# Where India stands now (snapshot)

* **Burden & trend:** India still accounts for ~**one-quarter** of global TB. Incidence has fallen ~**18% since 2015**; TB deaths down ~**24%** (to 2023). Progress resumed post-COVID but the 2025 “elimination” target (incidence <1/100,000) is not on track.
* **Drug-resistant TB:** WHO South-East Asia’s MDR/RR-TB numbers stabilized in 2023; India is rolling out **6-month BPaLM** nationally (bedaquiline-pretomanid-linezolid±moxifloxacin) with 2025 national DR-TB guidelines in force; early programme use is growing but uneven.
* **Prevention:** India has national **TPT guidelines** (household contacts, PLHIV, etc.) and is moving toward **short-course 3HP/1HP** where rifapentine access allows, but implementation gaps persist.
* **Social protection:** **Ni-kshay Poshan Yojana (₹500/month)** is nationwide; evaluations report **coverage gaps and delays**; revisions in 2024–25 aim to strengthen delivery. Catastrophic costs remain high for many households.
* **Pipeline:** **M72/AS01E TB vaccine** entered Phase-3 in 2024; recruitment completed across Africa & SE Asia (not India), results pending.

# Burning problems (actionable)

1. **“Missing” cases, esp. in the private sector** (large care share but variable notification; quality and standards inconsistent).
2. **Uneven BPaLM uptake & safety monitoring** (linezolid toxicity monitoring, eligibility screening, pharmacovigilance capacity).
3. **DST (drug-susceptibility testing) for the right drugs at the right time**—coverage and timeliness for fluoroquinolones, bedaquiline, and rifapentine remain patchy.
4. **TPT scale-up barriers**—rifapentine availability, regimen choice (3HP vs 6H), operational delivery to contacts and high-risk groups.
5. **Catastrophic costs & nutrition**—cash transfer delays, adequacy of ₹500/month, and leakage threaten adherence.
6. **Urban poor, migrants, and closed settings (prisons)**—screening continuity and treatment completion remain weak (evidence gap flagged in reviews).
7. **Paediatric & extrapulmonary TB**—diagnostic yield and non-sputum pathways lag; AI-CXR pilots exist but are not standardized.
8. **Data quality in Ni-kshay & outcome attribution**—incomplete contact investigation, deduplication, and delayed DBT linkage.
9. **Comorbidity integration**—diabetes, tobacco use, undernutrition: weak bidirectional screening & tailored adherence support. (Synthesis from India TB Report & reviews.)
10. **Supply-chain resilience**—for new/repurposed drugs (pretomanid, rifapentine) and cartridges; localized stock-outs reported informally; limited published, up-to-date audits (research gap).

# Research protocols you can field now

Each protocol includes PICO, design, sample & outcomes—built for NTEP settings and ethics-ready. Mix them per state context.

### 1) Private-sector notification & quality “nudge-bundle” trial

* **Question:** Do combined incentives + e-prescription + pharmacist linkage improve complete notification & standard-of-care?
* **Population:** Private chest physicians & pharmacies in 12 districts with high private TB load.
* **Intervention:** (a) On-the-spot Nikshay enrollment app + (b) pharmacist-triggered lab voucher + (c) quarterly feedback+benchmarking + (d) guaranteed DBT facilitation for patients + (e) Rs 1,000 PHCP incentive reminder.
* **Control:** Usual NTEP engagement.
* **Design:** **Cluster randomized trial** (district-quarters), 24 clusters, 12-month follow-up.
* **Primary outcome:** Proportion of microbiologically confirmed TB cases **notified within 7 days** of diagnosis.
* **Secondary:** DST completion, treatment initiation within 3 days, treatment success, catastrophic cost (WPRO tool).
* **Sample:** ~7,200 patients gives 90% power for +10-pp improvement (ICC 0.02).
* **Notes:** Use pharmacy sensitization evidence & notification barriers literature.

### 2) BPaLM implementation + pharmacovigilance (Pv) hybrid effectiveness study

* **Question:** What are real-world outcomes and AEs of **BPaLM** vs 9–11-month bedaquiline-containing regimens?
* **Population:** MDR/RR-TB adults eligible per 2025 DR-TB guideline.
* **Design:** **Type-2 hybrid** (prospective multicentre cohort + stepped Pv strengthening package: monthly CBC, neuropathy screen, optic check).
* **Sites:** 20 DR-TB centres across 8 states.
* **Primary outcome:** Treatment success at 12 months post-start.
* **Safety endpoints:** Grade 3–4 anemia/thrombocytopenia, peripheral/optic neuropathy, hepatotoxicity.
* **Sample:** 2,000 BPaLM vs 2,000 comparator; IPTW to reduce confounding.
* **Add-on:** **Therapeutic drug monitoring sub-study** (n=300) for linezolid exposure-toxicity modelling.

### 3) Fast-track DST study for all TB: Truenat/CBNAAT→ reflex FQ & Bdq DST

* **Question:** Does a **reflex DST algorithm** cut time-to-effective regimen and improve outcomes?
* **Design:** **Stepped-wedge** across 30 labs; each step adds upfront FQ resistance and targeted Bdq resistance testing for RR-TB.
* **Primary outcome:** Median days from sample collection to **appropriate regimen initiation**.
* **Secondary:** Loss-to-follow-up pre-treatment, mortality at 6 months, cost per patient.
* **Economic:** Provider + patient cost diary; budget impact for state.

### 4) TPT delivery models for household contacts: 3HP vs 6H operational trial

* **Question:** Among eligible contacts, does **community-delivered 3HP** achieve higher **completion** and fewer AEs than **facility-delivered 6H**?
* **Design:** **Pragmatic open-label RCT** at block level.
* **Primary outcome:** TPT completion (per WHO).
* **Secondary:** Incident TB at 24 months, AE-related discontinuation, cost-effectiveness.
* **Sample:** ~2,400 contacts (power to detect 10-pp difference).

### 5) Bridging the DBT gap: payments architecture A/B test

* **Question:** Do **auto-triggered, same-day DBT releases** (via Nikshay-PFMS API) + helpline reduce delays and improve adherence?
* **Design:** **Cluster randomized**, facilities as clusters; intervention adds instant eligibility checks and SMS nudges.
* **Primary outcome:** **Median days** from notification to first DBT credit.
* **Secondary:** Missed doses, weight gain at 2 months, default.
* **Qualitative:** Patient interviews on stigma & spend patterns for NPY funds.

### 6) AI-CXR vans + field molecular testing in urban slums/prisons

* **Question:** Do **AI-assisted CXR vans** with on-board Truenat and same-day linkage **increase case yield** and reduce pre-treatment LTFU vs periodic symptom camps?
* **Design:** **Controlled before–after** across matched hotspots & prisons.
* **Primary outcome:** Bacteriologically confirmed cases **per 1,000 screened**.
* **Secondary:** Time to treatment start, cost per case, positivity among high-risk groups (DM, elderly).

### 7) Paediatric TB diagnostic pathway evaluation

* **Question:** What is the incremental yield of **non-sputum sampling (stool, NPA), ultrasound-guided FNAC**, and **CAD-CXR** in children?
* **Design:** **Prospective diagnostic accuracy** study against composite reference standard across 10 paediatric sites.
* **Outcomes:** Sensitivity/specificity by specimen & age band; time-to-diagnosis; AE from procedures.
* **Policy hook:** Build national paediatric algorithm addendum.

### 8) Migrant-aware care cascades: longitudinal cohort

* **Question:** Where are the biggest **cascade losses** for **internal migrants** with TB?
* **Design:** **Cohort** of 3,000 PwTB tagged as migrants; **SIM-based contact tracing**, portability of care across states; compare to 3,000 non-migrants.
* **Outcomes:** Treatment interruption, transfer-out, success; qualitative barriers.

### 9) Diabetes-TB integrated management trial

* **Question:** Does **co-located glycaemic control** (meter, strips, basic meds + monthly counseling) **improve TB outcomes**?
* **Design:** **Cluster RCT** in 30 high-DM districts.
* **Primary outcome:** Unfavourable TB outcome composite.
* **Secondary:** HbA1c change, weight gain, severe AEs, cost. (Addresses high comorbidity burden flagged by NTEP/WHO.)

### 10) Catastrophic costs sentinel surveillance + policy simulation

* **Question:** What proportion of households face **catastrophic costs** today, and which policy levers (higher NPY, travel vouchers, sick-leave wage replacement) bend the curve?
* **Design:** **Sentinel patient-cost survey** (WHO tool) in 12 states + **microsimulation** of benefit packages.
* **Outcome:** Share of households with catastrophic cost; **equity impacts** by quintile; policy-ready budget scenarios.

### 11) Supply-chain readiness audit for BPaLM/TPT (rapid appraisal)

* **Focus:** Pretomanid, rifapentine, linezolid, moxifloxacin; cartridge stock; lab consumables.
* **Design:** **Cross-sectional structured audit** of 100 facilities + qualitative key-informant interviews.
* **Output:** Heat-map of stockout risk; reorder thresholds; vendor performance—directly actionable by states.

### 12) Vaccine preparedness & acceptance (M72 readiness)

* **Question:** What is **acceptability**, logistics readiness, and **targeting** strategy for an adult/adolescent TB vaccine?
* **Design:** **Mixed-methods** (community surveys, provider KAP, cold-chain audit).
* **Outcome:** Feasibility & comms blueprint to accelerate roll-out if/when M72 succeeds.

## Cross-cutting methods & ops details (for all protocols)

* **Sampling & power:** Use cluster-level coefficients from prior NTEP ops research (ICC 0.01–0.05). Conservative attrition 10–15%.
* **Data systems:** **Nikshay** integration for case IDs/outcomes; REDCap/ODK for study CRFs; PFMS webhook for DBT timing (where allowed).
* **Ethics:** Independent EC + state TB office nodal approval; adverse event reporting aligned to CTD Pv SOPs for BPaLM.
* **Economics:** Provider costing (ingredients method) + patient costing (WHO tool); present **cost-per-additional-success** and **budget impact**.
* **Equity lens:** Pre-specify subgroup analyses—sex, age, migrant status, urban slum residence, caste/tribe, and wealth quintiles.
* **Dissemination:** Interim dashboards to district/state TB cells each quarter; “policy brief” per study with 1-page recommendations.

## Immediate policy takeaways you can act on while research runs

* **Mandate reflex FQ DST with upfront molecular testing**; pilot Bdq DST where feasible.
* **Scale BPaLM with guardrails:** minimum monthly CBC + neuropathy/vision screens; hotline for AEs; track eligibility vs treated to find bottlenecks.
* **Accelerate TPT with 3HP where rifapentine is available**; in parallel, strengthen 6H supply and community delivery.
* **Fix DBT delays:** auto-trigger payments upon notification, publish TATs by district, and allow in-kind nutrition top-ups via Nikshay Mitra where banking hurdles persist.
* **Double-down on private sector:** pharmacy-linked notification, e-Rx standards, quarterly feedback, and routine audits.

If you’d like, I can turn any of the above protocols into a **full ethics/operations pack** (CRFs, SOPs, budget, Gantt, and power calcs) tailored to your state or district mix.