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CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

Reducing TB Mortality - What's priority?

AWACC, 30 October 2026

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UNIVERSITY of the WESTERN CAPE

Overview of presentation

- **Burden of TB mortality**
- Progress against the END TB Targets: 2026 Status update
- Unpacking TB mortality in SA health care settings
- Scientific advances for TB prevention, diagnosis & treatment
- Closing the implementation gap - what's priority?
- Conclusions and summary

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The perfect storm: TB & HIV

HIV

Globally
- 1.3 million new cases
- 630 000 deaths
- 25% of deaths due to TB

Africa
- 66% of new cases
- 390 000 deaths

South Africa
- 160 000 new cases
- 45 000 deaths

TB

Globally
- 10.7 million new cases
- 1.23 million deaths
- 12% of deaths in PLWHA

Africa
- 2.62 million new cases
- 423 000 deaths

South Africa
- 249 new cases
- 54 000 deaths
- 29000 (PLWHA) vs 25000 (HIV−)

DR-TB

Globally
- 390 000 new cases
- 150 000 deaths
- 20% of recurrent TB

Africa
- 57 000 new cases
- 40-55 000 deaths

South Africa
- 14 000 new cases
- 3 000 deaths

SA: 70% of deaths due to TB

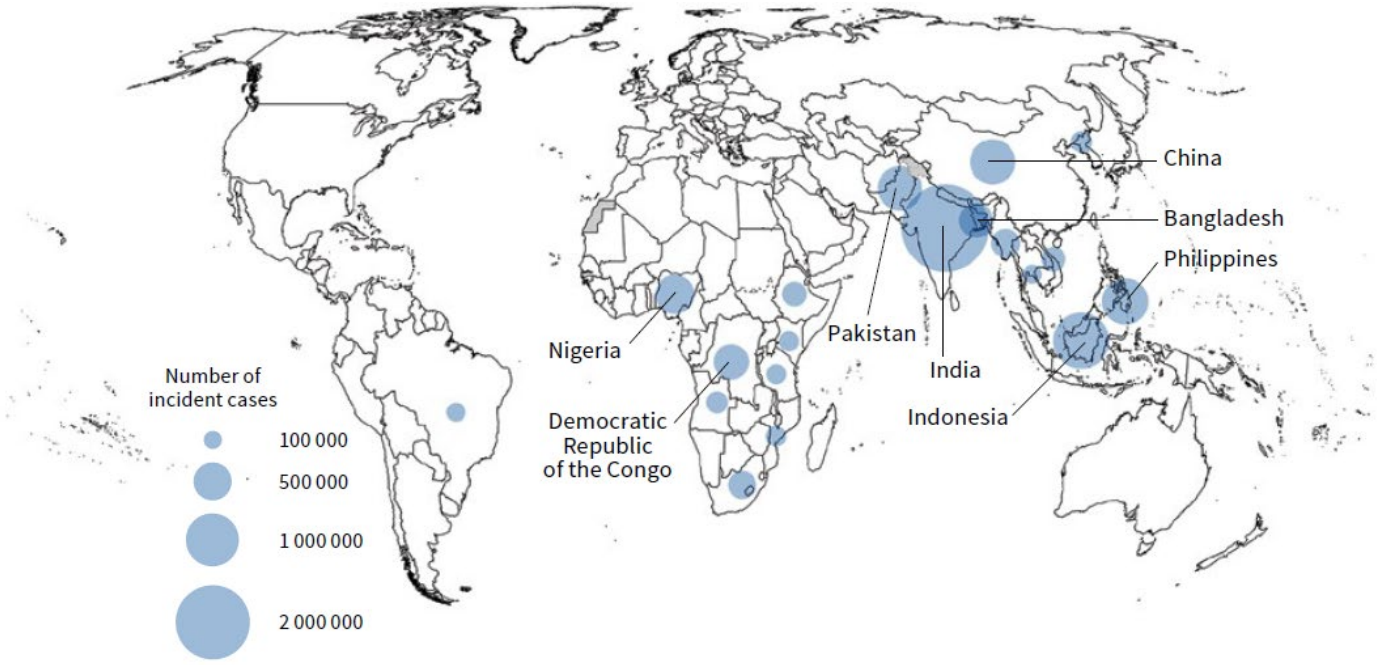
~53% of deaths in PLWHA

70% of deaths in PLWHA

Source: Global TB Report 2025

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Globally, eight countries account for 67% of TB



Country	Prop of Global TB Burden	HIV Prevalence
India	25%	3rd
Indonesia	10%	7th
The Philippines	6.8%	5th
China	6.5%	2nd
Pakistan	6.3%	8th
Nigeria	4.8%	4th
DRC	3.9%	6th
Bangladesh	3.6%	9th
South Africa	2.3%	1st

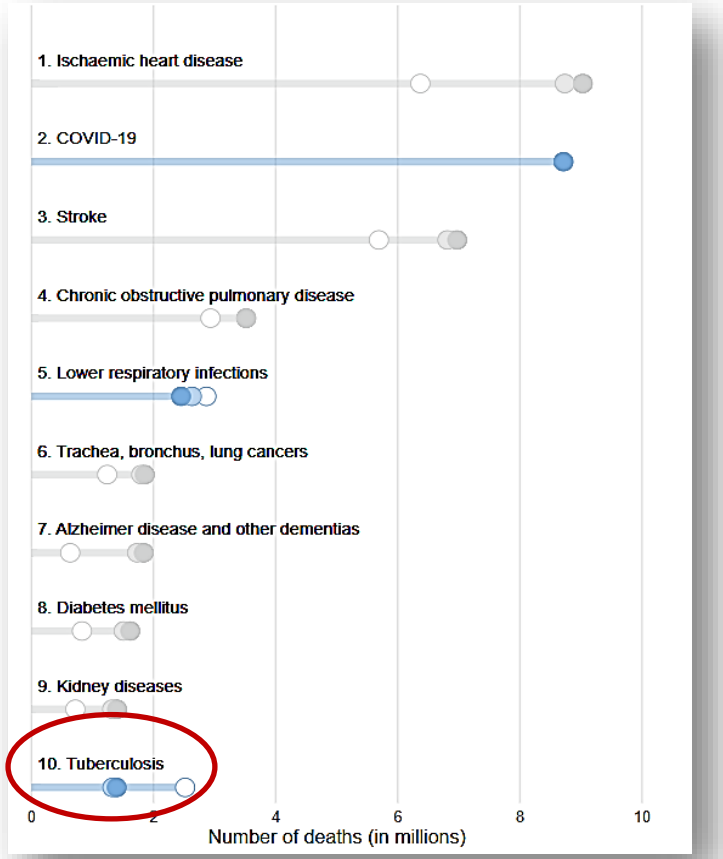
- 5.3% of all incident cases of TB occurred in PLWHA
- Co-infection highest in SA, approximately 59%

Source: Global TB Report 2025

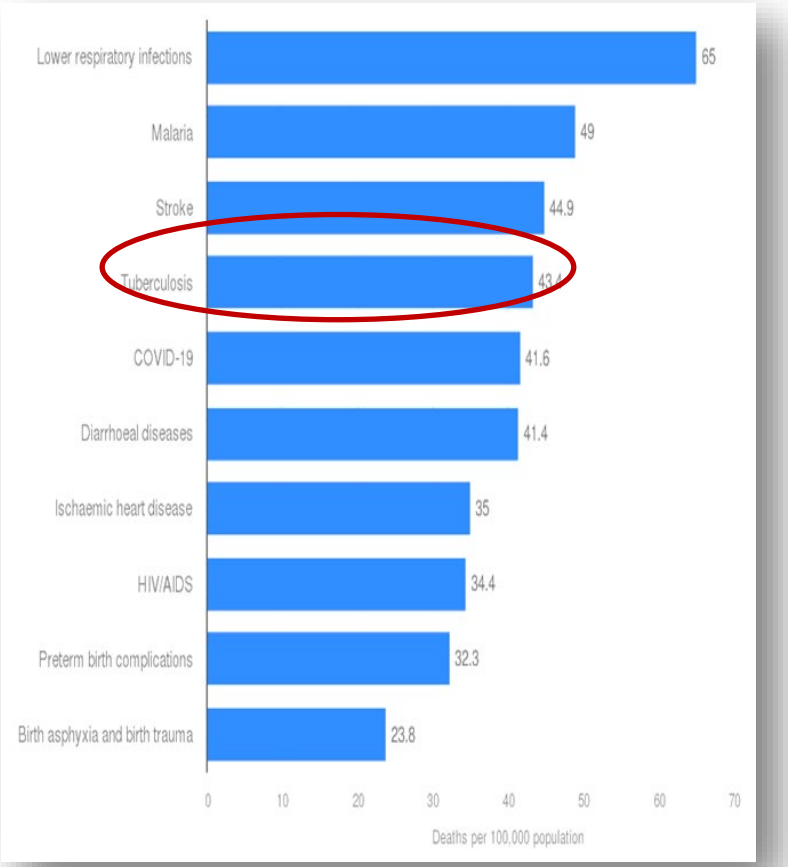
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Why sustain the momentum to end TB?

Global leading cause of death



Africa leading cause of death



Source: World Health Organization, Data, 2021

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TB mortality in SA in 2024

The ten leading underlying natural causes of death, 2022–2024*

Causes of death (ICD-10)	2022			2023			2024		
	Rank	Number	%	Rank	Number	%	Rank	Number	%
Diabetes mellitus (E10-E14)	1	33 126	6,7	1	27 967	5,8	1	28 767	6,1
Hypertensive diseases (I10-I15)	2	31 502	6,4	3	25 286	5,2	2	25 972	5,5
Cerebrovascular diseases (I60-I69)	3	29 084	5,9	2	25 844	5,3	3	25 539	5,4
Tuberculosis (A15-A19)	5	20 715	4,2	4	20 472	4,2	4	18 666	3,9
Human immunodeficiency virus [HIV] disease (B20-B24)	4	21 109	4,3	5	19 406	4,0	5	18 025	3,8
Influenza and pneumonia (J09-J18)	7	19 913	4,0	6	14 710	3,0	6	14 959	3,2
Other forms of heart disease (I30-I52)	6	20 513	4,2	7	14 211	2,9	7	14 059	3,0
Ischaemic heart diseases (I20-I25)	9	13 268	2,7	8	13 547	2,8	8	13 351	2,8
Chronic lower respiratory diseases (J40-J47)	10	11 993	2,4	10	12 090	2,5	9	12 081	2,5
Other viral diseases (B25-B34)	8	13 296	2,7	9	13 375	2,8	10	11 945	2,5
Other Natural		213 252	43,2		231 650	47,9		228 131	48,1
Non-natural		66 129	13,4		64 740	13,4		62 871	13,3
All causes		**493 900**	**100,0**		**483 298**	**100,0**		**474 366**	**100,0**

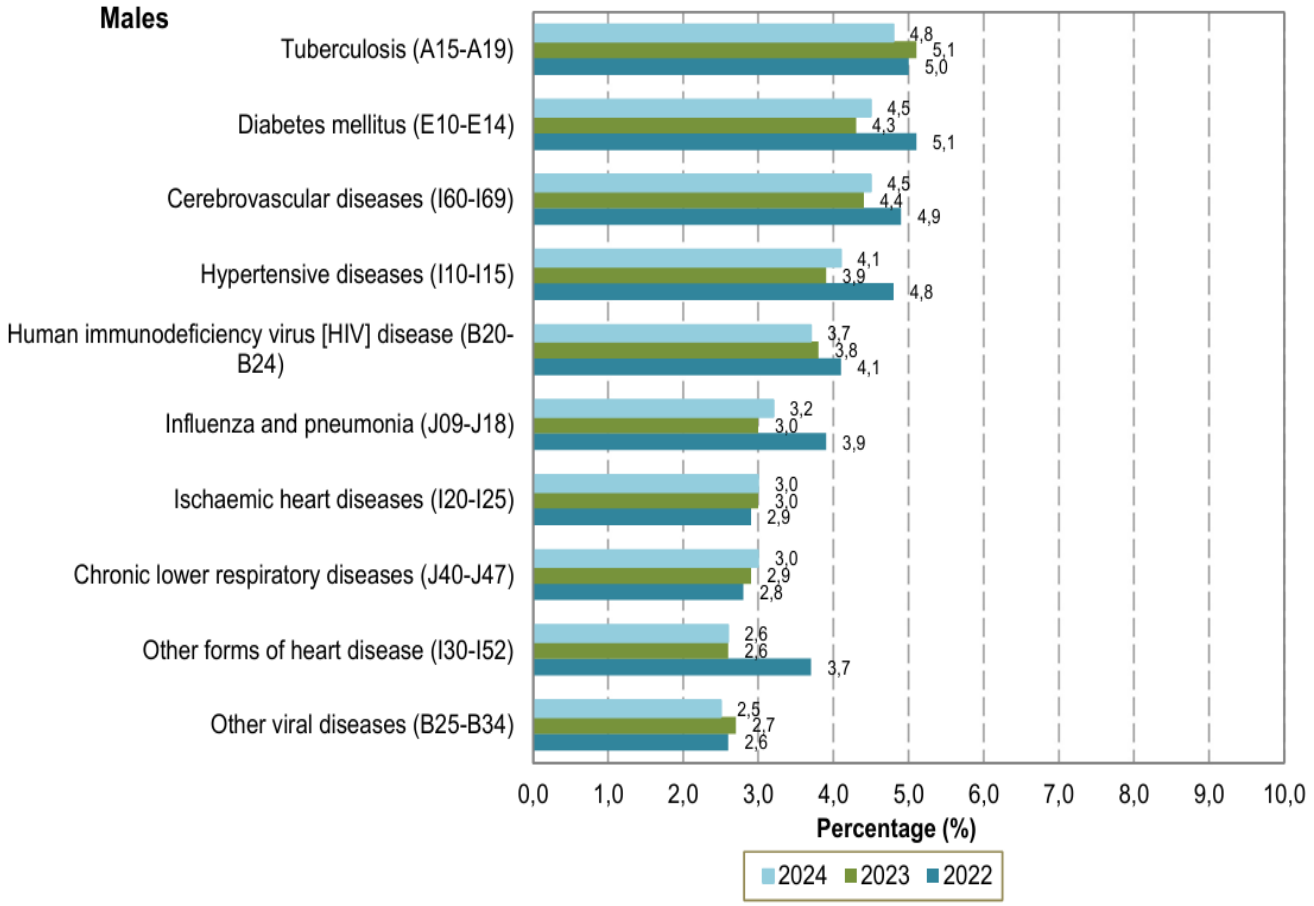
*Data from 2022–2023 have been updated with late registrations/delayed death notification forms processed in 2025/2026

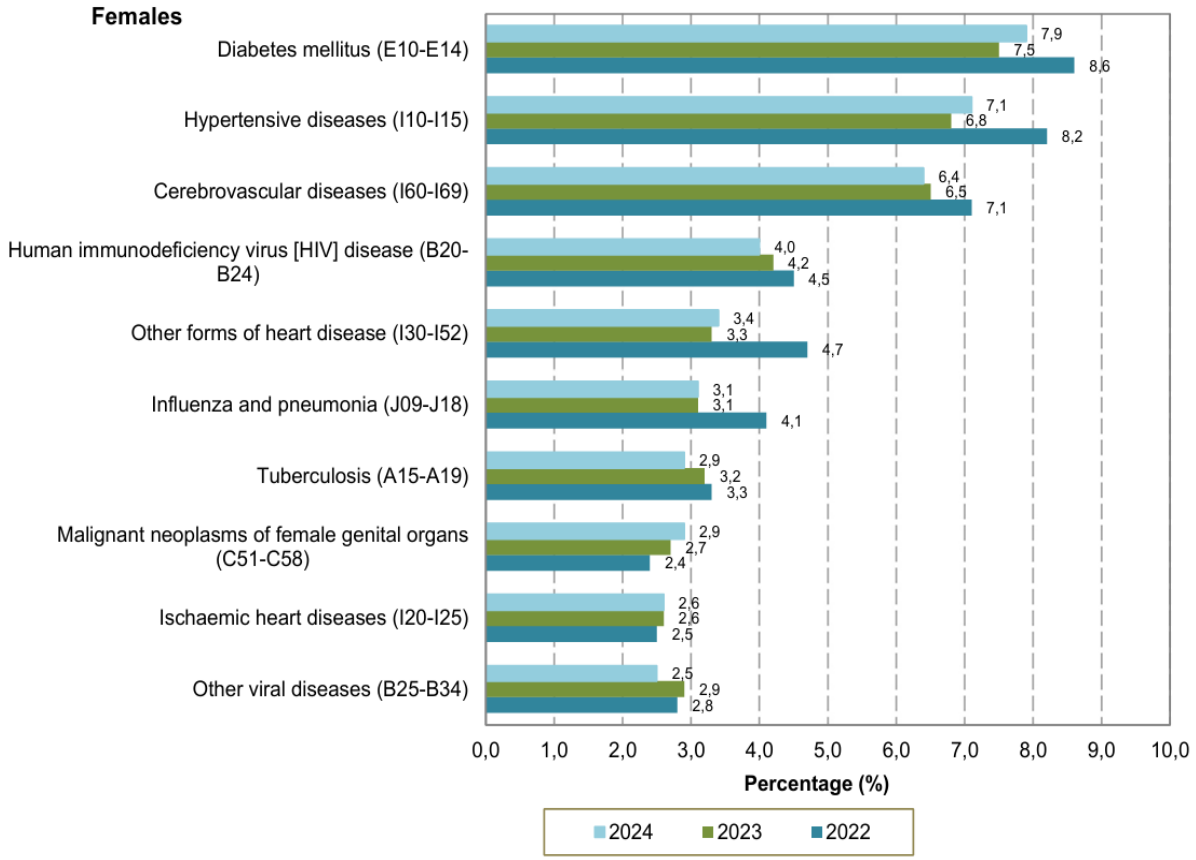
**Including deaths due to MDR-TB and XDR-TB

TB remains among South Africa's top five leading causes of death despite being preventable and curable

Source: Statistics South Africa. Mortality and causes of death in South Africa: Findings from death notification, 2024. Statistical release P0309.3. Pretoria: Statistics South Africa; 2026. p. 39

Distribution of deaths for the leading causes of death by sex, 2022–2024 in SA





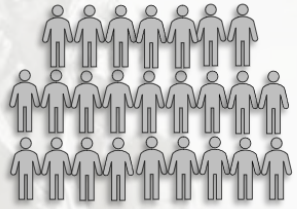
- *Tuberculosis ranked 1st among South Africa's leading causes of death among men*
- *TB is not a mystery disease. It is preventable & curable. Despite this - TB continues to kill at scale*

Source: Stat SA - Statistical release_Mortality and causes of death in South Africa: Findings from death notification 2025. p. 41

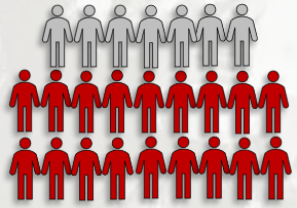
SA TB care cascade: From diagnosis to death — why we can't wait

Outcomes for the 249 000 people with TB in South Africa in 2024

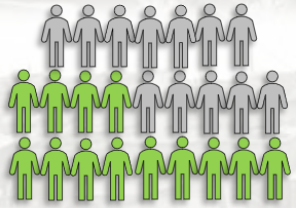
Successfully treated	**38%**
Lost to follow-up	**4%**
Died	**13%**
Unknown	**45%**



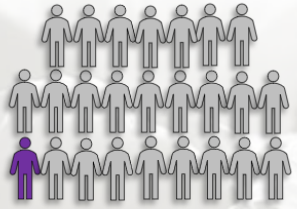
249 000 Developed TB



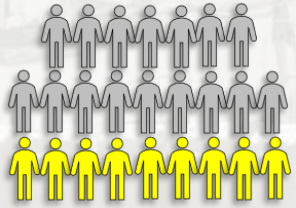
183 726/249 000 (74%) Diagnosed with TB



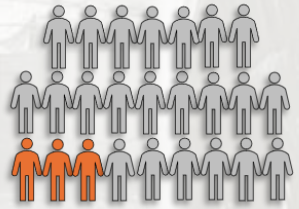
135 957/183 726 (74%) Linked to care



9517/135 957 (7%) LTFU



95 170/135 957 (70%) Successfully treated



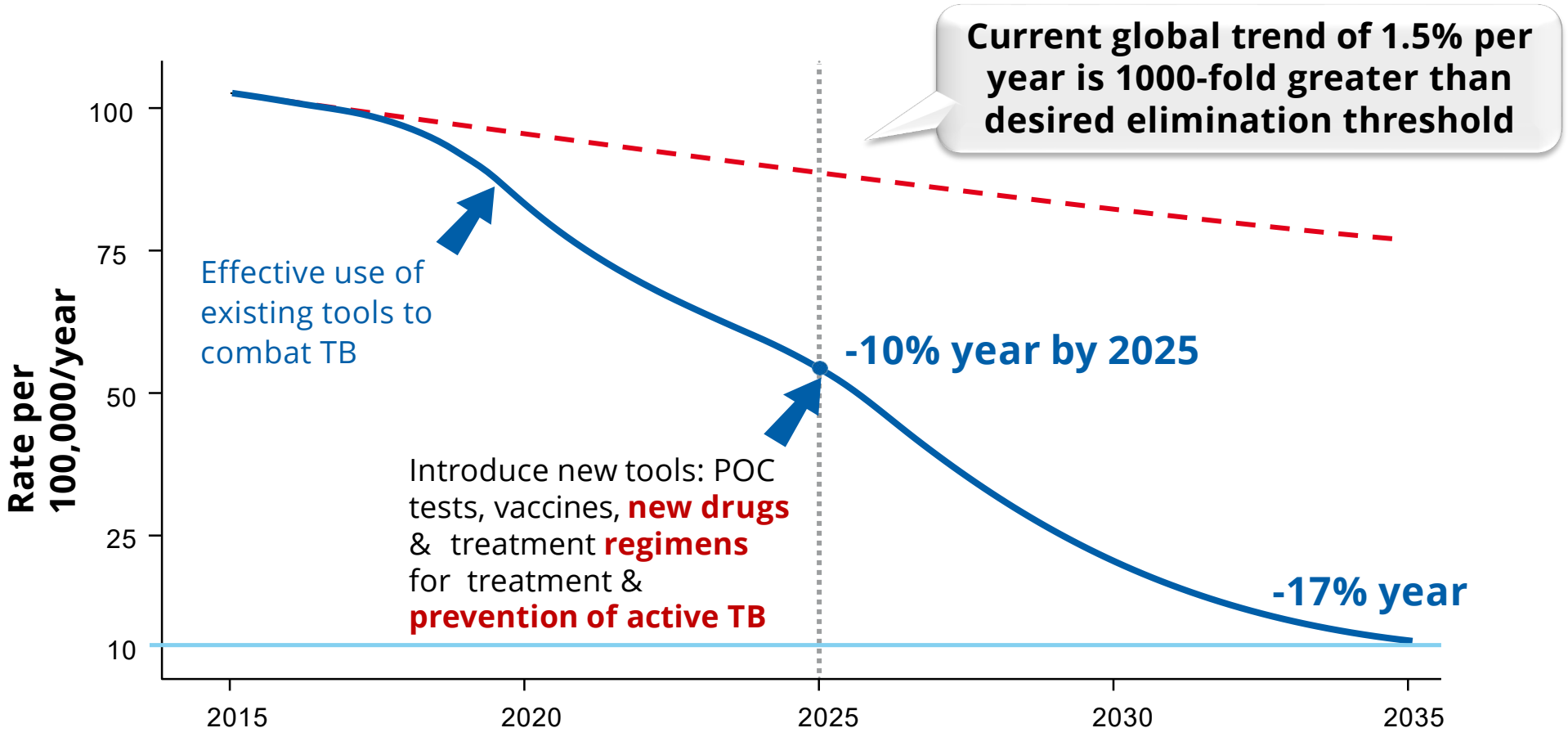
31 270/135 957 (23%) Confirmed deaths

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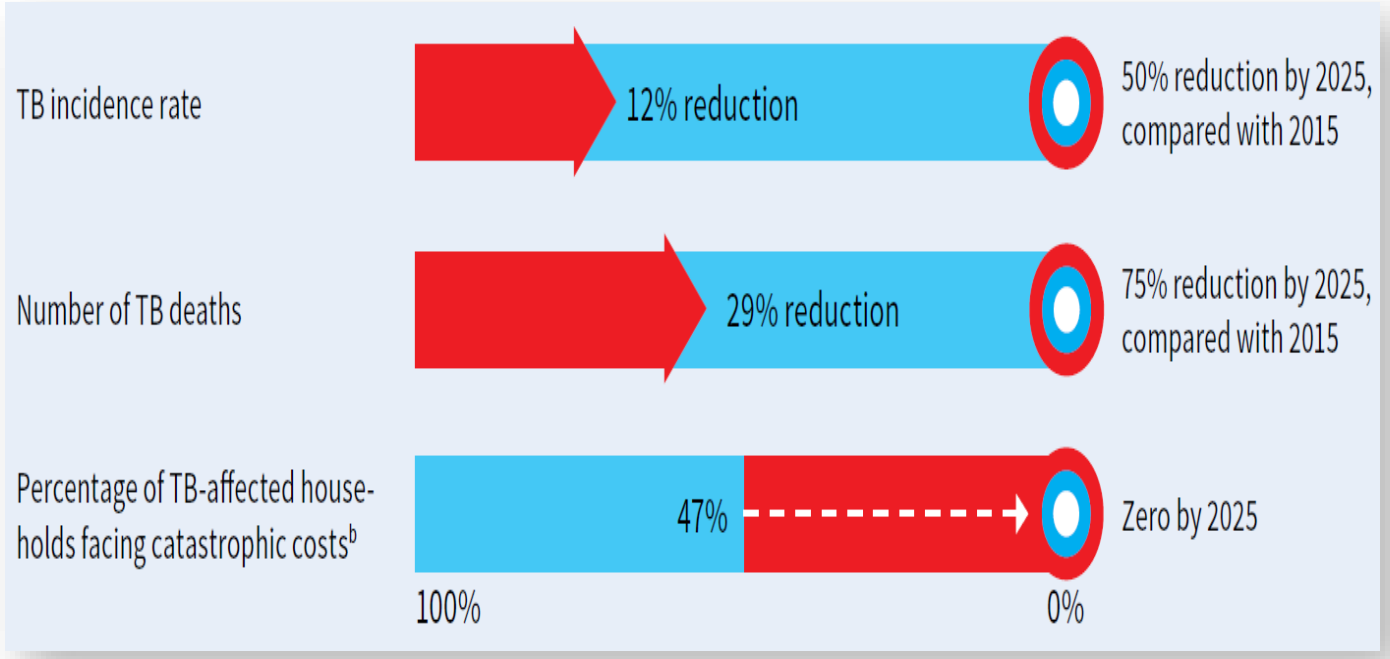
Ending the global TB epidemic by 2035 – are we on track?



The challenge: closing the gap between current trends & the End TB pathway

Sources: World Health Organization, 2015. National Department of Health, South Africa. End TB Plan 1.0 (2026); Global TB Report 2025

End TB Strategy, 2025 milestones



THE END TB STRATEGY



Vision:
A world free of TB
Zero TB deaths, Zero TB disease, and Zero TB suffering

Goal:
End the Global TB epidemic

	MILESTONES		TARGETS	
	2020	2025	SDG* 2030	END TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20%	50%	80%	90%
	(<85/100 000)	(<55/100 000)	(<20/100 000)	(<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	0%	0%	0%	0%

Rate of decline in TB incidence & mortality too slow to meet either SDGs or End TB Strategy targets

Source: Global TB Report 2025

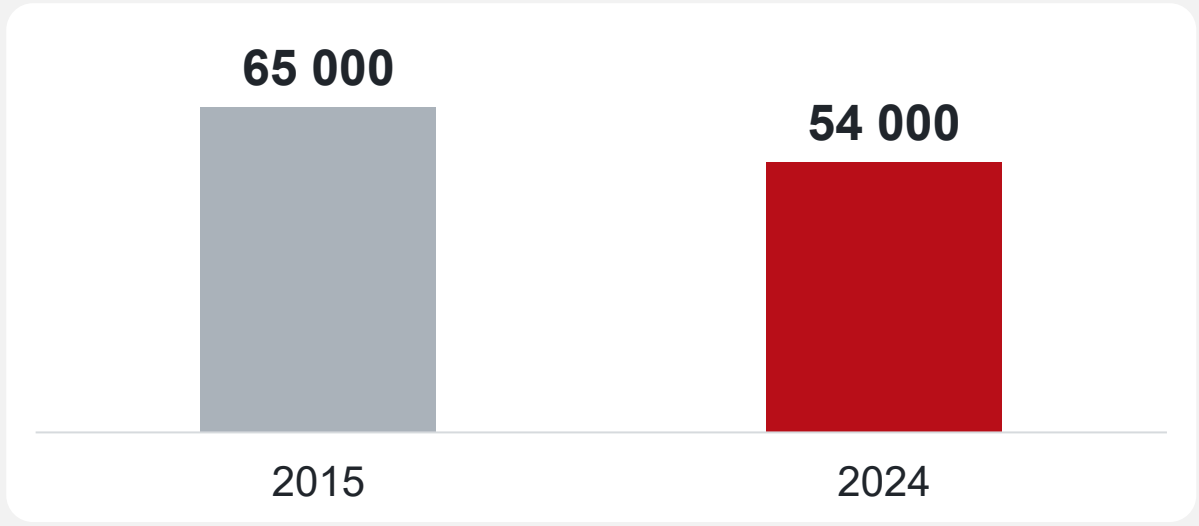
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Unpacking TB mortality in South Africa

54,000
Estimated TB deaths in 2024

29,000
Among people living with HIV

25,000
Among HIV-negative people



- 17% fewer deaths overall
- 36% decline among PLWHA
- 25% increase among HIV-negative people

TB deaths declined overall but increased among HIV-negative people

Sources: WHO Global tuberculosis report 2025. South African NDoH, End TB Plan 1.0 (2026), p. 6.
Rounded estimates. Total includes HIV-associated TB deaths, which WHO classifies under HIV/AIDS.

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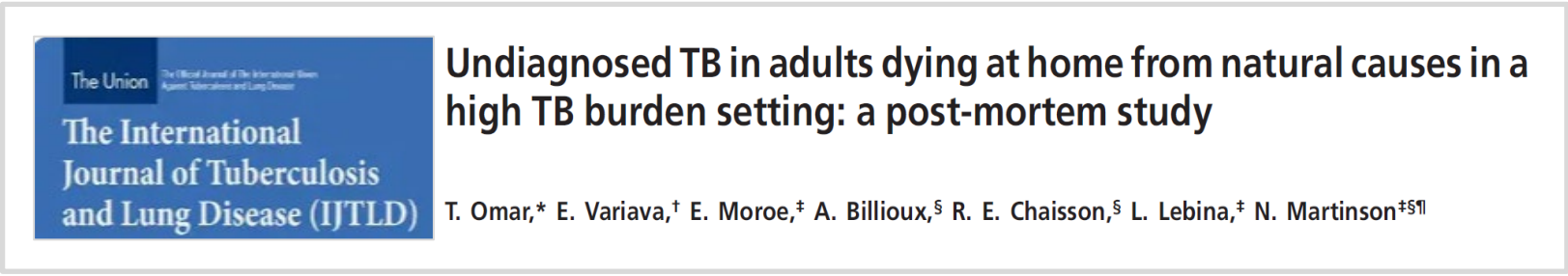
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1. TB mortality at post-mortem

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Evidence of undiagnosed TB at post-mortem



- Limited autopsy study of 85 adults: ≥18 years with no antemortem diagnosis, no recent hospital admission, no apparent CoD
- Performed: bilateral lung core biopsies, BAL→ MGIT and Xpert MTB/RIF
- *Mtb* identified in: 23.5% lung core biopsies; 25.9% BAL

- **TB prevalence**:
  - Xpert positive in 24.7% & MGIT culture in 27.1%

- Undiagnosed, potentially infectious TB was common, suggesting that routine reporting underestimates TB-associated mortality

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2. TB mortality in Primary health care settings

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Findings from the SUTHI trial

eClinicalMedicine
Part of THE LANCET Discovery Science

Mortality in HIV and tuberculosis patients following implementation of integrated HIV-TB treatment: Results from an open-label cluster-randomized trial

Kogieleum Naidoo,[a,b]* Santhanalakshmi Gengiah,[a] Nonhlanhla Yende-Zuma,[a,b] Regina Mlobeli,[a] Jacqueline Ngozo,[c] Nhlakanipho Memela,[a] Nesri Padayatchi,[a,b] Pierre Barker,[d] Andrew Nunn,[e] and Salim S. Abdool Karim[a,b,f]

High mortality among patients with tuberculosis accessing primary care facilities: secondary analysis from an open-label cluster-randomised trial

Kogieleum Naidoo,[a,*] Nonhlanhla Yende Zuma,[b,c] Mikaila Moodley,[b] Felix Made,[b] Rubeshan Perumal,[a] Santhanalakshmi Gengiah,[b] Jacqueline Ngozo,[d] Nesri Padayatchi,[a] Andrew Nunn,[e] and Salim Abdool Karim[a,f]

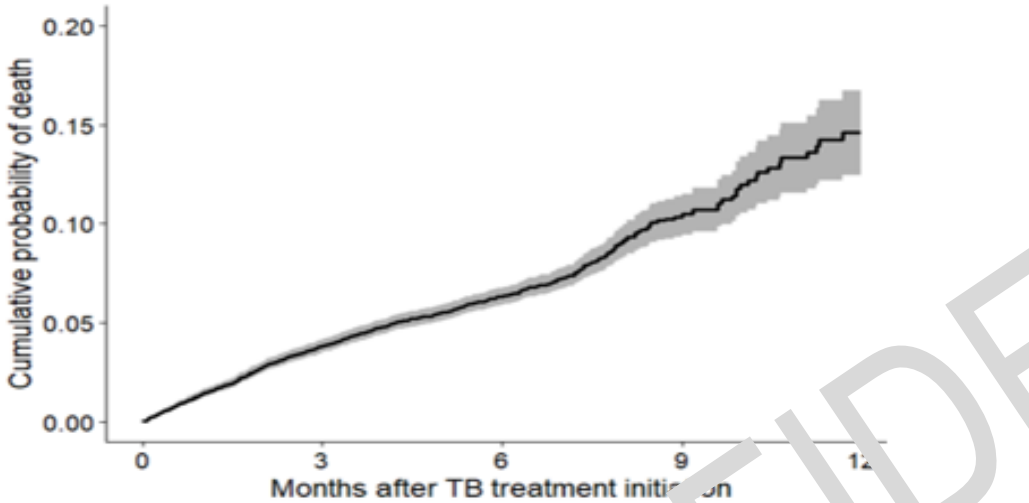
- Cluster–randomised trial in 40 rural KZN clinics conducted between 2016–2018; >21,000 patients
- Assessed mortality after QI-supported TB-HIV integration interventions at 12 and 18 months

- 12-month mortality among newly diagnosed with TB & HIV
- **Findings: Intervention vs SOC**
  - Overall: 4.5 vs 3.8 deaths per 100 person-years
  - HIV–TB coinfection: 10.2 vs 9.8 per 100 person-years

- 18-month TB mortality in newly diagnosed TB
  Findings:
- Overall, 90% deaths within 6 months of TB treatment initiation
- TB deaths: Overall (%): 9.5 vs 11.3
- TB deaths in PLWHA (%):
  - On ART: 10.8 vs 14.4
  - no ART: 18.6 vs 33.0
  - no VL: 22.4 vs 19.7
  - VL<200: 6.5 vs 11.5

- Ongoing high mortality in known TB patients enrolled in care
- Older males and vulnerable PLWHA esp in rural clinics at high-risk for mortality → Close clinical observation & early referral
- Greater demand for TB services and strengthened HIV/TB program implementation required

Risk factors for TB mortality



Kaplan-Meier estimates of cumulative probability of death in the 12-months after TB treatment start

- Assessed temporal trends and risk factors for TB mortality in 40 PHCs in KZN between 2016 – 2022
- >14,000 ambulatory patients accessing TB services

Findings:

- TB mortality: 6.7% overall
  - ↑ 4.8% in 2016 to 7.8% in 2022
- Risk factors for death (aOR): males: 1.22; 5-year increase in age: 1.21 & extrapulmonary TB: 1.6; unknown HIV/ART status: 3.7 & unsuppressed viral load at TB treatment start: 3.6

- Tuberculosis mortality did not decline over the seven-year period
- Risk factors for TB death: adult men, extrapulmonary disease, & viraemic PLWHA

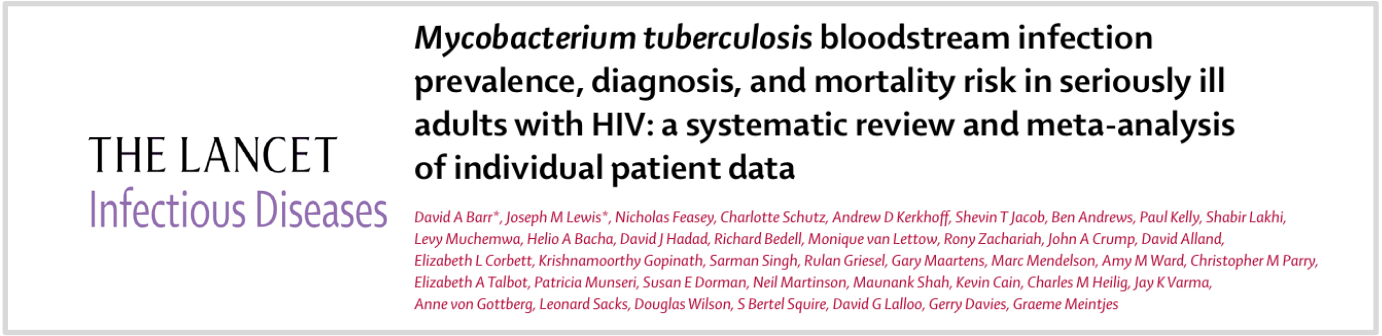
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3. TB mortality in hospitalised patients

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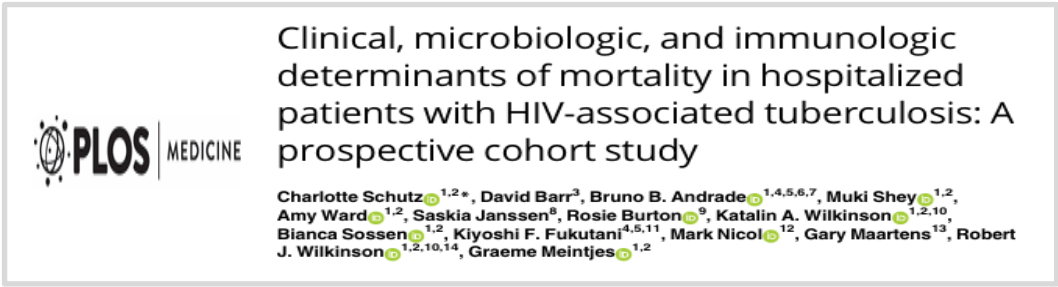
TB in the bloodstream predicts death



- 23 datasets and 5,751 patients
- Hospital inpatients with HIV-associated TB, WHO danger signs & CD4 count of 76 cells per ml^3 had a 45% predicted probability of *Mtb* BSI
- Diagnostic yield in patients with suspected *Mtb* BSI was 77% using sputum alone, increased to 89% (80–94) when combined with urine LAM
- Risk of death within 30 days in *Mtb* BSI vs no BSI was aHR: 2.48 vs 1.25
- HIV-TB co-infected patients with *Mtb* BSI > four-day delay in anti-TB treatment had 3-fold increased risk of death compared to those with no delay

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Early mortality in HIV-associated TB



- 576 hospitalised adults with HIV-associated TB (85% microbiologically confirmed)
- Median age 37 years & median CD4 count 58 cells/μL
- 98.3% started TB treatment, including 84.5% within 48 hours of enrolment
- **Findings:**
  - Mortality at 12 weeks: 21.5%; 37 % of all deaths occurred within seven days
  - Disseminated TB: Positive urine LAM, urine Xpert MTB/RIF, or TB blood culture in 79.6% who died vs 60.7% survivors (p=0.001)
  - Sepsis: Elevated lactate in 50.8% who died vs 28.9% survivors (p<0.001)
  - Rifampicin resistance: 16.9% who died vs 7.2% survivors (p=0.002)

- **Mortality high despite 84.5% starting TB treatment within 48 hours**
- **Disseminated TB, sepsis and rifampicin resistance were associated with death**
- **Early clustering of deaths points to very sick patients arriving late**

Source: Schutz et al. PLoS Medicine. 2019;16(7):e1002840. doi:10.1371/journal.pmed.1002840

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Scientific advances for TB prevention, diagnosis & treatment

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Advances: TB diagnostics pipeline



Emergence of TB-HIV co-infection 2002 & XDR-TB 2005

1882-1907

1882 – Robert Koch discovered TB using the microscope
1895 – Development of CXR
1907 – TST developed

1921-1974

1921 – BCG Vaccine
1936 – Solid culture for TB detection

Emergence of MDR-TB 1956

1980-2009

1980 – Liquid culture developed
2008 – GenoType MTBDR
2009 – ILED microscope and LPA developed

2010-2014

2010 – Xpert MTB/RIF test

2015-2016

2015 – Urine TB-LAM
2015 - Colourimetric DST
2015 – Xpert 2nd gen
2016 – VOC detection

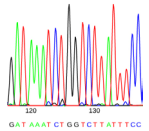


2017-2019

2017 - Xpert MTB/ RIF Ultra
2018 - DGE (platform)
2018 - QuantiFERON TB Gold Plus
2018 - T-SPOT.TB
2019 - Truenat MTB
2019 - RealTime MTB-RIF/INH Resistance

2020

2020 - Xpert Omni
2020 - Xpert XDR
2020 - SILVAMP TB LAM
2020 – FT-MTBDR



Covid-19 Pandemic

Emergence of AI-assisted TB diagnosis-2021
Shift to non-sputum TB testing-2022
Precision DR testing era-2023-present
Improved diagnosis of paucibacillary TB*

2021 - 2026

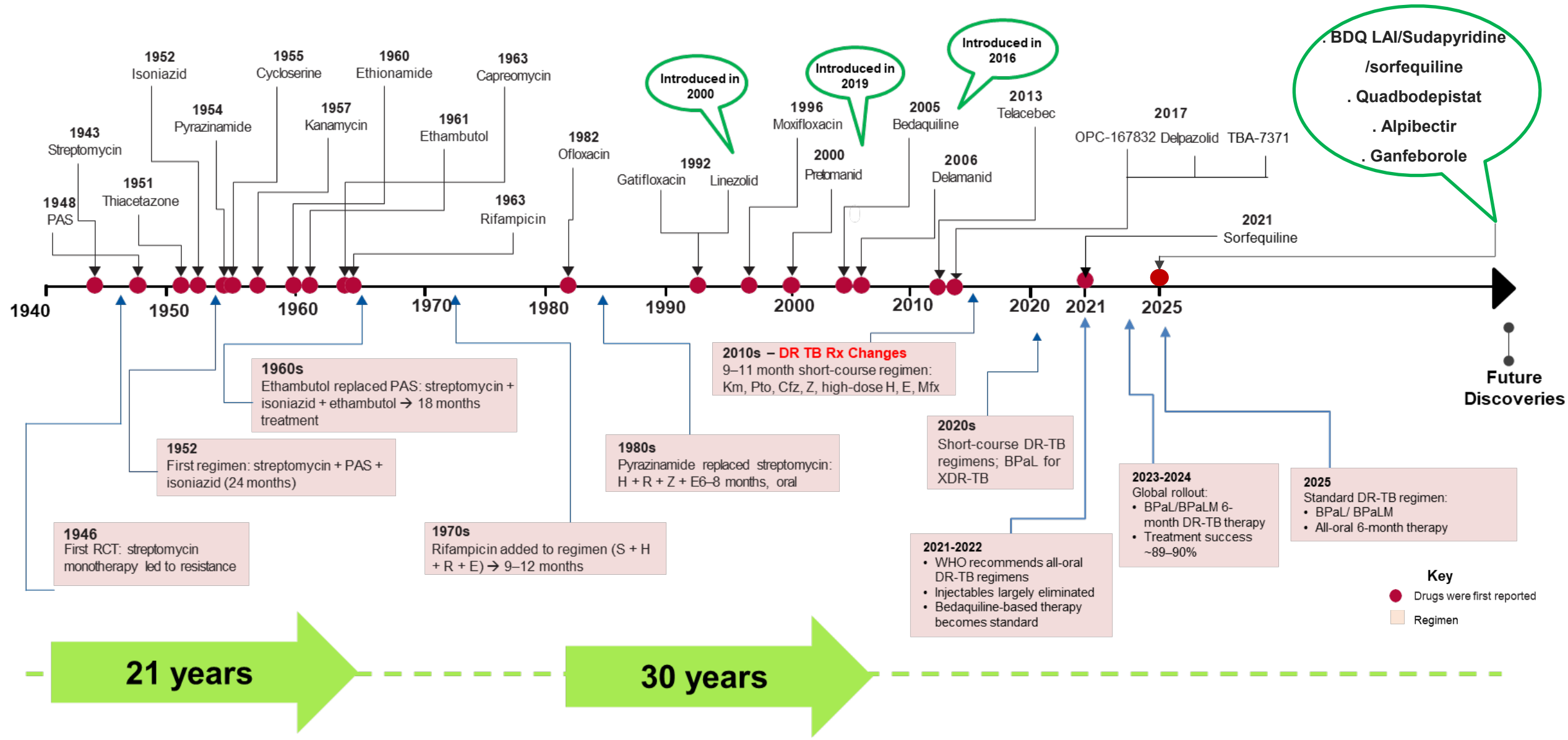
2021 – Xpert MTB/XDR rollout
2021 – Truenat scale-up
2021 – AI chest X-ray screening
2022 – WGS scale-up
2022 – Expanded TB-LAM use
2023 – Host biomarker tests
2023 – Non-sputum diagnostic development
2024 – CRISPR TB diagnostics (pilot)
2024 – Ultra-sensitive molecular assays
2025 – True point-of-care TB test (target)



Future Developments

26 Years
30 Years
54 Years
2 Years
5 Years
3 Years
01
02
03

TB drug discovery pipeline



Adapted from: Ma Z, Lienhardt C, McIlleron H, et al. Lancet. 2010

Strategies for improving treatment outcomes

- High mortality persists from severe TB, including TB meningitis, especially amongst PLWHA



- 6-month mortality 44.6% vs 40.7%
- More early deaths & hepatotoxicity, no neuro benefit
- High-dose RIF failed to improve TBM mortality outcomes



- Intervention: 6-8 weeks Dexamethasone
- 12-month mortality 44.1% vs 49.0%
- Adjunctive dexamethasone failed to improve TBM mortality outcomes

No impact on TBM Mortality with High Dose Rifampicin or with adjunctive Dexamethasone

Updates in Treating Severe HIV-Associated TB: Insights from DATURA

Determination of Adequate Tuberculosis Regimen in Patients Hospitalized With HIV-associated Severe Immune Suppression (DATURA)

ClinicalTrials.gov ID NCT04738812

OA-123: Intensification of TB treatment in Severely Immunocompromised Individuals with HIV (DATURA trial). Blanc F *et al*

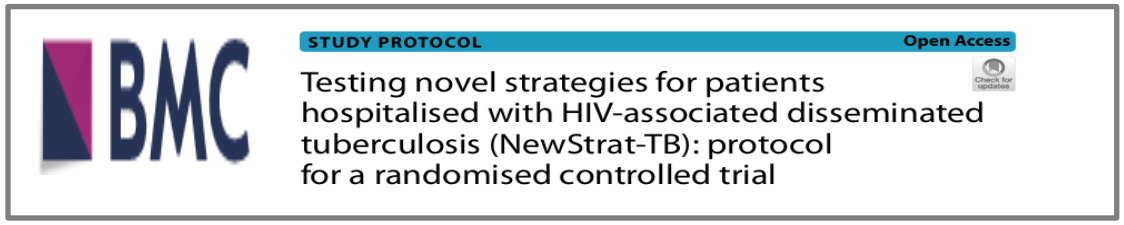
- **Phase III**, multicenter, two-arm, open-label, randomized superiority trial in five African countries
- 911 participants (≥15 yrs) hospitalised with TB and CD4 count < 100 cells/μL
- Intervention Arm: Intensified initial phase of TB treatment (High-dose rifampicin/isoniazid + corticosteroids) vs SOC

- **Key Findings:**
  - Mortality rate in intervention vs SOC arm at 48 weeks: 28% (129/454) vs 26% (119/454)

Conclusion: Intensifying the initial phase of TB treatment did not decrease the risk of mortality in severely immunocompromised PLWHA

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Updates in Treating Severe HIV-Associated TB: Insights from NewStrat-TB



OA-124 Adjunctive Prednisone for Inpatients with Disseminated HIV-Associated TB (NewStrat-TB trial). Namale P *et al*

- RCT of adult PWH admitted for disseminated TB (+urine LAM, urine Xpert Ultra and/or blood Xpert Ultra) at 3 hospitals in Cape Town, South Africa
- **Intervention**: Oral prednisone 1.5mg/kg/d vs placebo plus TB treatment (intensified TB regimen of RIF 35 mg/kg/d and levofloxacin)
- Overall, 732 participants; median age 36 years; 55% female
- Mortality at 12 weeks: 17.6% vs 19.2% (difference -1.6%; 95%CI; -7.5, 4.2)

Adjunctive prednisone with intensified TB treatment did not reduce mortality in PLWHA hospitalised with disseminated TB

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TB Vaccine Pipeline

Vaccine candidates under clinical development

There are 13 vaccine candidates in the pipeline as of July 2026, of which 8 are in active trials. The candidates are placed under the phase which corresponds to the most advanced ongoing or completed trial.

Platform

- Mycobacterial - Live attenuated
- Mycobacterial - Inactivated
- Viral vector
- Protein/Adjuvant
- RNA

Trial staus

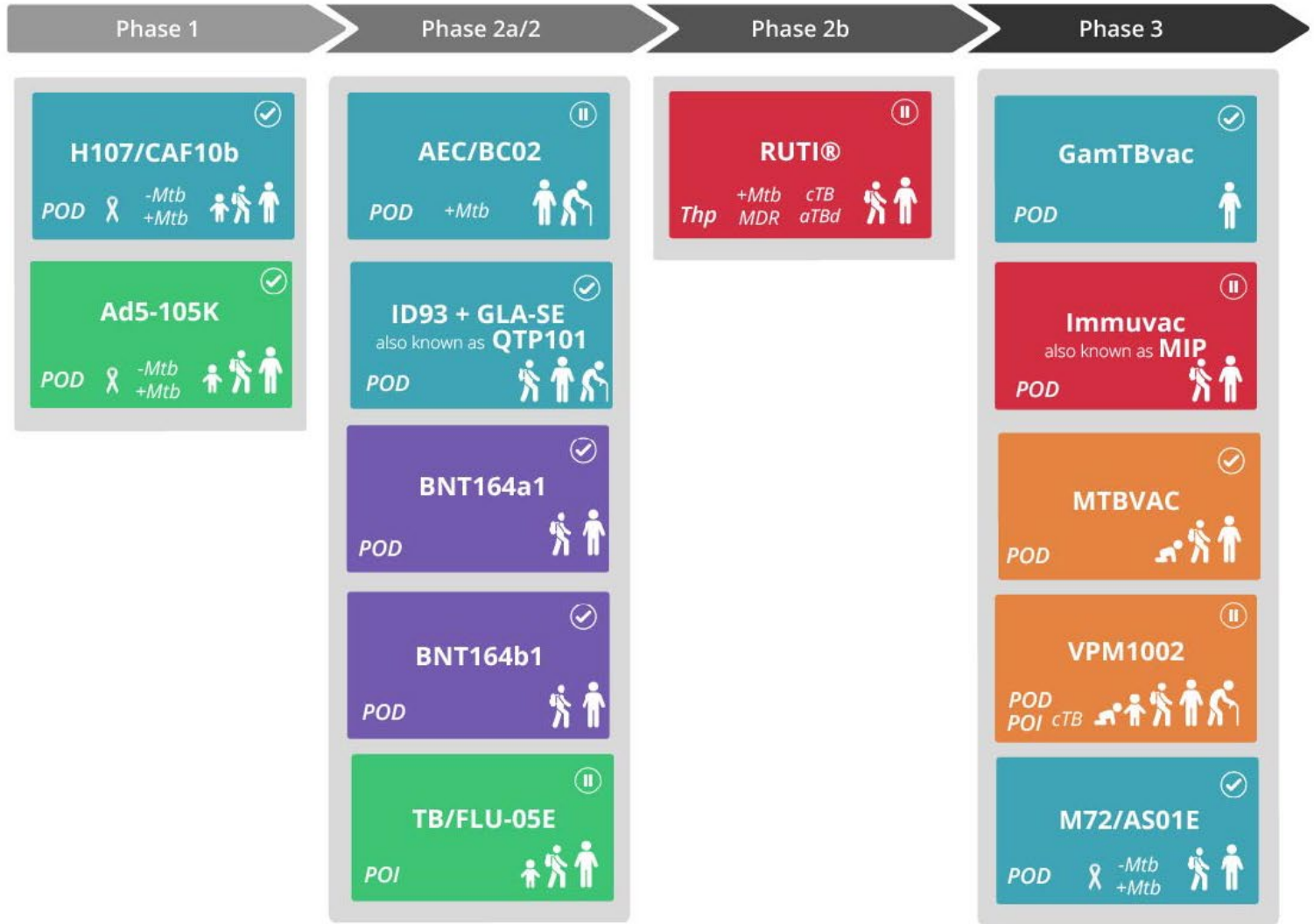
- Active trials
- No active trials

Candidate target population

- Elderly
- Adults
- Adolescents
- Children
- Infants
- People living with HIV
- -Mtb — People without Mtb infection
- +Mtb — People with Mtb infection
- aTBd — People with active TB disease
- MDR — People with MDR-TB
- cTB — People cured of active TB

Primary candidate indication

- *POI* — Prevention of Infection
- *POD* — Prevention of Disease
- *POR* — Prevention of Recurrence
- *Thp* — Therapeutic



Stop TB Partnership
WORKING GROUP ON NEW TB VACCINES

Information reported by vaccine sponsors or found in clinical trial registries or other public sources

Additional information, including the full list of clinical trials for each candidate, can be accessed via the QR code or at newtbvaccines.org/tb-vaccine-pipeline/

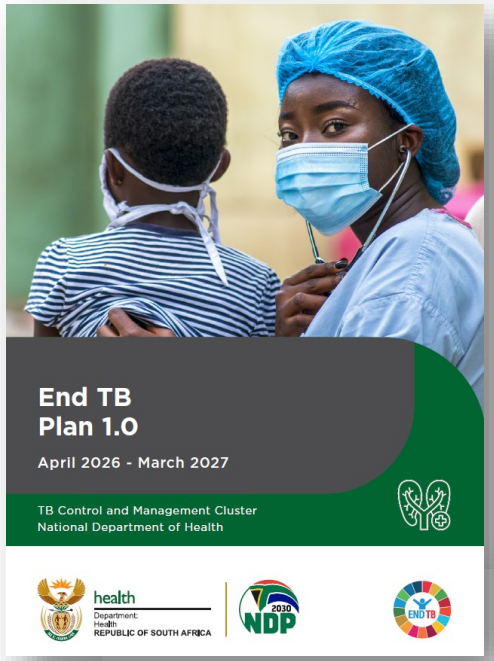
Last update: 27 July 2026

Overview of presentation

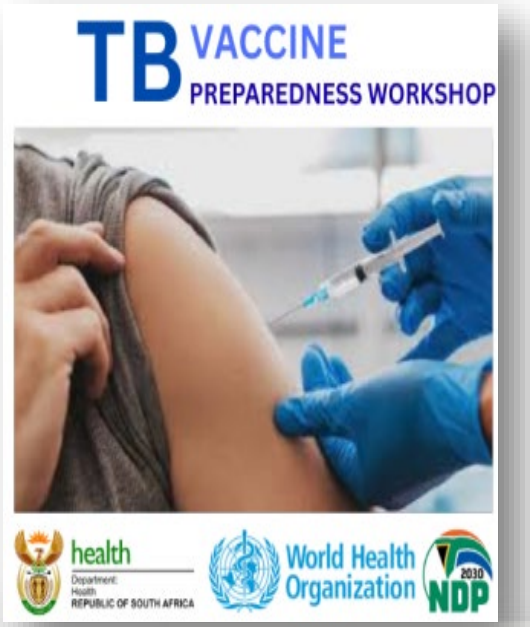
- Burden of TB mortality
- Progress against the END TB Targets: 2026 Status update
- Unpacking TB mortality in SA health care settings
- Scientific advances for TB prevention, diagnosis & treatment
- **Closing the implementation gap - what's priority?**
- Conclusions and summary

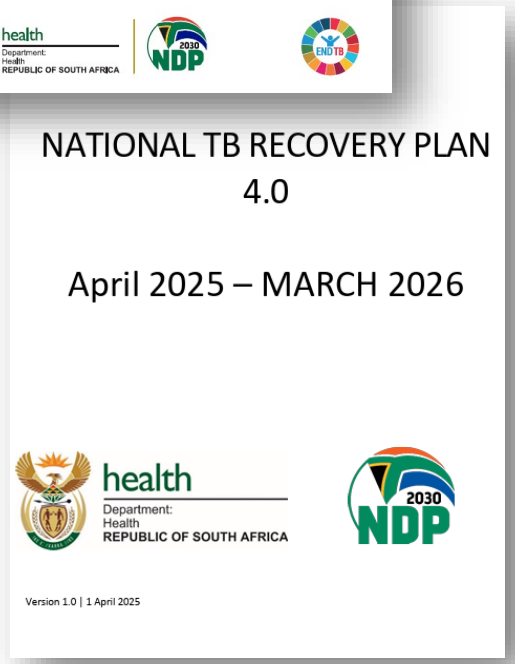
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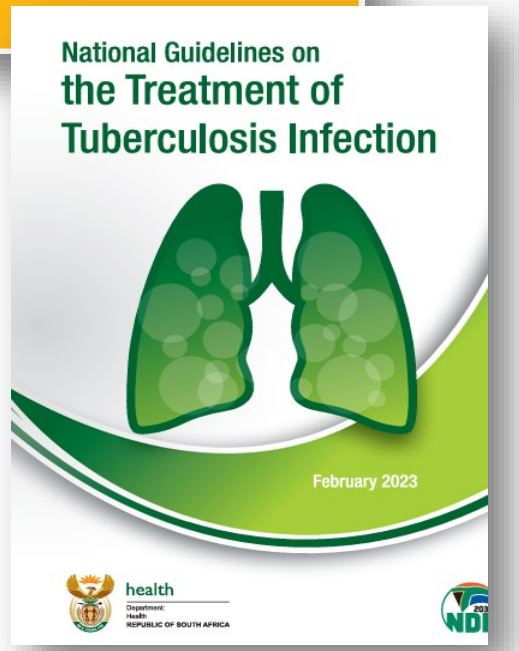
Responsibility, Transparency, Accountability & A call to Action (1)

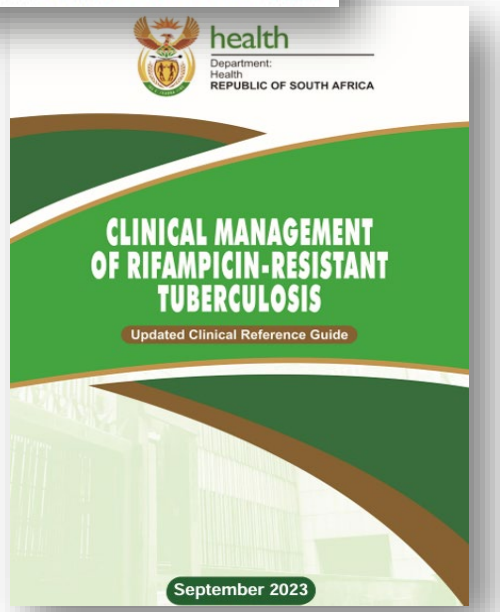








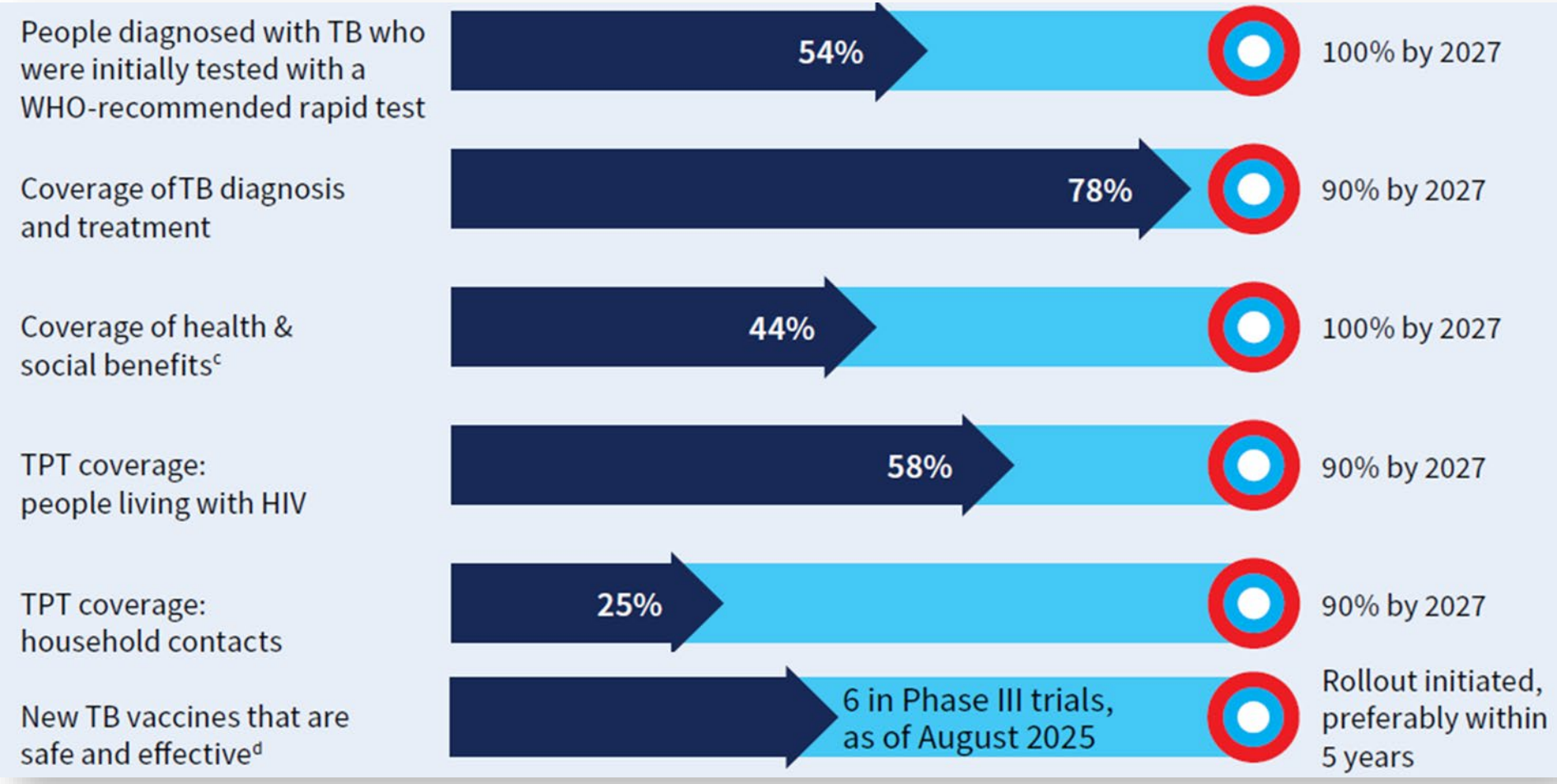




Wide-scale deployment of current Technologies (2)



Close Implementation gaps to reduce HIV-associated-TB morbidity & mortality (3)

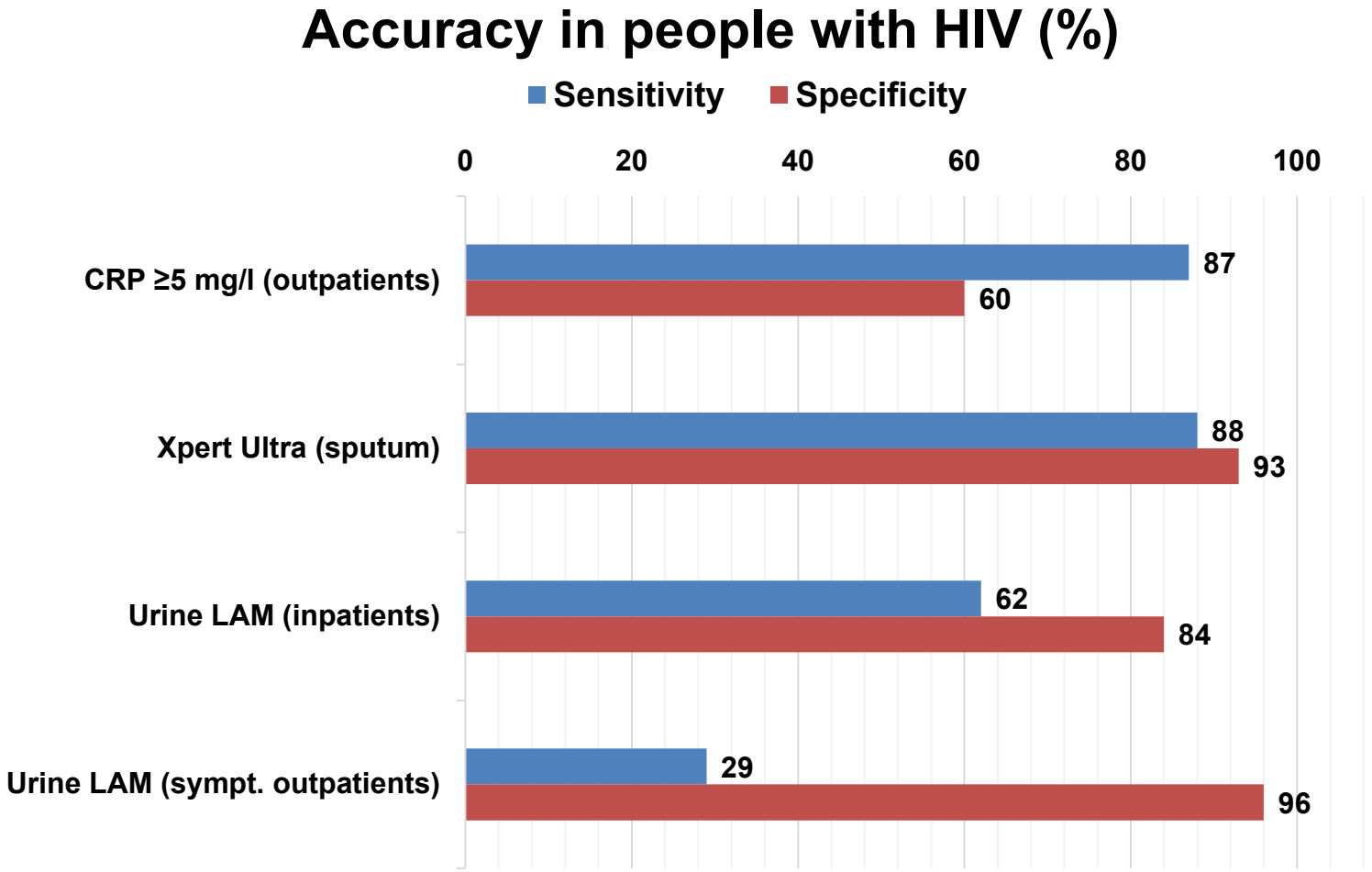


Tools exist but access, coverage & protection against TB remain insufficient

Source: Global TB Report 2025

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Find and treat TB faster (4): Screen and test



Screen at every visit: symptoms, CRP, chest X-ray or a molecular test, TUTT

Hospitalised PLWHA where TB prevalence is >10%: molecular test for all

Xpert plus urine LAM still misses ~28% of inpatient TB

WHO target for new screening tools: 90% sensitivity, 70% specificity

Source: Sossen et al, 2025. Int J Infect Dis

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ART in TB-HIV coinfected patients: Treat fast, start ART early (5)

Test early

- Sputum Xpert Ultra
- Urine LAM if inpatient
- Check rifampicin resistance
- CrAg if CD4 <200

Treat now

- RHZE 2 months, then RH 4 months
- Rifampicin-resistant: BPaL-M, 6 months
- Do not wait for culture

ART within 2 weeks

- Start or restart ART
- TB meningitis: wait 4–8 weeks
- CD4 ≤100: consider prednisone (TB-IRIS)

Protect & link

- Cotrimoxazole prophylaxis
- Pyridoxine
- Consider PCP and other diagnoses
- Link to care at discharge

TB meningitis: dexamethasone showed no survival benefit in PLWHA (trial may be underpowered)

Source: Sossen et al, 2025. Int J Infect Dis

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TB Prevention: ART first, then TPT

84% lower TB risk with effective ART, at any CD4 count (up to)

40% higher survival with rifamycin-based TPT (up to)

56% of PLWHA received TPT in 2023; target is 90% by 2027

Current WHO Recommended TPT Regimens

Regimen	Drugs	Duration	Dosing	DS/DR TB	Evidence strength
6H/12H	Isoniazid	6–12 months	Daily	Drug-susceptible	**Strong**
3HP	Rifapentine + isoniazid	3 months	Weekly	Drug-susceptible	**Strong**
3HR	Rifampicin + isoniazid	3 months	Daily	Drug-susceptible	**Strong**
1HP	Rifapentine + isoniazid	1 month	Daily	Drug-susceptible	Conditional
4R	Rifampicin	4 months	Daily	Drug-susceptible	Conditional
6Lfx	Levofloxacin*	6 months	Daily	Drug-resistant	**Strong***

INH = isoniazid. *For contacts of drug-resistant TB

Test for TB infection not required for TPT. NB. ART/TPT drug interactions; access to rifapentine limited

- Shorter regimens such as 3HP & 1HP improve adherence & completion
- Regimen choice should be individualized based on age, HIV status, weight, available formulations, ART interactions, susceptibility pattern of index patient & patient preference

Source: Sossen et al, 2025. Int J Infect Dis

Patient-Specific TTP Regimen Summary

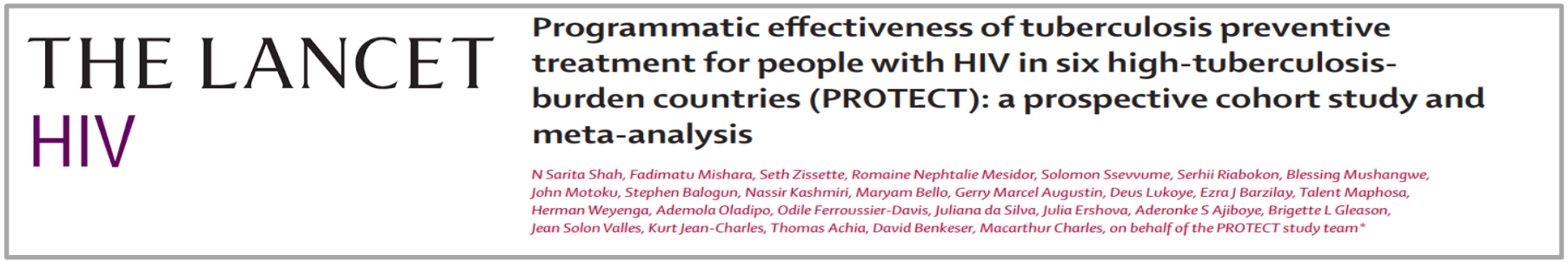
Category	What to Do	Regimen
Adults & Adolescents living with HIV ≥25kg	Exclude TB before TPT. Newly diagnosed HIV: start ART immediately, TPT within 2 weeks. Post-TB treatment: offer TPT. Retreatment after re-exposure: retest & give TPT. Pregnant women: evaluate and start TPT.	12H
Adults & Adolescents ≥25kg – HIV-negative	Evaluate close contacts and at-risk groups (anti-TNF, dialysis, diabetes, transplant prep, silicosis). Retreatment after re-exposure: retest & give TPT. Pregnant women: evaluate and start TPT once TB excluded.	3HP, 3RH, or 6H
Children living with HIV<25kg	Evaluate CLHIV >14 weeks old for TB and start TPT once TB excluded. Newly diagnosed: start ART immediately, TPT within 2 weeks. TB-exposed contacts: evaluate and start TPT regardless of previous treatment.	6H**
Children <25kg – HIV-negative	Evaluate TB-exposed children and start TPT once TB excluded. Evaluate other at-risk children (immunosuppressed, cancer, diabetes, transplant, dialysis, inherited immunodeficiency) and start TPT once TB excluded.	3RH

TPT Contraindications: *active TB disease; active acute or chronic liver disease; severe peripheral neuropathy (consider rifampicin-only (4R) regimen in such cases); previous adverse reactions to any TPT medications & excessive alcohol intake*

Source: National Guidelines on THE TREATMENT OF TUBERCULOSIS INFECTION, 2023

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Programmatic Effectiveness of TPT for PLWHA (PROTECT study)



- Target trial emulation involving 235 424 PLWHA comparing TPT effectiveness among those initiating TPT vs no TPT
- Two-year TB incidence and all-cause mortality. Results adjusted by year, age, sex, CD4 count, WHO clinical state, ART adherence, TB symptoms
- **Findings:**
  - 61% (HR 0.39; CI 0.34 - 0.43) reduction in TB incidence and 45% (HR 0.55; CI 0.51 - 0.58) reduction in mortality
  - Reduction in TB incidence and mortality held across diverse settings and risk groups

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Overview of presentation

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- **Conclusions and summary**

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Summary & conclusion

- Combating TB-associated morbidity & mortality remains our top priority
  - Death: 1 in 10 TB patients at PHCs; 1 in 5 with unknown HIV/ART status & 1 in 3 among viraemic PLHWA
    - 20% mortality in hospitalized patients, despite early TB Rx with most deaths occurring in the first 7 days
- Advanced diagnostics, shorter regimens, novel drugs, & SC TPT are available, offering huge promise in finding, preventing and treating TB effectively – access and coverage need to be improved
- Science translation is key for long-term reduction in TB incidents & mortality
- Cascade losses, & implementation gaps now a bigger constraint than lack of scientific innovation - need for transparency & health systems innovations
- Priorities to reduce TB mortality: Close implementation gaps: use existing tools & strategies to diagnose, Rx & prevent TB

Ending TB mortality will be determined not by discovery alone, but by delivery, surveillance, & sustained financial commitment