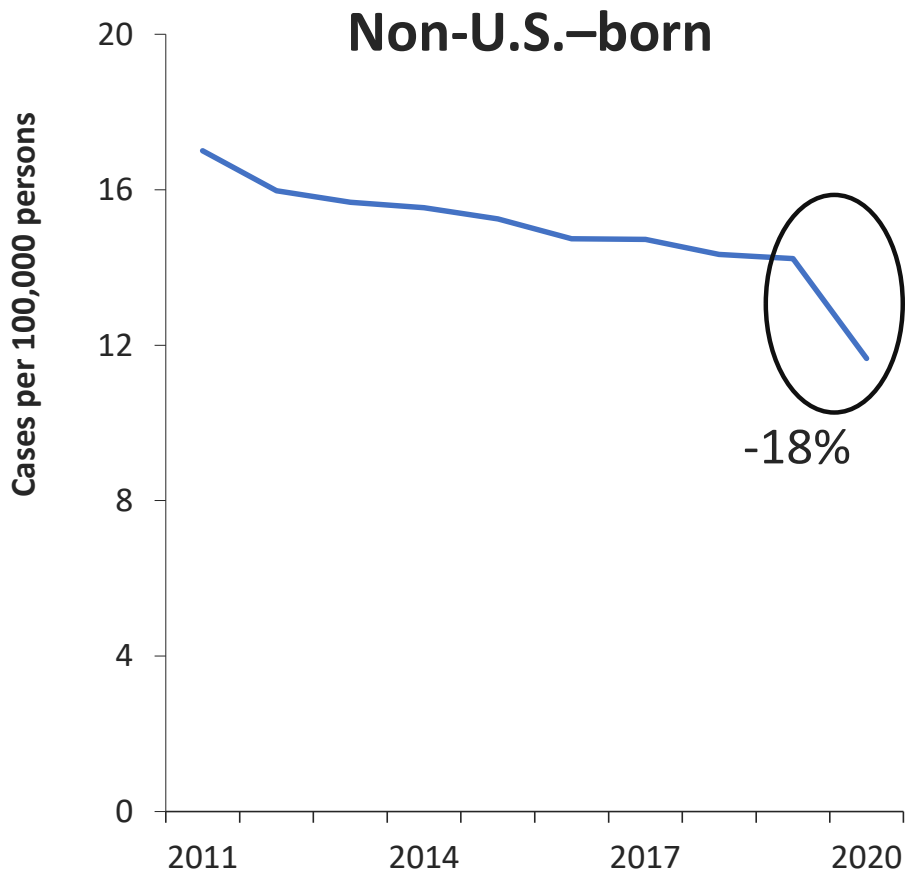
TB Incidence Rates and Annual Percent Change in Rate, United States, 2010–2020



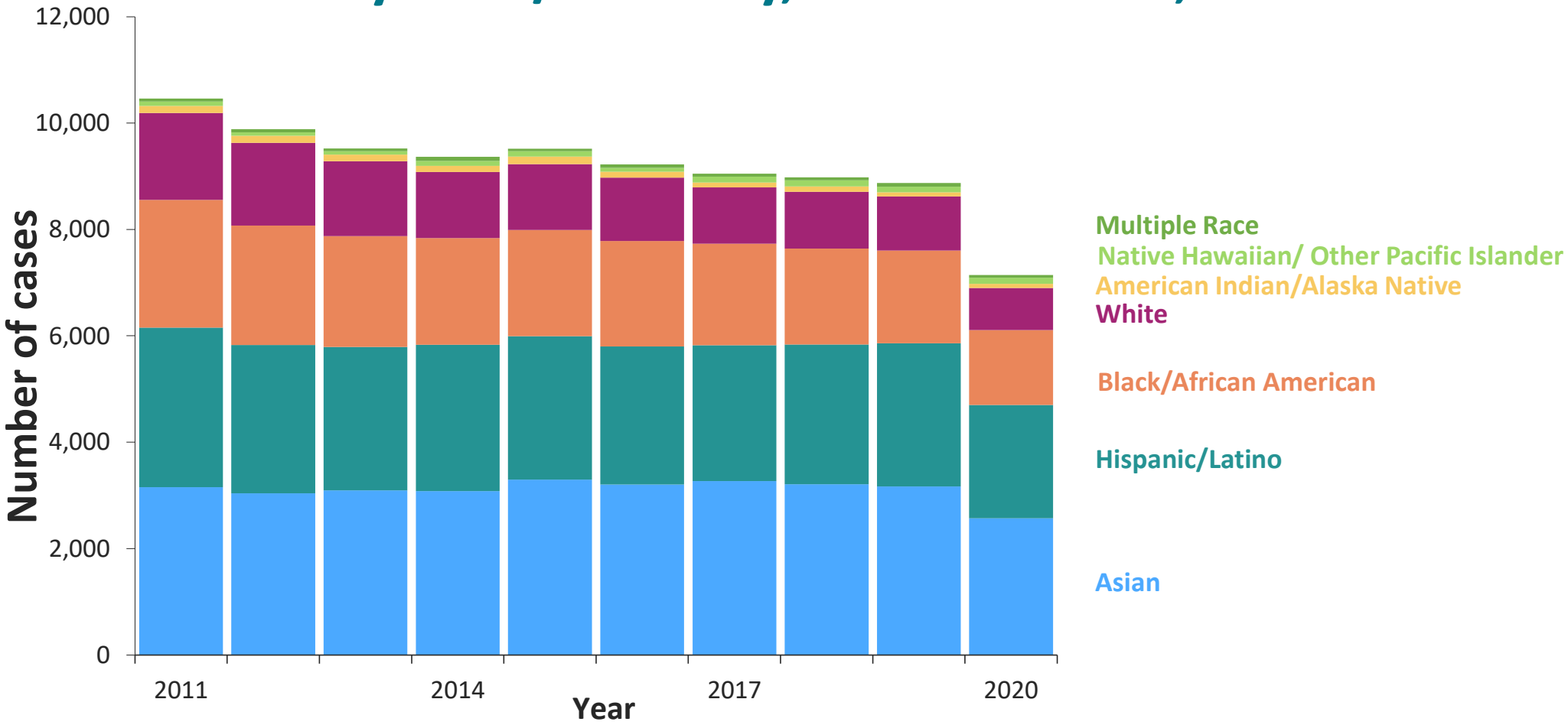
*Annual percent change in rate based on unrounded data

TB Incidence Rates by Origin of Birth, United States, 2011–2020



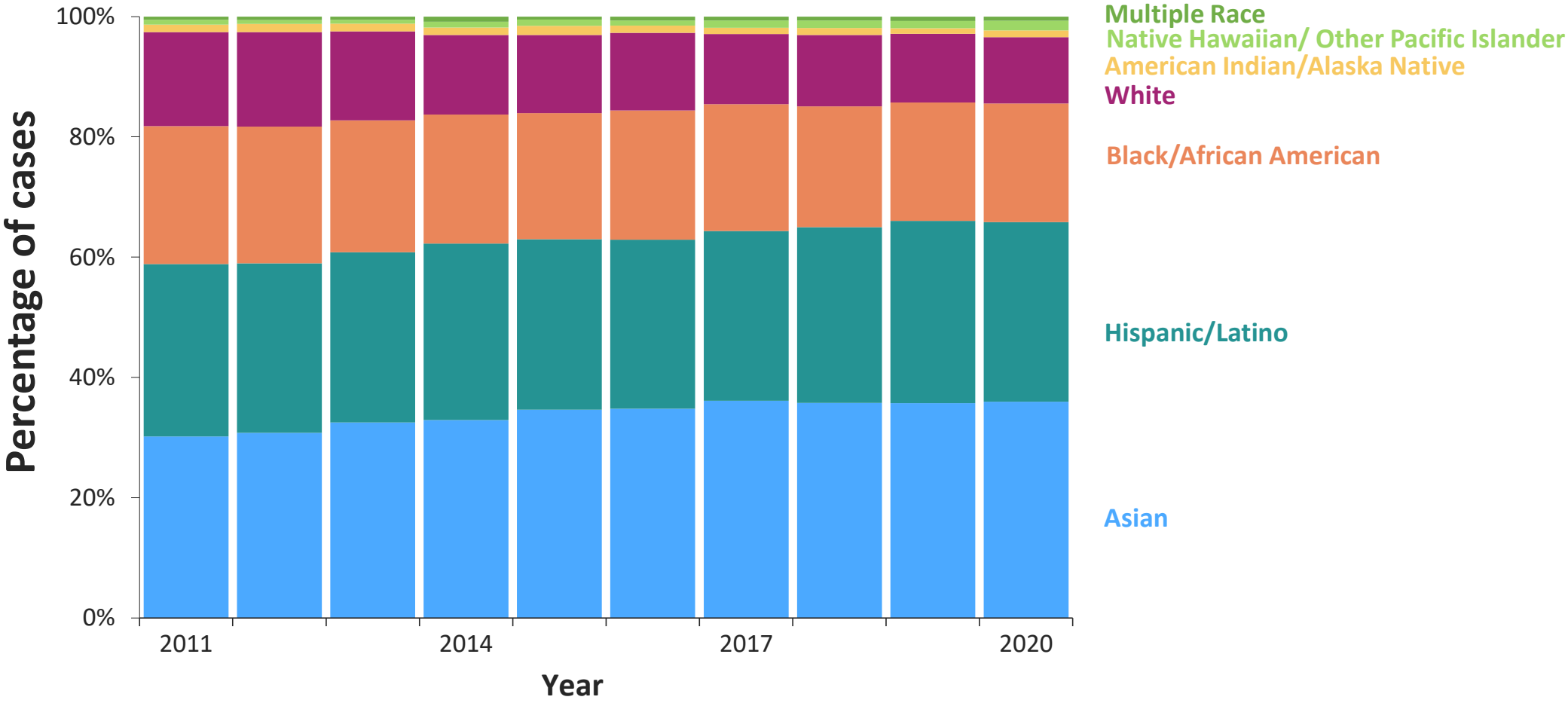


TB Cases by Race/Ethnicity,* United States, 2011–2020



*All races are non-Hispanic; multiple race indicates two or more races reported for a person but does not include persons of Hispanic or Latino origin.

TB Cases by Race/Ethnicity,* United States, 2011–2020



*All races are non-Hispanic; multiple race indicates two or more races reported for a person but does not include persons of Hispanic or Latino origin.

World Health Organization

Health Topics | Countries | Newsroom | Emergencies | Data | About WHO

Home / News / Tuberculosis deaths rise for the first time in more than a decade due to the COVID-19 pandemic

Tuberculosis deaths rise for the first time in more than a decade due to the COVID-19 pandemic

Русский

WHO estimates an extra 500,000 patients died of TB in 2020.

On World TB Day WHO calls for increased investments into TB services and research

Release of updated guidance on management of TB in children and adolescents

https://www.who.int/news/item/21-03-2022-on-world-tb-day-who-calls-for-increased-investments-into-tb-services-and-research

In 2020, an estimated 63 % of children and young adolescents below 15 years with TB were not reached with or not officially reported to have accessed life-saving TB diagnosis and treatment services;

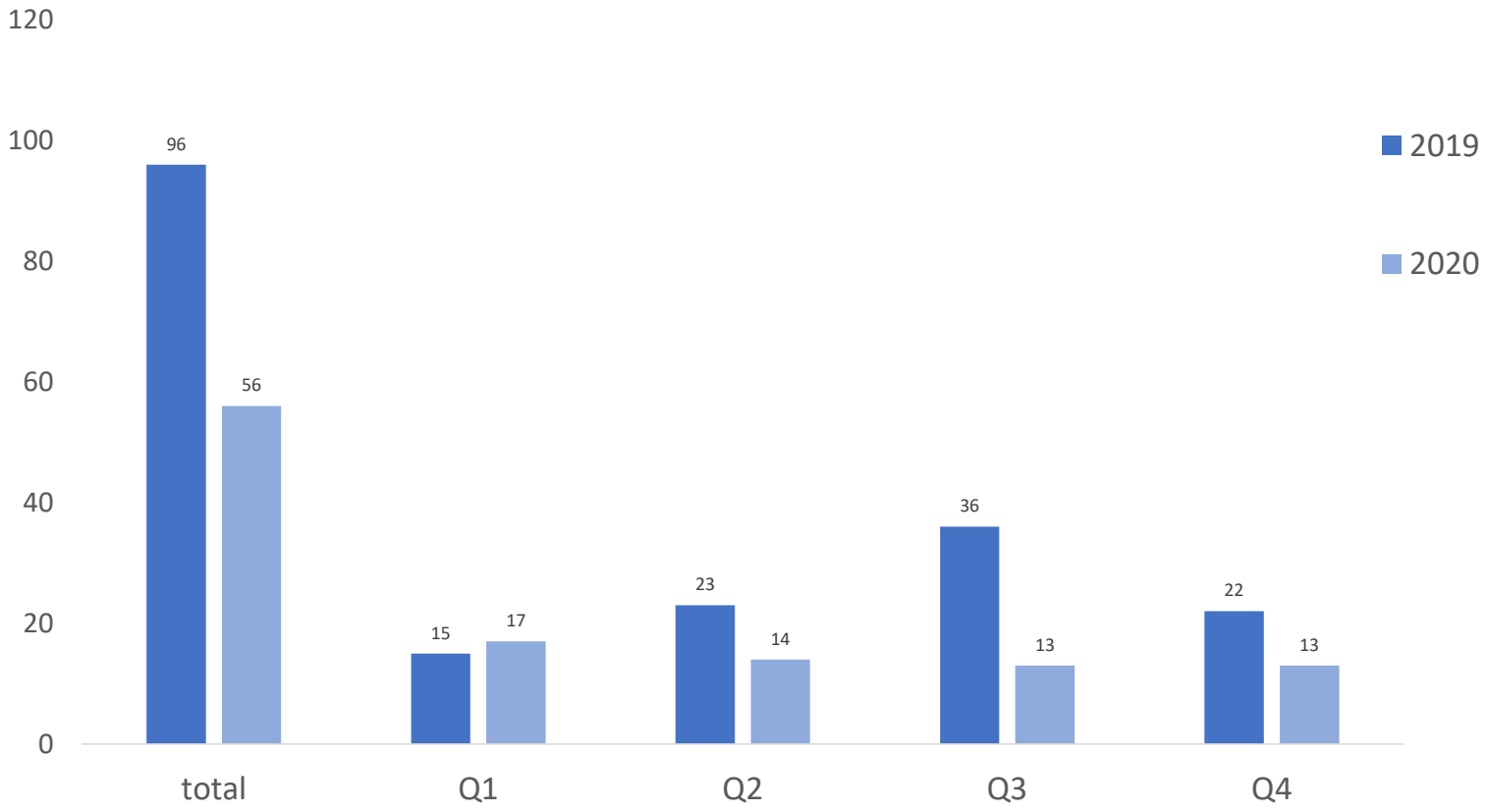
the proportion was even higher - 72% - for children under 5 years.

Almost two thirds of eligible children under 5 did not receive TB preventive treatment and therefore remain at risk of illness.

Why?

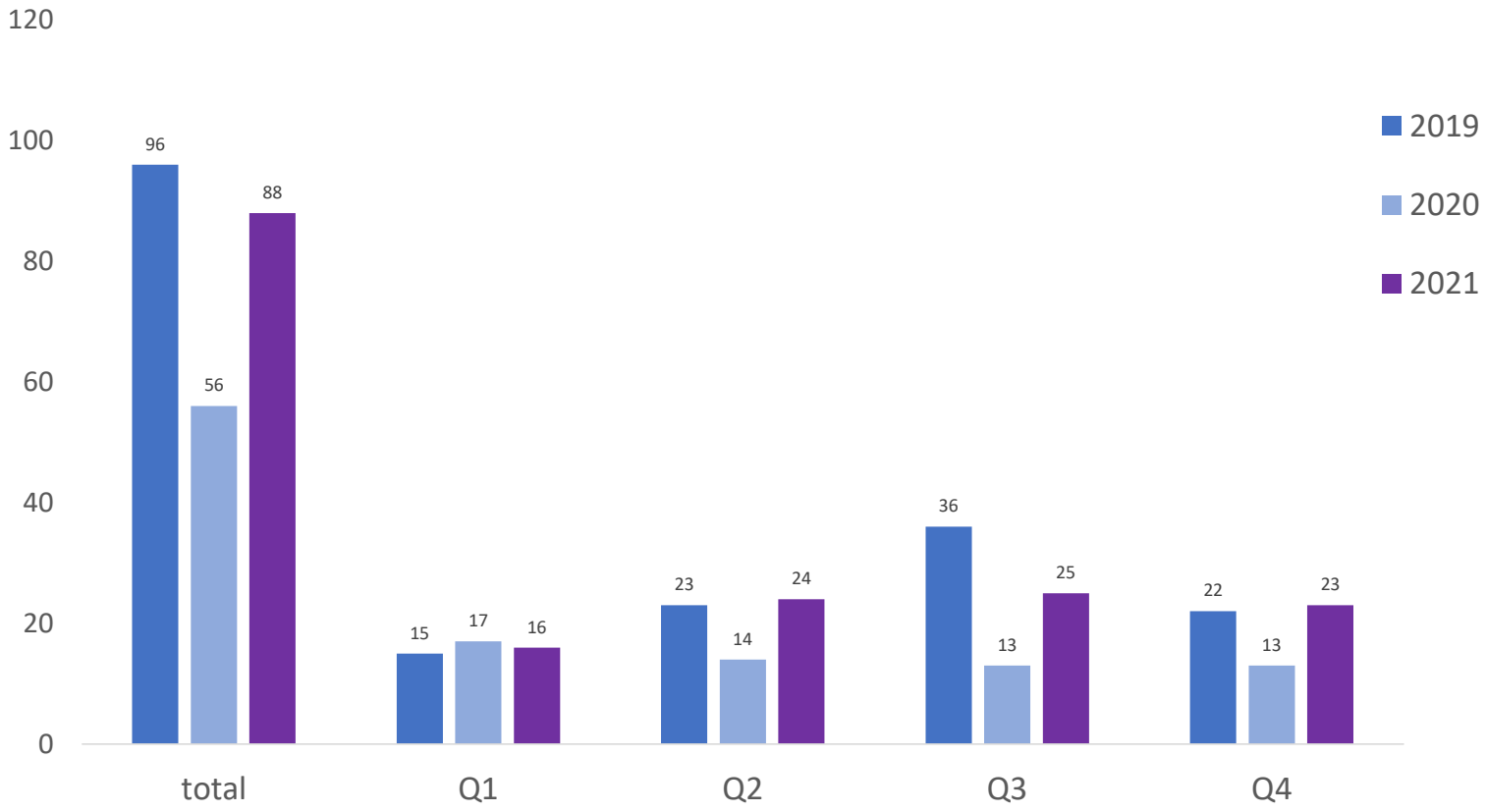
- Lock downs (one of the most impactful factors globally)
- Patients fearful of seeking care (and being tested repeatedly for Covid-19)
- Diversion of funds to Covid-19 response
- Diversion of ***staff*** to Covid-19 response

What about 2021?
TB patients at San Antonio Chest Clinic



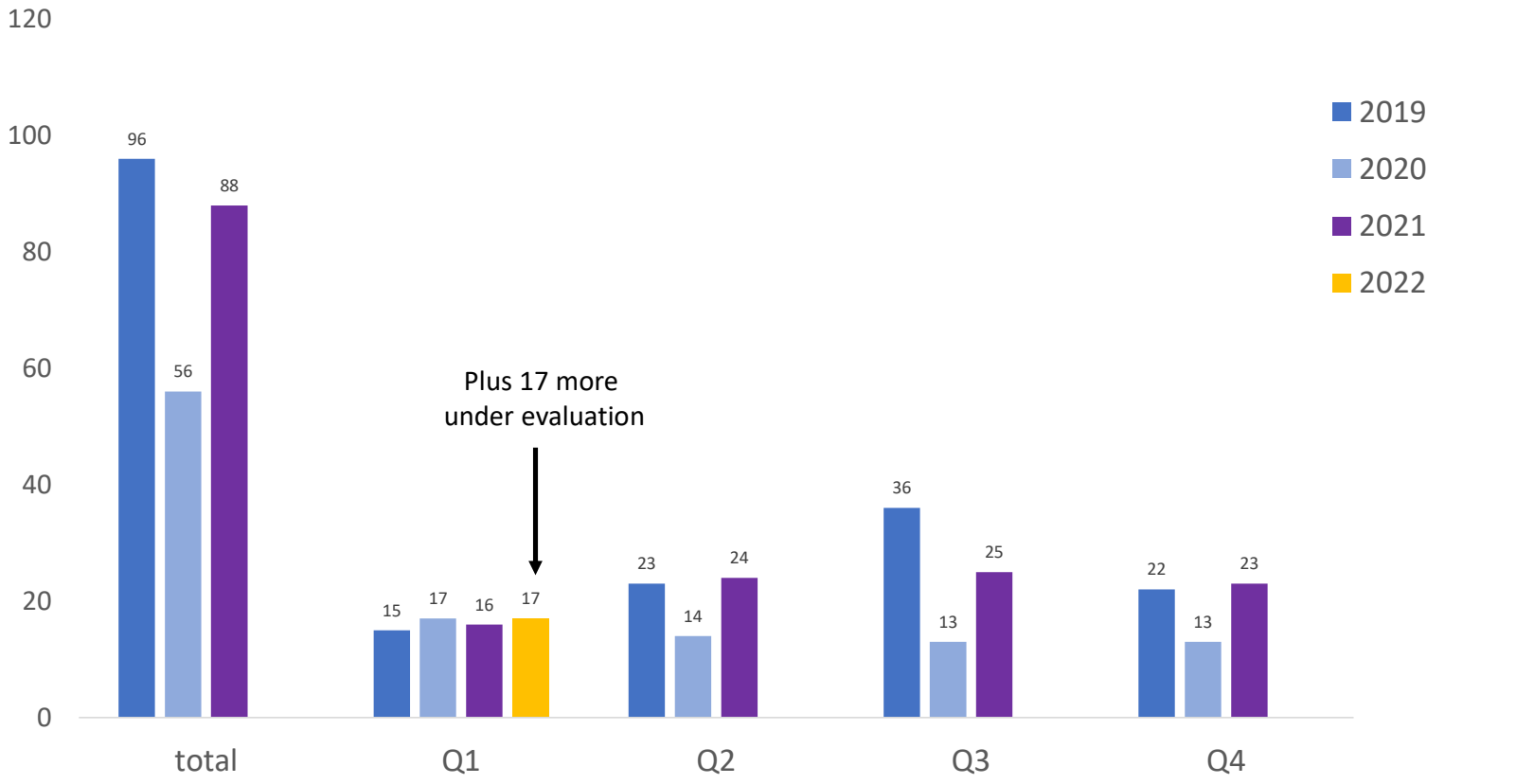
Provided by Norma Santos, Victoria Adams SAMHD

What about 2021?
TB patients at San Antonio Chest Clinic



Provided by Norma Santos, Victoria Adams SAMHD

What about 2021?
TB patients at San Antonio Chest Clinic



Provided by Norma Santos, Victoria Adams SAMHD

Things we don't know

- What effect does treatment for Covid-19 (steroids, 'malnutrition', the stress of severe illness) have on reactivation of TB infection?
- Where are the 'missing' TB cases now and how will they impact available resources in the coming years?
- How to optimize efforts to assure patients with TB disease and TB infection lost to care are brought back to care?
- What effect will public health burnout play in getting TB care back on track?

My patient was getting better on treatment,
now the lymph nodes are bigger and the pleural effusion is back.
She doesn't have HIV.

Dr. Seaworth, what's happening with my patient?

Immune Reconstitution Inflammatory Syndrome (IRIS) in non-HIV Immunosuppressed Patients with Tuberculosis

What is TB Non-HIV IRIS

- No precise definition –
- No diagnostic criterion agreed on
- What we can say:
  - **Characterized** by an Exaggerated and Dysregulated Inflammatory Response to various antigens or pathogens
  - **Caused** by Reconstitution of adaptive or innate immunity **Characterized** by high levels of inflammatory cytokines
    - ***A Shift from anti-inflammatory TH 2 to pro-inflammatory TH1 response***

What is IRIS?

- The result of a drastic expansion of *M. tuberculosis* in the poorly inflamed or anergic environment of an immunocompromised patient, followed by an exuberant antigen-specific inflammatory reaction after resolution of immunosuppression".

- Accordingly, TB-IRIS presents as an exacerbated inflammation, commonly including fever and lymphadenopathy as leading symptoms

Bell Int J Inf Dis 2015

How Is Non-HIV IRIS Manifested?

- **UNMASKING IRIS**
  - Disease becomes **Newly** apparent due to improved immune response
  - Disease **subacute, unrecognized and not treated** prior to reconstitution of immunity
  - **Requires a pathogen be identified** on culture from new lesions

- **PARADOXICAL IRIS**
  - **Worsening** of an already diagnosed clinical disease
  - **Occurs** while patient is **on appropriate therapy**
  - **Diagnosis of exclusion**; must exclude another infection or treatment failure

Potential Triggers for Non-HIV IRIS

- **Triggers:**
  - **Simply starting TB Medications**, especially in those with extensive TB disease
    - Interruption of disease-related immunosuppression.
  - **Recovery from immune suppressed state**
    - **ABRUPT** tapering of steroids or immunosuppressant medications
    - Withdrawal or reduced effects of TNF alpha blocker therapy
    - Postpartum state (3-6 weeks after delivery)
    - Initiation of dialysis?

Unmasking IRIS - Clinical Presentation

- Person who previously had subacute illness, just not well.
  - **Not diagnosed with TB**
- Presents with one or more of the following:
  - Abrupt onset of cough, shortness of breath, fever, night sweats,
  - Abdominal pain with new ascites
  - Chest pain with new pleural effusion
  - New neurological symptoms
  - Draining neck lesion

Paradoxical Reaction - Clinical Presentation

Patient **with TB and responding to treatment** now develops:

- Recurrent or worsening fever
- Worsening cough and SOB
- New or worsening pleural effusion
- New or worsening ascites
- Lymph nodes increase in size, become fluctuant, drain spontaneously
- New lymph nodes appear
- New neurological findings
- Radiographic progression of initial disease
- New lesions in previously uninvolved organs

Fujita - Respiratory Investigation 58: 2020

Pulmonary non-HIV IRIS – a Mini-review of Literature

(IRIS following white blood cell recovery excluded)

TB most frequent infection (17)
TNF alpha antagonist recipients (14)
Solid Organ transplant recipients (2)

Histoplasmosis (9)
Aspergillosis (5)
Cryptococcus (4)

TB IRIS occurred from 10 days to 3 months after reduced immunosuppression

10 cases PR; 6 Unmasking

Table 1 – Summary of reported cases of respiratory lesions as IRIS in non-HIV patients.

Cases	Authors (year)	Patient age and sex	Lung lesion	Underlying diseases	Factors	Specific treatment to IRIS	Outcome	Reference number
1	Asano (2000)	29 F	Tuberculosis	Kidney transplant recipient	Rifampicin decreases the level of cyclosporin A	None	Improved	[1]
2	Garcia Vidal (2005)	49 F	Tuberculosis	Rheumatoid arthritis	Infliximab	Surgery	Improved	[2]
3	Garcia Vidal (2005)	48 F	Tuberculosis	Rheumatoid arthritis	Infliximab	Surgery	Improved	[2]
4	Garcia Vidal (2005)	56 M	Tuberculosis	Ankylosing spondylitis	Infliximab	Steroid	Improved	[2]
5	Garcia Vidal (2005)	21 M	Tuberculosis	Crohn disease	Infliximab	NSAID	Improved	[2]
6	Belknap (2005)	73 F	Tuberculosis	Rheumatoid arthritis	Infliximab	None	Improved	[3]
7	Arend (2007)	24 M	Tuberculosis	Crohn disease	Infliximab	None	Improved	[4]
8	Place (2007)	28 F	Tuberculosis	Heart-lung transplantation	Triple-drug immune suppression	Steroid	Improved	[5]
9	Wallis (2009)	29 F	Tuberculosis	Rheumatoid arthritis	Adalimumab	Steroid	Improved	[6]
10	Yoon (2009)	38 M	Tuberculosis	Crohn disease	Infliximab	Surgery	Improved	[7]
11	Szerszen (2009)	70 M	Tuberculosis	Rheumatoid arthritis	Infliximab	Steroid	Improved	[8]
12	Melboucy-Belkhir (2010)	56 F	Tuberculosis	Ankylosing spondylitis	Infliximab	Steroid + Surgery	Improved	[9]
13	Troncoso Mariño (2010)	44 M	Tuberculosis	Ankylosing spondylitis	Infliximab	Steroid	Improved	[10]
14	Rivoisy (2011)	68 F	Tuberculosis	Crohn disease	Adalimumab	None	Improved	[11]
15	Dahya (2014)	36 M	Tuberculosis	Sarcoidosis	Adalimumab	Steroid	Improved	[12]
16	Miyoshi (2017)	78 F	Tuberculosis	Rheumatoid arthritis	Infliximab	Steroid	Died	[13]
17	Takata (2019)	75 M	Tuberculosis	Non-small cell lung cancer	Nivolmab	Steroid	Improved	[14]

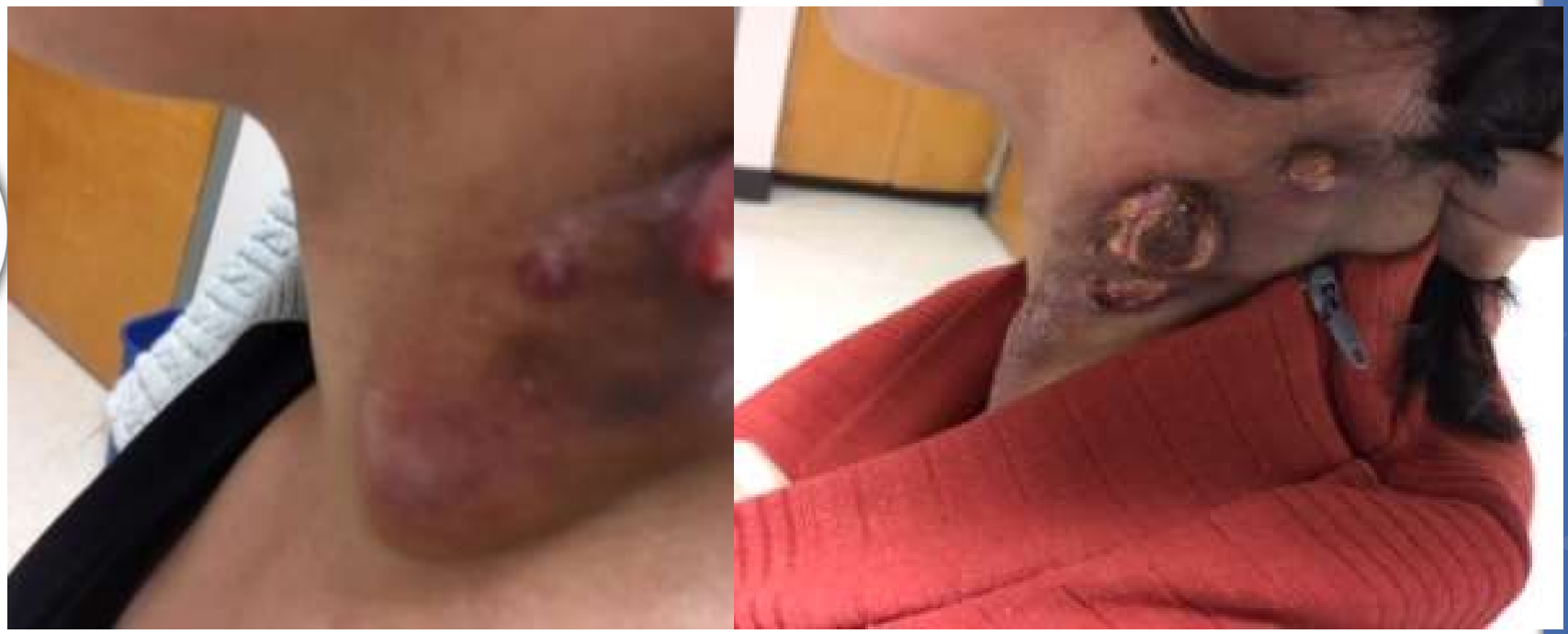
Large Lymph Node

Fluctuant, skin over node shinny, thin and erythematous

Spontaneous rupture is associated with scarring and draining fistula tract

Can avoid spontaneous rupture by fine needle aspirate

TB Lymph Node Disease after Start of RIPE
IRIS - Paradoxical Reaction

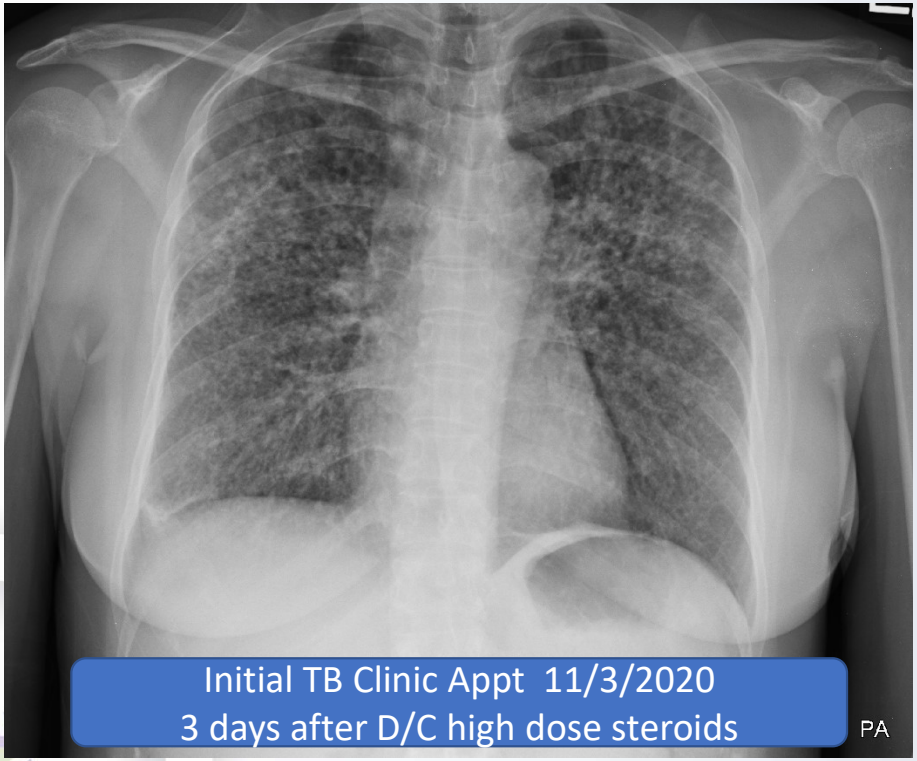


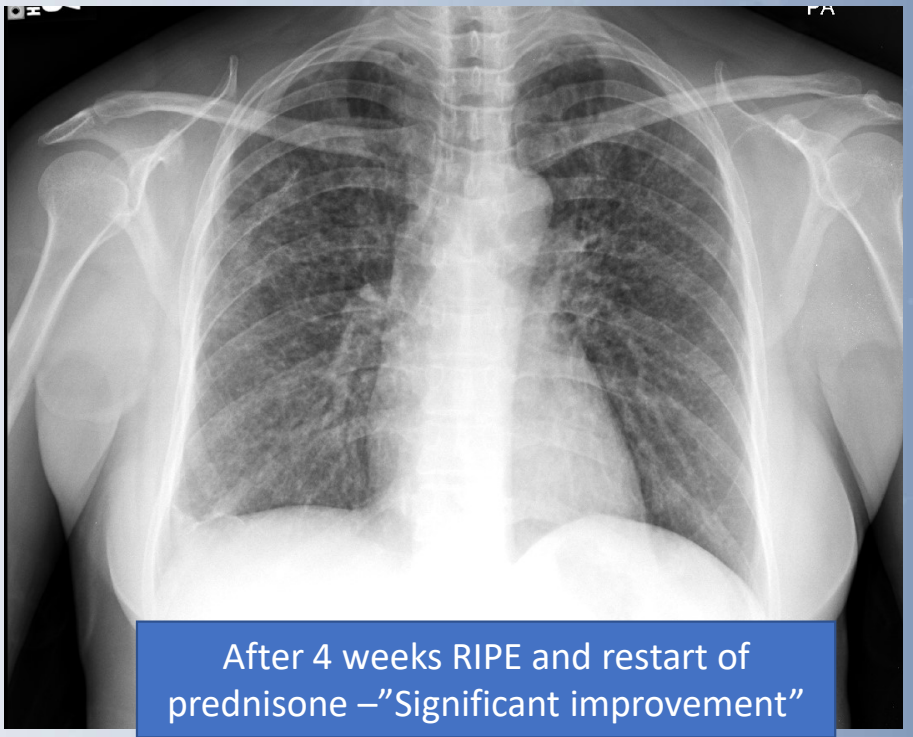
IRIS in CNS Tuberculosis

- Prevention Strategy Recommended
  - Routine steroids recommended at diagnosis with taper over 6-8 weeks (Treatment of TB: ATS, CDC, IDSA CID 2016)
    - Too rapid for some patients
- Paradoxical IRIS can cause recurrence of initial symptoms, enhanced or new CNS lesions
- Some patients require prolonged high dose steroids
- Some do not adequately respond to even high dose steroids
- TNF alpha blockers have been used successfully

Are there markers for these poorly responding patients?
Are there patients who should get TNF alpha blockers early?

Miliary TB of Lungs & Omentum in Pt with RA who had biologic stopped 2 months ago. High dose steroids restarted 1 month ago (Xray and clinical worsening) for possible sarcoid Steroids abruptly stopped 3 days prior to TB clinic visit when culture positive for MTB

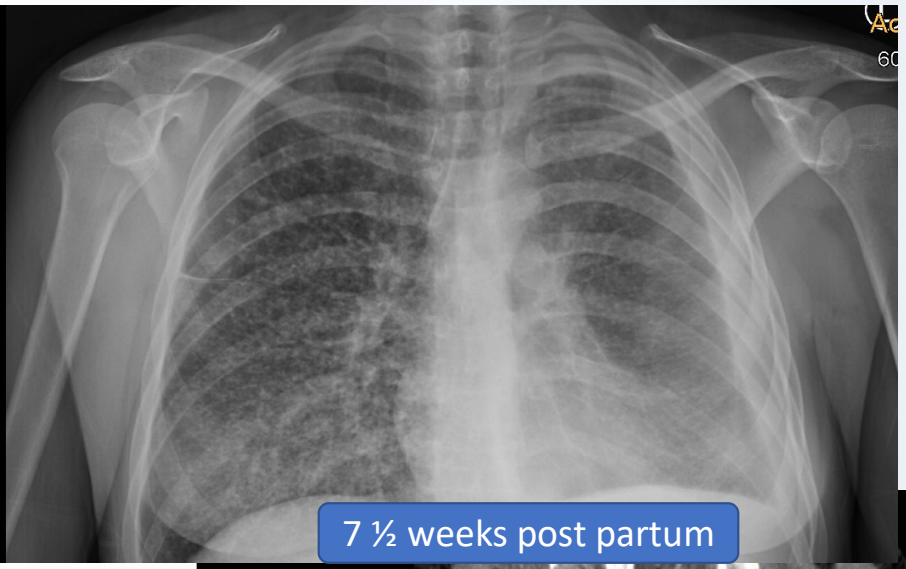




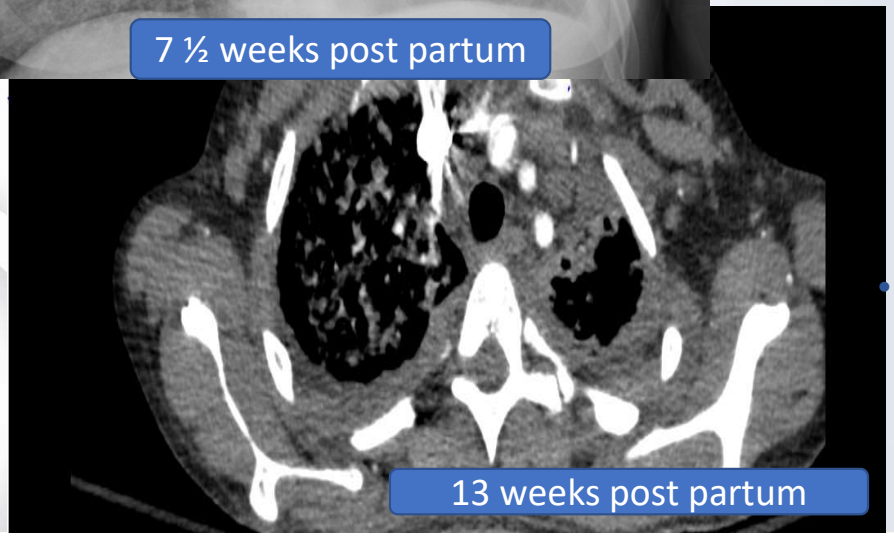
TB During Pregnancy and Postpartum

- **Pregnancy** is state of subtle immunosuppression
  - Physiological suppression of pro-inflammatory host responses that promote tolerance to fetal antigens
    - Increase in T regulatory cells (Treg) peaks in 2nd trimester then declines postpartum
    - Local immunoreactivity at maternal-fetal interface also shifts toward Th2 response
- **Postpartum**
  - Return to pro-inflammatory state: Th1 dominant response
- **TB in pregnancy is extrapulmonary in 5-10% of patients**
- **TB postpartum is extrapulmonary in 93% of patients;**
  - **69% central nervous system involvement** (Cheng - Eur J Clin Micro Inf Dis: 2003)

Postpartum



7 ½ weeks post partum



13 weeks post partum

- One month post partum history of fever, fatigue SOB, night sweats, rare cough, anemic, low albumin
  - **TST first trimester + 35 mm; now TST 00 mm**
- 6 weeks post-partum: SOB, Tachycardia, Fever, cough,

  Covid negative
- 7 weeks post partum: similar symptoms - now Covid +
- 13 weeks post partum: Admission – septic presentation, O_2 sat < 90%, T Spot +, AFB 4+ sputum and urine, albumin 1.7
- Arrested, CNS herniation
  - Sites involved: Lungs, lymph nodes, brain, adrenals, ascites, kidneys, heart (ejection fraction 35%), and positive blood culture
- **Unmasking IRIS**
  - **Non healing breast abscess still present at death**
  - **surgically addressed at delivery; cultures negative**

Treatment of non-HIV TB IRIS

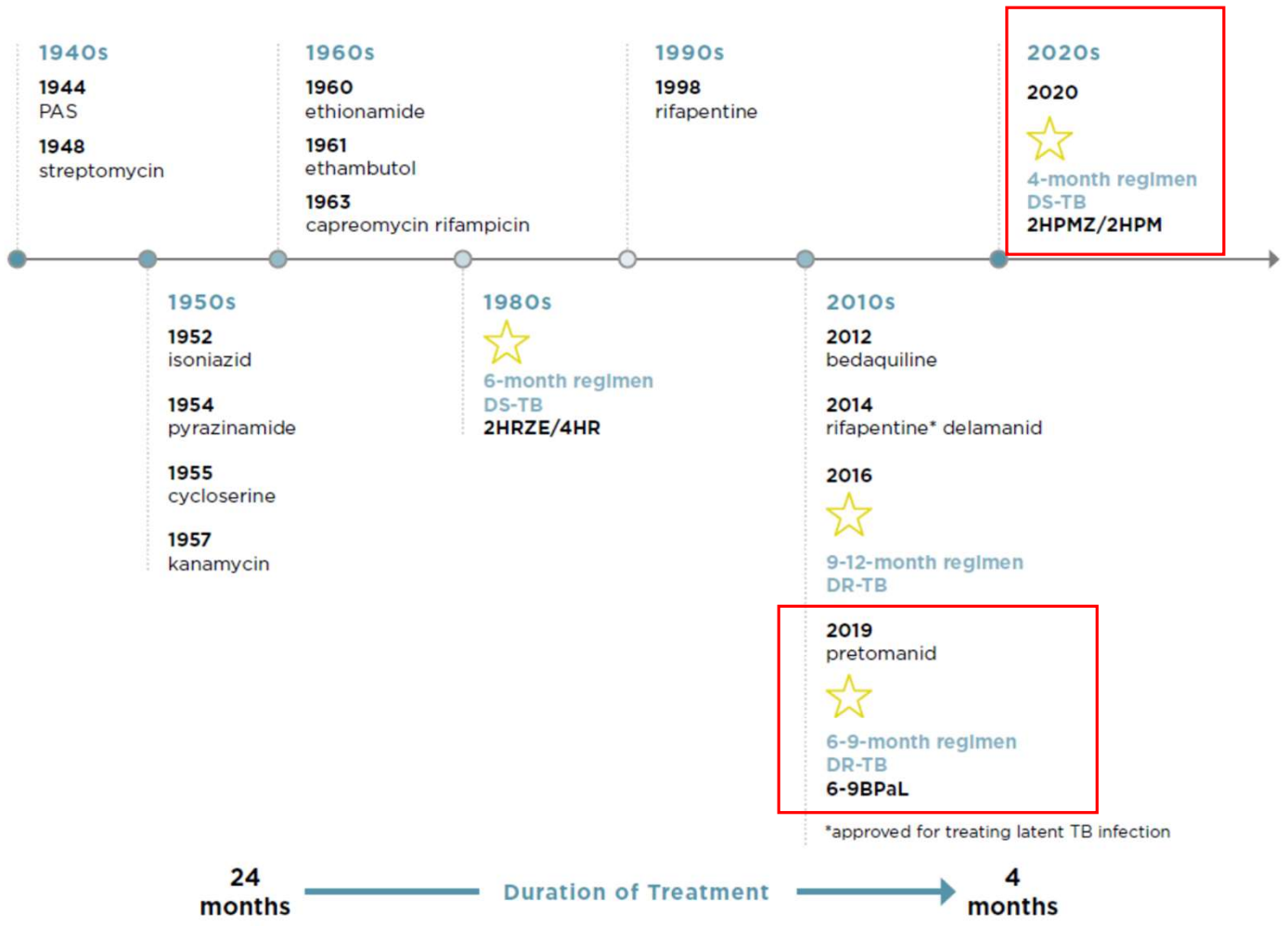
- No guidance available
- Based on patient's extent of disease, immune reaction and underlying illness
- Varies from observation to high dose steroids to TNF alpha inhibitors
- Duration of treatment – unknown
  - Individualized by patient

It has been a long time with the same treatment regimens.

Isn’t there a new, shorter option?

Study 31 Implementation – Important Considerations

FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES



https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/

Treatment shortening regimen – Drug Sensitive TB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

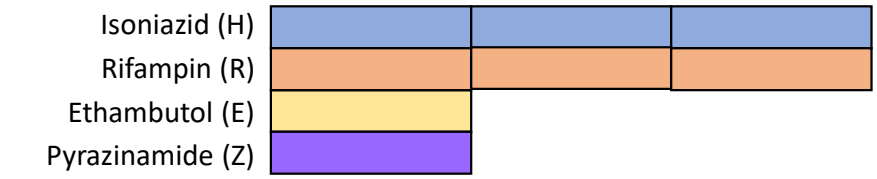
S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

2234 participants (194 PLHIV, 1703 with cavity on CXR)
Randomized 1:1:1 to 3 arms
Noninferiority study

N Engl J Med 2021;384:1705-18.

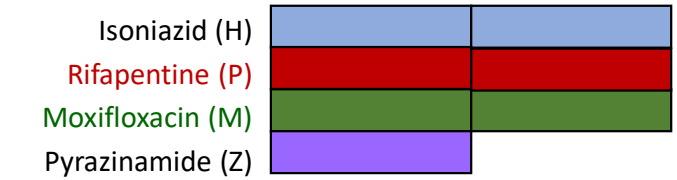
Study 31/A5349 (RPT-MOX)

Control
(2HRZE/4HR)



70 kg patient - 12 pills 4 pills

Control
(2HPZM/4HPM)



70 kg patient - 15 pills 11 pills

Safety and Efficacy Study 31/A5349

TABLE 1. EFFICACY AND SAFETY OUTCOMES IN S31/A5349

	EFFICACY		SAFETY	
Regimen	**Favorable outcomes**	**Unfavorable outcomes**	**Grade 3 or higher AEs**	**All-cause mortality**
Control (2HRZE/4HR)	90.4% (656/726)	9.6% (70/726)	19.3% (159/825)	0.8% (7/825)
RPT-MOX (2HPZM/2HPM)	88.4% (668/756)	11.6% (88/756)	18.8% (159/846)	0.4% (3/846)

TABLE 2. EFFICACY AND SAFETY OUTCOMES IN S31/A5349 AMONG PLHIV

	EFFICACY				SAFETY			
Regimen	**Favorable outcomes**		**Unfavorable outcomes**		**Grade 3 or higher AEs**		**All-cause mortality**	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Control (2HRZE/4HR)	84.7% (50/59)	90.8% (605/666)	15.3% (9/59)	9.2% (61/666)	21.4% (15/70)	19.1% (144/755)	2.9% (2/70)	0.7% (5/755)
RPT-MOX (2HPZM/2HPM)	91.4% (53/58)	88.1% (615/698)	8.6% (5/58)	11.9% (83/698)	13.9% (10/72)	19.3% (149/774)	0% (0/72)	0.4% (3/774)

https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/

Who It's For

- Recommended for
  - ≥ 12 y/o
  - ≥ 40 kg
  - Pulmonary TB
  - Not known or suspected to be drug-resistant
  - HIV (CD4 counts ≥100, receiving or going to receive efavirenz-based ART)
  - No significant drug-drug interactions

- NOT recommended for
  - < 12 y/o
  - < 40 kg
  - Pregnant or breastfeeding
  - Most extrapulmonary TB (think bone, CNS)
  - History of prolonged QT syndrome or QT-prolonging medications
  - Drug interaction or resistance to meds in the regimen (think *M. bovis,* any FQ)

https://www.cdc.gov/mmwr/volumes/71/wr/mm7108a1.htm

What's required

- Lab
  - Baseline assessment (microbiology, laboratory, clinical)
  - Respiratory specimen for AFB smear/culture (and monthly)
  - Molecular drug susceptibility testing followed by phenotypic DST
- Administration
  - Administered with food
  - 7 DAYS a WEEK (at least 5 days observed)
- Completion
  - 119 doses
  - 56 Intensive doses in 70 days
  - 63 Continuation doses in 84 days
  - 5 months to complete the whole regimen
  - Confirmation of continued drug susceptibility

https://www.cdc.gov/mmwr/volumes/71/wr/mm7108a1.htm

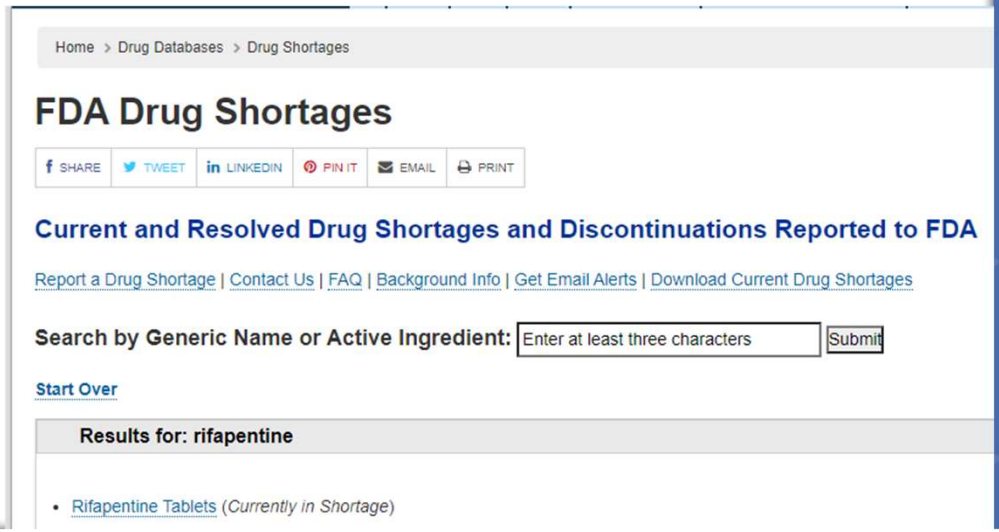
Might Want A Consult

- Consider a consultation if
  - In the past 6 months, patient has had
    - > 5 doses of treatment for TB disease
    - > 5 doses of treatment for TB infection
    - > 5 days of treatment with INH, rifampin, rifabutin, rifapentine, PZA or any FQ
  - Laboratory abnormalities at baseline
    - AST or ALT >3X ULN or total bili >2.5X ULN
    - Advanced liver disease
    - Renal insufficiency or end-stage renal disease (or creatinine >2X ULN)

https://www.cdc.gov/mmwr/volumes/71/wr/mm7108a1.htm

Challenges to Consider

- Pill burden
- Tolerability (versus safety, efficacy)
- Familiarity with the regimen
- EKG…?
- Rifapentine availability



Things we don't know

- What if all doses aren't completed in the required time?
- What if the patient is culture positive after ≥2 months of the 4 month regimen?
- What if the patient gets pregnant during the course of treatment?
- If the patient doesn't tolerate the treatment, can I give 'credit' for doses taken? What would that look like?

Is it MDR…XDR…IDK?

Changing the Definitions of Drug Resistant TB

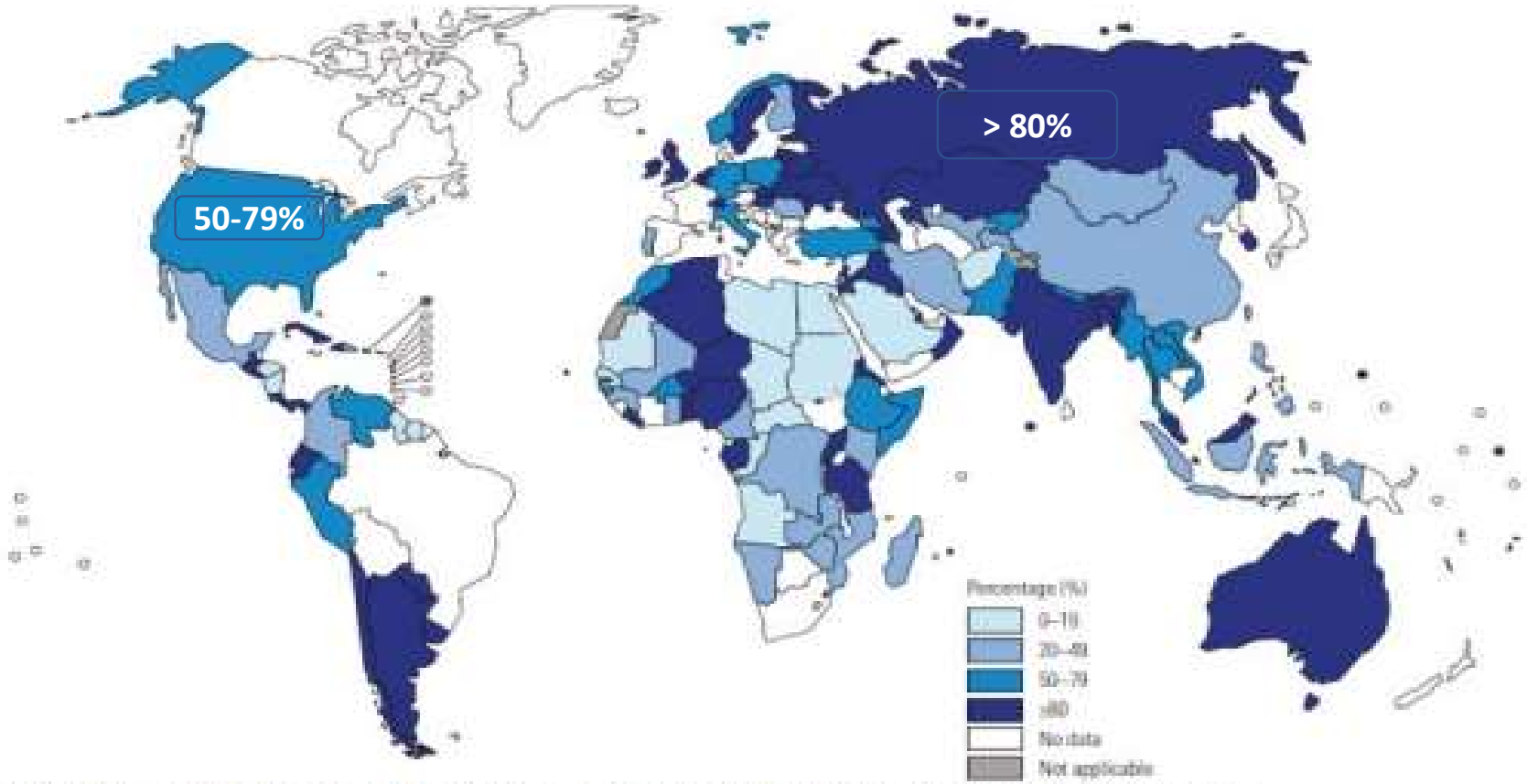
WHO and CDC 2021/2022

Why are Definitions Changing?

- Drug resistance increasing – simple MDR TB (INH/rifampin) less frequent
- New drugs that are stronger and less toxic
  - 2nd line injectable therapy has been discouraged by WHO and CDC
- Should support new diagnostics and therapeutics
  - Better, shorter, more well tolerated regimens
  - Implementation of molecular testing and DST for new medications (BDQ, Moxi, Linezolid, Delamanid, Pretomanid)
- Classifications should reflect groups with more serious disease, and which require different treatment regimens.

Fig. 1. Percentage of MDR/RR-TB cases tested for susceptibility to fluoroquinolones, 2019

Source: WHO, 2020.



MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; WHO: World Health Organization.

WHO Overarching Principals for New Definition of Drug Resistance

- **Simple:**
- **Measurable:**
- **Relevant to programs:**
  - Should signal a very serious form of TB and the need for such patients to have a regimen that is different from the regimen for patients with MDR-TB, or other less serious forms of DR-TB.
  - Should no longer include reference to injectable agents, given use is expected to be minimal in future
- **Future-proof:**
  - Accomplished by use of **"Group A"** drugs instead of specific drugs; allows new Group A drugs in the future.
    - **CDC definition includes linezolid and bedaquiline in place of Group A** designation; ignores delamanid and pretomanid and all future drugs

Grouping of medicines	Medicine
First line	RIF
	INH
	EMB
	PZA
Group A	LFX/
	MFX
	BDQ
	LZD
Group B	CFZ
	DCS
Group C	DLM
	IMP-CLN/
	MPM
	AMK
	STR
	ETO/
	PTO
	PAS

WHO consultation October 2020

WHO Terminology to Classify Drug Resistant TB

Old Terminology

- **Pre-XDR-TB:** No definition

- **XDR-TB: TB** that is resistant to any FQN and to at least one of three 2nd line injectable drugs (capreomycin, kanamycin and amikacin) in addition to multidrug resistance.

- * FQNs include levofloxacin and moxifloxacin.

January 2021: New Terminology

- **Pre-XDR-TB:** TB caused by M. tuberculosis strains that fulfill the definition of MDR/RR-TB and are also resistant to any fluoroquinolone*

- **XDR-TB:** TB caused by M. tuberculosis strains that fulfill the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone and **at least one additional Group A drug**.

-

- * FQNs include levofloxacin and moxifloxacin.

CDC Terminology to Classify Drug Resistant TB

OLD Terminology

- **Pre-XDR TB:** caused by an organism that is resistant to at least INH, rifampin, and a FQN **OR** by an organism that is resistant to INH, rifampin and a 2nd line injectable (amikacin, capreomycin and kanamycin)
- **XDR-TB:** caused by an organism that is resistant to INH, rifampin, a FQN, and a 2nd line injectable (amikacin, capreomycin and kanamycin)

Updated Terminology - January 2022

- **Pre-XDR TB:** caused by an organism that is resistant to at least INH, rifampin, and a FQN **OR** by an organism that is resistant to INH, rifampin and a 2nd line injectable (amikacin, capreomycin and kanamycin)
- **XDR-TB:** caused by an organism that is resistant to INH, rifampin, a FQN, and a 2nd line injectable **OR by an organism that is resistant to INH, rifampin, a FQN and BDQ or linezolid**

CDC Surveillance Definitions: XDR and pre-XDR Tuberculosis

- **January 18, 2022**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Centers for Disease Control and Prevention (CDC)

Memorandum

Resistance Classification	Drug Classes				
	Isoniazid & Rifampin	Fluoroquinolone (at least one)	Second-Line Injectable (at least one)	Bedaquiline	Linezolid
MDR TB	X				
Pre-XDR* TB	X		X		
	X	X			
XDR* TB	X	X	X		
	X	X		X	
	X	X			X

*Each row indicates one combination of drug resistance that meets the respective definition of pre-XDR or XDR TB.

If you have questions about this change or any other TB surveillance topic, please contact the DTBE Help Desk at 888-300-4261, ServiceNow or via email at DTBEsupport@cdc.gov. As always, we appreciate your dedicated efforts towards national TB surveillance. Please do not hesitate to contact us with any questions or concerns.

Key Differences between WHO and CDC Definitions

WHO

- RR/MDR
  - TB resistant to rifampin with or without INH resistance
- XDR-TB
  - RR/MDR plus also resistant to any FQN* and **at least one additional Group A drug**
  - * FQNs include levofloxacin and moxifloxacin.

CDC

- RR: not identified
- XDR TB
  - resistant to INH, rifampin, any FQN*, and **a 2nd line injectable OR by an organism that is resistant to INH, rifampin, a FQN and BDQ or linezolid**
  - * FQNs include levofloxacin and moxifloxacin

Thank you for being here.

Thank you for all that you do every single day.

You make a difference.