Original Article

Cost-effectiveness of multi-sample National Thalassemia Screening Programme *vs.* single-sample reflex DNA thalassemia screening in Malaysian schools: a comparative study in Sabah and Sarawak

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Background: Thalassemia poses a significant health and financial burden in Malaysia, highlighting the need for effective screening strategies to reduce the incidence of severe cases and associated costs. While the National Thalassemia Screening Programme (NTSP) for students has made progress in identifying carriers, challenges persist in preventing dropouts and ensuring timely diagnoses. This study assessed the cost-effectiveness of thalassemia screening and prevalence reduction using the single-sample reflex DNA approach comparing Sabah and Sarawak for Form Four or 16-year-old school adolescents. The existing National Screening approach (P1) uses multi-sample compared to the single-sample reflex DNA approach (P2), considering cost, effectiveness, potential cost savings on treatment expenses, and prevalence reduction.

Methods: The study employed a retrospective quantitative approach, using secondary data and non-probability sampling techniques. A purposive sampling method was used to select two states with contrasting prevalence levels: Sabah, with a prevalence rate above the national average, and Sarawak, with a lower-than-average prevalence. The sample comprised 36,860 test cases from Sabah and 35,161 from Sarawak, enabling a comparative analysis of the cost-effectiveness of P1 and P2. We conducted the analysis in three stages: (I) calculating screening and diagnosis costs, (II) comparing dropout rates and carriers identified under each approach, and (III) projecting the long-term impact on future treatment cost savings and prevalence reduction.

Results: The cost-effectiveness analysis using the incremental cost-effectiveness ratio (ICER) demonstrated that the additional cost per dropout averted was around RM 40. However, further analysis revealed substantial potential savings in future treatment costs associated with P2, suggesting significant savings for both Sabah and Sarawak. Depending on the assumed 2% to 6% probability of carriers marrying each other, the projected savings range from RM 691,000 to RM 11 million in Sabah and RM 200,000 to RM 2.2 million in Sarawak, based on the estimated reduction in new thalassemia births. Additionally, the study forecasts a potential 40% annual decrease in thalassemia cases, with the possibility of achieving minimal to zero new cases within 15 years of sustained implementation.

Conclusions: The single-sample reflex DNA approach is a cost-effective alternative to the existing NTSP. It offers a more efficient and rapid screening process, reducing dropout rates and time to diagnosis.

Implementing this approach could enhance the screening program's efficiency and contribute to reducing thalassemia prevalence in Sabah and Sarawak, providing a potential model for nationwide adoption.

Keywords: Thalassemia; screening; cost-effectiveness; Sabah; Sarawak

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Introduction

Background

The detection of Thalassemia in the early 1900s led to the development of various diagnostic tests to prevent the progression of this hereditary disease. Different screening programmes have been applied, from general population screening to targeted screening of high-risk males and adults and prenatal screening that may lead to pregnancy termination. Recently, upstream screening, like pre-implantation genetic screening, has also been explored. Several countries, including Sardinia, Iran, Iraq, Israel, Greece, Turkey, Oman, and Canada, have successfully reduced the incidence of thalassemia between 70% and 90%. North Cyprus has reported frequent zero cases annually in recent years. Many studies have supported the effectiveness of the various intervention programmes, showing that cost-saving treatments are possible if effective prevention is implemented. An example, the intervention programme in Israel has proven to be highly effective, resulting in savings of USD 76 million over ten years (1). It has been reported that treatment costs range from 23 to 65 times more expensive than the cost of the screening programme (2-6).

It is estimated that between 150 to 350 children have been born with beta-thalassemia each year in Malaysia in the last two decades (7). Despite various intervention programmes that have been implemented, including premarital, prenatal and retrospective counselling, thalassemia carriers have not shown significant decline in giving birth to children with thalassemia (8). The Ministry of Health (MOH) Malaysia introduced the Thalassemia Prevention and Control Programme in 2004 started with, cascade screening of family members, premarital and prenatal screening to reduce patient morbidity and mortality while decreasing the number of blood transfusion-dependent thalassemia cases (9). In 2016, the programme evolved into the National Thalassemia Screening Programme (NTSP), which the government fully funds. It targets secondary-four students aged 16 years, with high school coverage rates in this demographic. Schools were the ideal setting to reach most of the adolescent population. This age group was selected for two main reasons: first, students are not yet occupied with major school examinations, and second, it precedes the period when many adolescents begin courting and considering marriage. By implementing this screening programme in schools, Malaysia continues to raise awareness about thalassemia,

Highlight box

Key findings

- The single-sample reflex DNA (P2) approach offers a more cost-effective and efficient alternative to P1, Malaysia's current National Thalassemia Screening Programme (NTSP). By completing the diagnostic process from a single blood sample, it eliminates dropouts, reduces inter-carrier marriages, and lowers thalassemia prevalence. P2 has demonstrated potential savings of RM 691,000 to RM 15 million [United States Dollar (USD) 171 K to 3.72 M] in Sabah and RM 199,000 to RM 3 million (USD 49 to 743 K) in Sarawak by preventing future treatment costs. Although P2 costs 9–11% more upfront than the current method (P1), it improves carrier detection, reduces diagnostic delays, and accelerates outcomes. (Note: the 2018 average exchange rate was 4.0363 MYR/USD).

What is known and what is new?

- Global screening programs are effective in reducing thalassemia and are more cost-efficient than treatment. Malaysia's NTSP targets adolescents have been successful but suffers from significant dropout, limiting its impact. This study applies the incremental cost-effectiveness ratio (ICER) and desktop simulations to show that P2 can save treatment cost reductions in high-prevalence areas while improving diagnostic speed, reducing misdiagnosed carriers, and minimizing adolescent clinic visits. The results indicate P2 could lower thalassemia prevalence faster than the existing approach.

What is the implication, and what should change now?

- Policymakers should consider phased implementation of P2 in high-prevalence regions to reduce inter-carrier marriages and lower overall healthcare costs. A national rollout could follow, leveraging economies of scale to reduce unit costs and maximize impact in thalassemia prevention.

educate students about carrier status, and empower them to make informed decisions regarding marriage and family planning. This approach represents a proactive effort to break the cycle of thalassemia inheritance to reduce the burden on individuals, families, and the healthcare system.

In Malaysia, both α-thalassemia and β-thalassemia are prevalent: approximately 4–5% of Malaysians carry a β-thalassemia gene variant, and an equally high or higher carrier frequency is observed for α-thalassemia 17.3%, particularly single-gene deletions common in Southeast Asia (7,8,10). Although lower prevalence than α-thalassemia, β-thalassemia major often leads to severe disease requiring lifelong transfusions and chelation therapy, the NTSP has largely emphasised detecting β-thalassemia carriers (commonly indicated by elevated HbA_2). However, α-thalassemia remains clinically significant; for instance, couples who both carry the α^0 (double-gene) deletion risk having offspring with Haemoglobin Bart's hydrops foetal, which is typically fatal in utero or shortly after birth (11,12). Recognising the high carrier frequency of both types underscores the importance of a comprehensive screening approach to reduce the overall birth prevalence of severe thalassemia disorders in Malaysia.

Malaysia has a well-established public healthcare system supported by an extensive network of hospitals, clinics, and specialised laboratories capable of handling large-scale diagnostic testing across urban and regional centres (13,14). In particular, the NTSP has developed a coordinated network for sample collection, transport, and testing across states—including Sabah and Sarawak—ensuring that the entire screening process, from initial blood indices to confirmatory DNA testing, is performed efficiently (15,16). Although the population of Sabah and Sarawak is widely dispersed, major infrastructure such as schools and health clinics are often located near each other. Most primary healthcare centres, known as health clinics and staffed by medical doctors, supported with laboratory facilities, are situated close to schools (13). These clinics serve as collection points for samples gathered by school health teams. Full blood count (FBC) tests are conducted within four hours, within the health clinics, while samples for haemoglobin analysis (HbA) are transported to the nearest hospital within five days (17). This robust infrastructure mirrors the comprehensive screening models in countries such as Thailand, where integrated diagnostic workflows have led to rapid and effective results (18). By leveraging routine school health services to screen adolescents, the NTSP facilitates early carrier identification and aligns with Malaysia's public health priorities to reduce the birth of affected infants (19).

Rationale and knowledge gap

Initiating a screening programme is crucial to alleviating the burden of treating primary Thalassemia patients who require lifelong treatment, including blood transfusions and chelation therapy. Regular blood tests, such as complete blood counts, iron studies, and heart, kidney, and liver function tests, are necessary. Additionally, these patients often require consultations with various medical specialities. Hormonal investigations may also be essential for growth monitoring, increasing medical costs (20). Blood transfusions make up a significant portion of thalassemia treatment expenses. In Malaysia, one unit of packed red cells costs approximately RM 200 (21). According to recent research by Shafie *et al.*, the lifetime cost of treating patients with transfusion-dependent thalassemia (TDT) is estimated to be USD 606,665 (approximately RM 2,660,000), considering the cumulative healthcare costs over their lifetime (22). It is essential to note that these costs have increased significantly since then due to advancements in treatment and the prolonged life expectancy of thalassemia patients.

Detecting carriers of thalassemia is imperative to reduce its prevalence, facilitate and discourage inter-carrier marriages, and enable early prevention since thalassemia is preventable. Screening protocols accompany targeted counselling, which is especially important during adolescence—a critical period before individuals choose a life partner. Khurma's study highlighted the significant psychosocial burden faced by Indian adolescents with thalassemia, with concerns centred around future social interactions, education, and access to healthcare (23). The study emphasised the necessity of prioritising prevention while addressing the morbidities these adolescents experience. Conversely, Ghanizeh's research found that while psychiatric disorders, including major depressive disorder and suicidal behaviours, are present among adolescents with thalassemia, their prevalence is not higher than in the general population (24).

While NTSP has made significant achievements, it faces challenges with dropouts. The definition of dropouts refers to students who were identified for screening but did not attend the screening process, resulting in their exclusion from the statistics. A significant number of students who were flagged during the initial screening failed to return for

confirmatory testing. Administrative data from the MOH showed dropout rates as high as ~20% in some districts. The screening procedure is complex and involves various tests, requiring them to return for tests, including FBC and HbA, followed by DNA testing if necessary. This sequence took several months before a diagnosis was reached, and many students dropped out at various levels of the test before completing the screening and follow-up process. Previous studies have shown while health education increases awareness and knowledge about thalassemia, it does not necessarily motivate adolescents to undergo screening tests (25-27). Similarly, in Egypt, school-based screening programmes also report dropout issues. Doll *et al.*, [2013] revealed that while students are initially screened, follow-up rates suffer due to logistical challenges and socio-economic barriers, leading to an incomplete dataset on carrier prevalence. Egypt has considered strategies like incorporating thalassemia awareness into school curriculums and offering low-cost, streamlined testing to enhance retention and prevent new cases through early detection (28).

Several recent studies support the potential benefits of using single-sample reflex DNA testing for improving thalassemia carrier detection and screening efficiency, adding weight to its inclusion in public health programmes. Single-sample reflex DNA or, in some countries, using next-generation sequencing (NGS)-based techniques have demonstrated high detection rates, often exceeding 95%, particularly for thalassemia carriers who may be undetected in traditional screening methods. These studies have shown that NGS could detect silent and rare variants more accurately, making it advantageous in reducing false negatives and misdiagnoses commonly seen with conventional methods (29,30).

While the NTSP has made significant progress, challenges remain, particularly with dropout rates due to the multi-stage process. Recent advancements, such as single-sample reflex DNA testing, offer promising solutions by streamlining the workflow, reducing logistical barriers, and improving carrier identification. This study aims to evaluate the cost-effectiveness of this alternative approach and its potential to reduce dropouts and prevalence in high and low prevalence states.

Objective

Through desktop calculations, this study evaluated the cost-effectiveness of using the single-sample reflex DNA approach for thalassemia screening. It also aimed to address whether this approach can reduce dropouts and achieve the desired outcome of reducing births and the prevalence of thalassemia and potential cost savings. Ultimately, this strategy might be presented as a viable alternative to the existing NTSP. We present this article in accordance with the CHEERS reporting checklist (available at https://jhmhp.amegroups.com/article/view/10.21037/jhmhp-24-135/rc).

Methods

Research design

This study used purposive sampling to select two Malaysian states, Sabah and Sarawak, with contrasting thalassemia prevalence rates. Sabah, with a prevalence rate above the national average, had 36,860 test cases, while Sarawak, with a lower prevalence rate, had 35,161. This setup allowed for a meaningful comparison of the cost-effectiveness of two screening approaches, P1 and P2, in each region. The study's quantitative, retrospective design used non-probability sampling among adolescents aged 16 (Form-Four students) as part of the P1.

Sabah was purposively chosen not only for its high thalassemia prevalence but also for its higher dropout rates. In contrast, its neighbouring state, Sarawak, has similar dropout rates but a lower carrier prevalence. However, they share similar unique logistical challenges, including vast, sparsely populated areas and ethnically diverse communities, differentiating them from West Malaysia. By focusing on these states, the study captured the impact of the screening programmes in regions with specific logistical and demographic complexities, providing a framework for broader applications.

All samples were drawn from secondary data on NTSP test results collected from the MOH Malaysia, specifically from the Family Health Development Division database in 2019. It represented the 2018 cohort, the most recent year with complete and validated data available at the time of study design. This ensured a stable baseline for the cost-effectiveness analysis and avoided potential anomalies from subsequent program changes or disruptions. All recorded test cases from each state were included as study samples.

The retrieved data were subjected to the following analysis stages, shown in *Figure 1*. The first stage involved analysing screening costs, followed by the second, calculating the ICER. Subsequently, the third and fourth stages projected reductions in thalassemia prevalence and the associated cost savings. Finally, the fifth stage conducted

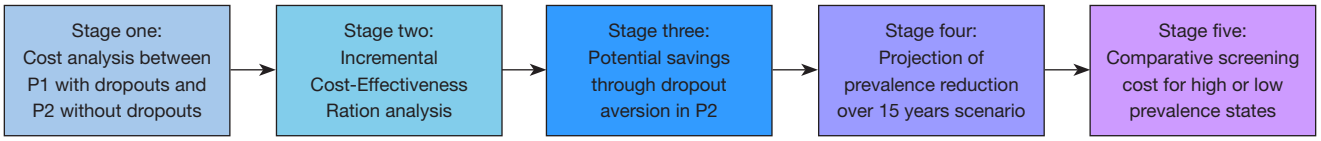

Figure 1 Flow chart of the five stages of P1, adopted in the methodology from Guidelines for Thalassemia Screening Among Form Four Students, Ministry of Health Malaysia, 2016. P1: existing National Screening approach; P2: single-sample reflex DNA approach.

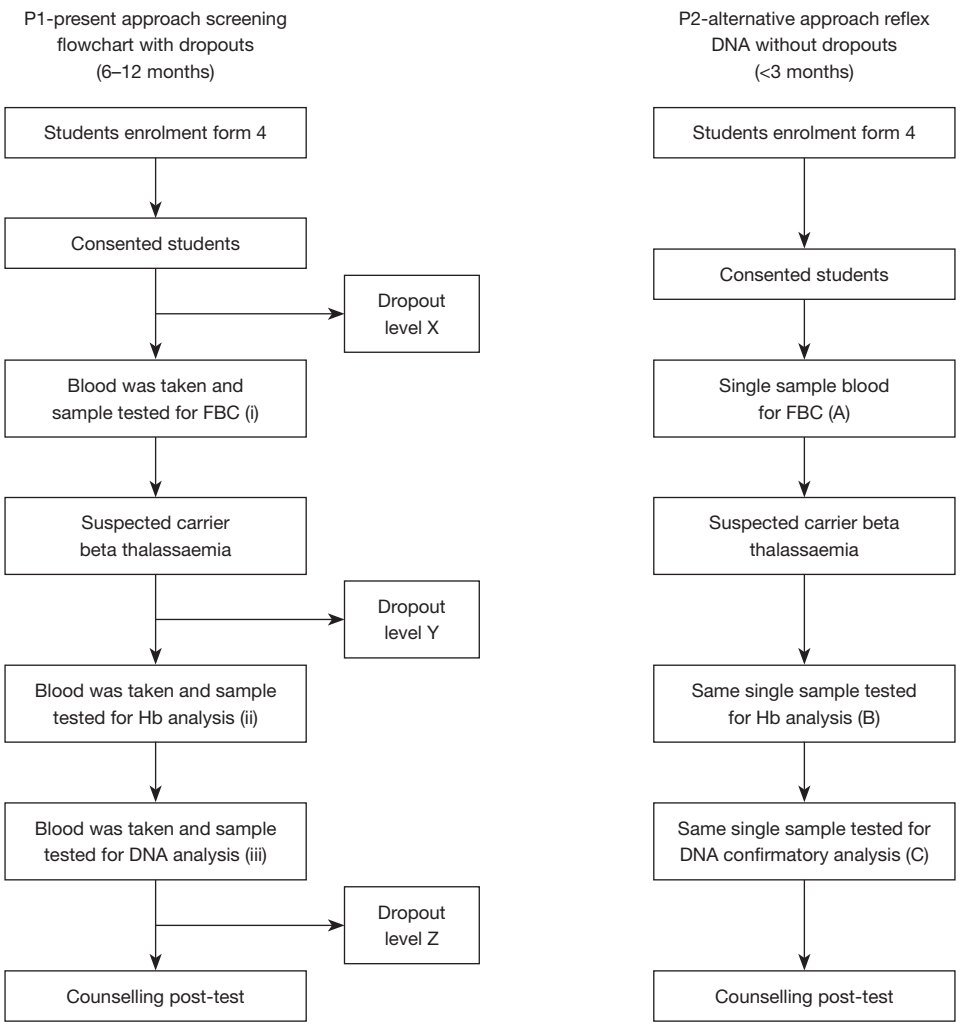

Figure 2 Flowchart of the first stage, comparing the screening process of P1 versus P2 identifying critical dropout points and estimated time taken to complete the steps. P1: existing National Screening approach; P2: single-sample reflex DNA approach. FBC, full blood count; Hb, haemoglobin.

targeted approach analyses, specifically comparing a low-prevalence state and a high-prevalence state to evaluate the implementation of the alternative approach.

Figure 2 illustrates the detailed thalassemia screening and testing processes for the current (P1) and the proposed single-sample reflex DNA (P2) to establish carrier status. The P1 flow chart demonstrated distinct stages where dropout rates were reported and labelled as Levels X, Y, and Z. P1 takes about 6–12 months before a diagnosis is made. Under P1, students undergo an initial blood screening FBC, HbA, and DNA analysis, requiring multiple visits over several weeks (13). In contrast, the alternative method,

the single-sample reflex DNA approach (P2), was projected to achieve zero dropout rates. This approach (P2) collects a single venous blood sample at the outset, removing the need for an additional blood draw or follow-up appointment. In this approach, testing is conducted sequentially, beginning with FBC, followed by HbA and DNA analysis on the same sample for individuals with abnormal FBC indices or elevated HbA. P2's efficient single-sample protocol provided enough blood sample for all necessary analyses. Hence, the test can be done within 3 months, if not lesser, removing the need for additional visits or recalls, which typically contribute to dropouts in multi-stage screening models.

For confirmatory DNA testing, positive screening samples were subjected to polymerase chain reaction (PCR)-based assays, specifically Gap-PCR, reverse dot blot (RDB), and PCR-Sanger sequencing for mutation-specific detection. Gap-PCR was employed to identify common α-thalassemia gene deletions, while RDB and PCR-Sanger sequencing were used to detect β-thalassemia point mutations. These methods were chosen due to their cost-effectiveness and compatibility with the existing infrastructure in Malaysian diagnostic laboratories, with an estimated cost per sample ranging between RM 150 and RM 200. Although NGS offers the advantage of identifying a broader range of mutations, including rare variants, its higher costs and the need for specialized instrumentation currently make it less feasible for routine population-based screening programs in Malaysia (13,16). As such, the use of these PCR-based assays provides a practical and sustainable option for large-scale implementation within Malaysia's public health system.

As shown in *Figure 2*, the Flowchart Comparing Dropouts in P1 and P2 for Sabah and Sarawak, the number of dropouts generated was as follows: students who consented but did not attend for FBC blood taking were categorised as dropouts at Level X. Those who consented but did not undergo HBA were classified as Level Y dropouts. Those identified as suspected carriers through DNA Confirmatory analysis and scheduled for counselling appointments were designated dropouts at Level Z.

Stage one: cost analysis

The cost analysis of activities for both the processes in P1 and P2 involved in diagnosing a carrier. These activities involved the costs of conducting a FBC, HbA, and DNA Analysis. The unit costs used for the respective steps are RM 4 (FBC), RM 50 (HbA), RM 100 (DNA), RM 9 for contact tracing, and RM52 for counselling. These unit costs for screening activities were obtained from the MOH's Family Health Development Division.

Data source for costs

The costs were obtained from the MOH Malaysia, which oversees the Thalassemia Screening Programme. The Ministry provided the average and estimated costs for each activity and allocated the costs accordingly. The captured costs include laboratory expenses and employee salaries, calculated based on the time required to perform each activity. The costs for FBC, HbA, and DNA analysis are incurred by the laboratory conducting these tests. The employee costs for conducting contact tracing and counselling for diagnosed thalassemia carriers are calculated, factoring in the employee's salary and the time required to perform these tasks. The average exchange rate in 2018 for 1 USD was 4.0363 MYR (31).

Stage two: ICER

The formula used the difference in costs and health effects (dropouts averted) between the alternative method (P2) and the present method. In this calculation, the ICER represents the additional cost per additional unit of health effect (dropouts averted) achieved by the alternative approach (P2); the formula is as depicted below (32).

$$\frac{\text{Cost of Single-sample Reflex DNA, P2} - \text{Cost of Current Screening, P1}}{\text{Effect of dropouts averted with P2} - \text{Effect of dropouts averted with P1}} = \text{ICER} \quad [1]$$

Stage three: estimating potential savings without dropouts

The goal was to compare P1 and P2 and determine potential cost savings. The analysis first quantifies the dropouts across all levels, as shown in *Figure 2*, and then estimate the number of carriers that could be missed. The methodology involved multiplying the number of dropouts reported for each state by the estimated carrier prevalence or percentage determined by the study. The study presented the results based on the sample population in two ways: (I) based on the total number of individuals who provided consent, and (II) based on the total student enrolment, with (I) being a subset of (II).

Stage four: projection of prevalence reduction

The projected reduction of thalassemia prevalence was estimated using a simple arithmetic approach, assuming

percentage decreases among carriers marrying each other at proposed rates of 2%, 5%, 10%, 20%, 30%, and 40% per year. For both states, these assumptions were used to estimate the resulting conception of thalassemia-affected babies over 15 years.

Stage five: comparative analysis of prevalence (high and low-prevalence states)

A comparative analysis was conducted to establish whether P2 would be more efficient to implement than P1 in high or low-prevalence states.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Malaysian Research Ethics Committee and registered under the National Medical Research Register Malaysia [NMRR ID-22-00985-D1X (IIR)] and the Family Health Development Division, MOH Malaysia provided the anonymised line listing of the study sample of Form 4 students and individual consent for this retrospective analysis was waived.

Statistical analysis

Descriptive and comparative analyses were performed using deterministic desktop modelling techniques based on secondary administrative data from the Ministry of Health Malaysia. The cost-effectiveness analysis was structured into five stages, each guided by defined economic modelling assumptions.

For each screening approach (P1 and P2), costs were calculated per activity using unit cost data provided by MOH Malaysia, while effectiveness was measured in terms of dropouts averted and carriers detected. The incremental cost-effectiveness ratio (ICER) was calculated to compare additional costs per dropout averted.

A scenario-based sensitivity analysis was conducted to test the robustness of projected cost savings by varying inter-carrier marriage probabilities (2%, 4%, and 6%). These rates were applied to Mendelian inheritance probabilities to estimate future thalassemia births and associated treatment costs under different assumptions.

Basic statistical calculations and projections were performed using Microsoft Excel, including prevalence estimates, dropout rates, and lifetime cost modelling. Where applicable, Fisher's Exact Test was used to compare dropout rates between Sabah and Sarawak due to their relatively small differences and unequal sample sizes.

Confidence intervals were not calculated because the study used fixed values from administrative data instead of simulating different possible outcomes using probabilities. Since the data came from the full population rather than a random sample, we focused on projected scenarios rather than statistical testing.

Results

The total enrolment and number of samples studied was 36,860 for Sabah and 35,161 for Sarawak. This represents 85% of the estimated total 16-year-old (33). However, only 33,142 (89.9%) and 32,848 (93.4%) consented. In P1, the screening flow involved many tests and was also the factor that resulted in dropouts (*Figure 3*). The total dropouts for P1 were from the sum of these three levels: Sabah, 2,940, and Sarawak, 2,836. To assess whether the difference in dropout rates between Sabah and Sarawak was statistically significant, Fisher's Exact Test was applied to the contingency table of dropout versus completion status. The resulting P value of 0.094 indicated that the difference was not statistically significant at the 5% level. As explained earlier, P2, the proposed single-sample reflex DNA approach, would not have any dropouts at all three levels from Level X to Level Z throughout the screening process.

Stage one

The detailed cost associated with each step involved with the screening was calculated as outlined in the flow chart in *Figure 3*. This is further elaborated in *Table 1*, which provides the breakdown of these costs for each defined activity. The cost analysis begins with P1, focusing on students listed in column C, row C, who provided consent. The FBC test, priced at RM 4 per test, resulted in total costs of RM 129,976 for Sabah and RM 125,016 for Sarawak. Similarly, the cost analysis was replicated for P2. The FBC screening identified 8,973 and 4,826 suspected thalassemia carriers for Sabah and Sarawak, respectively, as indicated in row D. For the subsequent HbA test in P1, there were 8,187 tests in Sabah and 4,356 in Sarawak. However, the study noted that 786 individuals in Sabah and 470 in Sarawak dropped out at Level Y.

The cost per HbA test was RM 50, leading to total expenditure after accounting for dropouts of RM 409,350 in

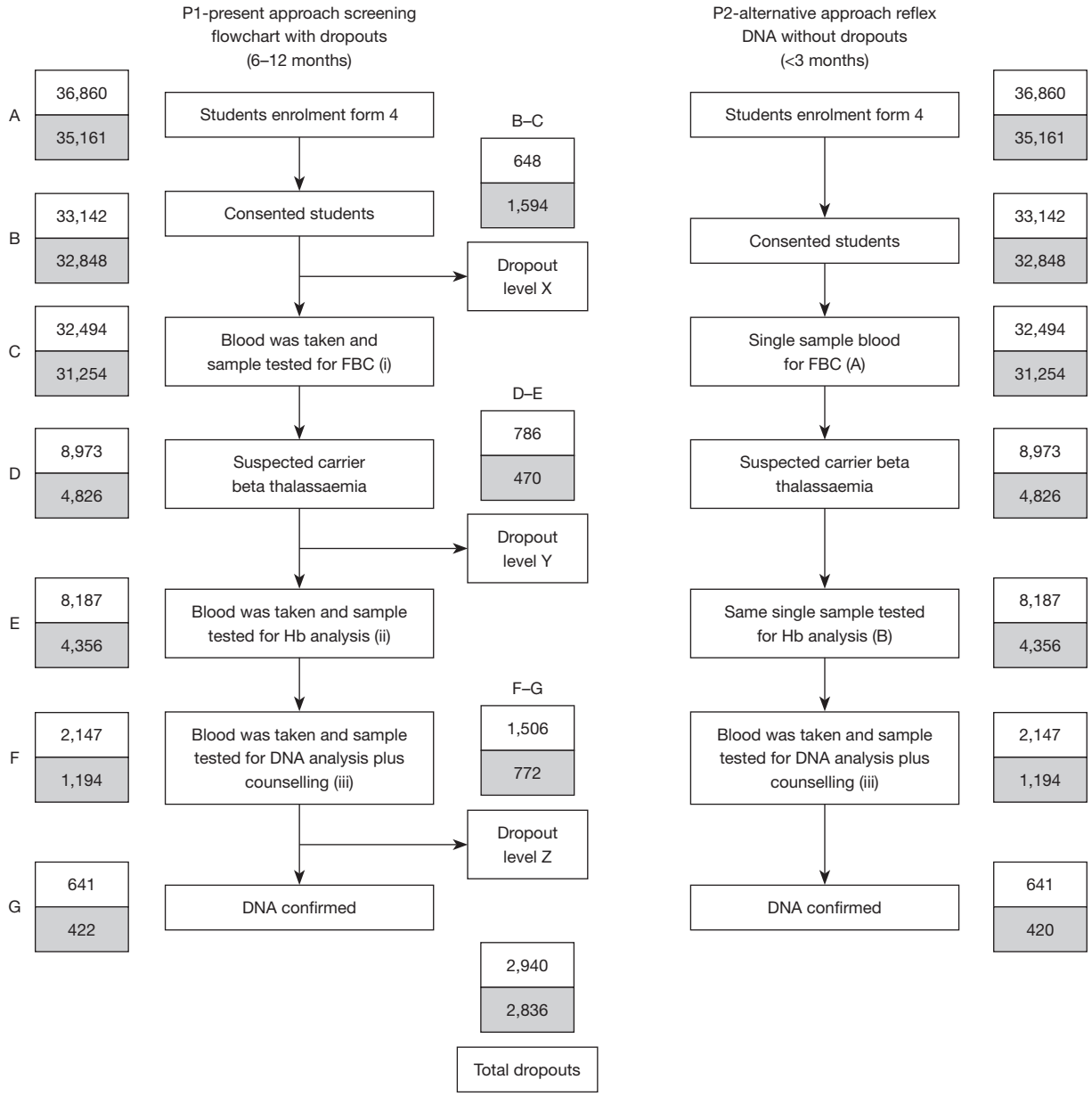

Figure 3 Flowchart comparing number of dropouts in P1 and P2 for Sabah (white box) and Sarawak (grey box). P1: existing National Screening approach; P2: single-sample reflex DNA approach. FBC, full blood count; Hb, haemoglobin.

Sabah and RM 217,800 in Sarawak. Notably, these dropouts incurred additional costs for contact tracing and follow-up activities at an average rate of RM 9 per contact. This added RM 7,074 in extra expenses for Sabah and RM 4,230 for Sarawak. It is crucial to highlight that the calculations for P2 assumed no dropouts.

For the subsequent HbA test in P1, the participant count was 8,187 for Sabah and 4,356 for Sarawak. Of these, 786 individuals in Sabah and 470 in Sarawak dropped out at Level Y. For RM50 per test, the total expenditure on HbA, after accounting for the dropouts, amounted to RM 409,350 in Sabah and RM 217,800 in Sarawak. It is essential to note that these dropouts incurred additional costs for tracing and follow-up activities, averaging RM 9 per contact tracing. This resulted in an additional expense of RM 7,074 for Sabah and RM 4,230 for Sarawak.

Table 1 Screening activities cost analysis for P1 and estimated for P2, for Sabah and Sarawak (for calculation reference, refer to *Figure 2* for each step)

Costing calculation	Sabah						Sarawak					
	P1			P2			P1			P2		
	a	b	c	d	e	f	g	h	i	j	k	l
	N	RM	RM	N	RM	RM	N	RM	RM	N	RM	RM
A) Enrolment of Form Four students	36,860	n/a	n/a	36,860	n/a	n/a	35,161	n/a	n/a	35,161	n/a	n/a
B) Students with consent for screening	33,142	n/a	n/a	33,142	n/a	n/a	32,848	n/a	n/a	32,848	n/a	n/a
C) Student screened for FBC[†]	32,494	4	129,976	32,494	4	129,976	31,254	4	125,016	31,254	4	125,016
D) Suspected thalassemia carrier[†]	8,973	n/a	n/a	8,973	50	448,650	4,826	n/a	n/a	4,826	50	241,300
E) Students with HbA[†]	8,187	50	409,350	n/a	n/a	n/a	4,356	50	217,800	n/a	n/a	n/a
F) Students default HbA [(D) – (E)]	786	n/a	n/a	n/a	n/a	n/a	470	n/a	n/a	n/a	n/a	n/a
G) Total dropouts-contact tracing family of confirmed Thal carrier	786	9	7,074	n/a	n/a	n/a	470	9	4,230	n/a	n/a	n/a
H) Students need molecular testing (DNA)[†] Level Y	2,147	n/a	n/a	2,147	100	214,700	1,194	n/a	n/a	1,194	100	119,400
I) Students with DNA analysis[†]	641	100	64,100	2,147	n/a	n/a	422	100	42,200	1,194	n/a	n/a
J) Students default DNA analysis [(H) – (I)]	1,506	n/a	n/a	n/a	n/a	n/a	772	n/a	n/a	n/a	n/a	n/a
K) Total dropouts-contact tracing family of confirmed Thal carrier	1,506	9	13,554	n/a	n/a	n/a	772	9	6,948	n/a	n/a	n/a
L) Counselling students with a diagnosis	2,147	52	111,644	n/a	n/a	n/a	1,194	52	62,088	n/a	n/a	n/a
Total cost (RM)	735,698[#]			793,326[@]			458,282[#]			485,716[@]		

The average exchange rate in 2018 1 USD was 4.0363 MYR (32). a: number of students enrolled for P1 in Sabah, based on *Figure 3*. b: cost per test for P1 in Sabah. c: total cost calculated by multiplying the number of students who consented to screening by the test cost for P1 in Sabah. d: number of students enrolled for P2 in Sabah, based on *Figure 3*. e: cost per test for P2 in Sabah. f: total cost calculated by multiplying the number of students who consented to screening by the test cost for P2 in Sabah. g: number of students enrolled for P1 in Sarawak, based on *Figure 3*. h: cost per test for P1 in Sarawak. i: total cost calculated by multiplying the number of students who consented to screening by the test cost for P1 in Sarawak. j: number of students enrolled for P2 in Sarawak, based on *Figure 3*. k: cost per test for P2 in Sarawak. l: total cost calculated by multiplying the number of students who consented to screening by the test cost for P2 in Sarawak. P1: existing National Screening approach; P2: single-sample reflex DNA approach. [†], data taken from the register. [#] Total cost for P1 Sabah (column c) and Sarawak (column i) = row 1 + row 3 + row 7 + row 9 + row 10. [@] Total cost for P2 Sabah (column f) and Sarawak (column l) = row 1 + row 2 + row 6. FBC, full blood count; HbA, haemoglobin analysis; n/a, not applicable.

Table 2 Parameters employed in cost-effectiveness analysis

Variables	Sabah	Sarawak
Cost of screening with P1	RM 735,698.00	RM 458,282.00
Cost of screening alternative method P2	RM 793,326.00	RM 485,716.00
Effect of dropouts averted with P1	0	0
Effect of dropouts averted with P2[†]	2,292	1,242
ICER	RM 25.14	RM 22.10

P1: existing National Screening approach; P2: single-sample reflex DNA approach. [†], dropouts of Hb analysis. Hb, haemoglobin; ICER, incremental cost-effectiveness ratio.

The analysis in this table on confirming carrier status for thalassemia noted that counselling activities were provided to 2,147 students in Sabah and 1,194 students in Sarawak, with an estimated cost of RM 52 per case. Despite the counselling efforts, an additional 1,506 students in Sabah and 772 students in Sarawak dropped out at Level Z, resulting in only 641 students in Sabah and 422 students in Sarawak proceeding to undergo the diagnostic DNA analyses at RM 100 per test (as shown in row G). These dropouts underwent contact tracing as per requirements of the standard operating procedures to comprehend their reasons for declining testing. The contact tracing activities cost RM 9 per case, amounting to RM 13,554 for Sabah and RM 6,966 for Sarawak.

For this stage, the overall cost analysis reveals that P2 incurred higher expenses than P1, with a difference of RM 57,628 for Sabah and RM 27,434 for Sarawak, as indicated in *Table 1*, P1's lower cost compared to P2 is attributed to its no-dropouts and thus excluding expenses related to the tests. However, P1 experienced dropouts of 2,940 in Sabah and 2,836 in Sarawak (as shown in *Figure 3*), which may create a misperception of cost savings for P1.

Stage two

The subsequent evaluation in Stage two entailed computing the ICER utilising the formula derived from the variables in *Table 2*. The ICER calculations for Sabah and Sarawak yielded positive values and were closely comparable, with both regions showing nearly identical figures. The ICER in P2 indicates that each additional unit of effectiveness in preventing dropouts' costs approximately RM 22.10 to 25.14, or an average of RM 25, more than the P1 approach. However, this interpretation should be approached with caution, as it does not account for the unmeasured costs associated with dropouts in P1.

Stage three

An analysis was conducted to estimate the number of potentially undetected thalassemia carriers in the population due to screening dropouts, as shown in *Table 3*. Two groups were analysed:

(I) Consented population (students who participated in the screening).
(II) Total enrolment (which reflects the entire target adolescent population).

Applying the observed carrier prevalence rates of 6.3% in Sabah and 1.8% in Sarawak, to both groups, the study estimated the number of missed carriers. Among the consented population, approximately 52 carriers in Sabah and 15 in Sarawak were potentially missed due to dropouts. When considering the total enrolment, the missed carriers were estimated to be 286 in Sabah and 57 in Sarawak.

To provide a more accurate projection of thalassemia-affected births and the associated treatment costs, Mendelian inheritance probabilities were applied alongside the consanguinity rate of 9.2% reported among parents of thalassemia parents (34). Additionally, another study by Nagaraj (35) reported a consanguinity rate of 11% in Sabah and Sarawak. Based on this studies, three conservative probabilities of 2%, 4%, and 6%, were assumed to represent the likelihood of two carriers marrying each other. Under Mendelian inheritance, when two carriers marry, each child has a 25% chance of being affected by thalassemia major. These probabilities were incorporated to estimate the financial implications of missed carriers, focusing on those marriages most likely to result in affected offspring.

In *Table 4*, the cost of treatment per person per lifetime is set at RM 2,660,000. The estimated costs of treatment were recalculated under different marriage probability scenarios, factoring in the 25% Mendelian inheritance risk:

❖ Based on the consented population, the potential

Table 3 Calculation of carrier prevalence and projected numbers in Sabah and Sarawak

States	(a) Number of screened	(b) Carriers detected through the program	(c) Estimated carriers' prevalence of population screened. [(b)/(a)] × 100%	(d) I) Number consented Scenario 1	(e) Estimate total carriers of consented population [(d) × (c)]	(f) Estimated missed carriers (consented population) [(e) – (b)]	(g) II) Number of enrolments (close to the estimated 16-year-old population) Scenario 2	(h) Estimated total carriers for the enrolment population [(g) × (c)]	(i) Estimated missed carriers (enrolment population) [(h) – (b)]
Sabah	32,494	2,036	6.30%	33,142	2,088	52	36,860	2,322	286
Sarawak	31,254	576	1.80%	32,848	591	15	35,161	633	57

a: number of students enrolled for P1 in Sabah, based on *Figure 3*. b: cost per test for P1 in Sabah. c: total cost calculated by multiplying the number of students who consented to screening by the test cost for P1 in Sabah. d: number of students enrolled for P2 in Sabah, based on *Figure 3*. e: cost per test for P2 in Sabah. f: total cost calculated by multiplying the number of students who consented to screening by the test cost for P2 in Sabah. g: number of students enrolled for P1 in Sarawak, based on *Figure 3*. h: cost per test for P1 in Sarawak. i: total cost calculated by multiplying the number of students who consented to screening by the test cost for P1 in Sarawak. P1: existing National Screening approach; P2: single-sample reflex DNA approach.

Table 4 Procedure for assessing potential savings in treatment costs through the identification of missed carriers by eliminating dropouts in Sabah and Sarawak

Parameter	Form four students	Sabah	Sarawak
(a)	Total enrolment	36,860	35,161
(b)	Consented population	32,494	31,254
(c)	Confirmed thalassemia carrier from screened identified by the study	2,036	576
(d)	Percent of thalassemia carrier (c)/(b)	6.3%	1.8%
Based on consented population—cost due to loss of carrier identification due to dropouts			
(e)	Possible missed carriers due to dropouts [(c) × (d)]	52	15
(f)	Estimated total carriers per consented population [(c) + (e)]	2,088	591
(g)	Cost of treatment/person/lifetime (ref)#	RM 2,660,000.00	RM 2,660,000.00
	The estimated cost of treatment if:		
(h)	2% of "f" marry each other [(2%) × (g) × (e)] ×25%	RM 691,600.00	RM 199,500.00
(i)	4% of "f" marry each other [(4%) × (g) × (e)] ×25%	RM 1,383,200.00	RM 399,000.00
(j)	6% of "f" marry each other [(6%) × (g) × (e)] ×255	RM 2,074,800.00	RM 598,500.00
Based on student enrolment—cost due to loss of carrier identification due to dropouts			
(k)	Possible missed carriers due to dropouts [(c) × (d)]	286	57
(l)	Estimated Total Carriers [*Table 3,* column (h)]	2,322	633
(m)	Cost of treatment/person/lifetime (ref)#	RM 2,660,000.00	RM 2,660,000.00
	The estimated cost of treatment if:		
(n)	2% of "f" marry each other [(2%) × (m) × (f)] ×25%	RM 3,803,800.00	RM 758,100.00
(o)	4% of "f" marry each other [(4%) × (m) × (k)] ×25%	RM 7,607,600.00	RM 1,516,200.00
(p)	6% of "f" marry each other [(6%) × (m) × (k)] ×25%	RM 11,411,400.00	RM 2,274,300.00

#, Shafie *et al.* 2021, Lifetime Cost of treatment RM 2,660,000 (22).

Table 5 Projected thalassemia case reduction over 15 years in Sabah and Sarawak under various annual reduction scenarios

Category	States	Year % reduction	2%	5%	10%	20%	30%	40%
Based on the consented population	Sabah	1st year	2,088	2,088	2,088	2,088	2,088	2,088
		10th year	1,706	1,250	728	224	59	13
		15th year	1,542	967	430	73	10	1
	Sarawak	1st year	591	591	591	591	591	591
		10th year	493	372	229	79	24	6
		15th year	445	288	135	26	4	0
Based on the enrolment population	Sabah	1st year	2,322	2,322	2,322	2,322	2,322	2,322
		10th year	1,897	1,390	810	249	66	14
		15th year	1,715	1,076	478	82	11	1
	Sarawak	1st year	633	633	633	633	633	633
		10th year	528	399	245	85	26	6
		15th year	477	309	145	28	4	0

lifetime treatment costs for Sabah range from RM 691,600 (2% probability) to RM 2,074,800 (6% probability), while in Sarawak, they range from RM 199,500 to RM 598,500.

- Based on total enrolment, the projected lifetime treatment costs for Sabah increase to RM 3,803,800 (2% probability), RM 7,607,600 (4% probability), and RM 11,411,400 (6% probability). In Sarawak, the costs range from RM 758,100, RM 1,516,200 and RM2,274,300, under the same scenarios.

These adjustments ensure that the estimated costs reflect more realistic probabilities of disease transmission and treatment burden. Furthermore, cases such as Bart's hydrops fetalis, which frequently result in foetal demise and do not incur long-term treatment costs, were considered to prevent overestimation.

The revised model offers a more accurate and nuanced understanding of potential cost savings from early detection programs like P2, strengthening the argument for its implementation to reduce future treatment costs.

Stage four

Under the assumption of adopting the P2 approach, the study predicted a gradual decrease in thalassemia cases over time based on a straightforward calculation shown in *Table 5*. It assumed that more individuals carrying the thalassemia gene would consciously choose not to marry each other, reducing the risk of having a child with thalassemia. The numbers are estimated using the rates between 2% to 40% each year. The projections began with an initial count of 2,088 cases in Sabah and 591 in Sarawak in the first year. Based on population data, additional estimates suggested these numbers could reach approximately 2,322 in Sabah and 633 in Sarawak. The analysis focused on three specific points: the 1st, 10th, and 15th years to observe the trend over time. By the 15th year, the projections suggested that Sabah might report only one new thalassemia case, while Sarawak could potentially see no new cases, given these assumptions.

Stage five

A comparative analysis was conducted between Sabah, characterised by a high prevalence of thalassemia, and Sarawak, characterised by a low prevalence of thalassemia carriers. This analysis aimed to determine the more cost-effective option regarding implementation cost to outcomes. *Table 6* compares the screening cost per positive carrier between these states. The proportion was calculated using the consented population. Notably, Sabah demonstrated a significantly lower cost at RM 379.95 per carrier detected, nearly half Sarawak's cost at RM 821.85 per identified carrier.

Discussion

The success of the NTSP in Malaysia, particularly in

Table 6 Calculation of screening cost per positive carrier in high and low prevalence states

States	Estimated total cost and carriers detected	Cost per carrier detected positive in RM/USD
Sabah	Est total cost of screening P1[†]: RM 793,326.00	RM 379.95/USD 84.43
	Est carriers detected[#]: 2,088	
Sarawak	The total cost of screening P2[†]: RM 485,716.00	RM 821.85/USD 182.63
	Est carriers detected[#]: 591	

P1: existing National Screening approach; P2: single-sample reflex DNA approach. [†], extracted from *Table 1*; [#], extracted from *Table 3*.

targeting secondary-four school children within the adolescent age group, has gained widespread recognition. The substantial attendance and wide coverage during its inaugural year, 2018, highlighted the programme's careful planning and execution of a voluntary screening initiative (36). This initiative has effectively achieved its objective of identifying carrier status among the screened students, with ongoing follow-up support to prevent intermarriage among carriers. While Tan *et al.*'s study supports the appropriateness of screening adolescents at 16, there is acknowledgement that health awareness should commence even earlier (19). To optimise the programme's efficiency, minimising dropouts becomes crucial to ensure every student has an equal opportunity for screening and understanding their status unless they have specific reasons to decline the National Programme's screening.

Numerous studies have shown the cost-effectiveness of a screening intervention programme for thalassemia. It is a common hereditary condition, and carriers are still prevalent worldwide, including areas in the Mediterranean, Middle East and Asian countries (12,37,38). However, the prevalence of thalassemia has been reduced successfully with the interventions implemented through various approaches to the screening programme by several countries (39,40). The thalassemia screening programme has been proven cost-effective in relation to the treatment cost, which can take up a substantial portion of the country's MOH Malaysia's budget annually. Leveraging this success is to progress towards a speedier reduction and perhaps near elimination.

The NTSP targets both α- and β-thalassemia, reflecting Malaysia's genetic diversity. However, β-thalassemia has a higher carrier rate (3–9%, depending on ethnicity) and imposes a greater clinical and economic burden due to the need for lifelong transfusions and chelation therapy (41). In contrast, while α-thalassemia is also screened, severe α-thalassemia, such as Bart's hydrops fetalis, usually results in in utero mortality, thus having lesser impact on long-term healthcare costs. This study focuses on β-thalassemia, which accounts for the majority of cases requiring sustained medical care. Emphasizing β-thalassemia in the screening strategy aligns with cost-effectiveness priorities and supports informed policy planning. Understanding these prevalence patterns is key to designing targeted prevention and management programs for Malaysia's public health needs.

Key findings

The ICER analysis showed that the additional cost per dropout averted with the P2 approach was approximately RM 25.

Based on lifetime treatment cost projections, P2 could yield substantial long-term savings:

- In Sabah, estimated savings range from RM 691,600 (2% probability) to RM 2,074,800 (6% probability) based on the consented population, and from RM 3,803,800 to RM 11,411,400 when applied to total enrolment.
- In Sarawak, savings range from RM 199,500 to RM 598,500 (consented population), and from RM 758,100 to RM 2,274,300 (total enrolment), under the same probability scenarios.

The study forecasts a potential 40% annual reduction in thalassemia cases, with the possibility of achieving minimal to zero new cases within 15 years of sustained P2 implementation.

Despite an initial screening cost increase of 9–11%, the P2 approach is projected to be a cost-effective and sustainable strategy for thalassemia prevention in Malaysia.

Strengths and limitations

The strengths of this study include the introduction of an innovative single-sample reflex DNA approach and a comprehensive cost-effectiveness analysis applying ICER

calculations. The approach demonstrates practical, scalable, and cost-effective screening improvements, especially for regions with higher thalassemia prevalence.

However, the study had several limitations. It relied on desktop calculations rather than real-world, large-scale implementation data, which may limit the generalizability of its findings. The focus on Sabah and Sarawak, while valuable for addressing logistical complexities, may not fully represent the diverse healthcare settings in West Malaysia.

Additionally, the study did not explore behavioural factors influencing dropouts or the psychosocial impact of screening and diagnosis on adolescents, leaving a gap in understanding potential stigma or emotional stress. While P2 reduces dropouts, its 9–11% higher upfront costs could be a barrier for national rollout without careful budget allocation.

The school-based thalassemia screening program maintains strict confidentiality and provides individualized counselling to minimize stigma (18,19). Results are disclosed privately by trained healthcare professionals to students and parents, ensuring carrier status remains confidential (42). Drawing from programs like the Tay-Sachs screening among Ashkenazi Jews, which normalized carrier status through education (43), the program emphasizes that being a carrier is common and not an illness. Identified carriers receive ongoing support, including referrals for reproductive counselling, prenatal diagnosis, and further care if needed (44). This approach aligns with the MOH Malaysia's ethical guidelines, promoting non-coercive, culturally sensitive counselling to safeguard autonomy and well-being (45).

Comparison with similar research

Several global thalassemia prevention programs provide relevant comparisons to Malaysia's NTSP and the proposed P2 approach. Iran's national thalassemia prevention program achieved a 70% reduction in beta-thalassemia births by implementing premarital screening and prenatal diagnosis (46). Similarly, Cyprus integrated premarital and prenatal screening with genetic counselling, dramatically lowering affected births (47). In Sardinia, Italy, Cao *et al.* demonstrated the cost-effectiveness of prenatal screening, reinforcing that early detection programs reduce healthcare costs significantly (48). Technological advances in Thailand, including single-tube multiplex PCR and reflex testing strategies—offer rapid, low-cost DNA diagnostics (49). These innovations align with Malaysia's proposed P2 strategy, which emphasizes efficiency and improved diagnostic accuracy. Adoption of these approaches has helped countries streamline their screening workflows and reduce dropout rates, mirroring the objectives of P2.

Explanations of findings

Cost-effectiveness of P2 in Sabah and Sarawak

The study findings reveal a noteworthy comparison in cost-effectiveness between the P1 and P2 screening approaches. While P2 incurs significantly higher initial costs (Sabah RM 793,326 and Sarawak RM 485,716 compared to P1's Sabah RM 735,698 and Sarawak RM 458,282), this upfront expense is strategically offset by the potential for long-term savings in healthcare costs associated with thalassemia care. Prior studies have shown that preventive genetic screening programmes, though costly at initiation, often yield substantial savings by reducing future health burdens. For instance, a cost-benefit analysis of a thalassemia disease prevention programme demonstrates that screening and prenatal diagnosis are cost-effective strategies for reducing the incidence of thalassemia (50).

The ICER analysis shows that P2 has an extra cost per health effect (dropouts averted of RM 25.14 for Sabah and RM 22.10 for Sarawak, aligning with the findings that ICER can guide policy decisions on resource allocation for this programme screening disorder. These values reflect the cost per additional dropout averted through P2's more intensive screening, underscoring the need for the MOH Malaysia to consider this additional cost in light of its budget threshold. Ultimately, this threshold will determine whether the anticipated health gains and future cost savings can justify the initial expense of P2.

The cost-effectiveness of the P2 strategy depends on the choice of DNA testing methods. This study uses Gap-PCR, RDB, and PCR-Sanger sequencing, providing reliable detection of common α- and β-thalassemia mutations. Although NGS offers broader mutation detection, its higher cost and technical requirements limit its feasibility for routine screening in Malaysia (16). The selected PCR-based methods balance accuracy and affordability, making P2 a practical and sustainable option within the NTSP.

Furthermore, P2's potential to avert 2,940 dropouts in Sabah and 2,836 in Sarawak is critical in reducing the risk of thalassemia-affected babies by identifying the potential carriers early. Population-based screening studies have highlighted the effectiveness of identifying carriers and preventing at-risk marriages to control thalassemia

prevalence. For example, Iran's NTSP, which includes prenatal screening and genetic counselling, has significantly reduced the incidence of thalassemia (46). Approximately 6.3% of averted dropouts in this study are likely carriers who might unknowingly marry other carriers, a risk that early screening and counselling can help mitigate. The preventive framework mirrors strategies in countries like Iran, where targeted education and counselling efforts led to marriage cancellation rates among carriers up 38% and 60% (2,51). If the MOH Malaysia sets a 40% marriage cancellation rate target among carriers, the P2 approach could feasibly reduce the number of thalassemia births to near zero within 10 to 15 years, a long-term benefit seen in similar programmes in other countries.

A critical observation in this study is the significant cost difference per carrier detected between high-prevalence (Sabah) and low-prevalence (Sarawak) regions. In Sabah, the cost per carrier detected under P2 is RM379.95, almost half of Sarawak's RM 821.85. This difference reflects the economy of scale, suggesting that screening in high-prevalence areas is more cost-effective, consistent with previous studies showing that cost per carrier decreases with prevalence due to economies of scale. This can be shown almost like a study on the cost-effectiveness of antenatal screening for sickle cell and thalassemia in primary care found that universal screening in high-prevalence areas is more cost-effective than targeted screening (52).

Given budget constraints, the MOH Malaysia may prioritise P2 implementation in high prevalence states as phasing high-burden areas first, a commonly recommended strategy for genetic disorder prevention programmes. This phased approach would allocate funds to areas where they can have the most immediate impact, enhancing the programme's cost-effectiveness and likelihood of success.

The screening program emphasizes that genetic counselling is meant to inform and empower, not to dictate marriage or reproductive choices; carriers maintain full autonomy (42). Support includes non-directive counselling, prenatal diagnosis, and, where legally and culturally acceptable, termination of pregnancy (53). Additional options like pre-implantation genetic testing and IVF with genetic screening are available for those seeking to reduce the risk of an affected child (54). This approach balances public health goals with respect for personal freedoms, autonomy, and Malaysia's cultural and legal frameworks.

Finally, the long-term benefits of P2 extend beyond immediate cost savings and dropout prevention. By integrating comprehensive speedy screening, counselling, and targeted awareness campaigns, P2 establishes a robust prevention strategy that addresses both present and future health challenges thalassemia poses. The potential to reduce thalassemia births and avoid costly treatments aligns with evidence supporting preventive approaches for genetic disorders as more cost-effective over time than reactive care. The adoption of P2 would reflect a commitment to proactive, cost-effective healthcare strategies prioritising the well-being of the country's future population. *Table 5* shows the projected 15-year case reductions under different annual percentage reductions (2–40%) for Sabah and Sarawak, based on consented and enrolment populations. The data highlights a gradual decline in cases, with higher reduction rates leading to faster decreases. For instance, in Sabah's consented population, cases may drop from 2,088 to 1,542 (2% reduction) and near zero (40% reduction) by the 15th year, illustrating the potential impact of varying reduction rates.

In summary, *Figure 4* encapsulates this study's stage-by-stage analysis and outcomes. It highlights the cost-benefit analysis of P2, its potential for significant cost savings, and its role in reducing carrier prevalence. The study concludes that P2, despite higher initial costs, presents a valuable approach for dropout aversion and long-term financial and public health benefits. This aligns with other research findings by Ahmadnezhad 2012, emphasising the impact of carrier management strategies like marriage cancellation on reducing new cases (2).

Impact of reducing dropout rates on patient care and public health outcomes

Reducing dropout rates in NTSP is critical for improving patient care and achieving public health outcomes. High screening completion rates ensure more carriers are identified and counselled, reducing the risk of inter-carrier marriages and subsequent thalassemia births. Countries like Cyprus and Iran demonstrate that effective screening programs, with coverage exceeding 90%, can nearly eliminate new thalassemia major cases (46).

In Malaysia, avoiding just a few new cases can lead to significant savings, given the RM 2.66 million lifetime treatment cost per patient. Reducing dropouts through P2 enhances program effectiveness, particularly in high-prevalence regions such as Sabah and Sarawak (16). By reducing dropout rates, NTSP can increase the effectiveness of screening programs, particularly in high-prevalence regions like Sabah and Sarawak, and contribute to reducing the national thalassemia disease burden (55).

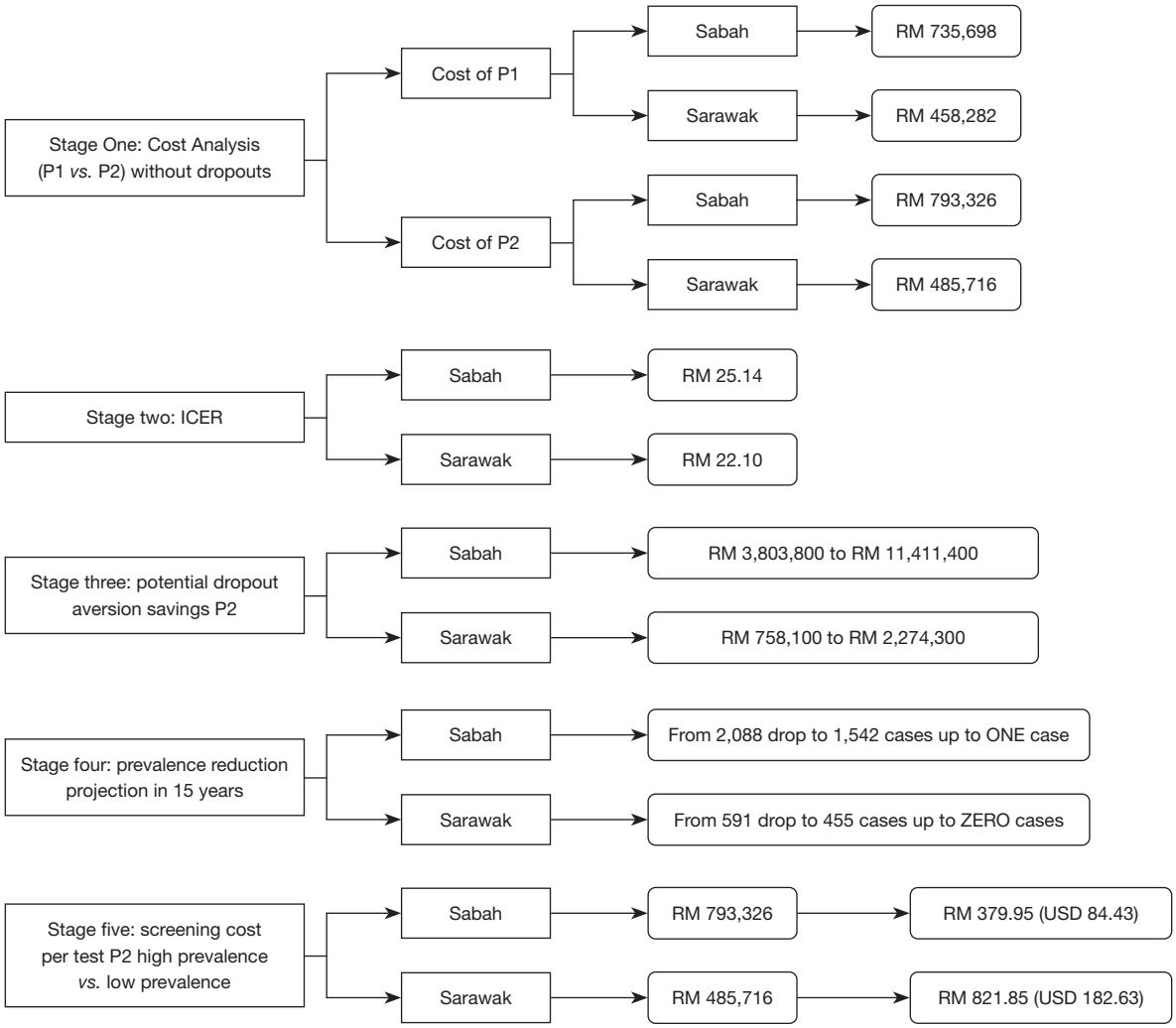

Figure 4 The summary findings for each stage of the research. This cost analysis compares two screening strategies: P1 (with dropouts) and P2 (without dropouts). Stage one shows that P2 incurs a higher upfront cost (Sabah: RM 793,326, Sarawak: RM 485,716) but is more efficient than P1. Stage two (ICER) estimates the additional cost per dropout prevented (Sabah: RM 25.14, Sarawak: RM 22.19). Stage three highlights potential savings from dropout aversion (Sabah: RM 3.8M – RM 11M, Sarawak: RM 758,000 – RM 2.3M). Stage four projects a reduction in thalassemia cases over 15 years with P2 (Sabah: 2,088→1,542→1, Sarawak: 591→455→0). Stage Five calculates per-test screening costs of P2 at RM 379.95 (USD 84.43), in high prevalence state was more cost-efficient. P1: existing National Screening approach; P2: single-sample reflex DNA approach. ICER, incremental cost-effectiveness ratio.

Summary of Stage one to Stage five

Figure 4 outlines a five-stage comparison between the current National Thalassemia Screening Programme (P1) and the single-sample reflex DNA strategy (P2). While P2 carries higher upfront costs, it achieves greater efficiency by preventing dropouts at lower incremental cost and generating substantial long-term savings. Projections show that P2 could significantly reduce, and in some settings nearly eliminate, new thalassemia cases over 15 years. In high-prevalence states, P2 is ultimately more cost-efficient per test, making it the more sustainable option despite its initial cost disadvantage.

Implications and actions needed

The findings from this study suggest clear, actionable steps to optimise the implementation and impact of thalassemia

screening in Malaysia. Firstly, a phased implementation of P2 is recommended, allowing for a more cost-efficient rollout by initially focusing on high-prevalence states. This approach would maximise early returns on investment by prioritising regions where screening has the highest cost-effectiveness due to a more significant number of carriers. Ranking the states from highest to lowest carrier prevalence and prioritising the top half, followed by the second phase, can be implemented nationwide if funding allows.

Secondly, establishing an electronic cohort register for carriers could substantially improve the programme's long-term effectiveness. Such a registry would enable systematic monitoring and follow-up for identified carriers, providing timely and personalised counselling throughout key life stages, including family planning. Additionally, the electronic registry will be an invaluable database to leverage analysis or make projections to improve impact over time.

Thirdly, conducting cross-sectional Surveys would offer insights into the family, social, economic, or political factors that influence dropout rates or contribute to gaps in programme participation. These surveys would allow the MOH Malaysia to remain responsive to evolving challenges and opportunities to enable continuous refinement of the screening and prevention programme.

Conclusions

This study demonstrates that the Single-sample Reflex DNA approach offers a cost-effective and efficient alternative to Malaysia's current NTSP. By reducing dropout rates and accelerating the diagnosis process, it has the potential to significantly lower thalassemia prevalence and future healthcare costs, aligning with successful international prevention models.

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Footnote

Reporting Checklist: The authors have completed the CHEERS reporting checklist. Available at https://jhmhp.amegroups.com/article/view/10.21037/jhmhp-24-135/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Ethical approval was obtained from the Malaysian Research Ethics Committee and registered under the National Medical Research Register Malaysia [NMRR ID-22-00985-D1X (IIR)]. The Family Health Development Division, MOH Malaysia provided the anonymised line listing of the study sample of Form 4 students and individual consent for this retrospective analysis was waived in accordance with national ethics guidelines and institutional review board policy.

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