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A Simulation-Based Cost-Effectiveness Analysis of Reflex DNA Versus Multi-Sample Adolescent Screening for Thalassaemia in East Malaysian Schools

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Summary
This study compares the cost-effectiveness of two school-based thalassemia screening protocols—multi-sample (P1) and Single-sample Reflex DNA (P2)—in Sabah and Sarawak using 2018 National Thalassaemia Screening (NTSP) data. Although P2 was 9–11% costlier upfront, it eliminated dropouts and improved carrier detection. Sabah, a high-prevalence state, demonstrated superior cost-effectiveness with P2 (RM379.95 per carrier detected) compared to Sarawak (RM821.85). Lifetime treatment cost savings for avoided births with thalassemia major were substantial. The findings support the phased implementation of P2, starting with high-prevalence states, to reduce the economic burden on Malaysia's healthcare system.

Keywords
Thalassemia, school-based screening, simulation-based analysis, Reflex DNA, drop-out rates

Introduction
Thalassemia remains a significant public health concern in Malaysia, with an estimated lifetime treatment cost of RM2.66 million per transfusion-dependent patient[1]. Since 2016, the Ministry of Health Malaysia has implemented the National Thalassemia Screening Programme (NTSP), targeting Form Four students through a school-based multi-sample approach (P1)[2]. However, the multi-stage workflow contributes to significant dropout rates. In 2018 alone, 2,950 students in Sabah and 2,836 in Sarawak discontinued the screening, resulting in missed carrier detection and a preventable disease burden. To address this, an alternative strategy Single-sample Reflex DNA approach (P2) was retrospectively modelled using 2018 data. This study aims to compare the cost-effectiveness of P1 and P2 in Sabah and Sarawak and evaluate the potential national impact of adopting P2.

Materials and Methods
A retrospective, simulation-based cost-effectiveness analysis used 2018 NTSP data involving 36,860 students from Sabah and 35,161 from Sarawak. Two protocols were compared as shown in Table 1.

Table 1: Comparing P1 and P2 steps involved

Step	Conventional Multi-Sample (P1)	Single-Sample Reflex DNA (P2)
Enrolment	Form 4 students enrolled	Form 4 students enrolled
Consent	Consent obtained	Consent obtained
Sample Collection	3 separate samples (Full Blood Count (FBC), Haemoglobin Analysis (HbA), DNA testing)	Single blood sample collected
Suspected Carrier	Identified after HbA	Identified after same sample tested
DNA Confirmation	Requires return visit	DNA test done reflexively from same sample
Dropout Risk	At 3 stages: FBC–Hb, Hb–DNA, before post-test	Zero dropout risk
Time to Completion	6–12 months	<3 months

As P2 was not implemented in 2018, a hypothetical simulation was applied assuming full compliance, zero dropout, and equivalent diagnostic sensitivity. Direct medical costs from a provider perspective were included, with no discounting due to the single group of students.

The effectiveness of Incremental Cost-Effectiveness Ratio (ICER)[3] was measured by comparing the cost difference and dropout reduction between P2 and P1, reflecting the additional cost per dropout averted using this calculation:

ICER = (Cost of P2 – Cost of P1) / (Dropouts averted by P2 – Dropouts averted by P1)

Cost per carrier and lifetime savings from prevented births were estimated using inter-carrier marriage rates of 2%, 4%, and 6% with a 25% inheritance risk[4]. Sensitivity analysis benchmarked P2's ICER against the WHO threshold (RM25,000–75,000)[5]. Crucially, nationwide scale-up requires real-world pilot studies to assess operational feasibility.

Results and Discussion

While P2 incurred higher upfront costs (Sabah: RM793,326; Sarawak: RM485,716) compared to P1, it proved cost-effective. The ICER per averted dropout was RM25.14 (Sabah) and RM22.19 (Sarawak), which is well below the WHO threshold of RM25,000–75,000 (1–3 times the GDP per capita), indicating excellent economic value. Additionally, the cost per carrier detected was lower in Sabah (RM379.95) than in Sarawak (RM821.85), reflecting greater efficiency in high-prevalence settings.

The P2 eliminated all dropouts, compared to 2,950 in Sabah and 2,836 in Sarawak under P1, and increased diagnostic yield. Further analysis estimated 286 and 57 additional carriers detected, respectively. This translates to a 12% increase in detection in Sabah and 5% in Sarawak. Fisher's Exact Test confirmed the statistical significance of dropout elimination ($p < 0.001$) (Figure 1).

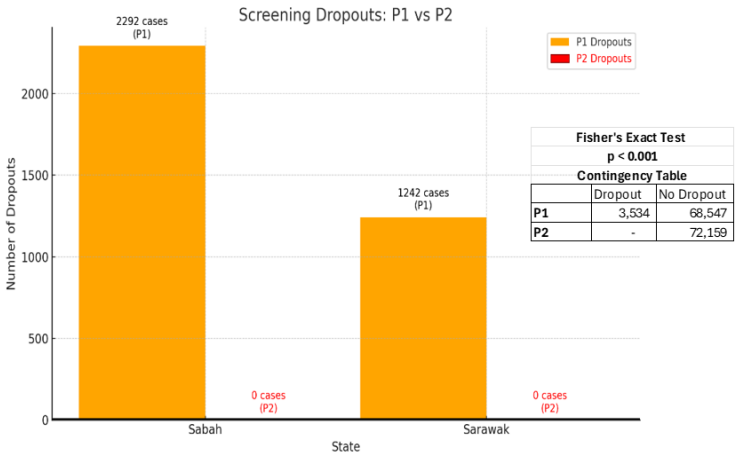

Figure 1: Dropout Comparison for P1 vs P2 Protocols using Fisher's Exact Test

Projected long-term savings were substantial. If the missed carriers under P1 entered inter-carrier marriages (2%–6%) (Figure 2), the lifetime treatment cost potentially avoided ranged from RM3.8 million to RM11.4 million in Sabah, and RM758,000 to RM2.3 million in Sarawak. These estimates were modelled using inter-carrier marriage probabilities and a 25% Mendelian inheritance risk[4].

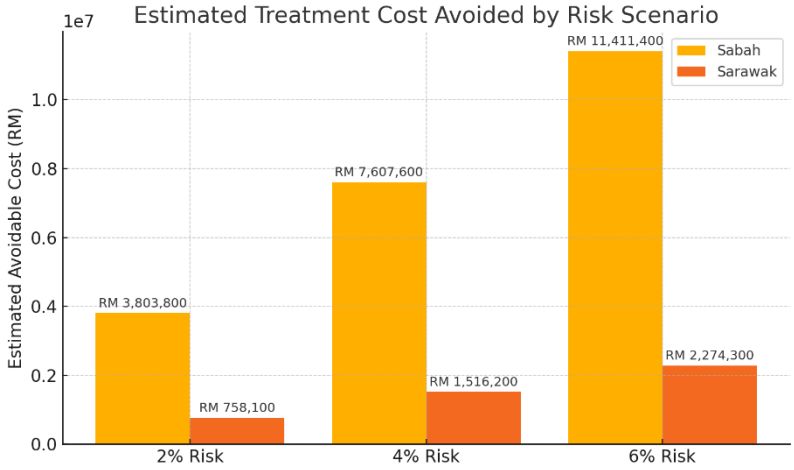

Figure 2: Estimated Avoidable Cost by Risk Scenario Under P1 Enter Inter-Marriages

With each thalassaemia major case costing RM2.66 million in lifetime treatment, the case for P2 is reinforced by both short-term diagnostic gains and long-term healthcare savings. Table 2 summarises the comparative performance of P1 and P2.

Table 2: Comparative Performance of Conventional (P1) vs. Reflex DNA (P2) Screenings

Item	**Conventional Multi-Sample (P1)**	**Single-Sample Reflex DNA (P2)**	**Gains with P2**
Dropouts	2,950 (Sabah) 2,836 (Sarawak)	0	100% dropout elimination
Carriers Detected (Est.)	~1,500 (Sabah) ~1,100 (Sarawak)	286 (Sabah) 57 (Sarawak)	12% (Sabah), 5% (Sarawak)
Cost per Carrier Detected	Not available	RM379.95 (Sabah) RM821.85 (5wk)	Lower in high-prevalence areas
ICER per Dropout Averted	Not available	RM25.14 (Sabah) RM22.19 (Sarawak)	Highly cost-effective
Preventable Treatment Costs	Not available	RM3.8M–11.4M (Sabah) RM758K–2.3M (Sarawak)	Significant long-term savings

Conclusion

The P2 approach demonstrates superior cost-effectiveness and operational efficiency compared to the P1 strategy, particularly in high-prevalence states such as Sabah. While based on modelled projections using retrospective data, these findings justify phased implementation, preceded by pilot studies, to reduce thalassaemia births and generate long-term savings across Malaysia's healthcare system.

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