# A systematic review on thalassaemia screening and birth reduction initiatives: cost to success

**Azrin Syahida Abd Rahim, MBAHM[1], Nour El Huda Abd Rahim, PhDMSc[2], Safurah Jaafar, MScPH[3]**

[1]Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Bandar Tun Razak, Kuala Lumpur, Malaysia, [2]Department of Basic Medical Sciences, Kulliyyah of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia, [3]School of Medicine, Business Healthcare Management, International Medical University, Kuala Lumpur, Malaysia

**ABSTRACT**

**Introduction: Thalassaemia has been prevalent with high morbidity and mortality rates since 1925. Although there is a lack of systematic review on the costs of prevention that has yielded reductions in thalassaemia prevalence, this review will show a widespread presence of complex but effective strategies in reducing national thalassaemia prevalence.**

**Materials and Methods: A systematic search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020). Designated keywords were combined with search functions and Boolean operators in databases like Scopus, Web of Science and several other search databases.**

**Results: The search identifed 5425 potential articles. Most countries reported a decline in thalassaemia prevalence after implementing intervention programmes for several decades. The screening methods, however, varies, and the speed of reductions depends on the type of screening approach that involves blood screening of adolescence and antenatal mothers and, in some countries, includes termination of pregnancy. In addition, the cost of these initiatives varies as it was challenging to find a common denominator. However, the endpoint concedes that the cost of screening, although substantial, would be offset by the cost of reduction of cases. In some countries, cost-effectiveness analyses have been reported to support the initiatives of thalassaemia screening and prevention in the long run.**

**CONCLUSION: The results showed significant variations in success rates with a significant reduction in the prevalence of Thalassaemia. Most successful are countries with comprehensive and aggressive prevention and control programmes that engaged with lab screening, counselling, and termination of pregnancy as a package.**

**KEYWORDS:**
*birth reductions, prevalence, thalassaemia, programme cost, screening methods, treatment cost*

## INTRODUCTION

Countries conducting thalassaemia screening and prevention programmes took several years to witness the decline in thalassemia births. The cost of a national screening programme that must be borne upfront is often high and needs to contend with other competing priorities. Hence, it requires political decisions based on sound evidence of the cost-effectiveness of screening to make a financial commitment to initiate these programmes. However, such commitment is not a one-off but a continuous undertaking of birth reduction aiming for zero new thalassaemia birth when the budget allows.

Cao et al., reported that the global prevalence of thalassaemia is still high.[1] In 2013, 56,000 children were born with thalassaemia major, where approximately 30,000 were affected by beta-thalassaemia, and 3,500 succumbed perinatally from the debilitating hydrops foetalis syndrome. The global incidence of symptomatic individuals is estimated to be one in 100,000.[2] Kadhim et al.,[3] stated that thalassaemia occurs in 4.4/10,000 live births. As reported in 2017 by Origa R, approximately 68,000 children are born with various thalassaemia syndromes yearly.[4]

Countries with high prevalence have made impressive thalassaemia prevention and control. There are several approaches adopted, and studies have reported the various outcomes of these initiatives at the country level. A successful initiative has been demonstrated in North Cyprus. They started with high carrier rates of thalassaemia. Two studies in 1946 and 1973 reported thalassaemia carrier rates of 18.2% and 15%, respectively. North Cyprus made an unprecedented decision to introduce a screening programme. It started in 1979 to screen high-risk families. The following year, pre-marital screening became legally required in 1980. Prenatal diagnosis began with foetal blood sampling techniques in 1984. Later in 1991, DNA techniques replaced foetal blood sampling. Since the prenatal diagnosis began, affected birth rates have dropped dramatically, compared to an average of 18-20 cases per year. North Cyprus has earned the honour as the first country to achieve a satisfactory reduction in carriers and thalassaemia major newborns. Between 1991 and 2001, only five thalassaemic babies were born, or only one every 2-3 years. No thalassaemic babies were born between 2001 and 2007.[5] In another study reported by Şanlidağ et al.[6], since the mandatory pre-marital screening in North Cyprus, there was a successful depletion of new thalassaemic babies born since 2001.

A study in Iran has shown the importance of screening, in which those who were positive carriers have voluntarily cancelled their marriage intention. Between 2002 and 2006,

*This article was accepted: 01 April 2024*
*Corresponding Author: Azrin Syahida Abd Rahim*
*Email: ajeansyahida09@outlook.com*

the average rate of marriage cancellation among the carrier couples was reported at 53%, with a minimum rate of 38% in 2003 and a maximum rate of 69% in 2006.[7]

The importance of initiating a thalassaemia screening and prevention programme is to lighten the cost burden of treating primary thalassaemia patients, which need lifelong treatment, including life-long blood transfusions and chelation therapy. In addition, complete blood counts, iron studies, and heart, kidney, and liver tests are required. Often cases need to be referred to medical specialists such as paediatricians, haematologists, and endocrinologists. Such follow-ups incur additional charges, such as hormonal investigations for growth monitoring.[8] In 2011, a decade ago, the total expenses throughout life for a patient with thalassaemia major were projected to be GBP219,608.[9] In Malaysia, Shafie et al.,[10] reported that the lifetime cost per Transfusion Dependent Thalassaemia (TDT) patient was USD606,665 extracted from the sum of lifetime healthcare costs. The price has increased many folds since, with these patients living longer and the increased treatment cost.

To the best of our knowledge, systematic reviews on thalassaemia screening, birth reduction initiatives, and relation to the programme's cost have not been reported. This study provides a comprehensive summary of the retrieved literature through a systematic search of various screening of thalassaemia initiatives in several countries. Therefore, the shared birth outcomes and costs incurred or saved can help administrators make decisions based on high-quality evidence of the intervention costs and outcomes. In addition, the quality of the included literature was evaluated by employing the updated PRISMA 2020 and Mixed Methods Appraisal Tool (MATT) method.

## MATERIALS AND METHODS

*Review Protocol*

A systematic search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) Statement guidelines of quantitative and qualitative studies.[11] The authors used several methods to identify synonyms and related terms for four main keywords related to screening programmes, birth, cost and success and narrowed them down to topics like thalassaemia screening and birth reduction initiatives, including prevalence, burden, challenges, impact, declining, prenatal, children, born, success and family. These keywords were combined with search functions and Boolean operators in databases like Scopus and Web of Science and identified 5,425 potential articles. The authors also manually searched databases like Science Direct, Emerald, Taylor Francis, Springer Link and Sage Journals.

*Formulation of Research Question*

The formulation of the research question was based on PICO, a tool that assists authors in developing a relevant research question for the review. PICO is based on three main concepts: Population or Problem, Interest and Context. Based on these concepts, the authors have included three main aspects in the review, namely thalassaemia patients (Population), treatment cost-effectiveness (Interest) and screening programmes (context) which then guide the authors to formulate its main research question—What are the costs and the outcomes of the thalassaemia screening programme in reducing the birth incidence of thalassaemia?

*Screening and Eligibility Criteria*

The eligible inclusion criteria of the literature met the following: (a) Thalassaemia patients as the target population; (b) articles expressing comparison birth numbers after the intervention was implemented; (c) the study contained economic evaluation where results expressed with the cost comparison between pre-and post-intervention as well as (d) articles published between 1992 until December 2022. In addition, non-original articles (e.g. drafts, case studies, conference posters or abstracts) were excluded. This systematic review only considered full-text articles in the English language.

## RESULTS

Figure 1 illustrates the identification process of studies collected and screened. In total, 5,425 were from electronic databases. We removed 4,905 articles, including non-published articles, those published before 1984, non-English and did not meet the criteria by browsing the titles and abstracts. This includes another 21 duplicates, which then came to 499 full-text articles eligible for review. Further article exclusion was made on those which do not focus on the four main keywords used for searching the database, based on screening the title (n=260), abstract (n=65) and content (n=6). Another 118 articles were excluded after quality appraisal. Finally, 50 full-text studies were included and analysed in this review.

*Quality Appraisal*

With the assistance of two co-authors, the corresponding author assessed each article's methodological and analytical rigour. Each article was carefully read, focusing on its methodology section and the analysis undertaken. Then, guided by the Mixed Methods Appraisal Tool, the authors scrutinised the articles, searching for the consistency of the sampling and analysis undertaken (e.g., random sampling vs inferential analysis). Each article was assessed based on five criteria with three options provided in presenting their answers: 'yes', 'no' and 'do not know/cannot tell'. The articles were included in the review if they passed at least three criteria. All decisions on the assessment were based on mutual agreement.

*Study Characteristics*

The essential characteristics of the 50 included full-text studies are reported in Table I. These studies were performed in 21 different countries, including Iran (n=9),[12-20] Malaysia (n=4),[9-10,20,21] and Cyprus (n=3),[5,6,23]. Iraq,[3,24] Canada,[25,26] Turkey,[27,28] Israel,[29,30] Sri Lanka,[31,32] Thailand,[33,34] Greece,35,36 India,[37,38] Palestine,[39,40] and Italy[41-42] each contributed two publications. Publications from the remaining countries each have a single citation:, Singapore,[43] Omani,[44] Saudi Arabia,45 France,[46] Taiwan,[47] Maldives[48] and China[49]. Iran, Malaysia, and Cyprus accounted for most studies, between three to eight articles.

**Table I: Articles included for review according to themes**

| No. | Author | Year | Countries | Title | Themes |
|---|---|---|---|---|---|
| 1. | Longinotti et al.[41] | 1994 | Italy | A 12-year preventive program for β-thalassaemia in Northern Sardinia | Theme 1: Prevalence |
| 2. | Haque et al.[21] | 2015 | Malaysia | Thalassaemia: Level of awareness among the future health care providers of Malaysia | |
| 3. | Ibrahim et al.[22] | 2020 | Malaysia | Observational study on the current status of thalassaemia in Malaysia: a report from the Malaysian Thalassaemia Registry | |
| 4. | Gholam Hasan et al.[12] | 2013 | Iran | Frequency of Thalassaemia in Iran and Khorasan Razavi | |
| 5. | Miri et al.[13] | 2013 | Iran | Thalassaemia in Iran in the last twenty years: the carrier rates and the births trend | |
| 6. | Canatan[27] | 2011 | Turkey | Haemoglobinopathy prevention program in Turkey | |
| 7. | Kattamis et al.[54] | 2020 | - | Changing patterns in the epidemiology of β-thalassaemia | |
| 8. | Şanlidağ et al.[6] | 2016 | Cyprus | Prevalence of Thalassaemia Trait & Iron Deficiency Anaemia during Infancy in 2011–2013 in a Thalassaemia Prevalent Region: North Cyprus | |
| 9. | Wong et al.[43] | 2009 | Singapore | Prevalence of haemoglobinopathies in Singapore | |
| 10. | Safdar et al.[48] | 2017 | - | Economic Burden of Thalassaemia on Parents of Thalassaemic Children: A Multi-Centre Study | |
| 11. | Mustafa et al.[55] | 2020 | Maldives | Genetic epidemiology of beta-thalassaemia in the Maldives: 23 years of a beta-thalassaemia screening program | |
| 12. | Voskaridou et al.[35] | 2019 | Greece | National registry of hemoglobinopathies in Greece: updated demographics, current trends in affected births, and causes of mortality | |
| 13. | Bozkurt[5] | 2007 | Cyprus | Results from the North Cyprus thalassaemia prevention program | Theme 2: Birth reduction |
| 14. | Koren et al.[29] | 2014 | Israel | Prevention of β-thalassaemia in Northern Israel-A cost-benefit analysis | |
| 15. | Alkindi et al.[44] | 2010 | Omani | Forecasting hemoglobinopathy burden through neonatal screening in Omani neonates | |
| 16. | Kadhim et al.[3] | 2017 | Iraq | Prevalence, incidence, trend, and complications of thalassaemia in Iraq | |
| 17. | Saffi et al.[28] | 2015 | Turkey | Exploring the Effectiveness of Mandatory Premarital Screening and Genetic Counselling Programmes for β-Thalassaemia in the Middle East: A Scoping Review | |
| 18. | Samavat et al.[14] | 2004 | Iran | Iranian national thalassaemia screening programme | |
| 19. | Chern et al.[56] | 2006 | - | Impact of a national β-thalassaemia carrier screening program on the birth rate of thalassaemia major | Theme 3: Screening |
| 20. | Saba et al.[42] | 2017 | Italy | Non-invasive prenatal diagnosis of beta-thalassaemia by semiconductor sequencing: a feasibility study in the Sardinian population | |
| 21. | Sirdah et al.[40] | 1998 | Palestine | Screening secondary school students in the Gaza Strip for β-thalassaemia trait | |
| 22. | Langlois et al.[25] | 2010 | Canada | Carrier screening for thalassaemia and hemoglobinopathies in Canada | |
| 23. | Esmaeilzadeh et al.[15] | 2021 | Iran | Major Thalassemia, Screening or Treatment: An Economic Evaluation Study in Iran | |
| 24. | AlHamdan et al.[45] | 2007 | Saudi Arabia | Premarital screening for thalassaemia and sickle cell disease in Saudi Arabia. | |
| 25. | Colah et al.[37] | 2017 | India | Burden of thalassemia in India: the road map for control | |
| 26. | Cowan[23] | 2009 | Cyprus | Moving up the slippery slope: mandated genetic screening on Cyprus. | |
| 27. | Karimi et al.[17] | 2007 | Iran | Premarital screening for beta-thalassaemia in Southern Iran: options for improving the programme | |
| 28. | Lena-Russo et al.[46] | 2002 | France | Outcome of a school screening programme for carriers of haemoglobin disease | |
| 29. | Mitchell et al.[26] | 1996 | Canada | Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassaemia disease carriers in high schools | |
| 30. | Rahbari et al.[20] | 2014 | Iran | Dropouts and social determinants of health; policy for the prevention of school dropout, qualitative study of the causes and interventions | |
| 31. | Tarazi et al.[39] | 2007 | Palestine | Obligatory premarital tests for β-thalassaemia in the Gaza Strip: evaluation and recommendations. | |
| 32. | Jameela et al.[9] | 2011 | Malaysia | Thalassaemia screening among students in a secondary school in Ampang, Malaysia | |

**Table I: Articles included for review according to themes**

| No. | Author | Year | Countries | Title | Themes |
|---|---|---|---|---|---|
| 33. | Ostrowsky et al.[57] | 1985 | - | Cost-benefit analysis of a thalassaemia disease prevention program | Theme 4: Programme cost |
| 34. | Voskaridou et al.[36] | 2012 | Greece | A national registry of haemoglobinopathies in Greece: deducted demographics, trends in mortality and affected births | |
| 35. | Shafie et al.[10] | 2021 | Malaysia | The economic burden in the management of transfusion-dependent thalassaemia patients in Malaysia from a societal perspective | |
| 36. | Ginsberg et al.[30] | 1998 | Israel | Cost-benefit analysis of a national thalassaemia prevention programme in Israel | |
| 37. | Ghotbi et al.[18] | 2005 | Iran | Evaluation of the national health policy of thalassaemia screening in the Islamic Republic of Iran. | |
| 38. | Riewpaiboon et al.[33] | 2010 | Thailand | Economic burden of beta-thalassaemia/Hb E and beta-thalassaemia major in Thai children | |
| 39. | Sattari et al.[19] | 2019 | Iran | The financial and social impact of thalassaemia and its treatment in Iran | Theme 5: Treatment Cost |
| 40. | Ho et al.[47] | 2006 | Taiwan | Financial burden of national health insurance for treating patients with transfusion-dependent thalassaemia in Taiwan | |
| 41. | Pankaj et al.[38] | 2010 | India | Expenditure to Treat Thalassaemia: An Experience at a Tertiary Care Hospital in India | |
| 42. | Karnon et al.[31] | 2000 | Sri Lanka | Thalassaemia in Sri Lanka: implications for the future health burden of Asian populations. | |
| 43. | Karnon et al.[58] | 2012 | - | Lifetime Cost-Utility Analyses of Deferasirox in Beta-Thalassaemia Patients with Chronic Iron Overload | |
| 44. | Mutar et al.[24] | 2020 | Iraq | Thalassaemia Prevention Program in Iraq: Cost-Effectiveness and Applicability | Theme 6: Cost-effectiveness |
| 45. | Esmaeilzadeh et al.[16] | 2016 | Iran | Economic burden of thalassaemia major in Iran, 2015 | |
| 46. | Leech et al.[59] | 2018 | - | Use and misuse of cost-effectiveness analysis thresholds in low-and middle-income countries: trends in cost-per-DALY studies | |
| 47. | Bang et al.[60] | 2014 | - | Cost-effectiveness analysis: a proposal of new reporting standards in statistical analysis | |
| 48. | Amarasinghe et al.[32] | 2022 | Sri Lanka | Redesigning new policy options for thalassaemia prevention in Sri Lanka | |
| 49. | Laoarayawat et al.[34] | 2020 | Thailand | Effectiveness Analysis of Prenatal Screening Program for Thalassaemia Between Semi-accelerated Screening Step and Current Program | |
| 50. | Leung et al.[49] | 2004 | China | Cost-effectiveness of prenatal screening for thalassaemia in Hong Kong | |

*Data Extraction and Analysis*

The articles were thematically analysed, given that the review relied on diverse research designs, presenting the best ways to integrate the differences by performing a qualitative synthesis.[50] While several qualitative syntheses could be applied, the present review relied on the approach suggested by Flemming et al.,[51] who stressed the suitability of thematic synthesis for synthesising data from diverse research designs due to its flexible mode. Furthermore, thematic analysis attempts to identify and notify the pattern of existing studies by detecting any similarities or relationships that could exist in available data.[52] In this review, the thematic synthesis was based on the steps suggested by Kiger et al.[53]

Firstly, agreement and disagreement were quickly settled via discussion among the authors. Based on this process, all authors agreed that all selected articles passed the minimum quality requirement regarding the methodology and analysis. Secondly, the generation of codes was conducted. Data were organised at a granular and specific level. During this stage, selected articles and extracted any data related to the main research question. The third process involved theme generation. The researchers practised inductive coding frameworks and attempted to note any interests, similarities, and connections between the extracted data. The themes developed were associated with the original data and reflective of the entire data set.[52] During this process, six main themes were developed.

*Developing the Themes*

The thematic analysis was undertaken on 50 articles. It resulted in six main themes (a) prevalence and thalassaemia burden, (b) birth reduction, (c) screening methods, (d) programme cost, (e) treatment cost and (f) cost-effectiveness. Based on the results, six themes provided answers to the main research question of this SLR, 'how do the thalassaemia screening programmes help reduce the birth and cost burden of the country?' The background of the selected studies is explained in the following section.

Findings from the review concluded six thematic areas in analysing the success of thalassaemia screening in reducing birth. The six main themes are (1) prevalence and thalassaemia burden, (2) birth reduction, (3) screening

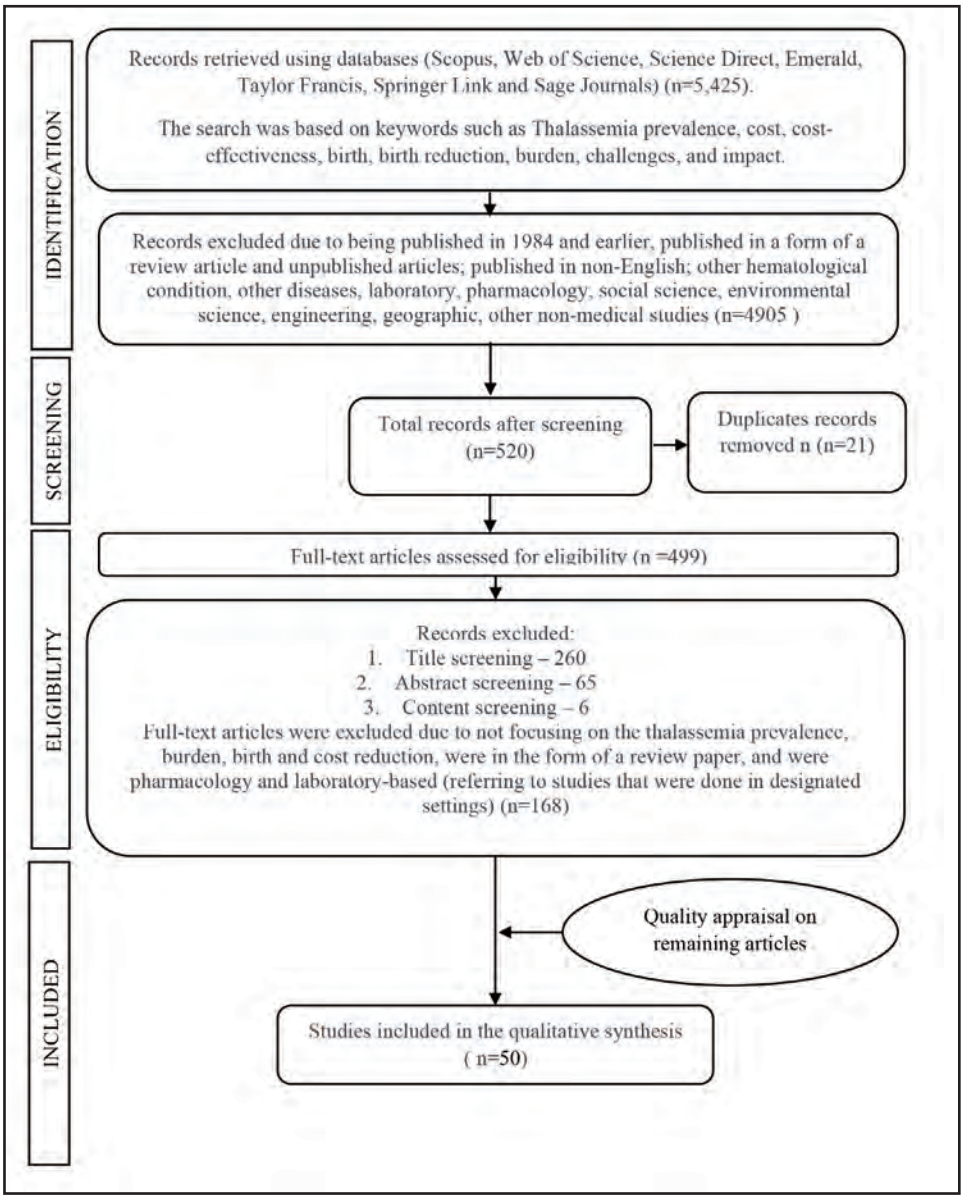


**Fig. 1:** PRISMA flow diagram

methods, (4) programme cost, (5) treatment cost and (6) cost-effectiveness. Figure 2 represents the six thematic areas and the articles associated with each category. A detailed listing of the articles included is provided in Table I.

## DISCUSSION

*Prevalence of Thalassaemia*

The prevalence of a condition is the percentage of people in a population who have that condition at a particular time or over a period of time. In this systematic review, the authors have analysed the prevalence of thalassaemia in several countries, including Cyprus, Iran, Maldives, Malaysia, Sardinia, Singapore, and Turkey. It provides a more objective measurement and mitigation effectiveness and facilitates ease in comparing data from different populations.

The prevalence of thalassaemia is exceptionally high in certain parts of the world, known as the 'thalassaemia belt'.[61] This belt includes countries in the Mediterranean region, Southeast Asia, and parts of Africa where the frequency of carriers of the thalassaemia gene is high. In these countries, thalassaemia is a significant public health issue, as the high prevalence of carriers in the population leads to a high incidence of the condition.

*Global*

Thalassaemia, a debilitating inherited haematological disorder, was first identified in the early 1900s in the United States and Italy. As screening for the condition has become more widespread, the number of people diagnosed with thalassaemia has increased. According to Origa R,[4] thalassaemia is highly prevalent, with an estimated 1.5% of the global population carrying the gene for the condition. This translates to around 80 to 90 million carriers worldwide.

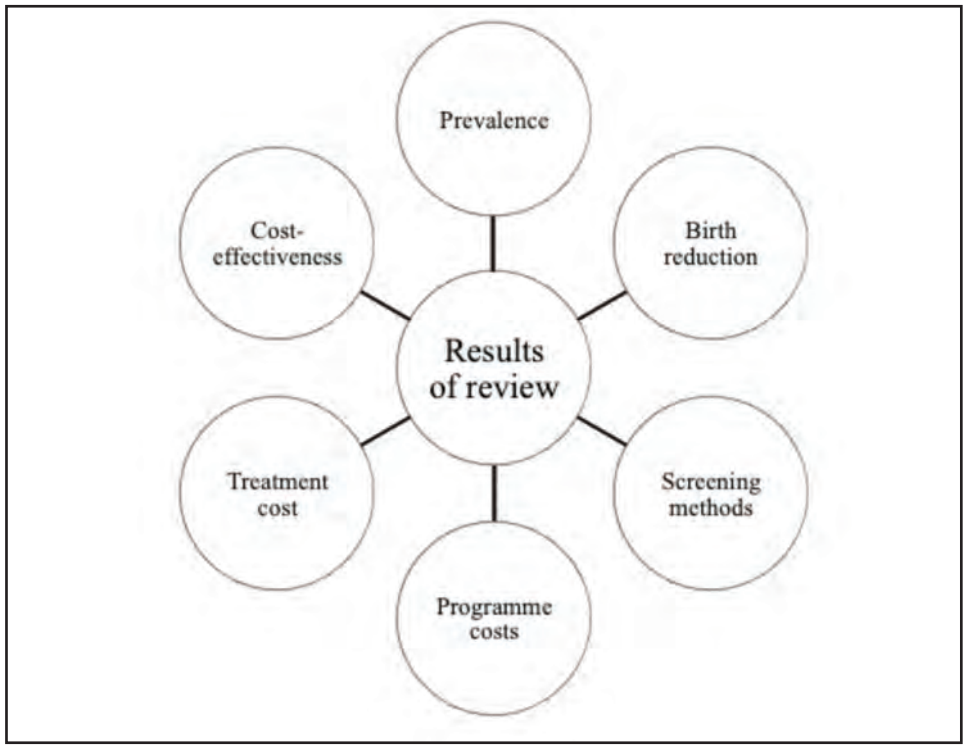


**Fig. 2:** Six thematic areas

Thalassaemia is prevalent in many parts of the world, particularly in the 'thalassaemia belt', which stretches from the Mediterranean basin to Southeast Asia. It is also found in Central Asia, Southern China, and the Far East, as well as in North Africa and South America. The highest carrier frequency has been reported in Cyprus (14%), Sardinia (10.3%), and Southeast Asia (3-5%).[62]

*The Mediterranean*

In the Mediterranean region, thalassaemia is especially prevalent in countries such as Cyprus, Greece, Italy, Iran and Turkey. The prevalence of carriers in these countries ranges from 10% to 25%.[27,54] This high prevalence is due to the high frequency of carriers in these populations. In addition, consanguineous marriages (marriages between close relatives) are more common in these countries, increasing the risk of thalassaemia.

Published articles on thalassaemia in North Cyprus, conducted in 1946 and 1973, found frequencies of 18.2% and 15%, respectively.[6] A more recent study conducted in 2013 found a frequency of 7.9%, representing a 50% decline in the prevalence of thalassemia compared to the 1973 study. In Sardinia, Cao et al. reported that the estimates of thalassaemia prevalence in Sardinia were between 10.3% and 15.7% and attributed that the factors of high prevalence may be related to genetic and demographic factors.[1] It was also reported that the 10.3% prevalence was contributed by a high prevalence of HbE-beta-thalassaemia in four regions of Sardinia.[41] In Iran, the overall prevalence was much lower at 4% in 2013.[12] However, in some localities, the Ministry of Health in Iran has reported that the provinces of Hormozgan, Sistan and Baluchistan, and Mazandaran have an average prevalence of 9%, 8.5%, and 8%, respectively.[13]

*Maldives*

The Maldives has a high prevalence of thalassaemia, with a reported rate of 18% of the population.[55] This is a significant number considering the smaller size of the Maldivian population. In addition, the migration of Maldivian citizens to other countries has also contributed to the prevalence of thalassaemia in those countries. For example, there is a reported prevalence of 16% in Cyprus and 3-8% in the populations of China, Bangladesh, and Malaysia.[48]

*South-East Asia*

The prevalence of thalassaemia in Asian countries is significantly lower. For example, according to Wong et al.[63], the prevalence of thalassaemia carriers in Malaysia is 4.5-6%. It was noted that individual perception and stigma towards thalassaemia could contribute to the rising prevalence of the condition. Approximately 4.5% of the population is estimated to be carriers of beta-thalassaemia in Iran.[13] Moreover, the prevalence rate of beta-thalassaemia in Malaysia is similar to Iran and higher among Malay ethnicity.[22] In Singapore, the nearby neighbour also reported in 2009 a 3.7% prevalence for thalassaemia and other haemoglobinopathies.[43]

*Thalassaemia Birth Reductions*

It is difficult to provide a specific percentage of thalassaemia birth reductions worldwide, as the incidence of thalassaemia varies widely from region to region and depends on several factors, including the prevalence of the thalassaemia gene in a population, access to genetic testing and counselling, and the availability and uptake of prevention measures.

*The Mediterranean Region*

In the Mediterranean region, Thalassaemia preventive initiatives have successfully lowered the number of Thalassaemia major births in Italy, Greece and Cyprus. Between 1972 and 1984, the preventative programme in Italy had a success rate of 62%, whereas Greece's had a success rate of 52%.[48] In its first epidemiological study, Cyprus reported that the prevalence of thalassaemia carriers was 17.2%.[64] Implementing a thalassaemia prevention programme in Cyprus, including compulsory premarital screening and prenatal diagnosis, has led to a significant decline in thalassaemia births. A 2011-2013 study found that the prevalence of thalassaemia trait in infancy in the region was around 7.9%, with no new cases reported since 2001.[5] The success rate of the prevention programme in Cyprus has been estimated to be 96%.[48] To hasten the reduction initiative, the government implemented a legal provision for premarital screening tests to be made compulsory for couples. This policy effectively reduced the birth rate of thalassaemic babies in the Turkish Cypriot population.[5] In Sardinia, an expanded thalassaemia screening programme was conducted among adults in the province of Sassari from 1980 to 1991. The programme screened 6.3% of adults, and the results showed that the prevalence of beta-thalassaemia was 15.7%.[41] In Iran, a study published by Samavat et al.[14] showed that the intervention programme significantly decreased the birth rate of thalassaemia patients from 1998 to 2002. The success rate of the thalassaemia prevention programme was estimated to be 82.3% in 2009, with the number of newborn thalassaemia patients falling from 1087 cases in 1989 to 239 in 2009.[13] It is estimated that, in Turkey, an average of four or five therapeutic abortions would be performed each year, given a 25% incidence of affected foetuses. These measures effectively reduce the number of thalassaemia births in other countries and could potentially be successful in reducing the number of thalassaemia births in Turkey.[28]

Therapeutic abortion, often a subject of intense ethical debate, intersects with the principle of non-maleficence, or the obligation to do no harm. In the realm of medical ethics, the decision to terminate a pregnancy for therapeutic reasons requires careful consideration of both the physical and mental well-being of the mother, as well as potential harm to the foetus.[65] Discussions surrounding non-maleficence in the context of therapeutic abortion often delve into deeply held beliefs about the sanctity of life, autonomy, and the rights of both the mother and the unborn child. Some argue that allowing therapeutic abortions upholds the principle of non-maleficence by preventing greater harm to the mother,[66] while others contend that terminating a pregnancy violates the inherent dignity and right to life of the foetus.[67] Ethical considerations in this realm necessitate a nuanced understanding of medical, social and cultural factors, as well as a commitment to balancing the well-being of all involved parties.

For the thalassaemia programme, therapeutic abortion pertains to the deliberate termination of a pregnancy upon the diagnosis of thalassaemia in the foetus, either through prenatal testing or during antenatal care. Various countries adopt distinct approaches to define the terms and conditions under which termination is permissible. For instance, in Germany, abortions are permitted up to the 22nd week for foetal abnormalities after a 3-day waiting period, and up to the 12th week with counselling or physician approvals, while recent Cyprus legislation allows abortions up to 12 weeks with a mandatory psychological consultation.[68] In Israel, abortion regulations have undergone multiple revisions, allowing termination under the age of 18 with the approval of an appointed committee, potentially extending beyond 24 weeks.[68,69] Iran permits selective abortion up to 15 weeks as part of its prevention programme, resulting in a significant reduction in the prevalence of new thalassaemia cases.[70,71] Similarly, Turkey allows termination at a younger gestational age of 10 weeks, with the possibility of extension based on stringent health criteria.[72]

Therapeutic abortion has been integrated into the national prevention and intervention programmes of several countries, including Cyprus, Israel, Iran and Turkey. Despite facing criticism from religious factions or segments of the population regarding abortion, these nations have achieved significant reductions in new thalassaemia births.[28] Remarkably, there is no evidence to suggest that these countries intend to reverse their decision on therapeutic abortion. This underscores the effectiveness of incorporating abortion services into comprehensive healthcare strategies aimed at mitigating the prevalence of genetic disorders like thalassaemia.

*Asian Region*

From 2007 to 2011, there were 1483 affected births in Malaysia, which decreased to 214 between 2017 and 2018. This declining trend is likely due to increased public awareness and initiatives like free early population screening and health education. Prenatal screening for thalassaemia is also available upon request in government hospitals, though the screening rate remains low.[22] Since 2019 the National Prevention and Control programme has been expanded to include 14-year-old. The success of the reduction will be appreciated once this cohort starts to give birth. In Singapore, the success rate of the thalassaemia prevention programme was found to be 90%, with the number of new cases falling from an average of 37 per year in the 1980s to less than five per year in 2000.[43]

*Screening Methods*

Thalassaemia screening was first introduced in the early 1970s as a national initiative.[56] Over the decades, the growth of innovation and technology has seen techniques made simpler with lesser steps and faster turnaround time with greater accuracy. As a result, several types of screening have been on the market. However, in this review, the selected articles were able to find only three types of screening that were adopted which include (1) pre-pregnancy / in the early stage of pregnancy/pre-gestational screening/pre-marital, (2) prenatal diagnosis/antenatal diagnosis, (3) population screening approach.

*Pre-conception Screening*

Pre-pregnancy screening for preventing beta-thalassaemia and other hemoglobinopathies has been done in Northern Israel since 1987.[69] Pregnant women were screened on their

first visit to community Mother and Child Health Clinics, and subsequently, the husbands of the affected women were also screened. Other nations have laws requiring premarital thalassaemia testing for all couples before marriage approval, including Iran since 1991.[14,73] The pre-marital screening began in Cyprus as early as the 1980s and was mandated by the Cypriot Orthodox Church for Greek Cypriots before they could get married.[23] In 1993, this form of mandatory pre-marital thalassaemia screening also continued to be a policy in the Palestinian Territories in 2000,[39] and Saudi Arabia in 2003.[45] The Taiwan government conducted a National Screening Programme to reduce the birth rate of thalassaemia major. It involves obstetricians routinely screening pregnant women's complete blood count.[74] These nations implemented the programme backed by legal provisions to reduce the prevalence of thalassaemia.

*Pre-natal Diagnosis*

As early as 1974, Greece started their prenatal diagnosis screening under the Greek National Prevention Program for thalassaemia and other haemoglobinopathies. The National Prevention Program provides services through the general hospital, which consists of a specific haematology unit and a prenatal diagnosis unit.[75] Both pre and post-test counselling are essential for prenatal diagnosis programmes to eliminate irrational fears among people, particularly regarding stigmatisation. It also helps individuals and families at risk come to terms with the situation and consequences of the disorder.[37] Cyprus started legislating 1980 mandatory thalassaemia carrier screening, and a prenatal diagnosis programme was started by the end of 1984.[76] In Sardinia, the married couples who were carriers of the c.118C4T variant in the HBB gene were counselled for prenatal diagnosis via peripheral blood screening.[42] In Israel, couples at risk of having affected offspring are referred for genetic counselling and prenatal testing starting in 1987.[69]

*Student Screening*

Thalassaemia screening is also offered to secondary high school students. A thalassaemia screening programme was conducted in India among high school students between 1984-1988, and 5682 students were screened. Out of which, 153 (2.7%) were found to have beta-thalassaemia.[78] In a similar programme on screening over 25,000 high school students in Montreal, Canada, from 1972 to 1992, 693 students were detected as carriers (1 in 36). The carriers identified in the high school programme remembered their status, had their partners tested and opted for prenatal diagnosis if required.[25,79] Another study from the Marseille region in France evaluated a screening programme for secondary school children from 1978 to 1985.[80] The study assessed the partner's uptake for testing by sending a letter along with an anonymous questionnaire to all the carriers. In total, 86% of them knew they had to test their partners. Six carrier couples were identified, and four requested prenatal diagnosis. Cross-sectional studies were conducted in Palestine[40] and Malaysia.[9] This screening exercise showed that thalassaemia carriers are common and are feasible to carry out a screening programme for secondary high school students and will impact the prevalence of thalassaemia.

Treatment and prevention are complementary and can reduce healthcare expenditure, particularly in the case of thalassaemia, to improve quality of life. Practical preventive approaches have demonstrated success in the above countries described. However, screening programs need to be backed by public education and a combination of regulatory frameworks to provide people with the information they need to make wise decisions and guarantee that people are not subjected to discrimination because of the findings of their tests. The screening programme is usually packaged with genetic counselling for individuals at risk, offers carrier testing to individuals with a family history of the disorder and provides prenatal diagnosis for pregnant women at risk of having a child with thalassaemia.

*Programme Cost*

The lifetime healthcare costs of transfusion-dependent thalassaemia from countries (such as the United Kingdom, United States, Italy, Iran, Thailand, Taiwan and India vary between USD363,149 and USD720,201.[10] This may include home infusion service, chelating agent, stay in the hospital, operation, outpatient visits, laboratory tests and therapist.[30] In addition, studies have demonstrated that screening and prevention initiatives reduce the number of newborns with thalassaemia but are also cost-effective compared to providing people with thalassaemia who depend on blood transfusions with lifelong supportive care.[10]

The World Health Organization committee emphasised a significant economic value that would could result from preventing thalassaemia in several European populations with a high incidence of the disease.[80] In Cyprus, the annual cost of operating the screening and prenatal diagnosis programme is about the same to the cost of treatment of existing patients for five years. Meanwhile, in Sardinia, it is estimated that a reducing the prevalence of thalassaemia by 90% would allow the establishment of a prevention programme to be paid off in three years from the start of the services; thereafter, the total cost of treatment would steadily reduce to one-fifth of the projected cost of treatment over the next five years.[57]

Thalassaemia Prevention Programme operates differently in different countries. Without prevention, annual treatment costs could rise to over USD150 million annually for one birth in Iran. The estimated annual cost of prevention in Iran is USD7,730 compared to the cost of treating thalassaemia, which is USD12,387.[16] Referring to the annual number of 1251 births of thalassaemia major here, the cost difference of USD3 million was saved by implementing the prevention screening programme.

The Israel National Screening Programme for Thalassaemia costs USD900,197, amounting to USD4.6 million for 13 homozygotes born. However, if the screening programme is not implemented, the lifetime medical care costs for 26 homozygotes would amount to USD7.5 million.[30] In another study by Koren et al., the cost of preventing one affected newborn was USD63,660 compared to USD1,971,380 for treating a patient for 50 years (mean annual cost: USD39,427).[29] Therefore, the preventative programme still benefits USD76 million over ten years, even after deducting the cost of the prevention programme (USD413.80/year). Therefore, each case prevented could cover the cost of screening and prevention programmes for 4.6 years.

The annual cost of carrier screening for thalassaemia trait in Montreal was USD26,648. The total undiscounted sum of these costs for the first 25 years of treatment is USD176,426 or USD7,057/per patient per year.[57] In Greece, there are several programmes in place to prevent the occurrence of thalassaemia. The total annual cost of the prevention programme is calculated to be only about EUR1,400,000, while the cost of treatment per thalassaemia major patient was approximately EUR2,229-4,371 per month.[36] In Iraq, it was reported in 2016 that each patient's management cost is USD1,428-3,785/month, an average of USD2,606.5 per month, with USD31,278 per year. The incidence of thalassaemia in Iraq in 2015 was 335 patients. If these cases were prevented, assuming the value of the preventive measures of USD63,660 would be much more cost-effective than case management.[24]

*Treatment Costs*

The various journals that reported treatment costs showed varying approaches in presenting their findings. Therefore, from the selected journals discussed in this paper, the contents for this theme on treatment costs are grouped into six ways how the cost are reported, namely, (a) prevention of one affected child/patient, (b) the annual cost of prevention, (c) cost per patient per month, (d) the annual cost per patient, (e) average treatment cost, (f) the lifetime cost of treatment and the lifetime cost of treatment.

As the treatment modalities vary between countries, which depends on the health infrastructure and resources employed, the policy or clinical guidelines that are followed, and the GDP for the different years, this article does not intend to compare costs between countries directly. Instead, it will share the findings to explain the costs incurred. The treatment cost is vital information as they significantly impact the economy and costs to the family problems, notwithstanding the societal problems that the disease may compound.

A study conducted by Koren et al., in Israel reported that preventing one case of affected β-thalassaemia new-born was only one-third the cost of treatment; USD 63,660 compared to USD 1.981,380 for treatment of beta-thalassaemia for over a lifetime of 50 years.[29] We could not find another country to compare this cost. However, Ostrowsky et al. reported that the annual cost of carrier screening for the thalassaemia trait in Montreal was USD26,648, which appeared to be far cheaper than reported by Koren et al.[29,57] In Greece, a study in 2012 showed the total annual cost of the prevention programme is calculated to be only about EUR1,400,000 or USD1,089,340 (Av exchange rate 1 USD in 2012:0.7781 EUR).[36] The scope of the screening prevention programmes in these countries may be very different to make a fair comparison.

Greece has started focusing on thalassaemia screening and treatment since the 1970s. This has given a positive outcome, given medical and supportive management, and it has provided an overall survival rate of 65% at the age of 50 years. Voskaridou et al.[36] 2012 estimated the cost of treatment per thalassaemia major patient to be approximately EUR2,229-4,371 per month. In Iraq, Mutar et al., shared that each patient's management cost is USD1,428.00-3,785.00/month; this includes blood transfusion and drugs, as this is calculated for life.[24]

In India, de Silva et al. found that the treatment cost includes costs of blood and its preparation, chelating agents, essential investigations, and hospital visits, and calculated that the average cost of treatment for the patient for a year is about INR175,000 (USD2,465).[81] A recent Indian study showed that the treatment of TDT was estimated to be USD1,135 annually.[82] While this study showed that in Thailand, the annual average cost of treatment from a societal perspective was approximately USD950 (at the year 2005 prices), of which 59% was direct medical cost, 17% was direct non-medical cost, and 24% was indirect cost. The total undiscounted costs for the first 25 years of treatment are USD176,426 or USD7,057 per patient-year.[33]

Taiwan reported that the undiscounted lifetime cost of treating TDT study was estimated at USD561,208.[47] Shafie et al., noted that in Malaysia, a TDT patient is expected to incur. Therefore, the lifetime cost of TDT patients is estimated to be USD 606,665.[10] In the United Kingdom, Karnon et al. in 1999, reported that the undiscounted lifetime cost of treating a beta-thalassaemia major patient was estimated to be GBP803,002.[31] However, when the costs were discounted at a rate of 6%, the lifetime cost was reduced to GBP219,068.

*Cost-Effectiveness of Prevention*

From the various papers screened on thalassaemia, it was noted that many studies commonly reported, among others, prevalence, the cost and financial burden, and the screening methods, though not all were covered in one paper. Most sparingly, however, are studies on cost-effectiveness. Cost-effectiveness analysis compares the costs and outcomes of different strategies to determine which provides the greatest value, responding to the need to manage health care's significant economic burden and high costs of medical interventions.[60] This review found only a few studies that have reported the cost-effectiveness of the intervention programme at the country level. As the approaches reported between these countries are dissimilar, this review will share the findings of each study in their respective countries.

Israel started their screening and intervention programme in 1987. In 2014, Koren et al., conducted a cost-effectiveness study and found that the cost of preventing one affected newborn was USD63,660 compared to the treatment cost, which is almost 30 times more, USD1,971,380 for the treatment of a patient for 50 years (the mean annual cost: USD39,427).[29] His study concluded that USD88.[5] million of net savings to the health budget over 10 years prevented 45 new thalassaemia cases, plus an additional USD76 million over 10 years after deducting the cost of the prevention programme (USD413,795/year).[83]

Iran started the minor thalassaemia screening programmes and intervention in 1997, a decade after Israel. It was a solid political commitment requiring thalassaemia screening test results before approval for official marriage registration. Esmaeilzadeh et al., compared the cost of screening and treatment.[15] The study found that screening techniques prevented 26.97 patients with thalassaemia major, and the

cost of prevention for each birth was estimated to be USD32,624 compared to the treatment cost of USD136,532 per year. For context, Koren et al., reported significantly lower mean annual treatment cost of USD39,427 in Israel.[29]

In Hong Kong, Leung et al., conducted a cost-effectiveness study that retrospectively reviewed the prenatal screening programme from 1998 to 2002 and compared the screening cost against the treatment cost.[49] The study estimated that the total expenditure for the screening programme would cost HKD10.0 million, much less than the postnatal service costs, which were HKD40.4 million for 18 beta-thalassaemia major foetuses if they were born. Hong Kong started with an indirect approach of serial ultrasound and, subsequently, invasive tests for definitive diagnosis in participating prenatal clinics. This approach provided 100% sensitivity and a low false positive rate of 2.9%. The study recommended that running a universal prenatal screening programme in an area where both β-thalassaemia and α-thalassaemia are prevalent is cost-effective. In addition, the indirect approach can effectively avoid an invasive test in unaffected pregnancies.

In 2020, a study in Thailand conducted the cost-effectiveness of prenatal screening thalassaemia between two methods; a semi-accelerated screening programme was compared with the current conventional programme. It was found that the new modality could detect many more cases 34 versus only eight by the current programme. Thus, the expected costs of the semi-accelerated screening programme were higher than the current programmes, with a difference of THB609.[29] and THB462.44.[34] However, the cost-effectiveness of the benefits or potential future reduction of the cases was not discussed.

Amarasinghe et al., have comprehensively analysed the cost-effectiveness of thalassaemia prevention in Sri Lanka.[32] In 2022, the study was conducted in five districts where the screening programme was implemented. The intervention package involved three elements: a) an education programme, b) nationwide screening and c) antenatal screening with the termination of pregnancy. The study found that the previous policy of promoting 'safe marriages' could reduce one thalassaemia major birth whilst the new policy package of a, b and c were able to minimise births by 14, 35 and 48, respectively. Although the cost per prevention was USD 20,084 through termination of pregnancy, the authors suggested that a less legal approach to the intervention is taking an island-wide screening that will cost USD22,324 and mass education costing USD12,420. As a combo approach, improving uptake and making it less objectionable to the community is cost-effective.

## LIMITATIONS

The decline in thalassaemia births can also be attributed to the declining population growth rate, and the success of birth control programmes can mask the actual decline of the programme during the same period. This can be shown by the study in Iran, which showed a declining trend in the number of birth cases of thalassaemia during the period from 1989 to 1995, when the prevention programme was not yet in place. Since the implementation of the prevention programme in 1996, the rate of thalassaemia births has declined.[13] The thalassemia prevention programme in Iran has impacted reducing the number of thalassaemia births in the country. Health decision-makers must continue reviewing and improving the programme to reduce the number of affected patients. Similar scenarios may be common in many countries. However, thus far, no studies have shown the rate of decline in isolation by the two effects, namely birth control and the screening programme.

## CONCLUSION

This systematic review found that the thalassaemia intervention and control programmes in selected countries have reduced thalassaemia births. They include countries in the Thalassaemia Belt and others with a high prevalence of thalassaemia traits. North Cyprus, Iran, Iraq, Greece, Turkey, Oman and Canada have shared their success in reducing the incidence between 50% and 90%. North Cyprus, in particular, with no reported new cases in recent years. Previous studies supported the various intervention programmes showing treatment cost-savings if effective prevention has been implemented. However, treatment costs range from 23 to 65 times more expensive than the cost of the screening programme.

This systematic review concluded that countries that have invested in screening and control programmes could enjoy savings on treatment costs and an appreciative reduction in thalassaemia incidence and morbidity. However, the screening modality must be tailored to the local culture and respect the religious values and sensitivities to earn a generous response from the community. The main limitation was the matching of the incidence, cost of prevention and treatment, which are collated from different authors for different years for the country understudied.

## DECLARATIONS

**Ethics approval and consent to participate.**

No ethical approval was required for the conduct of this systematic literature review as it is based on published research and does not involve any new studies of human participants or animals performed by any of the authors.

**Availability of data and material**

Data sharing does not apply to this article as no datasets were generated during the current study.

**Declaration of Conflicting Interests**

The authors declared no competing or conflict of interest concerning this article's research, authorship and publication.

**Funding and ethical approval**

The authors wish to convey that this study was conducted without the aid of any financial support. No grants or funds were received from public, commercial or non-profit funding entities to facilitate this study.

**Authors' contributions**

All authors have reviewed the manuscript, believe it represents valid work, and approve it for publication. In addition, all authors participated in the research design, the research performance, data analysis and manuscript writing.

## REFERENCES


1. Cao A, Kan YW. The prevention of thalassemia. Cold Spring Harb Perspect Med 2013; 3(2): a011775.
2. Shawky RM, Kamal TM. Thalassemia intermedia: An overview. Egyptian J Med Hum Genet. 2012; 13(3): 245-55.
3. Kadhim KA, Baldawi KH, Lami FH. Prevalence, incidence, trend, and complications of thalassemia in Iraq. Hemoglobin 2017; 41(3): 164-8.
4. Origa R. β-Thalassemia. Genet Med 2017; 19(6): 609-19.
5. Bozkurt G. Results from the north cyprus thalassemia prevention program. Hemoglobin 2007; 31(2): 257-64.
6. Şanlidağ B, Çağin B, Özenli Ö, Şahaloğlu Ö, Dalkan C, Galip N, et al. Prevalence of thalassemia trait & iron deficiency anemia during infancy in 2011–2013 in a Thalassemia Prevalent Region: North Cyprus. Iran J Public Health 2016; 45(8): 1038.
7. Ahmadnezhad E, Sepehrvand N, Jahani FF, Hatami S, Kargar C, Mirmohammadkhani M, et al. Evaluation and cost analysis of national health policy of thalassaemia screening in west-azerbaijan province of iran. Int J Prev Med 2012; 3(10): 687-92.
8. Kantharaj A, Chandrashekar S. Coping with the burden of thalassemia: Aiming for a thalassemia free world. Glob J Transf Med 2018; 3(1): 1-5.
9. Jameela S, Sabirah SO, Babam J, Phan CL, Visalachy P, Chang KM, et al. Thalassaemia screening among students in a secondary school in Ampang, Malaysia. Med J Malaysia 2011; 66(5): 522-4.
10. Shafie AA, Wong JHY, Ibrahim HM, Mohammed NS, Chhabra IK. Economic burden in the management of transfusion-dependent thalassaemia patients in Malaysia from a societal perspective. Orphanet J Rare Dis 2021; 16(1): 157.
11. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021; 372.
12. Gholam Hasan K, Nasrin F, Masumeh S. Frequency of thalassemia in Iran and Khorasan Razavi. Int J Pediat 2013; 1(1): 45-50.
13. Miri M, Tabrizi Namini M, Hadipour Dehshal M, Sadeghian Varnosfaderani F, Ahmadvand A, Yousefi Darestani S, et al. Thalassemia in Iran in last twenty years: the carrier rates and the births trend. Iranian J Blood Cancer 2013; 6 (1): 11-8.
14. Samavat A, Modell B. Iranian national thalassaemia screening programme. BMJ 2004; 329(7475): 1134-7.
15. Esmaeilzadeh F, Ahmadi B, Vahedi S, Barzegari S, Rajabi A. Major thalassemia, screening or treatment: an economic evaluation study in Iran. Int J Health Policy Manag 2021; 11(7): 1112-9.
16. Esmaeilzadeh F, Azarkeivan A, Emamgholipour S, Sari AA, Yaseri M, Ahmadi B, et al. Economic burden of thalassemia major in Iran, 2015. J Res Health Sci 2016; 16(3): 111-5.
17. Karimi M, Jamalian N, Yarmohammadi H, Askarnejad A, Afrasiabi A, Hashemi A. Premarital screening for beta-thalassaemia in Southern Iran: options for improving the programme. J Med Screen 2007; 14(2): 62-6.
18. Ghotbi N, Tsukatani T. Evaluation of the national health policy of thalassaemia screening in the Islamic Republic of Iran. Eastern Med Health J 2005; 11 (3): 308-318.
19. Sattari M, Sheykhi D, Nikanfar A, Pourfeizi AH, Nazari M, Dolatkhah R, et al. The financial and social impact of thalassemia and its treatment in Iran. Pharm Sci 2019; 18(3): 171-6.
20. Rahbari M, Hajnaghizadeh F, Damari B, Adhami B. Dropouts and social determinants of health; policy for the prevention of school dropout, qualitative study of the causes and interventions. Int J Prev Med 2014; 5(11): 1396.
21. Haque A, A'thirah bt Puteh F, Osman N, Amilin Z, Zain M, Haque M. Thalassaemia: Level of awareness among the future health care providers of Malaysia. J Chem Pharm Res 2015; 7(2): 896-902.
22. Ibrahim HM, Muda Z, Othman IS, Unni MNM, Teh KH, Thevarajah A, et al. Observational study on the current status of thalassaemia in Malaysia: a report from the Malaysian Thalassaemia Registry. BMJ Open 2020; 10(6): e037974.
23. Cowan RS, editor Moving up the slippery slope: mandated genetic screening on Cyprus. American Journal of Medical Genetics Part C: Seminars in Medical Genetics; 2009: Wiley Online Library.
24. Mutar MT, Hameed MM. Thalassemia Prevention Program in Iraq: Cost-Effectiveness and Applicability Assessment. Baghdad Med J Students 2020 1(1): 1-9.
25. Langlois S, Ford JC, Chitayat D, Désilets VA, Farrell SA, Geraghty M, et al. Carrier screening for thalassemia and hemoglobinopathies in Canada. J Obstetr Gynaecol Canada 2008; 30(10): 950-9.
26. Mitchell JJ, Capua A, Clow C, Scriver CR. Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassemia disease carriers in high schools. Am J Hum Genet 1996; 59(4): 793.
27. Canatan D. Haemoglobinopathy prevention program in Turkey. Thalassemia Reports 2011; 1(1): 9-11.
28. Saffi M, Howard N. Exploring the effectiveness of mandatory premarital screening and genetic counselling programmes for β-thalassaemia in the Middle East: a scoping review. Public Health Genomics 2015; 18(4): 193-203.
29. Koren A, Profeta L, Zalman L, Palmor H, Levin C, Zamir RB, et al. Prevention of β thalassemia in Northern Israel - A cost-benefit analysis. Med J Hematol Infect Dis 2014; 6(1): e2014012.
30. Ginsberg G, Tulchinsky T, Filon D, Goldfarb A, Abramov L, Rachmilevitz E. Cost-benefit analysis of a national thalassaemia prevention programme in Israel. J Med Screen 1998; 5(3): 120-6.
31. Karnon J, Zeuner D, Brown J, Ades AE, Wonke B, Modell B. Lifetime treatment costs of β-thalassaemia major. Clin Lab Haematol 1999; 21(6): 377-85.
32. Amarasinghe N, Amarasena A, Thabrew A, Werawatte P, Premawardhena A, Malik F, et al. Redesigning new policy options for thalassemia prevention in Sri Lanka. Thalassemia Reports 2022; 12(4): 135-42.
33. Riewpaiboon A, Nuchprayoon I, Torcharus K, Indaratna K, Thavorncharoensap M, Ubol B-o. Economic burden of beta-thalassemia/Hb E and beta-thalassemia major in Thai children. BMC research notes 2010;3(1):29.
34. Laoarayawat T, Bamrungsawad N, Dilokthornsakul P, Wong P, Upakdee N. Cost-Effectiveness Analysis of Prenatal Screening Program for Thalassemia Between Semi-accelerated Screening Step and Current Program. Ramathibodi Med J 2020; 43(1): 13-23.
35. Voskaridou E, Kattamis A, Fragodimitri C, Kourakli A, Chalkia P, Diamantidis M, et al. National registry of hemoglobinopathies in Greece: updated demographics, current trends in affected births, and causes of mortality. Ann Hematol 2019; 98(1): 55-66.
36. Voskaridou E, Ladis V, Kattamis A, Hassapopoulou E, Economou M, Kourakli A, et al. A national registry of haemoglobinopathies in Greece: deducted demographics, trends in mortality and affected births. Ann Hematol 2012; 91(9): 1451-8.
37. Colah R, Italia K, Gorakshakar A. Burden of thalassemia in India: the road map for control. Pediatr Hematol Oncol J 2017; 2(4): 79-84.
38. Pankaj K M, Jadab C S. Expenditure to treat thalassaemia: an experience at a tertiary care hospital in India. Iran J Public Health 2010; 39(1): 78-84.
39. Tarazi I, Al Najjar E, Lulu N, Sirdah M. Obligatory premarital tests for β-thalassaemia in the Gaza Strip: evaluation and recommendations. Int J Lab Hematol. 2007; 29(2): 111-8.
40. Sirdah, Bilto, Jabour E, Najjar. Screening secondary school students in the Gaza strip for β-thalassaemia trait. Clin Lab Haematol 1998; 20(5): 27983.
41. Longinotti M, Pistidda P, Oggiano L, Guiso L, Frogheri L, Dore F, et al. A 12-year preventive program for β-thalassemia in Northern Sardinia. Clin Genet 1994; 46(3): 238-43.

42. Saba L, Masala M, Capponi V, Marceddu G, Massidda M, Rosatelli MC. Non-invasive prenatal diagnosis of beta-thalassemia by semiconductor sequencing: a feasibility study in the sardinian population. Eur J Hum Genet 2017; 25(5): 600-7.
43. Wong WC, Lee J, Mok KY. Prevalence of haemoglobinopathies in Singapore. Singap Med J 2009; 50(6): 623-6.
44. Alkindi S, Al Zadjali S, Al Madhani A, Daar S, Al Haddabi H, Al Abri Q, et al. Forecasting hemoglobinopathy burden through neonatal screening in Omani neonates. Hemoglobin 2010; 34(2): 135-44.
45. AlHamdan NA, AlMazrou YY, AlSwaidi FM, Choudhry AJ. Premarital screening for thalassemia and sickle cell disease in Saudi Arabia. Genetics in Medicine 2007; 9(6): 372-7.
46. Lena-Russo D, Badens C, Aubinaud M, Merono F, Paolasso C, Martini N, et al. Outcome of a school screening programme for carriers of haemoglobin disease. J M Screen 2002; 9(2): 67-9.
47. Ho W, Lin K, Wang J, Hwang JS, Chung C, Lin DT, et al. Financial burden of national health insurance for treating patients with transfusion-dependent thalassemia in Taiwan. Bone Marrow Transplant 2006; 37(6): 569-74.
48. Safdar S, Mirbahar A, Sheikh MA, Taseer I-u-H, Mustafa A, Ali Z, et al. Economic burden of thalassemia on parents of thalassemic children: a multi-centre study. Pak J Med Res. 2017; 56(3): 68-72.
49. Leung K, Lee C, Tang M, Lau E, Ng L, Lee Y, et al. Cost-effectiveness of prenatal screening for thalassaemia in Hong Kong. Prenatal Diagn 2004; 24(11): 899-907.
50. Whittemore R, Knafl K. The integrative review: updated methodology. J Adv Nurs 2005; 52(5): 546-53.
51. Flemming K, Booth A, Garside R, Tunçalp Ö, Noyes J. Qualitative evidence synthesis for complex interventions and guideline development: clarification of the purpose, designs and relevant methods. BMJ Global Health 2019; 4(Suppl 1): e000882.
52. Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qual Res Sport Exer Health 2019; 11(4): 589-97.
53. Kiger ME, Varpio L. Thematic analysis of qualitative data: AMEE Guide No. 131. Med Teach 2020; 42(8): 846-54.
54. Kattamis A, Forni GL, Aydinok Y, Viprakasit V. Changing patterns in the epidemiology of β-thalassemia. Eur J Haematol 2020; 105(6): 692-703.
55. Mustafa I, Firdous N, Shebl FM, Shi Z, Saeed M, Zahir Z, et al. Genetic epidemiology of beta-thalassemia in the Maldives: 23 years of a beta-thalassemia screening program. Gene 2020; 741: 144544.
56. Chern JP, Lin KH, Su YN, Lu MY, Jou ST, Lin DT, et al. Impact of a national β-thalassemia carrier screening program on the birth rate of thalassemia major. Pediatr Blood Cancer 2006; 46(1): 72-6.
57. Ostrowsky JT, Lippman A, Scriver CR. Cost-benefit analysis of a thalassemia disease prevention program. Am J Public Health 1985; 75(7): 732-6.
58. Karnon J, Tolley K, Vieira J, Chandiwana D. Lifetime cost-utility analyses of deferasirox in beta-thalassaemia patients with chronic iron overload. Clin Drug Invest 2012; 32(12): 805-15.
59. Leech AA, Kim DD, Cohen JT, Neumann PJ. Use and misuse of cost-effectiveness analysis thresholds in low-and middle-income countries: trends in cost-per-DALY studies. Value Health 2018; 21(7): 759-61.
60. Bang H, Zhao H. Cost-effectiveness analysis: a proposal of new reporting standards in statistical analysis. J Biopharm Stat 2014; 24(2): 443-60.
61. Weatherall D, Clegg JB. Inherited haemoglobin disorders: an increasing global health problem. Bull World Health Organ 2001; 79(8): 704-12.
62. Gafer AA, Al-Rabeei NA, Al-Awar MS. Factors affecting health-related quality of life among thalassemia patients, 2020, Sana'a-Yemen. Res Sq: 2021.
63. Wong LP, George E, Tan J-AMA. Public perceptions and attitudes toward thalassaemia: Influencing factors in a multi-racial population. BMC Public Health 2011; 11: 193.
64. Kyrri AR, Kalogerou E, Loizidou D, Ioannou C, Makariou C, Kythreotis L, et al. The changing epidemiology of β-thalassemia in the Greek-Cypriot population. Hemoglobin 2013; 37(5): 435-43.
65. di Giacomo E, Pessina R, Santorelli M, Rucco D, Placenti V, Aliberti F, et al. Therapeutic termination of pregnancy and women's mental health: Determinants and consequences. World J Psychiatry 2021; 11(11): 937-53.
66. Egan BM. Abortion as a moral good? Contrasting secular and judeo-christian views and a potential pathway for promoting life. Health 2021; 13(1): 9.
67. Lan NT. The right to life of a fetus: Abortion is a serious moral and social problem of the young people in Vietnam. Int J Res 2021; 10(15): 47-63.
68. Kivity S, Barnoy S. Women's intention to abort a fetus diagnosed with a genetic disease: results from Israel, Cyprus, and Germany. Sage Open 2023; 13(3): 21582440231184974.
69. Koren A, Profeta L, Zalman L, Palmor H, Levin C, Zamir RB, et al. Prevention of β thalassemia in northern Israel - a cost-benefit analysis. Mediterr J Hematol Infect Dis 2014; 6(1): e2014012.
70. Ghodrati F, Saadatmand N, Gholamzadeh S, Akbarzadeh M. Investigation of the prevalence and causes and of legal abortion of teenage married mothers in Iran. Int J Adoles Med Health 2020; 32(1).
71. Karimi M, Johari S, Cohan N. Attitude toward prenatal diagnosis for β-thalassemia major and medical abortion in southern Iran. Hemoglobin 2010; 34(1): 49-54.
72. Keskin A, Türk T, Polat A, Koyuncu H, Saracoglu B. Premarital screening of beta-thalassemia trait in the Province of Denizli, Turkey. Acta Haematologica 2000; 104(1): 31-3.
73. Karimi M, Jamalian N, Yarmohammadi H, Askarnejad A, Afrasiabi A, Hashemi A. Premarital screening for β-thalassaemia in Southern Iran: options for improving the programme. J Med Screen 2007; 14(2): 62-6.
74. Chern JP, Lin KH, Su YN, Lu MY, Jou ST, Lin DT, et al. Impact of a national beta-thalassemia carrier screening program on the birth rate of thalassemia major. Pediatr Blood Cancer 2006; 46(1): 72-6.
75. Voskaridou E, Kattamis A, Fragodimitri C, Kourakli A, Chalkia P, Diamantidis M, et al. National registry of hemoglobinopathies in Greece: updated demographics, current trends in affected births, and causes of mortality. Ann Hematol 2019; 98(1): 55-66.
76. Bozkurt G. Results from the North Cyprus thalassemia prevention program. Hemoglobin 2007; 31(2): 257-64.
77. Colah R, Thomas M, Mayekar P. Assessing the impact of screening and counselling high school children for beta-thalassaemia in India. J Med Screen. 2007; 14(3): 158.
78. Mitchell JJ, Capua A, Clow C, Scriver CR. Twenty-year outcome analysis of genetic screening programs for Tay-Sachs and beta-thalassemia disease carriers in high schools. Am J Hum Genet 1996; 59(4): 793-8.
79. Lena-Russo D, Badens C, Aubinaud M, Merono F, Paolasso C, Martini N, et al. Outcome of a school screening programme for carriers of haemoglobin disease. J Med Screen 2002; 9(2): 67-9.
80. World Health Organization. Community control of hereditary anaemias: memorandum from a WHO meeting. Bull World Health Organ 1983; 61(1): 63-80.
81. de Silva S, Fisher C, Premawardhena A, Lamabadusuriya S, Peto T, Perera G, et al. Thalassaemia in Sri Lanka: implications for the future health burden of Asian populations. Lancet 2000; 355(9206): 786-91.
82. Amita Moirangthem AM, Phadke S. Socio-demographic profile and economic burden of treatment of transfusion dependent thalassemia. Indian J Pediatr 2018; 85(2): 102-7.
83. Koren A, Zalman L, Palmor H, Ekstein E, Schneour Y, Schneour A, et al. The prevention programs for beta thalassemia in the Jezreel and Eiron valleys: results of fifteen years experience. Harefuah 2002; 141(11): 938-43.