

Beyond Drug Efficacy: Diagnostic Informatics as a Hidden Driver of Therapeutic Value in Multidrug-Resistant Tuberculosis

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ABSTRACT

This conceptual review examines whether published cost-effectiveness models of bedaquiline and delamanid account for diagnostic and pretreatment delays in multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB). Evidence was retrieved through targeted searches of an AI-assisted medical evidence platform indexing Springer Nature, Wiley, NEJM Group, and JAMA Network. Searches covered five domains: diagnostic delays in Bandung's MDR/RR-TB care cascade; clinical and epidemiological consequences; the structure of six bedaquiline/delamanid cost-effectiveness models; evidence for diagnostic and informatics interventions; and precedents for incorporating delays into economic models. Thirty-two unique studies were included. A four-year Bandung cascade analysis found that fewer than one in ten estimated MDR/RR-TB cases were diagnosed; this finding is specific to that study and is not a national estimate. Evidence from comparable high-burden settings links delays to greater disease severity, poorer treatment outcomes, and prolonged infectiousness. None of the six identified drug cost-effectiveness models formally parameterized diagnostic delay or diagnostic informatics performance. Their simulated horizons began at treatment initiation, while sensitivity analyses emphasized drug prices, outcome probabilities, and adverse-event costs. However, discrete-event simulation and related approaches have incorporated treatment waiting times into economic models in oncology and bloodstream infections. This review does not develop or validate a new economic model. It proposes a conceptual framework positioning diagnostic informatics as a determinant of therapeutic value in MDR/RR-TB. The framework aims to guide empirical research incorporating locally observed delay distributions into cost-effectiveness models for Indonesia and other high-burden settings.

1. Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a major public health problem in Indonesia, one of the countries with the highest tuberculosis and drug-resistant tuberculosis burden worldwide [1]. Bedaquiline and delamanid, two newer second-line drugs, show favorable cost-effectiveness in several high-burden countries [2], [3], [4]. Whether these findings translate into real-world therapeutic value in Indonesia is a separate question. The uncertainty comes

from a structural gap in how these economic evaluations are built, not from doubts about drug efficacy.

Indonesian studies document delay across the MDR/RR-TB care cascade. Diagnostic and treatment-initiation intervals span several days to several weeks across settings, and rural residence, financial barriers, and health-system fragmentation drive much of this delay [5], [6], [7]. A four-year care cascade analysis in Bandung found that fewer than one in ten estimated

true drug-resistant tuberculosis cases were diagnosed, and only a quarter of diagnosed patients completed treatment successfully [8]; this finding describes the Bandung cascade specifically and should not be read as a national figure. These delays carry clinical consequences. Studies from comparable high-burden settings link longer diagnostic and treatment-initiation delay to greater disease severity at treatment onset, lower treatment success, higher mortality, and prolonged infectiousness that sustains community transmission [9], [10], [11].

A structural inconsistency follows from this evidence. Six published cost-effectiveness analyses of bedaquiline and delamanid, spanning the United Kingdom, Germany, China, South Africa, and sp, begin their model structure at the point of confirmed diagnosis and treatment initiation, treating the interval between diagnosis and treatment as fixed [2], [3], [4], [12], [13]. Their sensitivity analyses concentrate on drug acquisition price, treatment outcome probabilities, and adverse event costs as the dominant drivers of the incremental cost-effectiveness ratio (ICER) [12]. None of these six models incorporates diagnostic delay, time-to-treatment-initiation, or diagnostic test performance as a varied parameter, despite epidemiological evidence that such delays alter the clinical trajectory these models are meant to capture.

This omission is not a methodological ceiling. Health-economic models in other disease areas already parameterize diagnostic delay and time-to-diagnosis. Discrete-event simulation has incorporated treatment wait-time directly into ICER estimation for chimeric antigen receptor T-cell therapy, and wait-time shifted projected quality-adjusted life years and cost-effectiveness estimates depending on payment-timing assumptions [14]. Rapid diagnostic testing models for bloodstream infections build time-to-effective-therapy directly into their decision-analytic structure, and methodological guidance for economic evaluation of diagnostics names time-to-correct-diagnosis as a modelable value driver [15], [16].

A spectrum of diagnostic and informatics-based interventions can reduce this delay, with evidence maturity that varies by technology. Molecular diagnostics such as Xpert MTB/RIF and line probe assays show the most direct and quantified reductions in diagnostic and treatment-initiation delay [17], [18]. Consensus guidance on molecular drug-resistance testing points to further gains from next-generation sequencing platforms for second-line resistance profiling [19]. Artificial intelligence-based approaches, including machine-learning genotypic resistance prediction and deep-learning chest radiograph triage, show strong diagnostic accuracy, but prospective evidence linking their deployment to shortened time-to-treatment remains limited [20], [21]. Indonesia's national tuberculosis information system, SITB,

exemplifies the digital infrastructure that could close this gap, though its quantitative effect on delay reduction in Indonesia has not been documented [22].

These five bodies of evidence point to a specific, addressable gap: cost-effectiveness models for bedaquiline and delamanid treat the diagnostic informatics environment as external to therapeutic value, when the evidence reviewed here shows it helps determine that value. This paper's contribution is conceptual. It proposes a framework that repositions diagnostic informatics as a determinant of therapeutic value in multidrug-resistant tuberculosis and sets out the mediating and moderating pathways through which this occurs, with direct relevance to the Indonesian health system.

2. Research Method

This paper is a conceptual review, not a systematic review. It builds an argument that connects two established but previously unlinked bodies of evidence, rather than cataloguing every study within a single domain. A conceptual review does not require pre-registration or formal risk-of-bias assessment, but the search process is reported here in enough detail to allow verification.

Evidence was retrieved between 14 and 15 September 2026 using an AI-assisted medical evidence retrieval platform (OpenEvidence) that indexes and synthesizes peer-reviewed content, including material from Springer Nature, Wiley (including the Cochrane Database of Systematic Reviews), NEJM Group, and JAMA Network. No publication-year or language filter was applied; all retrieved sources were in English. Searches were structured around five thematic domains, each queried with one narrowly scoped question:

Domain 1, magnitude of diagnostic and treatment-initiation delay for MDR/RR-TB in Indonesia, queried with the terms diagnostic delay MDR-TB Indonesia, time from symptom onset to diagnosis, and time from diagnosis to treatment initiation, returned 9 unique studies.

Domain 2, clinical and epidemiological consequences of delay, queried with diagnostic and treatment initiation delay, clinical outcomes MDR-TB, and treatment success, mortality, disease severity, transmission, returned 16 unique studies (with overlap with Domain 1).

Domain 3, parameter structure of published bedaquiline/delamanid cost-effectiveness models, queried with bedaquiline delamanid cost-effectiveness model, diagnostic delay as model parameter, and sensitivity analysis drivers ICER, returned 12 unique studies, including 6 primary cost-effectiveness analyses.

Domain 4, evidentiary maturity of diagnostic and informatics-based delay-reduction interventions, queried with AI-based diagnostic tools, machine learning drug susceptibility prediction, digital chest X-ray screening, and automated resistance genotyping, returned 21 unique studies.

Domain 5, precedent for incorporating delay into health-economic models in other disease areas, queried with diagnostic delay as ICER parameter, time-to-diagnosis health economic model, and diagnostic informatics quality treatment value, returned 10 unique studies.

After removing duplicates across domains, 32 unique studies were included in this review. Where a domain search returned model-specific findings, for example the parameter structure of a named cost-effectiveness model, the underlying primary study was identified by name and checked against its original publication before its findings were used to support this paper's argument. This targeted approach does not provide the exhaustive, reproducible coverage of a systematic review, and the findings below are stated with that limitation in mind: claims about what published models do or do not include describe the models identified in this review, not the full universe of published models on this topic.

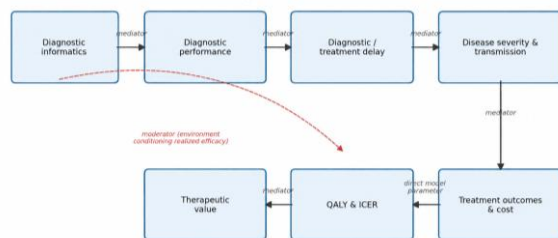


Figure 1. Conceptual framework linking diagnostic informatics to the therapeutic value of multidrug-resistant tuberculosis treatment. Dashed arrow denotes the moderating pathway; solid arrows denote the mediating chain.

Figure 1 summarizes the conceptual framework this review builds toward. Diagnostic informatics affects therapeutic value through two distinct pathways. As a mediator, it acts through a chain: diagnostic informatics shapes diagnostic performance, which shapes diagnostic and treatment-initiation delay, which shapes disease severity and transmission, which shapes treatment outcomes and cost, which enters QALY and ICER calculations, which determine therapeutic value. As a moderator, diagnostic informatics also conditions how much of a drug's trial-derived efficacy is realized in practice, independent of the mediating chain: the same drug, at the same acquisition price, carries different real-world value depending on the diagnostic environment into which it is deployed. In current bedaquiline and delamanid cost-effectiveness models, only the segment from treatment outcomes to

QALY/ICER is modeled as a direct parameter; every upstream link is absent from the model structure.

3. Result and Discussion

3.1. Magnitude of Diagnostic and Treatment-Initiation Delay in Indonesia

Indonesian studies document delay at multiple points in the MDR/RR-TB care cascade, and the magnitude depends on which point in the cascade is measured and which diagnostic technology is in use. In an urban Bandung cohort, the median interval from symptom onset to confirmed TB diagnosis, the diagnostic delay, was 62 days, following a median of 30 days from symptom onset to first provider contact; patients typically visited multiple providers before diagnosis [7]. After Xpert MTB/RIF became the primary diagnostic tool, the registration-to-diagnosis interval fell to a median of one day in a pre-post intervention study across three provincial hospitals [23]. The treatment-initiation delay, the interval from diagnosis to treatment start, has proven harder to close: a West Java retrospective cohort found second-line treatment started at a median of 41 days after RR-TB diagnosis [5], and a Jakarta-based mixed-methods study reported a median of 24-26 days [6]. In the Bandung cascade-of-care analysis, only 9.8% of estimated true drug-resistant tuberculosis cases were ever diagnosed, and only 25.5% of diagnosed patients completed the full cascade through successful treatment [8]; again, this is a finding specific to Bandung. Rural residence, lack of insurance, and reliance on private providers were independently associated with longer delay in more than one of these studies [5], [7]. Table 1 summarizes the design, population, delay definitions, and key findings of the Indonesian delay studies identified in this review.

Table 1. Indonesian studies on MDR/RR-TB diagnostic and treatment-initiation delay identified in this review

Study, setting	Delay measured	Duration	Key finding
Lestari et al. [7], Bandung (urban, general TB)	Symptom onset to diagnosis	Median 62 days (35-113)	30-day median to first provider contact; multiple visits typical
van Kampen et al. [23], 3 provincial hospitals	Registration to diagnosis	Median 1 day (0-4), post-Xpert	Xpert MTB/RIF sharply cut turnaround
Soeroto et al. [5], West Java (RR-TB)	Diagnosis to treatment start	Median 41 days (29-70)	Rural residence predicted delay
Silitonga et al. [6], Jakarta (MDR/RR-TB)	Diagnosis to treatment start	Median 24-26 days	Comorbidities, unemployment linked to delay

Study, setting	Delay measured	Duration	Key finding
Lestari et al. [8], Bandung (4-yr cascade)	Full cascade, diagnosis to cure	9.8% ever diagnose d; 25.5% of those cured	Largest reported gap; specific to Bandung

3.2. Clinical and Epidemiological Consequences of Delay

Delay at both the diagnostic and treatment-initiation stages associates with worse clinical outcomes across high-burden settings, though the strength of this association is not always statistically robust after adjustment. In Shanghai, treatment initiation within 60 days of drug susceptibility testing was independently associated with favorable outcomes [24]. In Yangon, longer treatment delay was significantly associated with higher sputum smear grade, resistance to a greater number of drugs, and longer time to culture conversion, all surrogate markers of greater disease severity [9]. In Hunan Province, China, progressive shortening of diagnostic timelines after rapid molecular diagnostics were introduced tracked with a stepwise decline in the cumulative hazard of poor treatment outcomes across successive treatment cohorts [10]. Because delayed effective treatment prolongs infectiousness, diagnostic and treatment delay is increasingly recognized as a principal driver of ongoing MDR-TB transmission; some analyses rank it above acquired resistance as the epidemic's primary driver [11], [25]. Indonesian national treatment success rates for MDR-TB have stayed below the WHO target of 80%, ranging from 48% to 58% across recent cohorts, against the backdrop of the delay intervals reported above [26]. None of these outcome studies is drawn from an Indonesian cohort that directly links delay duration to mortality or transmission; the mechanistic link presented here draws on regional and global evidence applied to the Indonesian delay data in Section 3.1.

3.3. Absence of Delay Parameters in Cost-Effectiveness Models of Second-Line TB Drugs

The six bedaquiline and delamanid cost-effectiveness analyses identified in this review, spanning the United Kingdom, Germany, Hong Kong, South Africa, and one multi-country analysis of seven high-burden settings, do not include diagnostic delay or time-to-treatment-initiation as an input parameter or a sensitivity-analysis variable [2], [3], [4], [13], [27]. Each model's simulated time horizon starts at confirmed diagnosis and treatment initiation, treating that interval as fixed, and each model's sensitivity analysis concentrates on drug acquisition price, treatment outcome probabilities, and adverse event management costs as the dominant drivers of the ICER [12]. Diagnostic test accuracy is likewise absent as a

formal sensitivity variable in these treatment-regimen models; it appears instead in separate diagnostic-strategy models that do not connect back to treatment-regimen valuation [28]. Table 2 lists the six models by country, model structure, perspective, time horizon, and whether delay is included as a parameter.

Table 2. Bedaquiline/delamanid cost-effectiveness models identified in this review (all use a healthcare-payer perspective and decision-analytic structure) and their treatment of diagnostic and treatment-initiation delay

Study, country	Time horizon	Key drivers	ICER	Delay parameter?
Wolfson et al. [2], UK	5 years	Outcome, hospitalization cost, AE cost		No
Wirth et al. [3], Germany	Full treatment course	Outcome probability, drug cost		No
Lu et al. [12], 7 countries	24 months	Drug price, favorable outcome rate		No
Fekadu et al. [4], South Africa (XDR-TB)	24 months	Outcome probability, drug price		No
Mpobela Agnarson et al. [13], South Africa	9-11 months	Regimen cost, outcome probability		No
Fan et al. [27], China (city-level)	2 years	Background regimen cost, outcome		No

3.4. Evidentiary Maturity of Diagnostic and Informatics-Based Delay-Reduction Interventions

Diagnostic and informatics interventions vary in how strongly they are shown to reduce diagnostic and treatment-initiation delay. Molecular diagnostics carry the strongest and most directly quantified evidence: a systematic review and meta-analysis of 45 studies found line probe assays reduced diagnostic delay by a mean of 40.1 days and treatment-initiation delay by 45.3 days compared with culture-based drug susceptibility testing [17]. Consensus guidance points to further turnaround gains from next-generation sequencing for second-line resistance profiling, particularly for drugs such as bedaquiline and linezolid, for which no rapid molecular assay exists outside sequencing-based platforms [19]. Machine-learning models trained on whole-genome sequence data reach high accuracy for resistance prediction and compress a process that traditionally took weeks into hours to days once sequence data is available, but the literature treats prospective validation of their effect on time-to-treatment as an open question [29]. Deep-learning chest radiograph triage tools perform comparably to human readers for TB screening; their authors propose, without directly measuring, that such tools could reduce time to diagnosis [20], [30]. Indonesia's national tuberculosis information system, SITB, belongs to the

category of digital infrastructure that multi-country qualitative assessment associates with automated result notification and reduced diagnostic delay, though no Indonesia-specific quantitative delay metric for SITB has been reported [22].

3.5. Precedent for Incorporating Diagnostic Delay into Health-Economic Models

Health-economic models in other disease areas show that diagnostic delay and time-to-diagnosis can be built into cost-effectiveness structures as formal parameters. Methodological guidance on economic evaluation of diagnostics names time-to-correct-diagnosis as a modelable value driver and points to discrete-event simulation combined with long-term lifetime modeling as one applicable approach [15]. Oncology offers a working example: a chimeric antigen receptor T-cell therapy model for pediatric acute lymphoblastic leukemia used discrete-event simulation to include wait-time between leukapheresis and infusion as an explicit parameter, and increasing wait-time changed projected quality-adjusted life years and the resulting ICER [14]. In infectious disease, cost-effectiveness models of rapid molecular diagnostic testing for bloodstream infections build time-to-effective-therapy directly into their decision-analytic structure and find such testing cost-saving when combined with antimicrobial stewardship [16]. Within tuberculosis, a decision-analytic model of computer-aided detection integrated into chest X-ray triage in Ghana modeled diagnostic pathway choice as the parameter driving incremental cost and quality-adjusted life years, and identified threshold configurations that were cost-saving relative to standard care [31].

3.6. Discussion

The five domains reviewed above point to a specific gap in how the therapeutic value of second-line tuberculosis drugs is assessed. Diagnostic delay in Indonesia's MDR/RR-TB care cascade is not marginal: it spans weeks at multiple points in the pathway, and its downstream consequences, greater disease severity, lower cure rates, prolonged infectiousness, are documented across comparable high-burden settings [9], [10], [11]. The cost-effectiveness models that inform decisions about whether bedaquiline or delamanid represent good value for a health system start their simulated clock only after this delay has already occurred, at treatment initiation [2], [4]. A determinant of real-world therapeutic value that is well characterized epidemiologically sits entirely outside the parameter architecture of the models built to quantify that value.

Diagnostic informatics should not replace drug efficacy, price, or adverse-event profiles as the primary levers of cost-effectiveness in these models. The claim here is narrower: diagnostic delay acts as a moderating variable that determines how much of a drug's trial-

derived efficacy is realized in practice. A regimen shown to be cost-effective under an implicit assumption of prompt treatment initiation may perform differently in a health system where diagnosis-to-treatment intervals commonly exceed three weeks and where the Bandung cascade data suggest fewer than one in ten true cases are ever diagnosed [8]. This distinction sits within the domain of pharmacology and therapeutics, since the same drug can carry different real-world value depending on the diagnostic informatics environment in which it is deployed, and not only within the domain of diagnostics.

The evidence reviewed here also suggests the fix does not require new technology. Molecular diagnostics with the strongest quantified delay-reduction effects, line probe assays and Xpert-based testing, already exist and are partly deployed in Indonesia [17], [23]. Artificial intelligence-based tools, including genotypic resistance prediction and radiographic triage, remain earlier-stage: prospective evidence linking their use to shortened time-to-treatment is still limited, and any framework should position them as promising rather than proven [20], [29]. What is missing is not primarily new diagnostic technology. It is the methodological step of connecting existing diagnostic informatics performance, at whatever level of maturity, to the economic models that shape formulary and reimbursement decisions.

Precedent from other disease areas shows this connection is achievable with existing methods. Discrete-event simulation has already incorporated treatment wait-time into an oncology cost-effectiveness model, with measurable consequences for the resulting ICER [14]. Rapid diagnostic testing models in bloodstream infection have built time-to-effective-therapy directly into their decision-analytic structure [16], and a tuberculosis-specific precedent exists in the Ghanaian computer-aided detection model, which parameterized diagnostic pathway choice as a driver of incremental cost and quality-adjusted life years [31]. The absence of delay parameters in bedaquiline and delamanid cost-effectiveness models reflects a gap in current modeling convention, not a methodological ceiling.

For Indonesia, this gap carries policy relevance. Health technology assessment processes that evaluate second-line tuberculosis drugs for national formulary inclusion, using models imported or adapted from higher-resource settings, risk overestimating real-world cost-effectiveness if the diagnostic informatics environment in which the drug will actually be deployed is left out of the model structure. Framing diagnostic informatics investment, whether in molecular diagnostics, digital notification systems such as SITB, or eventually AI-based triage, as a determinant of pharmacoeconomic value, rather than a separate public health infrastructure concern, could

strengthen the policy case for such investment by tying it directly to the value proposition of the drugs it supports.

This paper's contribution stops at the conceptual framework in Figure 1. It does not present a new model or dataset, and it does not quantify how much diagnostic delay changes the cost-effectiveness of bedaquiline or delamanid in Indonesia; no claim in this paper should be read as demonstrating that diagnostic informatics has already been shown to alter these drugs' therapeutic value in Indonesia. The framework instead sets the direction for that work: adapting the discrete-event simulation or survival-adjustment methods used in oncology and infectious disease [14], [32] to a bedaquiline or delamanid cost-effectiveness model built on Indonesian delay distributions [5], [6], with a sensitivity analysis that varies the diagnosis-to-treatment interval against locally observed ranges. That step would move this framework from conceptual argument to a quantified, testable model.

4. Conclusion

This paper has argued that diagnostic informatics This paper has argued that diagnostic informatics functions as a determinant of therapeutic value in multidrug-resistant tuberculosis, one that is documented in the epidemiological literature but absent from the six bedaquiline and delamanid cost-effectiveness models identified in this review. Indonesian evidence shows diagnostic and treatment-initiation delay to be substantial and clinically consequential, though the largest cascade figures cited here come from Bandung specifically and should not be generalized nationally without further data. The pharmacoeconomic models that inform formulary and reimbursement decisions continue to assume prompt treatment initiation as a fixed condition, and precedent from oncology and infectious disease modeling shows this gap reflects modeling convention rather than methodological limitation. The conceptual framework in Figure 1 is a starting point, not a finding: it has not been tested against Indonesian data, and it does not by itself demonstrate that diagnostic informatics changes the measured cost-effectiveness of these drugs. The next step is empirical: build a bedaquiline or delamanid cost-effectiveness model using locally observed diagnostic delay distributions as model inputs, and run a sensitivity analysis that varies the diagnosis-to-treatment interval to quantify its effect on the ICER for the Indonesian health system.

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