Biomarkers and New TB Diagnostics

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

Treatment monitoring biomarkers for patient-centered outcomes

Should culture matter so much…?

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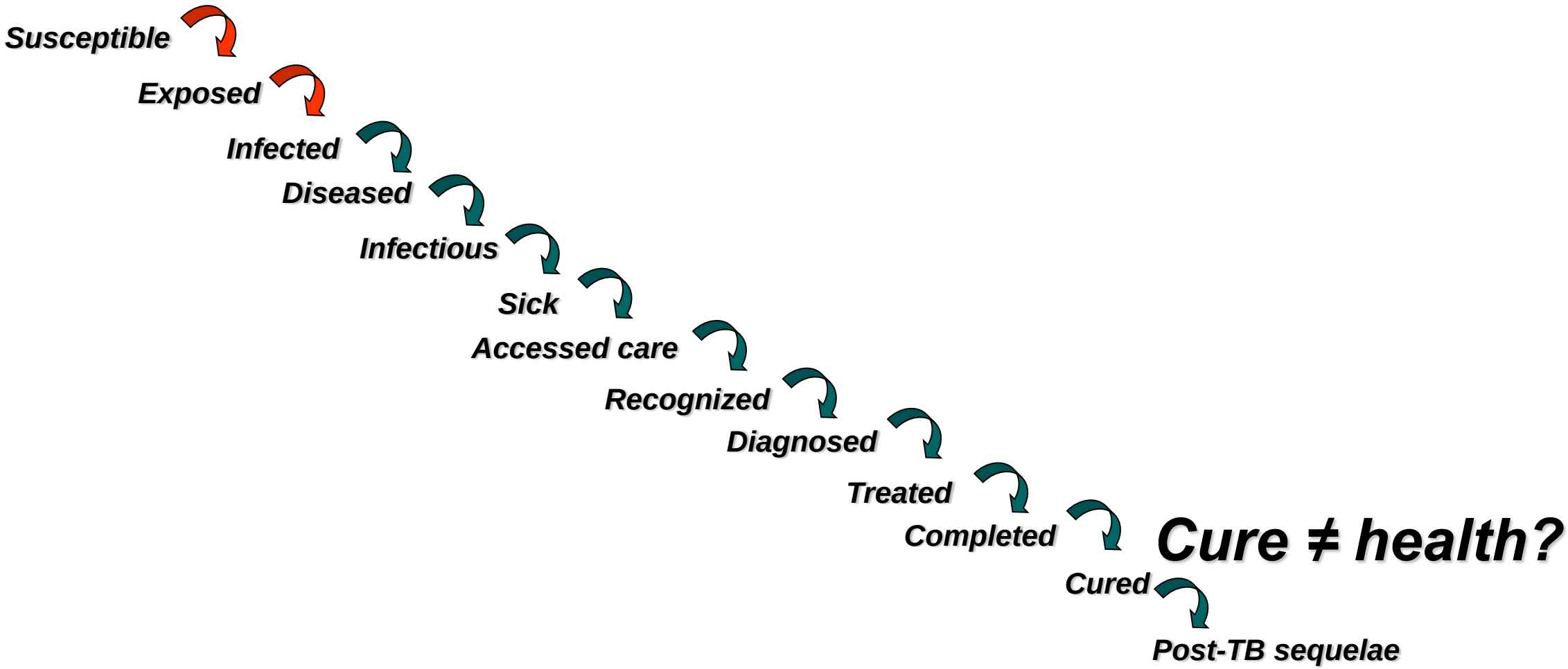
Prevention

Cascade of Care



Standard of Care (?) treatment Monitoring

Test	Limitations
Smear	LOD 5000 CFU/mL; nonviable organisms; 1882
Culture	42 day TAT
Symptoms	Paradoxical reactions
Albumin	Non-specific
Hemoglobin	Non-specific
Quantiferon	Non-specific
MBLA	Detects Mtb RNA; Predicts clinical relevant outcomes?

* Molecular Bacterial Load Assay

What should we be Monitoring?

Test	Implementation
Viable bacilli	Necessary but not sufficient for health; MBLA
Deadness	Not currently assessed
Cardiovascular	Not currently assessed
Respiratory	Rollout occurring
Cancer	Not currently assessed
Relapse risk	No *good* treatment monitoring tools
Well-being	SGRQ; 6 MWT

Viable organisms: 1882 vs 2025

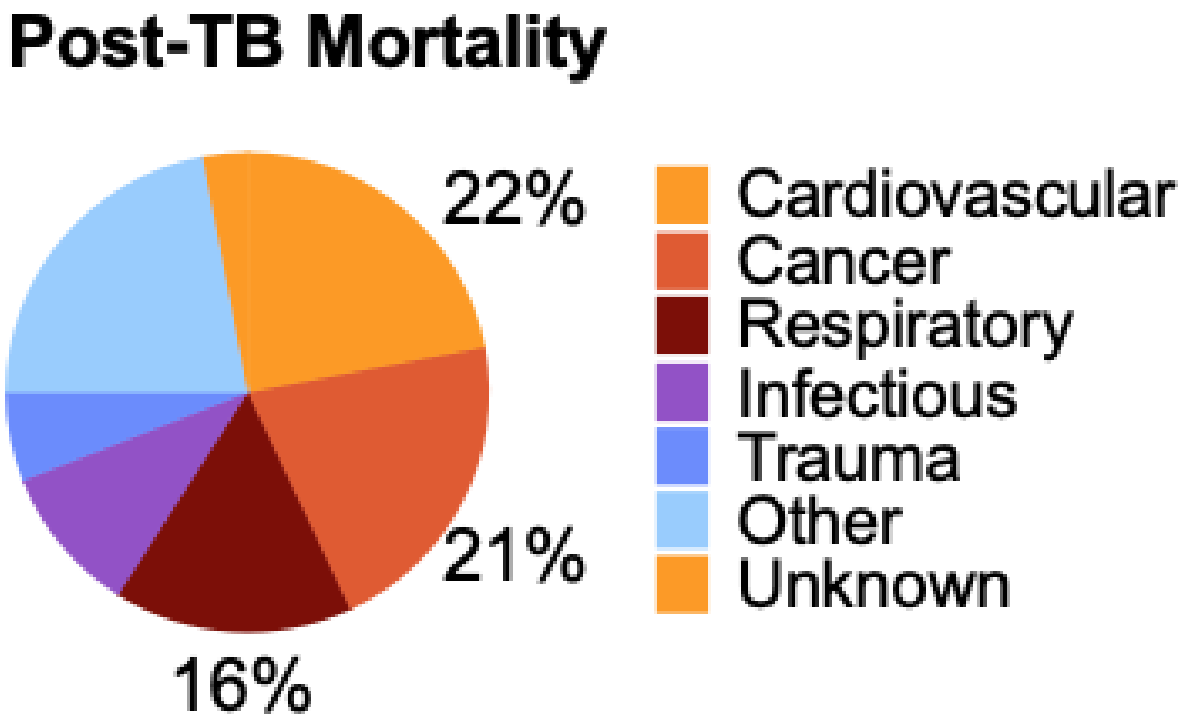
- 1882 option: culture w pDST
  - 6 – 12 week TAT
  - Costs: $50 - $500

- 2025 option: MBLA w tNGS
  - qPCR similar to Xpert
  - Detects Mtb RNA; 2-3 hr TAT
  - $20-50
  - tNGS: gDST in 2 day TAT for <$100

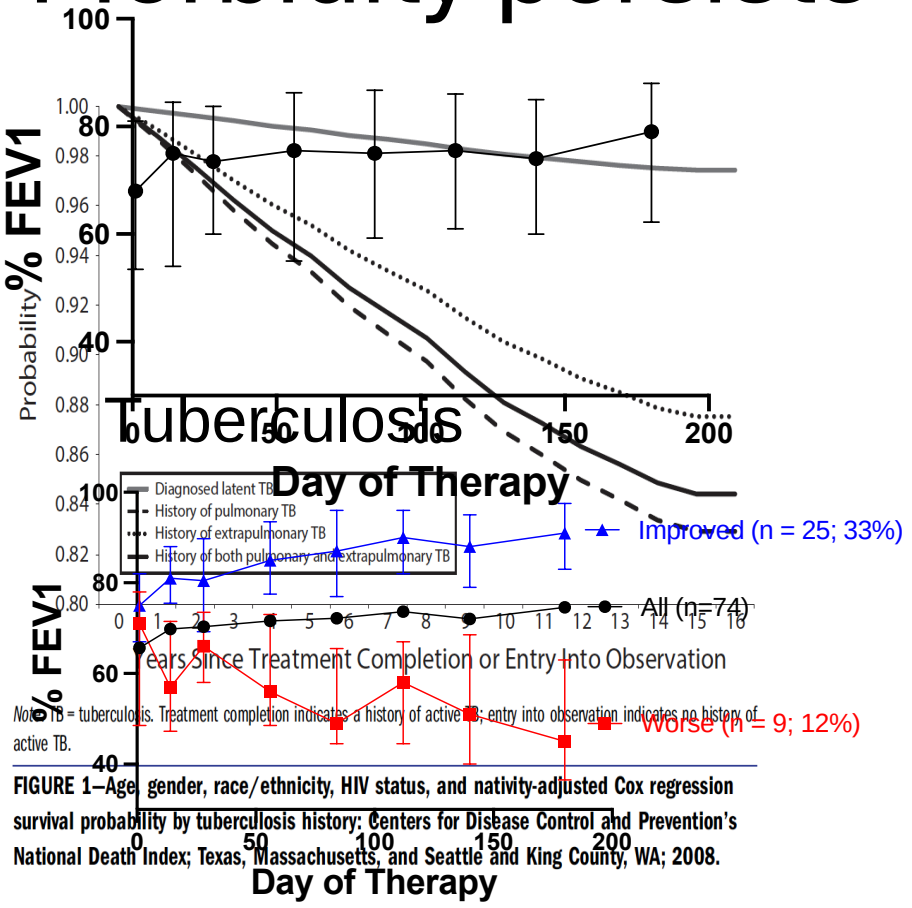
Molecular Bacterial Load Assay (MBLA)

Killing Viable organisms ≠ synonymous with improved health

Mortality risk



Morbidity persists

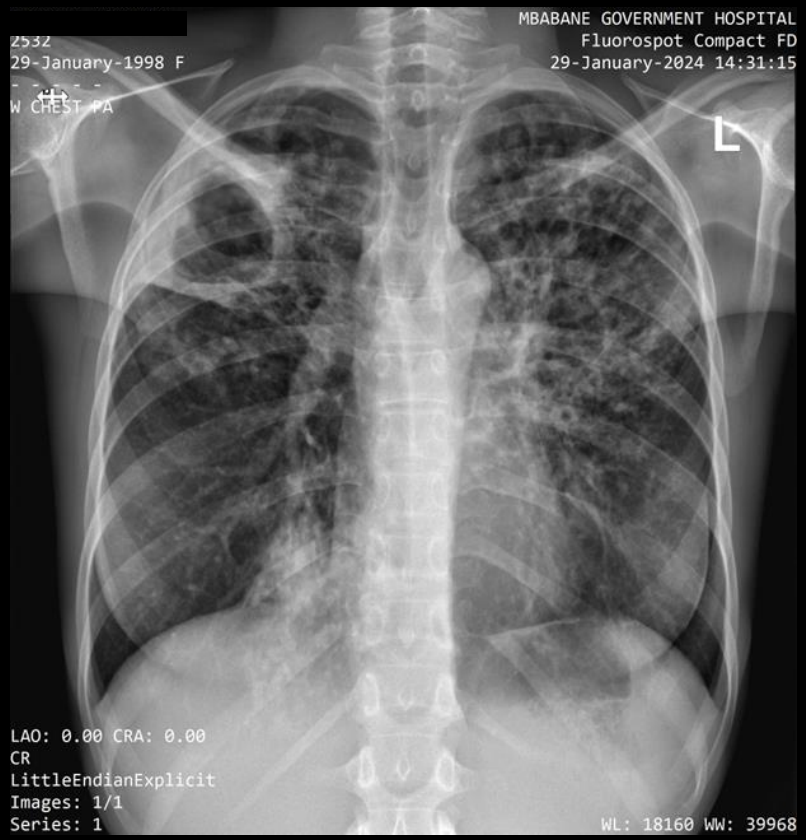


Baseline

Test1 2024-01-09 10:28

Parameter	Best	LLN	Z-sc.	%Pred
FVC[L]	4.76	3.22	1.21	115.8
FEV1[L]	3.59	2.62	0.40	105.6
FEV1/FVC	0.75	0.73	-1.17	
FEF2575[L/s]	3.68	1.90		104.9
PEF[L/s]	6.96	--		--
FET[s]	10.99			
FIVC[L]	4.11	3.22		100.1
PIF[L/s]	5.01	--		--

FEV1 Var = 247mL 6.9%, FVC Var = 774mL 16.3%
Test quality FEV1 - D, FVC - E
Normal spirometry

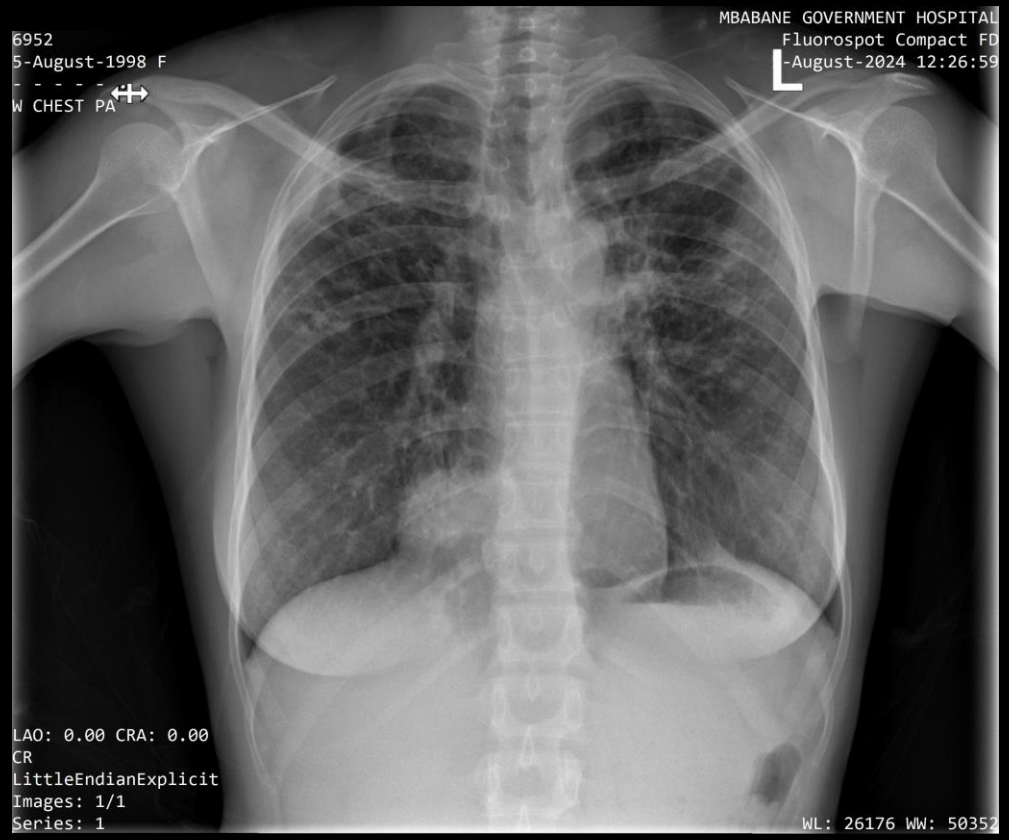


EOT

Test1 2024-07-16 10:45

Parameter	Best	LLN	Z-sc.	%Pred
FVC[L]	4.26	3.21	0.30	104.0
FEV1[L]	3.67	2.61	0.59	108.3
FEV1/FVC	0.86	0.72	0.56	
FEF2575[L/s]	4.46	1.88		127.6
PEF[L/s]	6.71	--		--
FET[s]	6.64			
FIVC[L]	4.13	3.21		100.7
PIF[L/s]	5.56	--		--

FEV1 Var = 48mL 1.3%, FVC Var = 129mL 3.0%
Test quality FEV1 - A, FVC - A
Normal spirometry



Baseline

Parameter	Best	LLN	Z-sc.	%Pred
FVC[L]	4.83	3.00	1.52	122.2
FEV1[L]	LLN 2.07	2.32	-2.15	66.0
FEV1/FVC	LLN 0.43	0.69	-5.72	
FEF2575[L/s]	LLN 0.46	1.12		15.4
PEF[L/s]	LLN 4.31	4.88		57.0
FET[s]	16.31			
FIVC[L]	3.84	3.00		97.2
PIF[L/s]	3.91	--		--

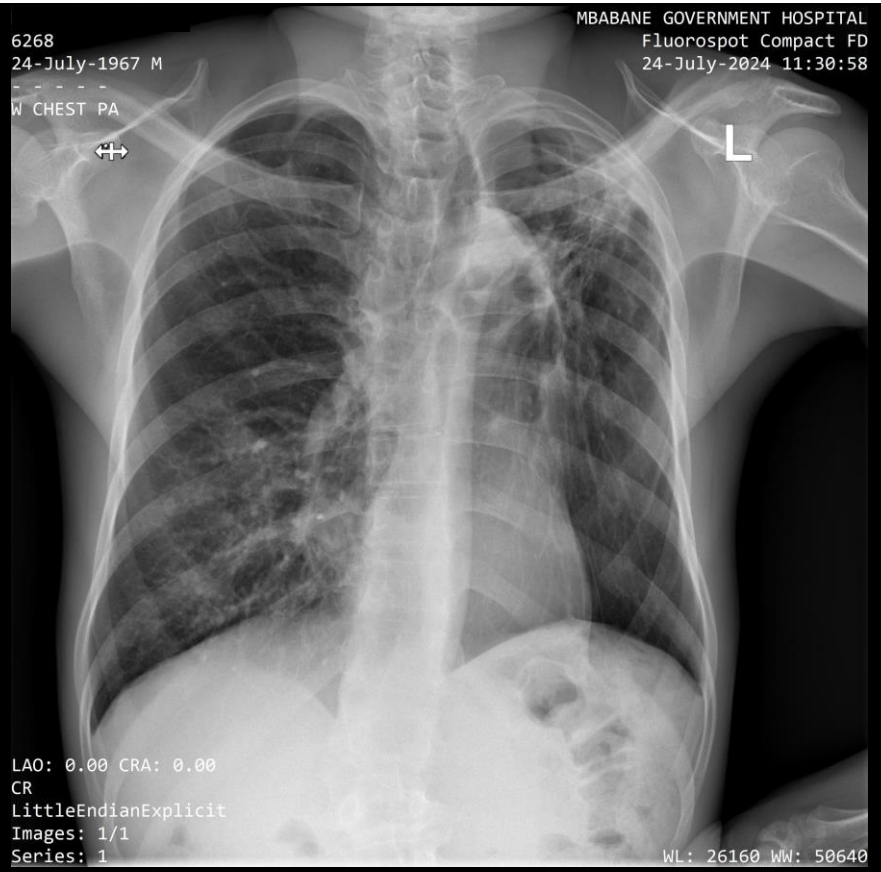
FEV1 Var = 34mL 1.6%, FVC Var = 503mL 10.4%
Test quality FEV1 - A, FVC - E
Moderate obstruction

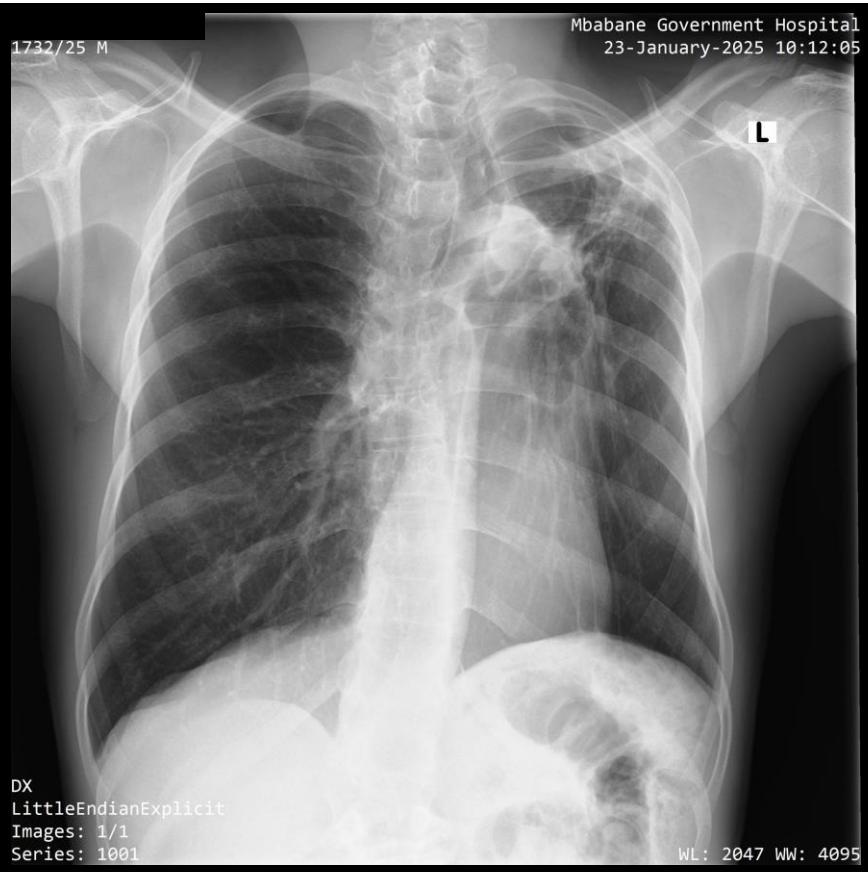
EOT

Parameter	Best	LLN	Z-sc.	%Pred
FVC[L]	5.31	2.92	3.38	143.4
FEV1[L]	2.32	2.24	-1.48	78.1
FEV1/FVC	LLN 0.44	0.67	-5.09	
FEF2575[L/s]	LLN 0.26	1.90		8.0
PEF[L/s]	LLN 5.27	6.01		70.4
FET[s]	16.22			
FIVC[L]	4.10	2.92		110.7
PIF[L/s]	3.64	--		--

FEV1 Var = 81mL 3.5%, FVC Var = 821mL 15.5%
Test quality FEV1 - A, FVC - E
Moderate obstruction

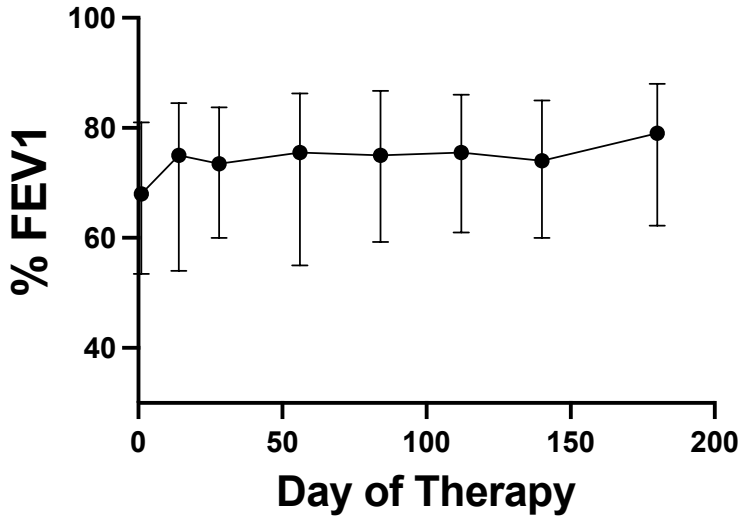
No improvement

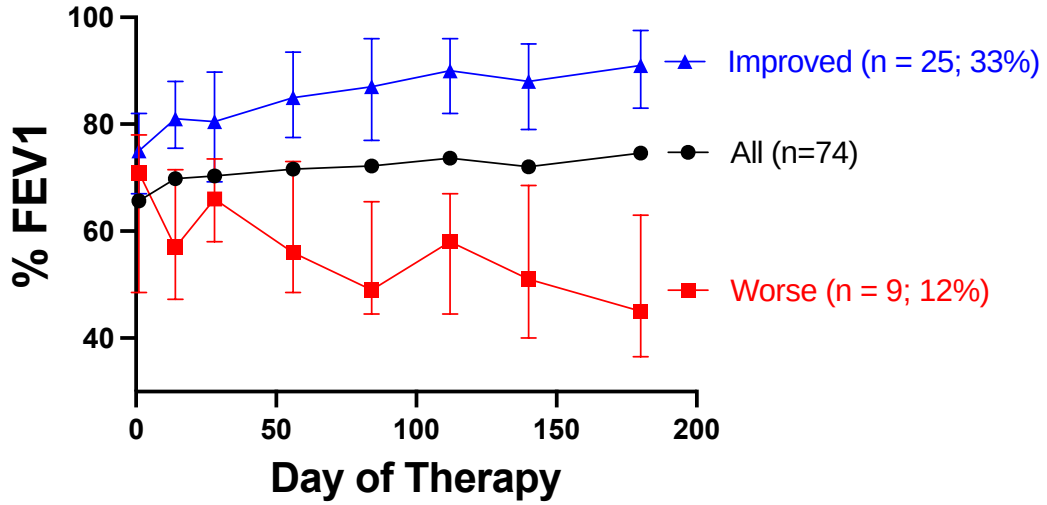




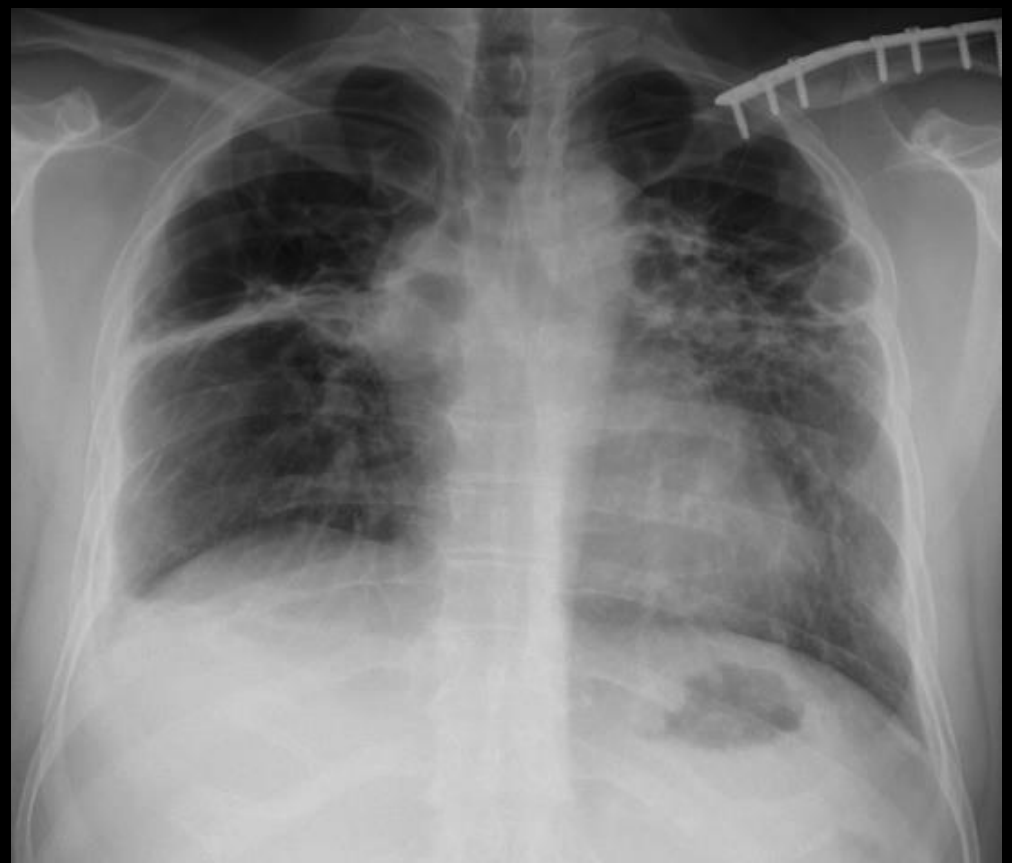
“Paradoxical” worsening

*Plitt 1999

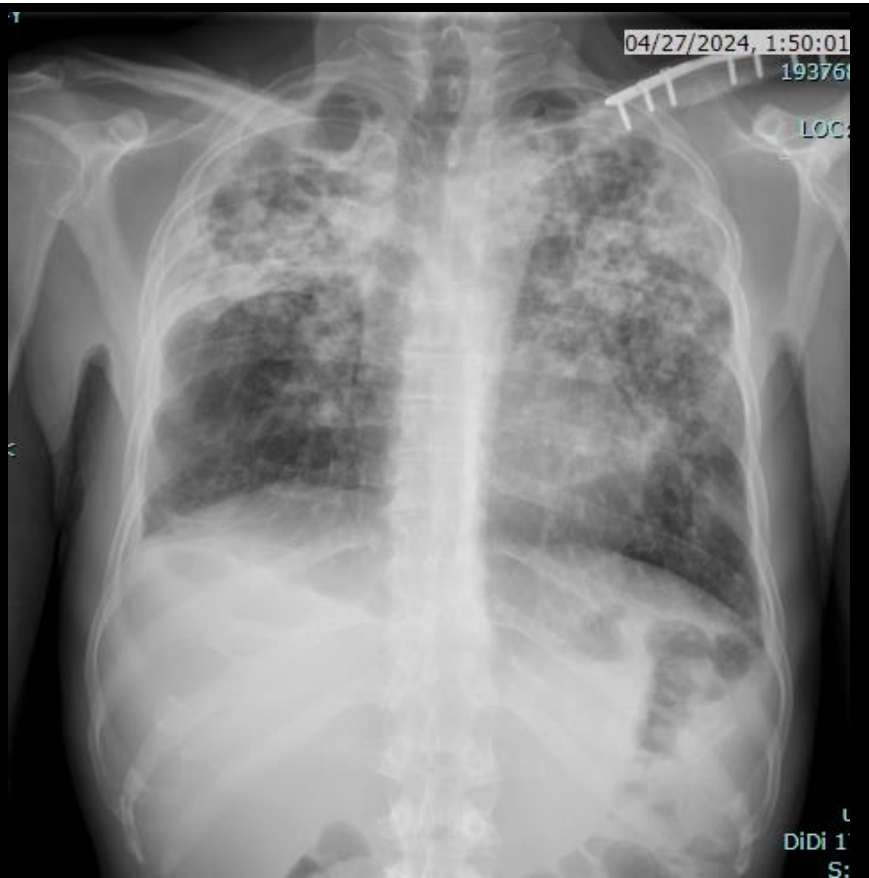




Baseline



2-Months



Treatment Monitoring for Lung Damage?

Molecular Pathology

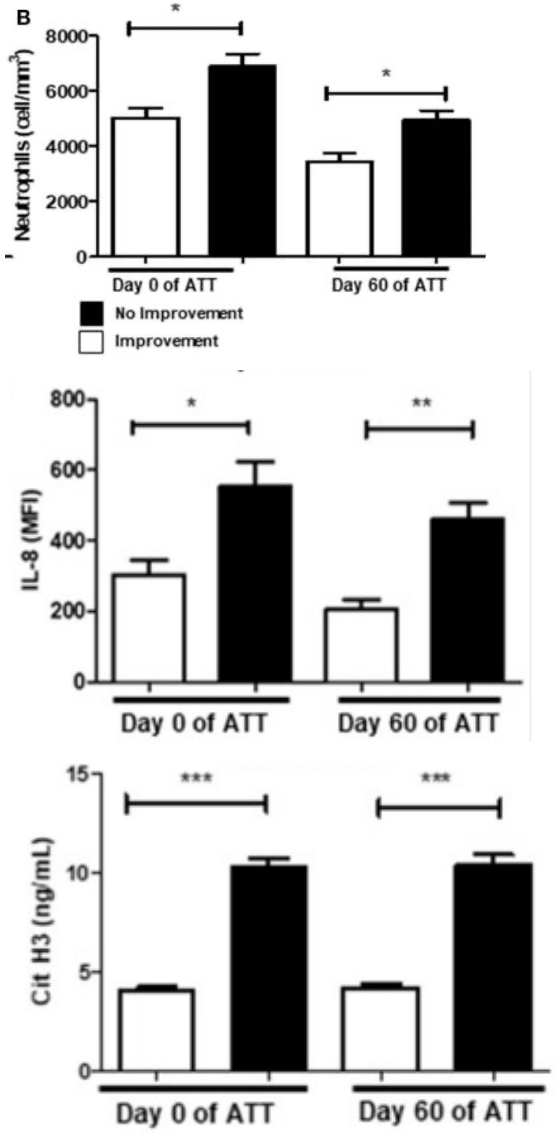
- NETosis
- Fibrosis

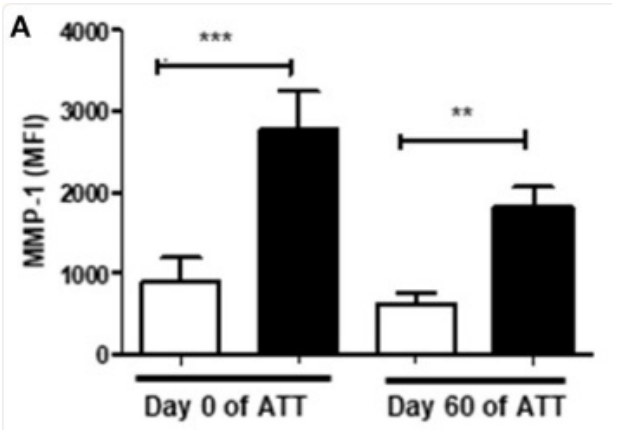
Histopathology

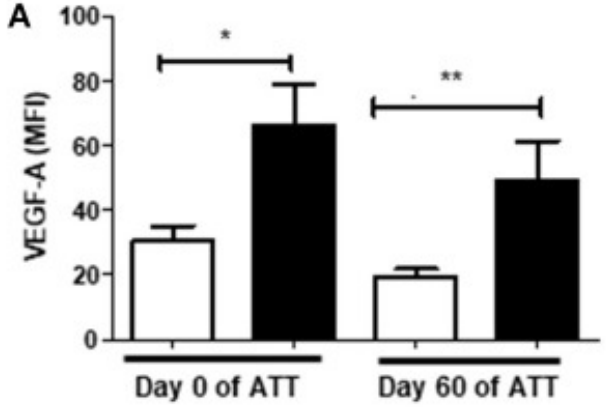
- Fibrosis
- Cavitation
- Bronchiectasis

Spirometry

- Obstructive
- Restrictive







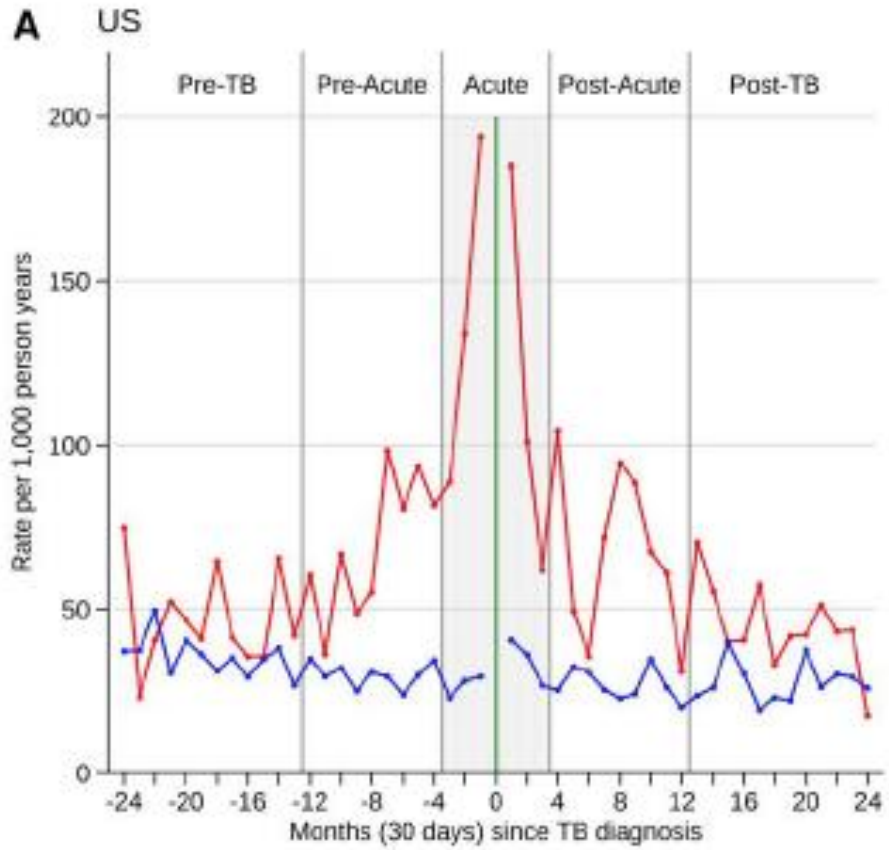
De Melo 2019;

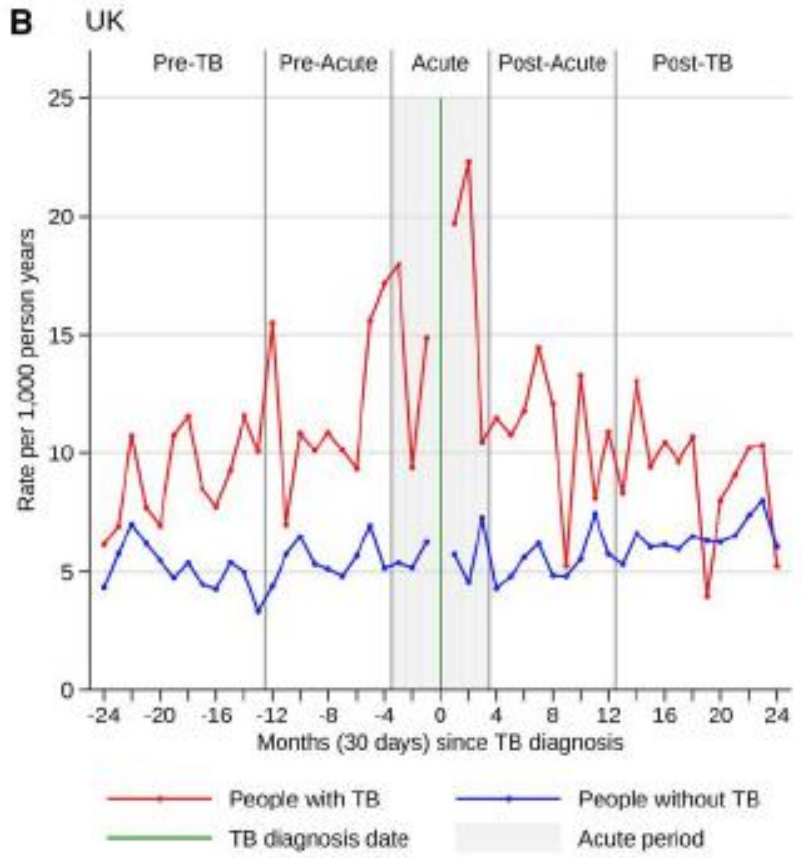
Post-TB assoc Cardiovascular Disease

2-3 fold increase risk before, during, and after TB

Why?

Biology?

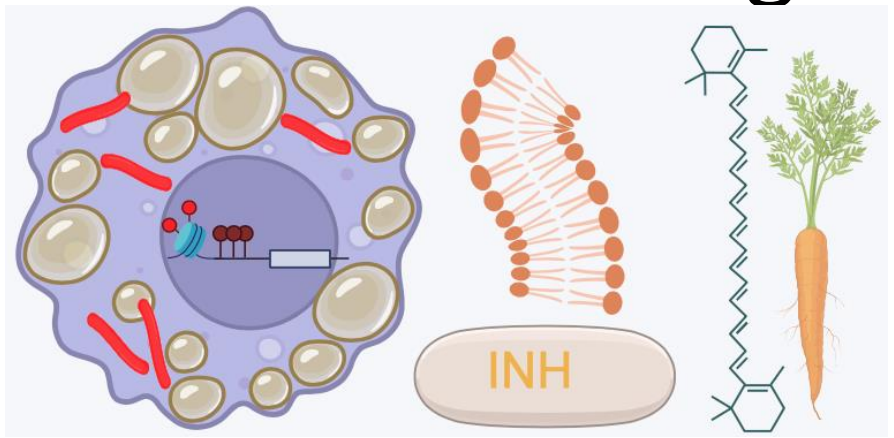


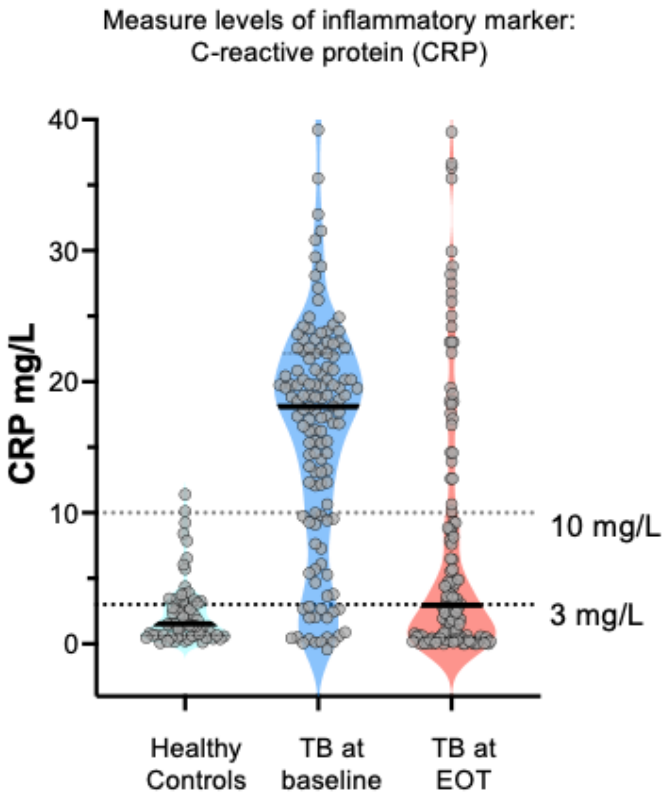


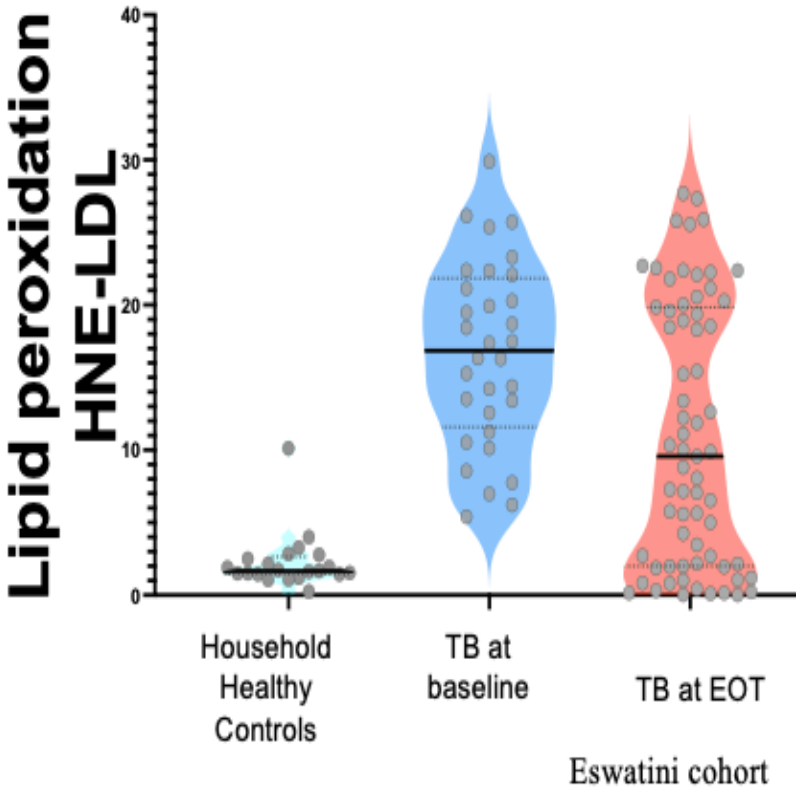
Critchley 2024

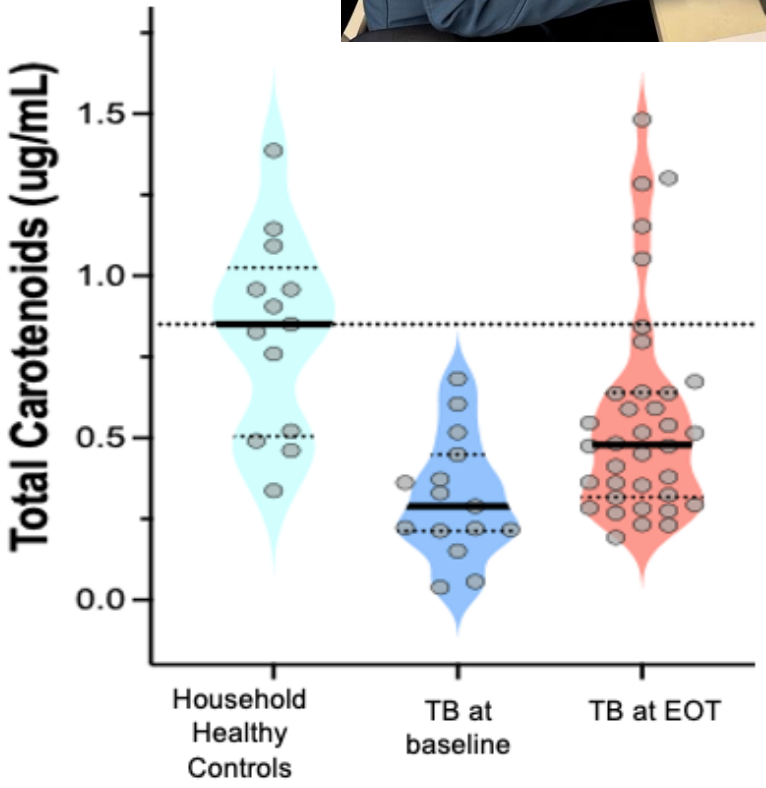
Evidence for Biomarkers for TB assoc. Cardiovascular Disease?

Lipid peroxidation driving CVD?





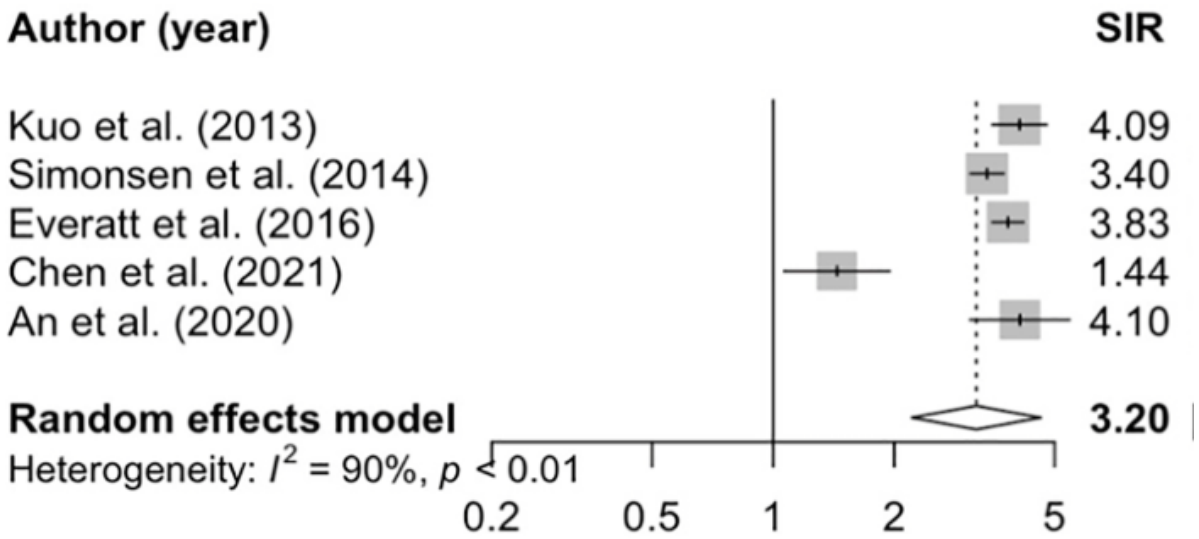


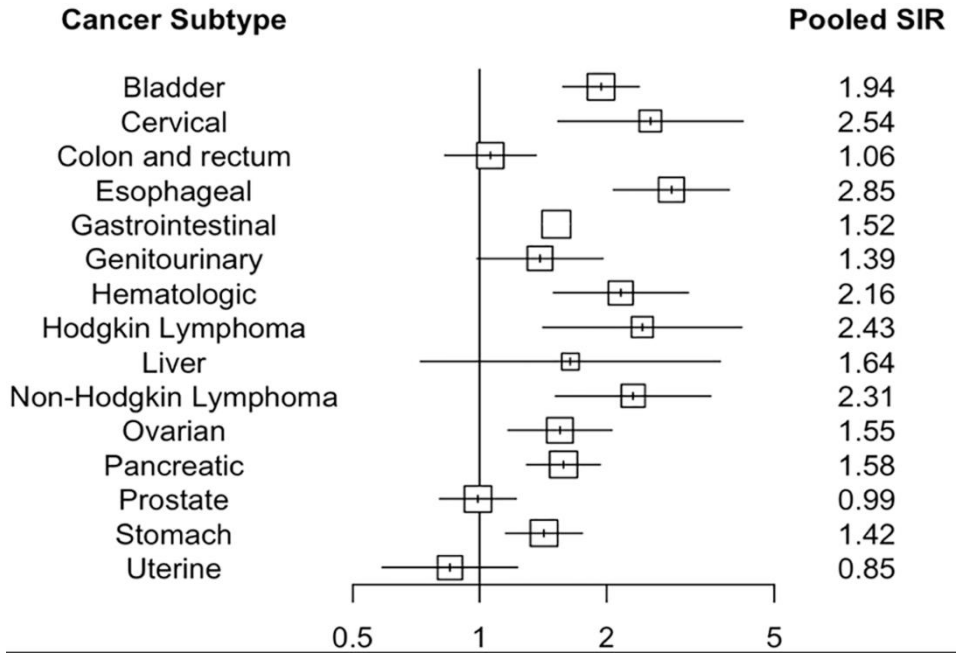


Post-TB assoc. Cancer

Time Post-TB	Pooled SIR (95% CI)
<1 yr	16.2 (8.6-30.7)
1-5 Yrs	3.0 (2.1 – 4.2)
> 5 Yrs	1.7 (1.3-2.3)
Overall	1.6 (1.3-1.9)

Lung Ca: SIR 3.2





Luczynski, Romanowski, Johnson, 2022

Evidence for Biomarkers for TB assoc. Cancer?

Potential mechanisms for post-TB Cancer

- Epigenetic changes
- Clonal hematopoiesis
- Infection induced anergy
- Oncoprotein upregulation
- Chronic inflammation

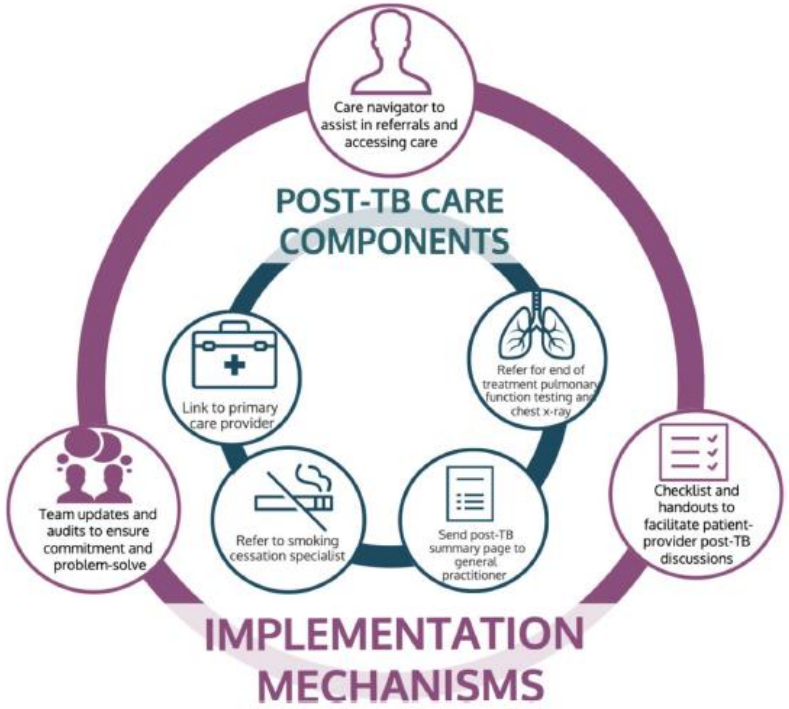
Reference	Mechanisms of Carcinogenesis	Cancer Sites	Infectious Agents
(17,19)	Chronic Direct and carcinogens inflammation	Hepatocellular carcinoma	HBV
(26)	Chronic inflammation	Hepatocellular carcinoma	HCV
(34,36)	Direct carcinogens	Burkitt's lymphoma, Nasopharyngeal carcinoma and Hodgkin lymphoma	EBV
(43)	Direct carcinogens	Carcinoma of cervix, vulva anus, oral cavity	HPV
(49)	Immune suppression	Kaposi sarcoma, non-Hodgkin lymphoma, carcinoma of the cervix	HIV
(52,56)	Chronic inflammation	Adenocarcinoma and lymphoma	H.pylori
(58)	Chronic inflammation	Colorectal cancer	S. bovis

Table 1: **Post-TB morbidity and mortality etiologies.**

Morbidity	Hazard (HR) or Incidence Rate ratio (IRR)	Putative biomarkers
Lung Dys-function	34-74% of TB survivors have abnormal spirometry [1, 2] By PET-CT, >80% of microbial cured TB survivors have persistent lung inflammation [4, 5].	IL-6,[6] TNF, CRP,[7] CXR[8], TGF-β[9], MMP-1,[10, 11] IL-1β[11], VEGF,[12] IL-8, cit-H3,[13]
Cardio-vascular disease	Compared to those without TB, people with TB have an IRR of 2.7-3.5 [14] Survivors of TB have a HR of 2.0 above controls without TB [15]	No existing studies have evaluated CVD-specific biomarkers associated with TB.
Cancer	Within first year of TB, SIR 4.7 (95% CI 1.8-12.2) for all cancers and 16.2 (CI 8.6-30.7) for lung cancer [16]	No existing studies have evaluated cancer specific biomarkers associated with TB
TB relapse	Relapse rate of 2.26 per 100 person years of follow up.[17]	IL6,[18] CXCL10,[19] IL-1β,[19]

How does Texas help close the gap in treatment monitoring?

- Continue follow up for10 years
- Universal roll-out of lung function evaluation as SOC
- TX-specific post-TB care package



RESEARCH Open Access

Using a theory-informed approach to guide the initial development of a post-tuberculosis care package in British Columbia, Canada

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Thank you…