4. REVIEWING THE EFFECTIVENESS OF THALASSAEMIA PREVENTION PROGRAMMES TIF'S PERSPECTIVE IN A GLOBAL SNAPSHOT

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INTRODUCTION

Patients with haemoglobin disorders continue to be born, in small or large numbers, as a result of a lack of effective control programmes across the world. Moreover, although improvements, to variable extents, in medical and public health services have occurred in many countries around the world which allow better survival of these patients, the suboptimal medical and social care provided to a great percentage of them, perhaps to the majority of them, leads to high levels of early, premature death. The rising number of annual affected births is a major contributing factor to providing suboptimal care services and continues to be the case in many, if not most, countries. This poses very serious challenges to health and social care systems, as patients with these disorders necessitate multiple elements of medical treatment and complex social care. The provision of care for these patients is, therefore, directly related to the level of the Human Development Index (HDI) of each country; the competencies of its healthcare and social welfare systems to address the needs of annually rising numbers of cases in the absence of prevention; and other competing public health priorities, particularly, but not confined to, communicable diseases. Although a new, long-awaited innovative gene-based curative treatment has been authorised recently (2019) (while others are in advance phases of research), it will take time and immense resources to be widely applied. Bone marrow transplantation, on the other hand, has been adopted as a cure of thalassaemia for decades, albeit this can address with sufficient safety and effectiveness to-date only 20–30% of the patient population who can secure absolute sibling matched donors. Furthermore, its level of success lies in specific patient criteria and importantly in the quality and experience of the providing transplant centre. Thus, effective prevention programmes still, to date, offer the most important means to achieving advances in the quality-of-care services.

Over the last 2–3 decades, the advances achieved in the area of clinical management of patients particularly with transfusion-dependent thalassaemia (TDT), as well as those with other haemoglobin disorders, have significantly improved their quality of life and impressively extended their life expectancy, and these have happened in countries that have implemented effective prevention polices at the national level. Unfortunately, however, such results are not seen across all affected countries. In fact, in the majority of countries of the world, where more than 80% of patients with these disorders live, even basic treatment is to-date for a large percentage of them, if not for the majority, suboptimally provided, resulting in the development of many and multiple complications, poor quality of life, and premature death. Mortality and morbidity rates are very rarely reported due to the lack of disease specific registries and patient health record systems, and even when these are published, this kind of information comes from countries or centres within a country that are able to provide fairly adequate management data and have adopted registries and surveillance programmes. Such information unfortunately does not come from countries or regions where the greatest challenges exist. Indicators that may predict in a country poor survival of these patients include a low HDI and weak economies, a high under-5 mortality rate, inadequate health insurance coverage, poor medical / public health and social service organisations, and an absence of effective nationally coordinated prevention and management programmes. More disease specific indicators related to poor survival include inadequate blood supply and/or blood safety, interrupted and suboptimally provided specialised monitoring of iron load and iron chelation therapy, and a lack of appropriate multidisciplinary care offered by healthcare professionals with high levels of expertise in the field. Moreover, the absence of universal healthcare coverage constitutes the one, if not, the most important

component that renders a country unable to provide any level of appropriate, even basic, clinical management to a chronic, particularly genetic disease such as thalassaemia. Even affluent countries, with their high HDIs, strong healthcare systems and social infrastructures, when addressing the complex needs and high costs of a multi-organ, lifelong chronic condition such as thalassaemia, in the absence of effective prevention programmes that achieve reduction of the annual affected births, are faced with great challenges. The annual increase in patient numbers, particularly in high prevalence countries with no effective nationally coordinated prevention programmes, obviously becomes more and more challenging, directly impacting on the standards and quality of care services for these disorders.

The direct relation between the reduction of annual affected births and the competency of health authorities to address the huge, multiple medical, public health, social, and economic repercussions of thalassaemia was first fully recognised in the 1970s by the Southern Mediterranean countries, notably Cyprus, Greece, and Italy. These are the first countries in the world to recognise thalassaemia and other haemoglobin disorders (mainly SCD) to be highly prevalent amongst their indigenous populations and to recognise their potentially severe repercussions if left inappropriately addressed. As a result, their governments, with the support and guidance of the World Health Organization (WHO), focused great efforts on identifying those elements and policies that could contribute to the reduction of annual affected births. That factor would facilitate the reallocation of resources and thus allow the improvement of health and other care of the existing patients, as well as engage scientists in more active research with the aim to continually improve patient outcomes.

One must underscore at this point, that the patients and particularly parents in these countries who started establishing support groups and developing strong, united voices, contributed substantially to engaging their governments in promptly developing prevention programmes. They, too, had recognised since then that reducing the annual affected births could indeed support the government to focus attention, research, and resources on saving the lives of their children (the majority were children at the time), acknowledging the fact that, until then, patients particularly with TDT were dying before reaching the second decade of their life.

Below is quoted some important guidance by the WHO through its disease specific resolution in support of its country members:

WHO EB118.R1 THALASSAEMIA AND OTHER HAEMOGLOBINOPATHIES [1]

Article 1.

(1) *The Executive Board urges Member States "to design, implement and reinforce in a systematic, equitable and effective manner, comprehensive national, integrated programmes for prevention and management of thalassaemia and other haemoglobinopathies, including surveillance, dissemination of information, awareness-raising and screening, such programmes being tailored to specific socioeconomic and cultural contexts and aimed at reducing the incidence, morbidity and mortality associated with these diseases".*

Article 2. The Executive Board requests the Director-General

(1) to raise awareness of the international community of the global burden of thalassaemia and other haemoglobinopathies, and to promote equitable access to health services for prevention and management of these diseases.

(2) to provide technical support and advice to Member States in framing of national policies and strategies for prevention and management of thalassaemia and other haemoglobinopathies.

Italy, Cyprus, and Greece initially, but later also followed by other countries (including Israel, Thailand, and India), fully acknowledged the value of prevention in safeguarding and continually improving the quality of care

of patients and their medical and public health resources (see below historical extracts of country specific statements).

Cyprus: The Case for Implementing a National Prevention Programme [2, 3]

Prof. George Stamatoyannopoulos, a medical geneticist at the University of Washington, was invited in 1972 by the Ministry of Health of Cyprus, in his capacity as a WHO Consultant at the time, to visit the island in order to provide guidance.

Prof. Stamatoyannopoulos stated in his report to the Ministry that "*... [by] offering the best available treatment regimens to the current population of patients, each patient would be likely to live into middle age. A not insignificant consequence would be that medical costs would escalate and would escalate further as [an average 60–80] new affected births would be born each year. Absent of a prevention programme, it is estimated that the prevalence of β-thalassaemia would go from 1:1000 to 1:138 in the next 50 years (v.2022), creating an increase of 300–400% in the demand for blood and 600–700% in the cost of treatment. Cyprus would soon find that the needs of its thalassaemic patients would completely engulf not just the available blood supplies but also the entire budget of the Ministry of Health*".

Greece: Realising the Future Public Health Burden of Thalassaemia [4, 5]

A series of studies conducted in Greece between 1962–1972 by Prof. Christos Kattamis, paediatrician at the University of Athens, showed that 21% of children suffering from congenital diseases who were hospitalised were thalassaemia patients. Prof. Kattamis concluded that this "percentage was extremely high and revealed the gravity of the problem".

It was estimated that the number of affected births in Greece between 1980–2009 would be more than 10,000. The government of Greece had already invested sufficient annual resources for the treatment programme of thalassaemia (since 1965), and, based on this new prospective analysis, subsequently ensued a policy (including community awareness) for the prevention of thalassaemia, founding the first Centre for the Prevention of Mediterranean Anaemia in 1975 in Athens, and subsequently establishing a premarital certificate policy in 1980.

Israel & Thailand: A Cost-Benefit Analysis of Prevention Vs. Treatment

In more recent times (2014), it has been estimated in Israel, with an anticipated 45 annual affected births, that the cost of preventing one affected birth is approximately USD 63,660 compared to an investment of USD 1,971,380 for treatment of a single patient for 50 years. This is related to a total health resource preservation of USD 76 million over ten years.

Respectively, in Thailand it has been estimated that, for every affected birth prevented, a total of USD 1,914.57 is saved, considering that the lifetime cost of treatment of a single patient for 30 years is USD 219,759.00. Thus, providing a benefit:cost ratio of 72:1 [6].

This essentially demonstrates that effectiveness in prevention is related to significant resource savings which can be allocated to improve the quality of treatment, social care, and many aspects of the public health infrastructure and services provided to existing patients.

India: Anticipated Future Costs Without Prevention [7]

It has been estimated that in the absence of prevention the thalassaemia population of India would rocket to a total of 275,000 by 2026.

This would require an annual blood supply equivalent to 9.24 million units and total treatment costs would surpass 19% of the Indian national health budget.

Historically, voluntary avoidance of new cases of thalassaemia was initially offered in the early 1970s, as previously mentioned, by countries of high disease prevalence in their indigenous populations, such as Greece, Cyprus, and Italy. This led to a reduction of annual affected births by more than 70% within 2–4 years and, in most of them, by over 80% within 5 years of implementation of such efforts (See Figures 1–4 & Table 1). At first the programmes of prevention addressed the at-risk couples as part of a national policy that involved mainly screening. The programme was gradually, however, and with the guidance of the WHO, extended to include additional components (as seen in Table 2) aiming to secure the programmes' effectiveness and sustainability. This policy was followed in subsequent years by many other countries across different cultures, healthcare and social service infrastructures, and economic robustness. Successful implementation of an effective programme, marked by the reduction of annual affected births, has, however, been quite poor across the world to-date, particularly in countries where political commitment, national organisation, and full financial coverage of policies have been absent or suboptimal. In conclusion, a comprehensive control policy should include both the components of provision of quality care for patients and a reduction of annual affected births, if effectiveness of a control programme to address haemoglobin disorders is the target.

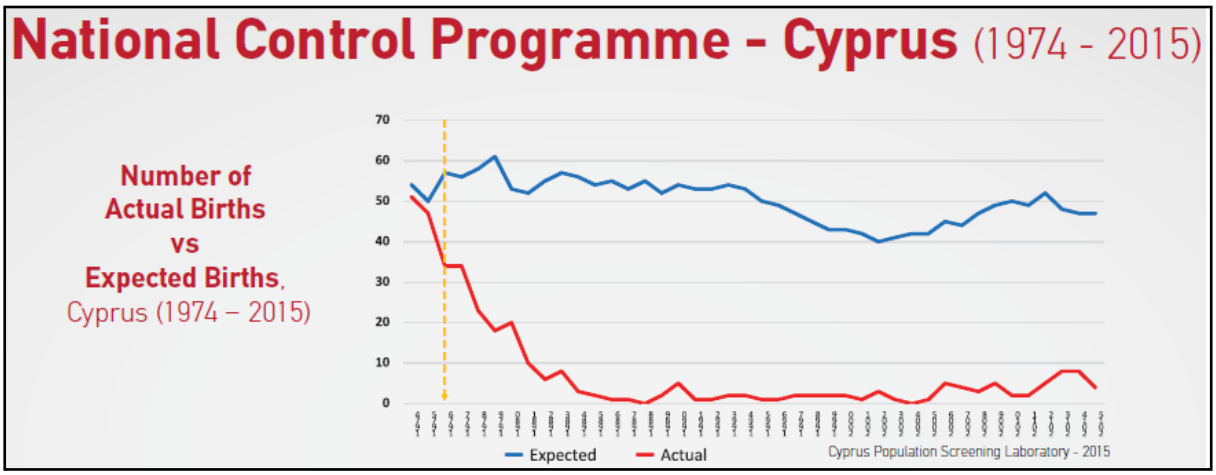

Figure 1. Cyprus national prevention programme results [8]

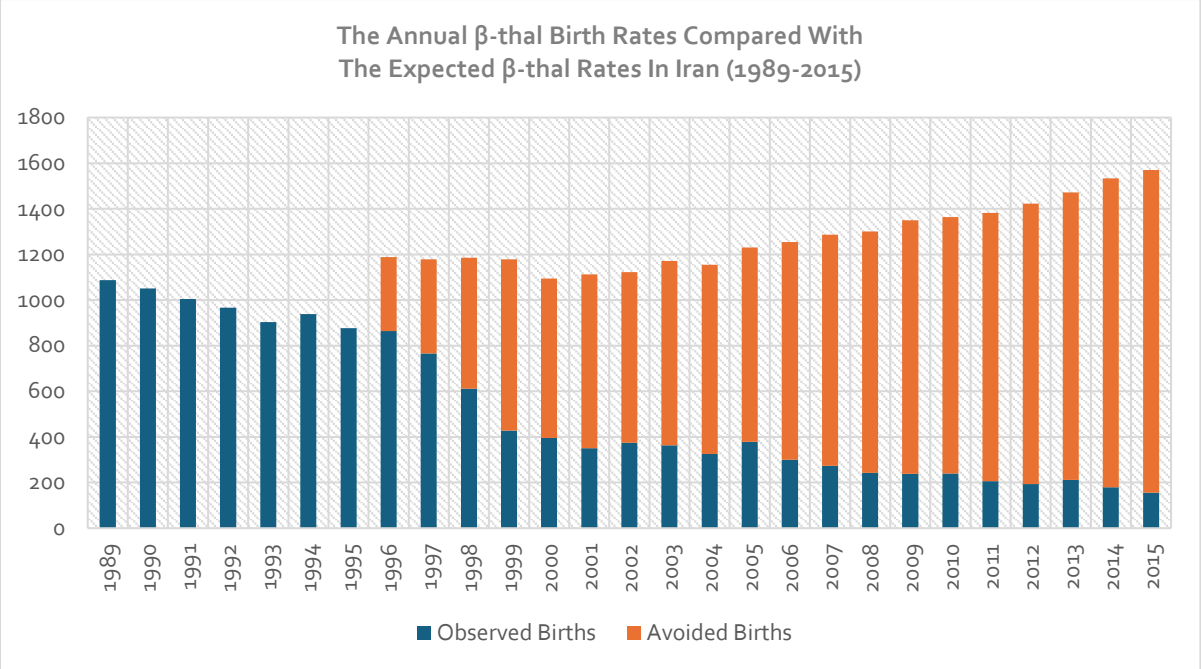

Figure 2. Iranian national prevention programme results (1989–2015) [9]

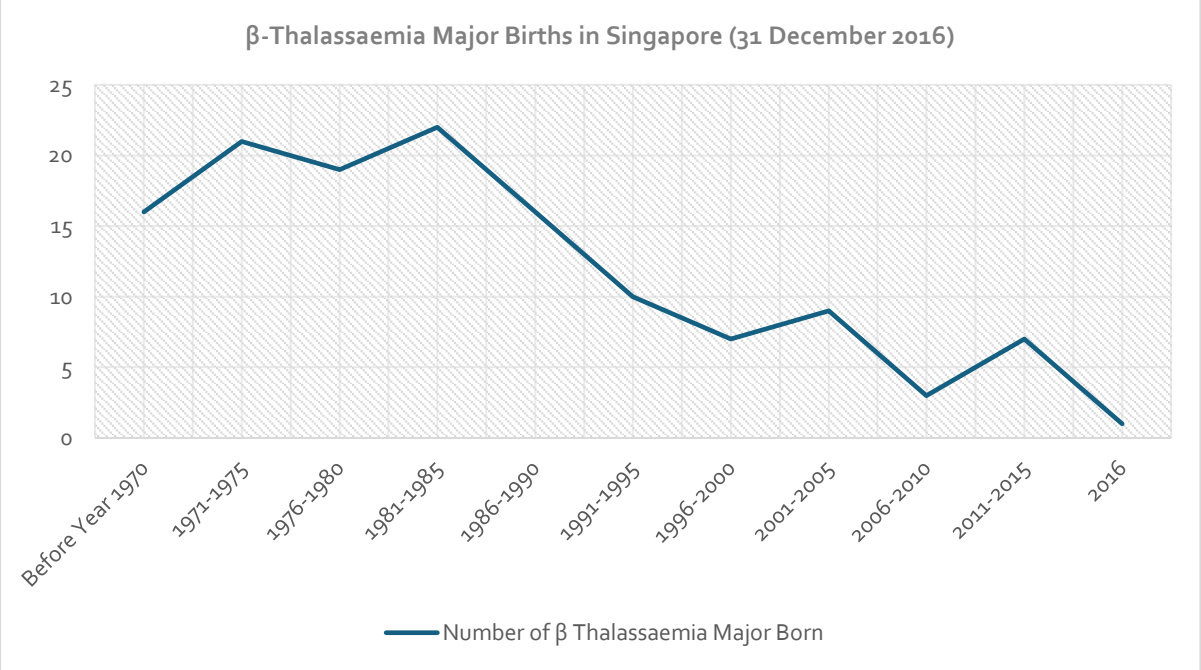

Figure 3. Singapore–Decrease in births (1970–2016) [10]

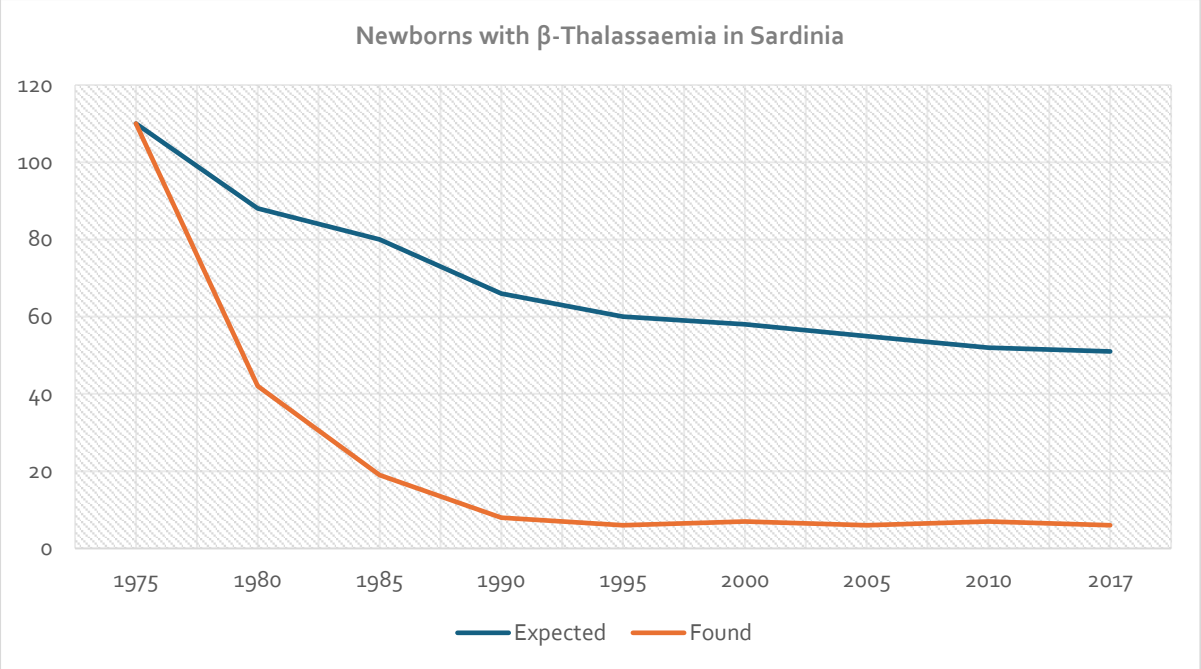

Figure 4. Fall in β-thalassaemia birth rate in Sardinia (1975–2017) [11]

Table 1. Longitudinal trends of annual births with β-thalassaemia (in 5-year intervals) during 1980–2009 for expected vs. observed and prevented births in Greece [4].

Period	Number of Newborns With β-Thalassaemia		
	Expected	Observed	Prevented
1980-1984	1,096	458 (41.7%)	638 (58.3%)
1985-1989	872	187 (21.4%)	685 (79.6%)
1990-1994	823	145 (17.3%)	678 (82.7%)
1995-1999	809	99 (12.2%)	710 (87.8%)
2000-2004	831	73 (8.7%)	758 (91.3%)
2005-2009	908	48 (5.2%)	865 (94.8%)
1980-2009	5,339	1,010 (18.2%)	4,334 (81.8%)

China

The thalassaemia carrier screening for about 1,645,000 couples dramatically decreased the incidence of thalassaemia in Guangxi Province and Guangdong Province from 21.7 and 44.6 per 10,000, respectively, in 2006 to 1.93 and 3.15 per 10,000 in 2017 [12].

The Global Picture

The Thalassaemia International Federation (TIF) has, as a pillar of its work, the promotion of nationally coordinated and fully funded control services (prevention and management) in every affected country. As a patient driven organisation, the rationale behind this is that improvements of medical and social care cannot happen in the absence of effective control of annual affected births.

In this chapter, we attempt to provide a crude snapshot of the current services and policies in some countries, members of TIF, across the different regions of the world, and their level of effectiveness with regards to prevention, mainly of transfusion-dependent thalassaemia. For this purpose, a simple scoring system, better described as a "ladder" model, was developed where those in the lower scores can rise or climb the ladder (should they wish or decide to do so) to reach higher scores and become more effective. **Such a scoring system does not aim, under any circumstances, to criticise the policies or results seen in the different countries across the world** and neither can it be considered as an accurate representation of the existing situation with regards to prevention of thalassaemia in a country. It may merely point out basic deficiencies that have been identified through published literature and/or TIF's work and to assist its members—national patients/parents associations—to encourage heathcare professionals and healthcare planners to optimise their national strategies related to the prevention of thalassaemia, recognising its value and contribution in the improvement of care services for their disorder(s).

METHODOLOGY USED

Retrieved Information

Current practices on prevention were investigated through a literature search, using publications recorded in PubMed and Google Scholar. Information from these sources on this theme is often unfortunately limited and/or outdated, mainly, as previously noted, due to the absence of national registries and/or updated epidemiological studies and micromapping. Therefore, this was supplemented by information contained in reports of TIF developed by advisors and collaborators (a variable group of medical/scientific professionals and expert patients at the national, regional, and international levels), who have been visiting, in the context of TIF's work and activities, countries across the six WHO Regions of the world over the years. Many of these reports are confidentially prepared by TIF in support of the work of health authorities and/or patient associations, and as such, they constitute unpublished information of TIF.

HbE was considered along with β-thalassaemia since it results in a thalassaemia syndrome of variable clinical severity. Other haemoglobin disorders, especially SCD and clinically significant α-thalassaemia, have been excluded from this discussion since, despite their geographical coincidence and the use of the same medical/public health/social services, different polices are usually necessary for their control, including neonatal screening.

Countries Included

A total of 51 countries across the six WHO Regions, with 100 national patient associations-members of TIF, were selected for this study, with variable estimated birth incidences of β-thalassaemia. These countries are heterogeneous in culture, needs, health priorities and socioeconomic development.

It is noted that:

- Those countries which are in active turmoil at this time, namely Syria, Afghanistan, and Yemen, are included in this list due to their high affected birth incidences. However, it is acknowledged that these have certainly no possibility, today or in the very near future, to formulate or apply any policy while the majority of their patients are displaced and struggling to survive.
- The Democratic Republic of China, with its large regional variations and high prevalence in most of the Southern provinces, is included in this study, through some of these provinces in which quite successful prevention programmes have been implemented in the last 10–15 years.
- A small number of both low and high prevalence countries for which reports and contacts are so limited that any data are considered quite unreliable (e.g., Tajikistan, Uzbekistan, Sudan) are omitted from this study.

Scoring System – Rationale

TIF has proceeded to develop, based on the rationale described below, a scoring or grading system to crudely assess the level of effectiveness of any prevention programme that exists in each of the countries included in this study. This work aims to provide a tool that may:

1. Support TIF in its work with governments, healthcare professionals' and patients' communities in advocating for the value of an effective national prevention programme;
2. Encourage, empower, and assist competent national health authorities to engage in a process of self-evaluation in regards to their existing prevention policies, with a view to facilitate the identification of areas for improvement and the better planning of those public health services that will be tailored/targeted to the country's national needs in the area of prevention.

Grading is an extremely difficult, challenging, and sensitive task to achieve satisfactorily, and it will of course never be absolutely accurate as previously mentioned, particularly in the absence of so much significant information and up-to-date data.

The main components that TIF recommends to comprise a national effective prevention programme (see Table 2) are those which have demonstrated to have contributed to the success of the prevention strategies established mainly by the governments of Cyprus, Greece, and Italy back in the early 1970s, and which a number of other countries have adopted and followed through the years. These strategies are primarily related to a significant decrease of incidence of annual affected births (as seen in Figs. 1–4 & Table 1).

In later years, in the mid-1980s, such programmes began to be adopted by other countries including the United Kingdom and France. These are countries which, since the 1950s, have hosted large numbers of immigrant workers from countries with high prevalence in haemoglobin disorders. Hence, these countries developed at national level either effective disease-specific policies of prevention and management (United Kingdom) or policies in the context of national rare disease plans into which haemoglobin disorders were/are included (France).

Strong surveillance programmes were developed by these countries as essential components to closely monitor the effectiveness of their national programmes and promote necessary adjustments, amendments, or corrective measures. The work and experience deriving from successful and effective prevention programmes contributed to TIF and others developing guidelines for the prevention of haemoglobin disorders [13]

Several others across the world, including many with significant cultural and religious constraints, have made efforts to develop prevention strategies, albeit with largely variable effectiveness.

Components of a Thalassaemia Prevention Programme considered by TIF in developing its scoring

Political commitment and a nationally coordinated, fully funded programme (policy or strategy) to cover the needs of the whole population is the pre-required component of any effective Thalassaemia Prevention Programme. In addition, any comprehensive prevention programme should encompass the following 5 pillars:

1. Public awareness & education campaigns/programmes
2. Laboratory screening programmes (to identify carriers)
3. Prenatal diagnosis/Gynaecological services/molecular studies
4. Surveillance system
5. Genetic counselling services

Further explanations of each of the above pillars are provided in Table 2.

TIF made an effort to "grade" the effectiveness of any programme and/or policies existing in a country with reference to the prevention of thalassaemia.

The grading methodology used is explained below:

- The existence of a nationally supported and funded programme (policy or strategy) for the prevention of thalassaemia in a country scores five (5) units, as this alone, underscores the existence of a strong political commitment to address a medical condition that is considered a health priority.
- Next each of the five pillars/services, as mentioned above in Table 2, is scored as follows:
    i. One (1) unit is allocated for the existence of the pillar/service to any extent;
    ii. Two (2) units are added if the pillar/service constitutes part of a national policy irrespective of its effectiveness and;
    iii. Two (2) units are further added for effectiveness of the pillar(s)/ service(s) as assessed from documentation (e.g., published literature).

Table 2. Components of a comprehensive programme on prevention of a genetic disorder.

No.	COMPONENT	EXPLANATION
1.	National programme (policy or strategy)	This implies national commitment, budgetary support and quality control.
2.	Public awareness & education	Without an informed and willing participating public, any strategy will meet obstacles. Well-coordinated public awareness and educational programmes to reach the larger society constitute an essential component of a national plan.
3.	Population screening	Identification of patients and carriers through quality-assured nationally designated laboratories, sufficient in number and with appropriate geographic distribution to cover the needs of the whole population across the country.
4.	Gynaecological and prenatal diagnosis services	Competent, well-trained, and sufficient in number gynaecologists and laboratories in nationally assigned centres to cover the needs of those who wish to perform prenatal diagnosis (PND), irrespective of their decision on how to act on the results.
5.	Surveillance system	Policies that lead to actions at a public health level require a system of continuous monitoring and systematic evaluation, not only to know the results but also to act as guides to any necessary upgrades or modifications the programme may need.
6.	Genetic counselling	To inform and offer choices to at-risk couples and carriers is vital to allow couples to make informed choices. In addition, the provision of reliable genetic information is essential to identify / diagnose patients in order to facilitate their decisions on the next steps in life. This service requires experienced, well-trained, and sufficient in number genetic counsellors.
Note: Preimplantation diagnosis is a possible choice where technology is available and costs are financially feasible. Based on in-vitro fertilisation (IVF), this technology allows the selection and implantation of healthy embryos, not affected by thalassaemia.		

In an ideal situation, therefore, each pillar could score a maximum of five (5) units and a total maximum of 30 units if and when each pillar/service scores the maxixum (i.e., 5 x 6). A score of 30 would indicate a prevention programme that is effective in reducing greater than or equal to 70% of the anticipated annual affected births within about 5 years of its implementation. Such information, of course, should be based on reliable, nationwide published data, deriving from the surveillance system component of the programme; otherwise, the score of 2 units for the effectiveness of the programme cannot be added to the score (Table 3).

Effectiveness is defined by TIF in the context of this grading exercise as the competency of the pillar/service to cover the needs of ≥70% of the country's population in the context of a national policy.

Table 3. TIF's grading system for the assessment of thalassaemia prevention programmes

Open No.	Component	Indicator	Score
1.	National Programme	A National Policy, Programme, Strategy Exists With Official Status, Publicly Announced, Government-Controlled And Fully Funded	5
2.	Public Awareness/ Education	Exists	1
		Exists Within a National Programme	2
		Nationwide or Covers at Least 70% of the Population	2
3.	Screening	Exists	1
		Exists Within a National Programme	2
		Nationwide or Covers at Least 70% of the Population	2
4.	Pre-Natal Diagnosis Services	Exists	1
		Exists Within a National Programme	2
		Accessible and Available to Cover ≥70% of the Needs of the Population Within the National Programme	2
5.	Surveillance	Exists	1
		Exists Within a National Programme	2
		Nationwide or Covers at Least 65% of the Population	2
6.	Genetic Counselling	Exists	1
		Exists Within a National Programme	2
		Nationwide or Covers at Least 65% of the Population	2
	According to the score of each pillar/service. a total score is given to each country (as seen in Annex I)		

Based on this scoring system, four (4) broad categories (A–D) of effectiveness emerged as shown below in Table 4.

Table 4. Score interpretation

Grade	Interpretation
A **≥ 20 Units**	Describes countries which have established a programme that demonstrates a very good effectiveness reflected in ≥70% reduction in the annual affected births.
B **19–15 Units**	Describes countries which demonstrate a programme of good effectiveness with considerable but not sufficient national coordination and support but, with a good potential to upgrade its programme to grade 'A' with targeted improvements.
C **14–10 Units**	Describes countries which demonstrate a programme with some disease-specific policies but with no national coordination and with weak to poor effectiveness.
D **≤ 9 Units**	Describes countries which demonstrate serious weaknesses, gaps and challenges calling for many and multiple actions to be taken at the national level.

RESULTS

Based on the information and data collected (as previously described) for each component/service in each of the 51 countries included in this study (as shown in Annex I), TIF's scoring system (as shown in Table 3 & 4) was applied, and each country was given a grade between A and D (as shown in Table 5, separated by Region, and in Annex I, by country).

The countries included in this study reflect about 51% of the global population in 2019. In addition, the number of thalassaemia patients in these countries, as reported in the literature and by TIF's estimations, constitute about 85% of the global patient community. Therefore, based on the results of the crude Grading System implemented by TIF for the purposes of this study, effective national prevention programmes are implemented in only 12% of the countries examined. The affected annual births in those countries represent only 3–4% of the global annual expected births, indicating that a great number of thalassaemia-affected births are happening across the world and that effective prevention programmes are still widely lacking [13].

Annex I comprehensively presents the prevention policy scores for each of the 51 countries, justified according to TIF's scoring rationale and methodologies.

Table 5. Summary of the implementation of TIF's grading system for thalassaemia prevention programmes in 51 countries (as described in Annex I)

WHO Region	Grade A	B	C	D
Europe	Cyprus, Greece, Italy	Azerbaijan, France, Turkey, United Kingdom	None	Albania, Austria, Belgium, Bulgaria, Germany, Romania, Sweden
Eastern Mediterranean	Iran, Palestine	Jordan, Kuwait, Lebanon, Oman, UAE, Qatar, Saudi Arabia	Iraq, Egypt Pakistan, Tunisia	Afghanistan, Morocco, Syria, Yemen
West Pacific	Singapore	Malaysia, Thailand	Vet Nam	Cambodia, Laos
Southeast Asia	None	Maldives	India, Sri Lanka	Bangladesh, Indonesia, Myanmar, Nepal
Americas	None	None	None	Argentina, Brazil, Canada, Trinidad & Tobago, USA
Africa	None	None	None	Algeria, Mauritius

DISCUSSION

Disease prevalence, in most cases, has been the driving factor guiding political commitment to address the prevention of this disorder rather than the national HDI or the level of the country's economy. This contrasts with the area of management, where the HDI level has proven to be the decisive factor in the provision of appropriate health and other care.

Through the analysis performed on the existing situation with regards to prevention in 51 countries members of TIF, across six WHO regions of the world, as shown above, one can evidence the immense heterogeneity; significant success for example has been achieved in areas with high thalassaemia prevalence but with

important cultural and religious challenges (e.g., Iran). On the other hand, success has also been achieved in areas with high thalassaemia prevalence but long-term political instability and low HDI (e.g., Palestine). Also, smaller areas with very low prevalence but a robust healthcare infrastructure and a high HDI (v. Singapore) have achieved effective prevention, and as such it is singled-out in the entire region for its effectiveness.

These, together with the countries in the southern Mediterranean, including Italy, Cyprus, and Greece, for which there is ample reference throughout this chapter, are included in **SCORING CATEGORY A,** characterising those countries that have demonstrated effectiveness in their prevention strategies.

The countries in **SCORING CATEGORY B** have also focused appropriate efforts and work on addressing the control of haemoglobin disorders, and in their case too, high prevalence has been the key driver for achieving political commitment to develop disease-specific policies. Although published data to-date have not documented the level of effectiveness with regards to prevention (as defined as a decrease by ≥70% of annual affected births at a national level) many and significant steps have been taken through the years in these countries across each pillar (as described in Table 2) of the prevention programme. These include for example many public awareness initiatives, large screening studies, and implementation of genetic counselling services to a smaller or greater extent. In most of these countries, the services related to the component of PND were not satisfactorily addressed and have not reached neither all those in need nor at least a significant proportion of at-risk couples. This has happened in some countries as a result of cultural and religious norms, but in many others this has occurred on account of medical and healthcare infrastructure challenges and poor economies, in addition to other important health priorities (including communicable diseases) that needed to be addressed.

In some countries of this category, the small to medium geographic size of the country and/or population, good public health infrastructure, and/or strong scientific interest provide significant potential for their programmes to reach effectiveness in the near future, including Malaysia, Maldives, and Sri Lanka. Despite the huge steps taken in Thailand over the years, as well as the implementation of many disease-related policies, the country has unfortunately not achieved the goal of effective nationwide prevention. This has been the result of not only vast genetic and thus phenotypic heterogeneity of haemoglobin disorders in the country but also on account of the country's size and the level of the population's health literacy and education in passing out information and awareness in rural or remote parts of the country and the wide and variable distribution of haemoglobin disorders, especially in rural areas. Other countries in this category, mainly in the European Union and across the extended European region, including the United Kingdom, France, Turkey and Azerbaijan, have exhibited reasonably effective programmes. The former two (i.e., United Kingdom and France), being countries with robust healthcare infrastructures and strong economies, felt that it was essential and cost-effective to address the prevention of haemoglobin disorders, which were of high prevalence among their immigrant populations; while for the latter two, Turkey and Azerbaijan, the high prevalence in their indigenous population was the driving element for political commitment to take significant steps in order to reduce the annual affected births whilst acknowledging the great benefit this would have on their patients' quality of care and the amelioration of the burden on their public health infrastructures. In countries of Scoring Category B, and although very limited published data is currently available, reductions of annual affected births have occurred but not quite to levels as those defined by TIF as effective.

SCORING CATEGORY C includes countries with a great focus on haemoglobin disorders as well as the existence of strong political interest in addressing the control of haemoglobin disorders. These have led to the promotion and development of many and multiple disease-specific policies and programmes. However, these countries (including India and Pakistan), on account of large populations, diverse ethnic backgrounds, geographic challenges (e.g., size, terrain), other competing health priorities, weak health and social care infrastructures, and/or weak economies, have to-date shown poor results in the prevention component of haemoglobin disorders. In other countries of this category cultural and/or religious beliefs to a large extent have perhaps hindered the implementation of a national programme and the achievement of a good level of effectiveness with regards to the prevention of haemoglobin disorders. On the other hand, Iraq, a country with

a very long history of interest in haemoglobin disorders and long-term planning for an effective prevention programme, has been unable to adopt a national strategy thus far due to political turmoil and instability, which has suffocated the country for more than two decades now.

Other countries, including Viet Nam, are still quite in the early stages of planning, however political commitment does exist for such a programme to proceed. Tunisia, included in this category, is a country with a long history of interest and quality work done in the area of both management and prevention of thalassaemia since the early 1990s. Unfortunately, the country has suffered political turmoil in the last 20 years, which has not only allowed the strengthening of such strategies but has also, sadly, resulted in their regression. Noteworthy is the fact that all the countries in this category have made important progress in the clinical management of these disorders.

The countries included within **SCORING CATEGORY D** represent those which have not focused enough efforts and have not to-date prioritised the prevention of haemoglobin disorders at any level. In this Scoring Category, many, if not all, countries have focused work only on the clinical management of the disorders; some of them with great, but many with very limited, success. The countries in this category are of variable levels of HDI, different capacities of medical / public health infrastructures and different levels of thalassaemia prevalence. This category includes the USA, Canada, Austria, Belgium, Sweden, and Germany, which all countries have low to medium prevalence mainly within their immigrant population groups, very high HDI, and strong and robust medical and public health infrastructures. In two of these countries (v. Austria and Sweden), these disorders have only very recently been introduced and thus constitute very rare disorders. In contrast Bulgaria, Romania, and Albania have low to medium thalassaemia prevalence in their indigenous populations but weak economies and healthcare infrastructures. Their focus has been confined to providing medical and public health services to the patients. Morocco, with a medium prevalence and medium HDI, has also focused more on clinical management and very confined work on prevention strategies. Nepal, on the other hand, with medium to high thalassaemia prevalence but fragile economy and weak healthcare infrastructure, coupled with many geographic challenges, has focused more, albeit with limited success, on clinical management and has not addressed to any extent any of the essential components of prevention. Across the spectrum, Yemen, with medium to high prevalence of the disease, very low HDI, and almost a completely destroyed healthcare infrastructure, consequent to the ongoing civil war, has lost every hope of strengthening and continuing the work it started some 25 years ago to control thalassaemia. Finally, Brazil, Argentina, and Trinidad & Tobago are countries of the South American region with medium to high HDI and variable prevalence of haemoglobin disorders, historically confined to immigrant groups. These have since become integrated into the respective indigenous populations of each country, thus peaking the interest of governments in addressing as a priority the medical and social care of patients with these disorders and less on disease-prevention strategies.

New data for the 2024 update:

EGYPT has initiated a national programme which mainly includes family screening [14], and included premarital and school screening in 2023.

JORDAN is an example of a country with a long-standing national prevention programme based on premarital screening, yet it is not fully effective. A recent study concerning awareness among university students indicated that, whereas 90% are aware that premarital screening is available, 23% would not be deterred from marrying their anticipated partner and believed engaging in an at-risk marriage was a valid idea. This is not a negative result, but it is indicative of a cultural influence in choosing a life partner [15]. These observations are similar to a previous study from Jordan [16].

INDONESIA: A national prevention programme has been initiated: Phase 1 consists of a free family screening programme, and this has already started (immediate family members of patients and of all ages are included). This will be followed by Phase 2, which will include the extended family, and then Phase 3 will be offered to the public, mainly as a way to minimise at-risk marriages. The challenges to this plan include:

- The test is not required before marriage.
- There is limited access for couples living in remote areas.
- The population is huge and diverse, with many religious and cultural groups.
- The education level in much of the population is poor.
- There is a culture of not believing in hospitals.
- Resources are limited.

These points were discussed with TIF in a virtual meeting in October 2022.

MALAYSIA: The national programme (initiated in its present form in 2016) attempts primary prevention by screening school pupils at the age 16 years. There is no difficulty in obtaining parental consent for this, but despite students being given a card with the result, this is not remembered in many cases at the time of choosing a partner for marriage. Since there is a lack of qualified genetic counsellors, lab staff, who do not fully know about the disease, mainly advise parents and children who are detected to be carriers in screening. Genetic counselling courses must be made available (2023). A policy as to who can be a counsellor is needed.

Antenatal clinic screening is carried out as a secondary measure. If the pregnant mother is found to be a carrier, then her husband is tested. One major drawback is that many appear in the antenatal clinic after the 20th week and cannot benefit from PND.

PND is offered in hospitals, and at-risk pregnancies are referred, but this service is not offered in all hospitals; for example, in Kuala Lumpur only two hospitals have free of charge PND. There are, therefore, still gaps in the prevention programme, which need to be addressed. Reduction in birth incidence is not yet recorded.

Information supplied mainly by Dr Saidatul from the Ministry of Health of Malaysia, September 2022.

MALDIVES: Prevention has been a national policy for many years, but in recent years it has not been progressing as well as it should. The COVID epidemic may have diverted attention. Public awareness is still an obstacle. The MTS/MBS have conducted webinars for professionals but not for the public. Prenatal diagnosis is not offered locally, and some couples travel abroad for the service. Technically, in terms of gynaecological and molecular services, it is possible to set up PND in the Maldives. A fatwa has allowed termination of affected pregnancies in the first 120 days. Many couples accept this. As matters stand at present the new affected births recorded (Dr Umar) were:

- 2019 – 11 births, 2020 – 5 births, 2021 – 22 births (expected births are calculated to as high as 50/year).

PAKISTAN: The Punjab Prevention Programme remains the most organised effort on prevention. This programme was initiated in 2009. It includes Public Awareness on Thalassaemia and other Genetic Disorders, Screening of Carriers (extended family screening), as well as Pre-Marital Screening for the General Public, Genetic Counselling, Prenatal Diagnosis, and Research. To date almost 300,000 individuals have been screened and almost 6,000 prenatal tests performed (This information came from the director of the programme on 4 November 2022).

CONCLUSION

In conclusion, until science and medicine can offer decision-makers other solutions that can be implemented readily, easily, and without great cost and technological challenges available, preventing annual thalassaemia affected births remains the only effective tool to safeguard both the survival and quality of life of existing patients and the sustainability of medical and public health infrastructures and resources.

Notwithstanding the existence of a disease-specific WHO Executive Board decision, the ample knowledge and experience available on how to develop an effective prevention programme, the plethora of WHO programmes, resolutions, and declarations (including those on non-communicable diseases, blood and patient safety, etc.), the United Nations Declaration of Human Rights aspiring for equal access to quality healthcare, and the prioritisation of universal health coverage as a Sustainable Development Goal 2030, the global situation calls for more structured actions on behalf of national health authorities. The close collaboration of expert healthcare professionals, academia, and patient support groups, who are equal and invaluable partners in this effort, with the national competent authorities and under the guidance of the WHO, is urgently needed.

The global situation at present, regarding the implementation of effective prevention policies for thalassaemia, as seen from this study (please see also Map A and Table 6 at the end of this chapter), even when roughly assessed, is unsubstantial. This is despite the huge work done by the WHO and many national governments across the globe.

For TIF, effective prevention programmes remain a necessary tool that has proved beyond any doubt its substantial contribution to achieving better health and quality of life of patients with thalassaemia. Advocating for the implementation of effective prevention strategies therefore remains a key focus of TIF's work and activities across the world. The Federation's close and productive collaboration with the WHO; other official regional and global health bodies; medical, scientific/research, academic communities across the world; industry; and other relevant stakeholders is indeed regarded essential in achieving advances in this area.

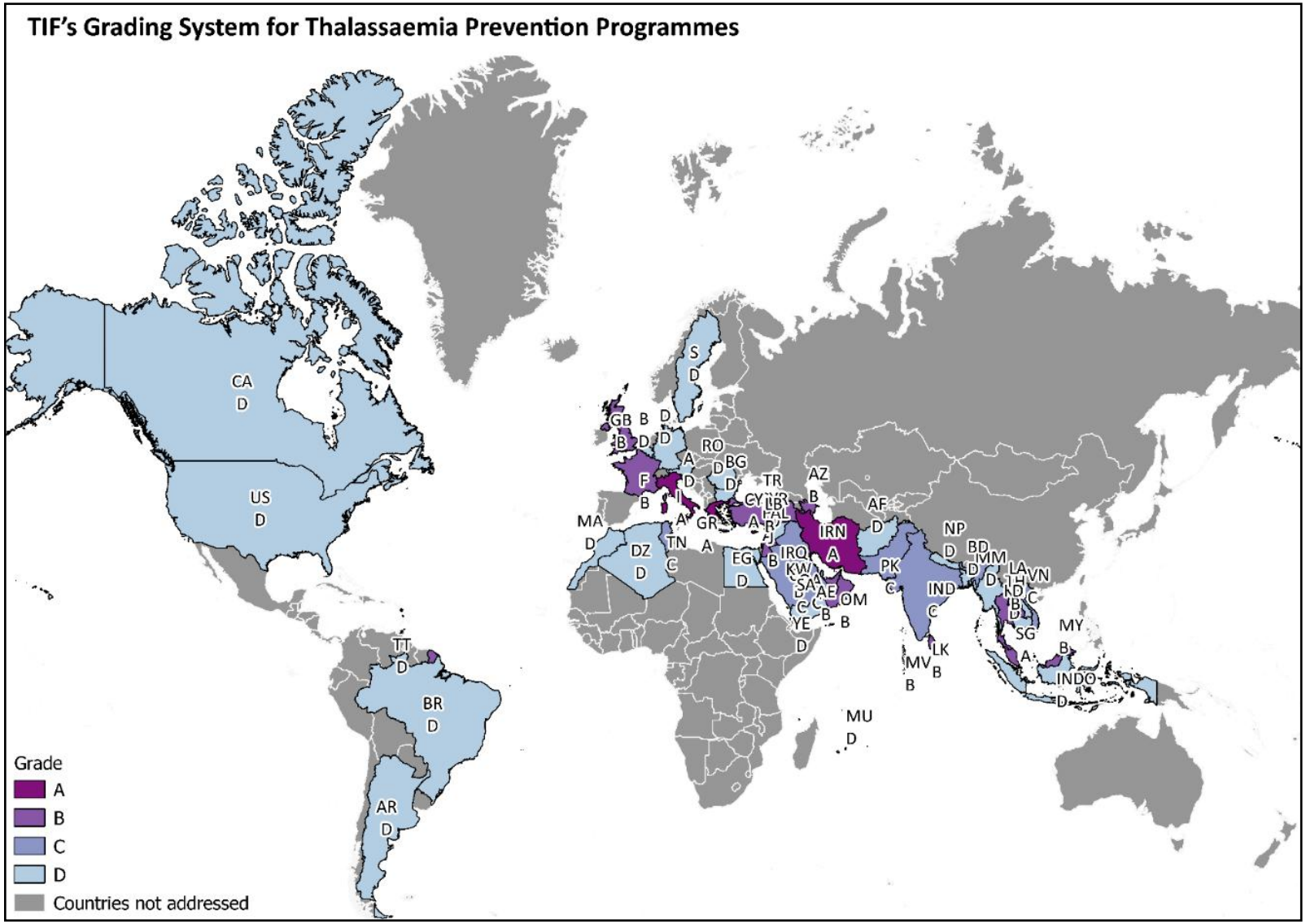

Figure 5. Map A

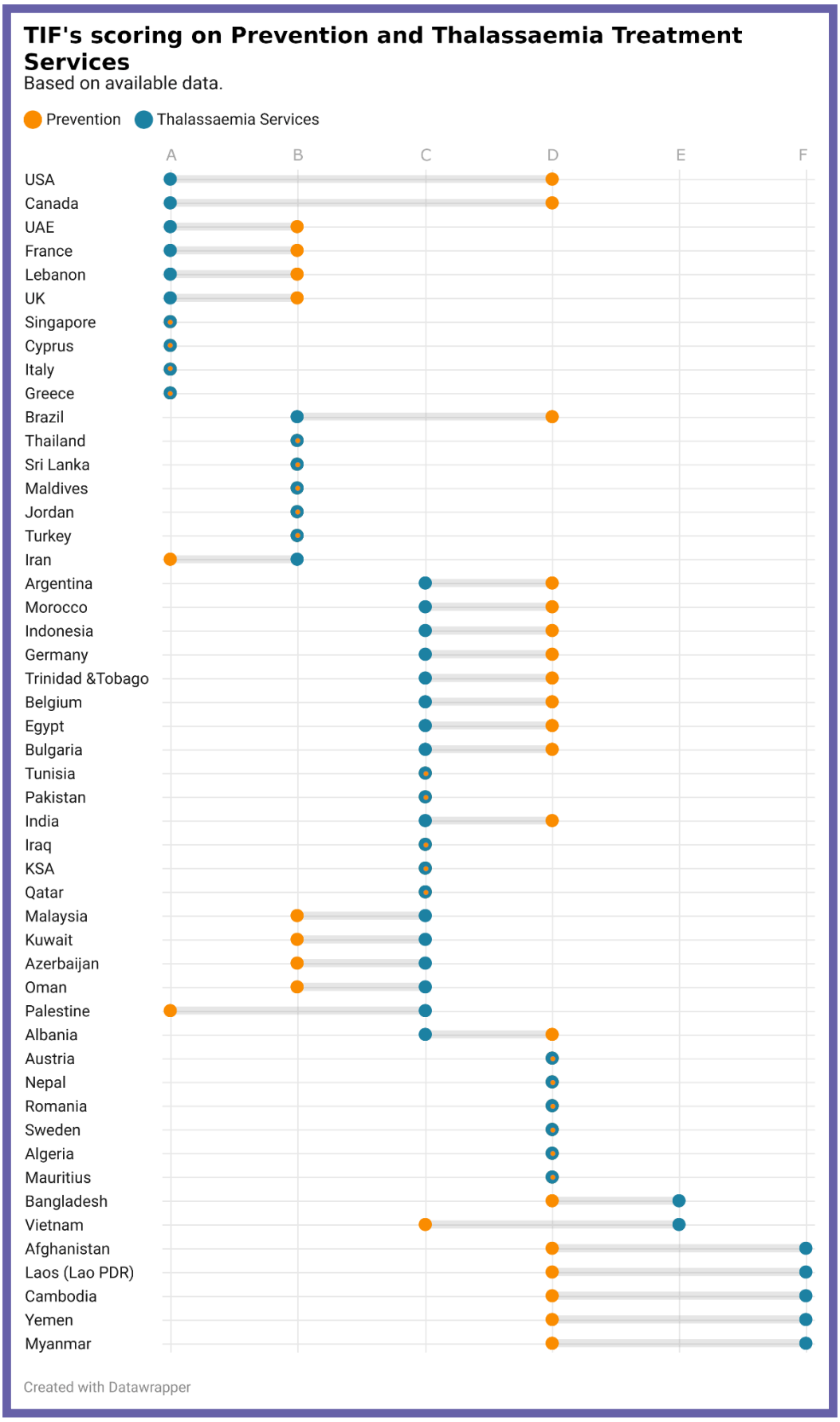

Figure 6. TIF's scoring on Prevention and Thalassaemia Treatment Services (based on available data)

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ANNEX

Country + Reference	Expected β-Thalassaemia Births/Year	National Policy	Public Awareness	Screening	PND	Surveillance	Genetic Counselling	Total/30	Category
Greece [19]	1.64/1000	5	3	5	5	5	5	28	**A**
Italy [11]	0.46/1000	5	3	5	5	5	5	28	**A**
Bahrain [20]	0.21/1000	5	5	5	3	5	5	28	**A**
Iran [21]	0.43/1000	5	5	5	3	5	5	28	**A**
Cyprus [22]	5.55/1000	5	2	5	5	5	5	27	**A**
Palestine [23]	0.4/1000	5	3	5	5	3	1	22	**A**
Singapore [24, 25]	0.2/1000	5	2	5	3	5	5	20	**A**
Oman [26]	0.286/1000	5	3	3	1	2	5	19	**B**
Azerbaijan [27]	0.344/1000	5	3	5	3	3	5	19	**B**
United Kingdom [28]	0.0018/1000	5	1	1	5	5	2	19	**B**
Lebanon [29]	0.132/1000	5	2	2	2	3	5	19	**B**
Turkey [30]	0.121/1000	5	1	3	3	5	1	18	**B**
Jordan [17]	0.306/1000	5	3	3	3	3	1	18	**B**
Maldives [31]	8.97/1000	5	3	5	0	5	1	18	**B**
France [32]	0.0016/1000	5	1	2	2	5	3	18	**B**
UAE [33, 34]	1.8/1000	5	2	5	1	1	3	17	**B**
Sri Lanka [35]	0.18/1000	5	3	3	3	3	1	17	**B**
Thailand [36]	0.21/1000 [An additional 3.57/1000 With Hbe/B Thalassaemia]	5	3	3	3	3	1	17	**B**
Kuwait [37, 38]	0.132/1000	5	2	5	1	3	1	16	**B**
Malaysia [39, 40, 41, 42, 43]	0.58/1000	5	2	2	1	5	1	15	**B**
Qatar [44]	0.225/1000	5	1	5	1	1	1	14	**C**
Viet Nam [45]	0.37/1000	0	2	2	3	2	5	14	**C**
Ksa [46]	0.25/1000	0	3	5	1	3	1	13	**C**
Iraq [47, 48, 49, 50]	0.576/1000	0	2	5	1	3	1	12	**C**
India [51]	0.58/1000	0	3	3	2	3	1	12	**C**
Pakistan [52, 53, 54]	1.0/1000	0	3	3	3	1	1	11	**C**

Country + Reference	Expected β-Thalassaemia Births/Year	National Policy	Public Awareness	Screening	PND	Surveillance	Genetic Counselling	Total/ 30	Category
Tunisia [55]	0.122/1000	0	2	1	2	3	2	10	**C**
Albania [56]	0.625/1000	0	1	1	3	3	1	9	**D**
Bulgaria [57]	0.156/1000	0	2	2	2	2	1	9	**D**
Egypt [58]	0.7/1000	0	3	1	1	3	1	9	**D**
Belgium [59]	0.002/1000	0	1	5	1	0	1	8	**D**
Trinidad &Tobago [60]	0.3/1000	0	2	2	0	3	1	8	**D**
Brunei D [61]	0.47/1000	0	1	3	0	3	1	8	
Bangladesh [62]	1.67/1000	0	1	1	2	2	1	7	**D**
Germany	0.0017/1000	0	1	1	3	0	2	7	**D**
Indonesia [63]	2.13/1000	0	1	3	1	1	1	7	**D**
Algeria [64]	0.1/1000	0	1	3	0	1	1	6	**D**
Sweden	0.0026/1000	0	1	1	1	1	1	5	**D**
Canada [65]	0.006/1000	0	1	1	1	0	1	4	**D**
USA [66]	0.004/1000	0	1	0	1	0	1	3	**D**
Mauritius [67]	0.371/1000	0	2	1	0	0	0	3	**D**
Myanmar [68]	0.66/1000	0	0	1	1	0	1	3	**D**
Romania	0.025/1000	0	0	1	1	0	0	2	**D**
Yemen [69]	0.484/1000	0	0	1	1	0	0	2	**D**
Cambodia [70]	3/1000	0	0	0	1	0	1	2	**D**
Lao [71]	5.7/1000	0	0	1	0	0	1	2	**D**
Nepal [72]	1.28/1000	0	0	1	0	0	0	1	**D**
Austria	0.0014/1000	0	0	0	1	0	0	1	**D**
Papua Ng [73]	0.65/1000	0	0	0	0	0	0	0	
Syria	0.625/1000							0	**D**
Afghanistan	0.361/1000							0	**D**
Morocco	0.07/1000							0	**D**
Brazil	0.042/1000							0	**D**
Argentina	0.046/1000							0	**D**