
INDIA
Delhi
Kolkata
Nagpur
Hyderabad
Mumbai
Bangalore
Chennai
Pondicherry
Arabian Sea
SRI LANKA
Colombo
AFGHANISTAN
Kandahar
OMAN
ARABIA
YEMEN
SOMALIA
INDIAN OCEAN
Diego Garcia
Seychelles (Br.)
Equatorial Current
MADAGASCAR
Diego Suarez
Antalaha
MAURITIUS
Port Louis
COMOROS
MALAWI
MOZAMBIQUE

2. THE GLOBAL EPIDEMIOLOGY OF THALASSAEMIA

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INTRODUCTION

According to Lilienfeld [1], epidemiology is the study of the distribution of a disease or a physiological condition in the human population and the factors that influence that distribution. An inherited disorder like β-thalassaemia has its own distinct geographical distribution, affecting certain populations more than others. Environmental factors have influenced the landscape of this genetic condition. To this interplay of genetic and environmental factors, other confounding factors, such as customary consanguineous marriages, prevention programmes, and population migrations, have influenced the prevalence of both carriers and actual clinically affected individuals globally. The most important environmental factor that has affected thalassaemia epidemiology is the protective effect the carriers have when infected by Plasmodium falciparum [2, 3]. This selective advantage has contributed to the survival of carriers with the mutated β globin gene, allowing them to increase in numbers in areas where the malarial parasite is or was most active. This correlation has been more strongly supported where the sickle cell gene and α-thalassaemia are concerned, but the geographical coexistence between β-thalassaemia and the malaria belt seems to confirm the same relationship. The well-known thalassaemia belt has been mapped through epidemiological studies:

It has been estimated that 5%–7% of the world's population carries a mutated gene affecting the production or function of the haemoglobin molecule [4]. This suggests that over 330,000 affected infants are born annually of which 83% have sickle cell disorders and 17% have thalassaemias (around 56,000). These numbers and country specific figures come from data from published reports and collected by individuals and groups who maintain databases. These include Modell's Haemoglobinopathologist's Almanac [5] and the IthaMaps database maintained by the Ithanet project [6]. The Thalassaemia International Federation (TIF) keeps its own database of data not only from published surveys but also from information gathered through country visits and discussions with local experts. This report discusses about β-thalassaemia, even though the geographical distribution of this condition coincides with other haemoglobin disorders, mainly α-thalassaemia and sickle cell syndromes. There is no attempt in this report to provide data on the whole global picture. Countries were selected because of high birth incidence of beta thalassaemia or in order to study current population movements and their possible effect on services to the patient community.

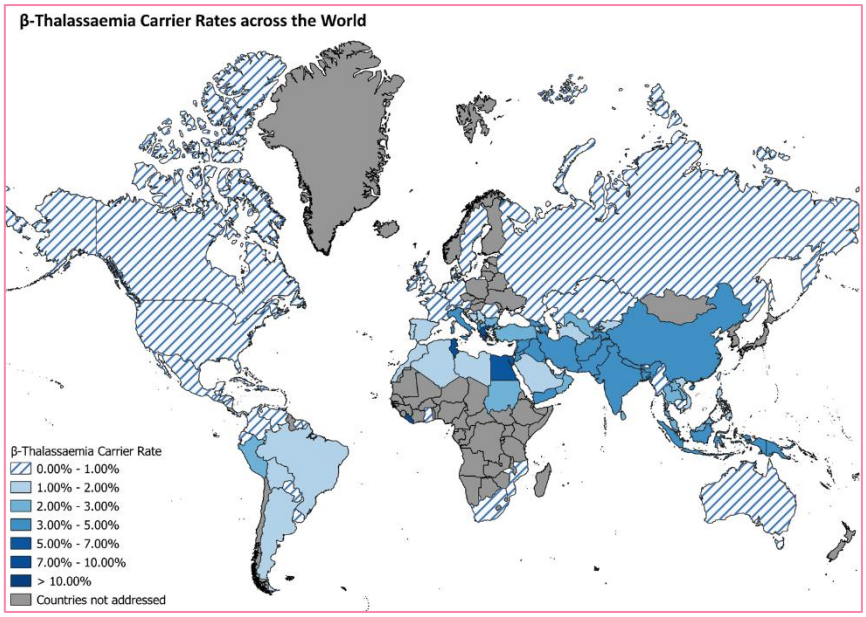


Figure 1. β-Thalassaemia carrier rates across the World, based on data gathered by TIF.

WHY ARE EPIDEMIOLOGICAL DATA IMPORTANT?

The importance of collecting data and supporting databases lies in the role that accurate epidemiological facts have in the development of health policies. Epidemiology is the basis of public health and policy-making and not an academic exercise, to quote an eminent epidemiologist and ex-director of the CDC, William H Foege emphasised that "epidemiology is no better than the information on which it is based" [7]. Indeed, complex chronic disorders such as β-thalassaemia require policies and strategies to provide a strong diagnostic infrastructure, day transfusion services, multidisciplinary care, cost-effective treatment modalities, centres of expertise and screening services that offer the possibility of preventing affected births [8]. In view of the economic pressures that such policies imply, providing policymakers with convincing information is a major step in advocating for change and service improvement for the benefit of the patient. In addition, such data enable further understanding of the social implications of disease. Epidemiological data provide invaluable information for monitoring and evaluating policies, as well as for studying the natural history and prognosis of syndromes and observing changes over time and place.

The collection of accurate figures (using surveys and registries) is therefore imperative, as is their correct interpretation (using probability and other statistical methods). However, the data collected by various databases are, in fact, not always of the quality that can assure accuracy or even approximation in many locations. Additionally, patient registries that are regularly updated are hard to come by. Survey data are often based on small projects, which cannot be representative of the whole population. In fact, approximations have become an accepted norm since carefully conducted surveys seem to be rarely applied. The question arises whether approximations are adequate to establish a health policy and plan adequate quality services.

The Thalassaemia International Federation (TIF) collects such epidemiological information to support its advocacy efforts in promoting national health service development for haemoglobin disorders. This role is fulfilled through the provision of tailored, evidence-based recommendations to competent national authorities for the development of policies and services that can improve the lives of patients. In addition, TIF develops and provides tools and resources that will assist national patient associations to better influence their local governments thus making them productive and active partners in the decision-making process. TIF is fully aware of the limitations of the data collected, which are explained below. The need to regularly review data is recognised, and the effort to reach as near to the truth as possible cannot be abandoned, as the unmet needs

of patients must be brought to the attention of policymakers to ensure that the appropriate resources are allocated to develop new policies or refine existing policies for patients with β-thalassaemia.

METHODOLOGY

The data which are collected for the TIF epidemiological database are listed in Table 1. The collective interpretation of these indicators provides a meaningful picture of the national landscape regarding α- and β-thalassaemia.
Information describing each country's development profile varies from year to year and is regularly updated, based on international databases, such as the World Bank and the CIA Factbook, as well as WHO sources.

Country indicators for major haemoglobin disorders	Subgroups
Overall carrier rates	α-thalassaemia (overall) β-thalassaemia HbE HbS HbC
Annual expected births/1000 live births	β-thalassaemia homozygotes HbE/β-thalassaemia HbS homozygotes HbS/β-thalassaemia
Total affected births expected annually	β-thalassaemia homozygotes HbE/β-thalassaemia patients Total β-thalassaemia syndromes (1+2) Sickle cell disease (SS+SC) HbS/β-thalassaemia Total sickle c ell syndromes (4+5)
Total number of known patients	β-thalassaemia syndromes Sickle cell syndromes
Country profile	
Population characteristics	Total population Crude birth rate Total annual births
Relevant health indices	Infant mortality rRate/1000 livebirths (LBs) Under-5 mortality rate/1000 livebirths (LBs) Consanguinity rate/coefficient
Country health development	Human Development Index (HDI) Income per capita Health expenditure per capita Universal health coverage

Table 1. Data collected for each country in the TIF database

In addition, a more detailed literature review was undertaken concerning the global epidemiology of both α- and β- thalassaemia, with the objectives to both update data and review the accuracy of the methods used in

various studies. This review was assigned to the Epidemiology Department of the University of Larissa (Greece). The research group conducted an overview of the research efforts made over the last decade (2009–2019), with the aim of establishing the prevalence and incidence of thalassaemia as a disease or of thalassaemia-related genes around the world. Three research databases were searched (namely PubMed, Scopus and Web of Science) for studies whose methodology involved sampling and screening the following conditions: thalassaemia, α-thalassaemia trait (α^+-thalassaemia and α^0-thalassaemia), haemoglobin H disease, Hb Barts hydrops fetalis, β-thalassaemia heterozygotes and β-thalassaemia homozygotes.

A total of 6,373 research articles were identified by the initial search. Their abstracts were then screened to decide if they contained relevant information. Of those, 432 articles were selected, which then underwent a more thorough evaluation process in which the full text of the articles were read in order to compose a final list. In the end, 116 studies were identified.

RESULTS

Literature review (2009–2019)

The Epidemiology Department of the University of Larissa, which undertook a targeted literature review as described in the Methodology section of this chapter, identified a total of 116 studies in 31 countries that fulfilled the search criteria. However, about two thirds of the studies occurred in only four countries, namely China, India, Thailand, and Turkey. Only three studies were nationwide (Brazil, Malawi, and Saudi Arabia).

One of the first objectives is to establish the proportion of the population at a given location that carries a thalassaemia gene. The elements for accurate estimation of carrier frequency include the following:

The laboratory methods used in surveys

Simple and adequate laboratory methods are used to identify carriers in the target population, with minimal error rates.

For thalassaemia, relatively simple techniques, suitable for testing large numbers of individuals, exist. In fact, these have been used extensively in screening programmes as well as in surveys [9]. Extensive heterogeneity existed among the studies about the way in which carriers or cases were ascertained. For example, in the case of β-thalassaemia minor, the commonest diagnostic method was measuring the levels of HbA2. However, different thresholds were applied. Although most studies used >3.5% as the cut-off point, some studies used 3.4%, 3.6%, 3.9%, or 4.0%. Furthermore, some studies used the naked-eye single-tube red-cell osmotic fragility (NESTROF) test, others used capillary electrophoresis to measure HbA2, while others still used high-performance liquid chromatography or reverse dot-blot hybridisation. Furthermore, other studies checked for specific β-globin gene mutations using DNA sequencing. Some studies had two stages of screening, in which they would check the levels of HbA2 and then perform DNA sequencing on those who were positive in the first stage. This diversity of methodology is understandable since each diagnostic test has a different cost and each research team in each of the studies did not have the same amount of funding or resources available to them. However, this precludes an accurate comparison of different studies. Therefore, any comparisons that do occur should be made with caution.

In the literature reviewed, the sample size varied from 120 participants to 4.6 million. The median sample size was 1,272 participants.

CARE NOT TO INTRODUCE BIAS

The sample size is adequate and unselected to reflect the defined population.

The way population samples were selected varied, and a variety of methodologies were employed. The vast majority were cross-sectional (over a period of a few months) or prospective studies (lasting more than one year). Recurring themes included (a) screening camps in specific rural/tribal communities, (b) blood donors, (c) pregnant women visiting antenatal clinics, (d) couples seeking premarital screening (mandatory or voluntary), (e) healthy subjects receiving routine health checks, and (f) screening newborns and students. Very few studies applied multi-stage clustered or stratified sampling, which would be the most reliable way to minimise the risk of bias. Furthermore, many studies were not very clear as to how they selected their participants and the sampling methodology was only implied or omitted completely. This means that an assessment of the risk of bias cannot be made with confidence and thus there is significant uncertainty about the external validity (generalisability) of the results. It is important to mention that studies were excluded if they involved participants who were referred for thalassaemia screening specifically because they had anaemia, there was clinical suspicion of thalassaemia, or they had a known family history. Such a sample would be heavily biased, prohibiting an estimation of thalassaemia prevalence that is representative of the general population.

STATISTICAL ANALYSIS

In this recent review of the literature, the most striking finding was that only three studies reported 95% confidence intervals along with their point estimates. Considering that science is the study of uncertainty, well-established methods should be applied to quantify this uncertainty. Another observation was that since most samples were non-probabilistic, weighting could not be applied to the individual measurements. In the case of probabilistic sampling, it was not always clear if and how weighting was applied.

MICROMAPPING

The importance of micromapping cannot be overemphasised, since even in relatively small countries the distribution of thalassaemia is uneven, with some areas or tribal groups being more affected than others. This observation was recognised many years ago and has been related to a possible relationship with the historical prevalence of malaria in a specific region [10]. To more accurately estimate the number of carriers, the number of at-risk couples, and the need for service planning, the local data for a country are good indicators of where to locate services and the size of services to meet real needs. Micromapping is an essential exercise that is rarely found in practice [11]. Examples of such efforts are given below, including those of Iran and Azerbaijan. Micromapping provides information about geographic variations and should provide more accurate prevalence data on which to base calculations concerning birth incidence and other indicators of the burden of disease.

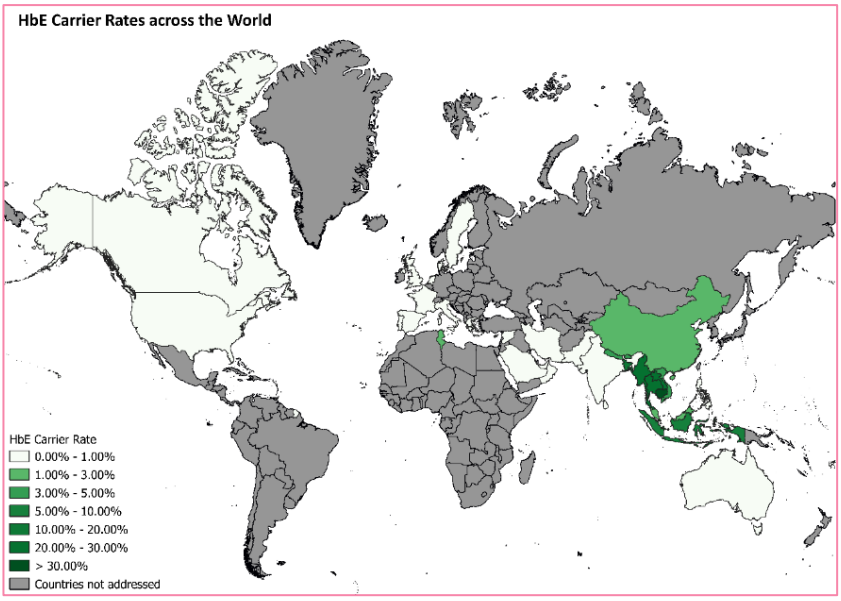


Figure 2. HbE carrier rates across the world, based on data gathered by TIF

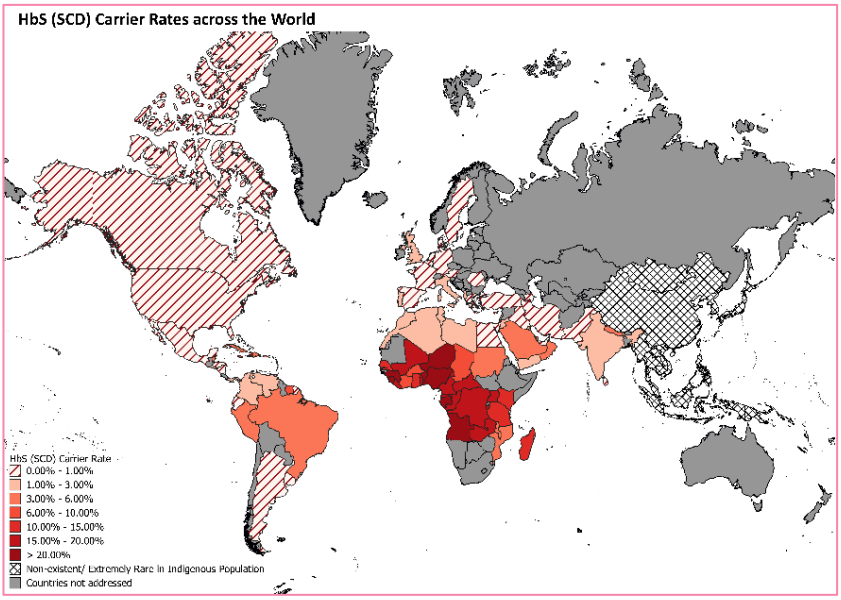


Figure 3. HbS (SCD) carrier rates across the world, based on data gathered by TIF.

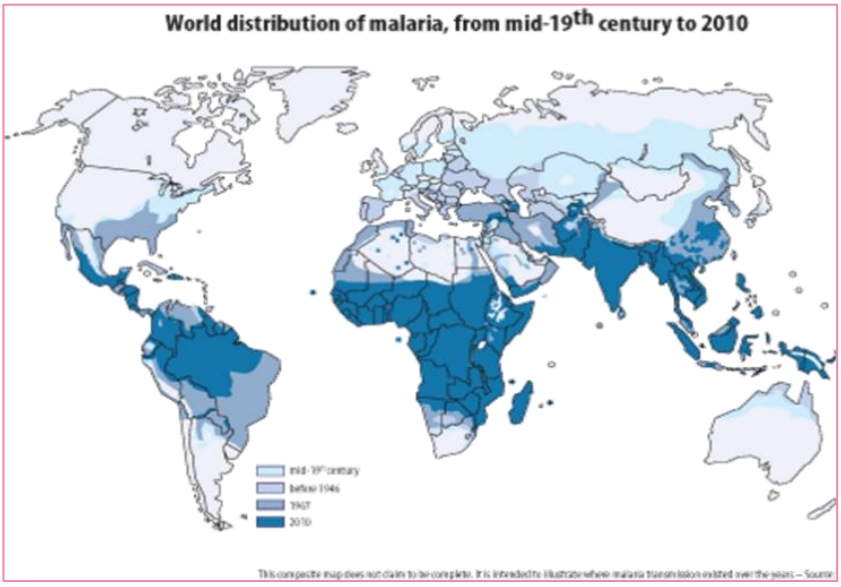


Figure 4. World distribution of Malaria, from mid-19th century to 2010.

PART 1 - THE EPIDEMIOLOGY OF B-THALASSAEMIA AND SICKLE CELL ANAEMIA

The following portraits are of selected countries with a significant birth incidence of β- thalassaemia patients for which data have been collected. In addition, European countries that are affected by recent migrations have also been included. Data are derived from published literature, TIF country visits and reports (including those obtained in the course of conferences). Countries have been grouped in regions as defined by the World Health Organization.

EASTERN MEDITERRANEAN REGION

AFGHANISTAN

This high prevalence country has been influenced by the unstable political situation, including the political violence that was a feature of daily life. Chronic conditions like thalassaemia still suffer from poor attention by service providers. However, a country with a rough estimate of over 5,300 thalassaemia patients is a major hub for this severe condition. The political situation has resulted in a steady flow of refugees from Afghanistan to Pakistan and Iran, but mainly to Europe. 97% of the country's population is living below the poverty line while the biggest health programme (Sehatmandi) has lost financial support from the World Bank and others. Health performance is reflected in an infant mortality rate of 42/1000LBs and an under-5 mortality of 55.5/1000LBs.

With a current population of 38,415,100, 3.8% are estimated to be carriers of beta thalassaemia, with a homozygote birth rate of 1,118/year. No sickle cell or other variants are reported. In a recent survey the mean age of affected patients was 6.89 years [12], [13], [14], [15].

BAHRAIN

This is a small country of around 1.5 million people. It has a very high HDI and a health expenditure/cap. of over USD 11,000. IMR is 5.2/1000LBs and the under-5 mortality rate is 6.9/1000LBs. Sickle cell syndromes are predominant, but the β-thalassaemia carrier rate is also significant. The Hereditary Disease Programme started in Bahrain in 1984, and in 1991 a National Committee for Prevention of Genetic Disease was formed to plan the control programme of these diseases in the country.

In a sample of 60,424 students, the sickle cell trait was found to be 13.3%. This rate was confirmed in an unpublished survey of 82,000 pupils in 2012 (13.05%) (Al Arrayed and Al Mahdi, unpublished report). The β-thalassaemia carrier rate was reported as 2.9% in a survey of 5,685 pupils. For this reason β-thalassaemia is a significant contributor to the disease burden in Bahrain, with a significant number of children born with HbS/β-thalassaemia, as well as with homozygous β-thalassaemia.

The total consanguinity rate and the first cousin marriage rate in 1990 were 39% and 24%, respectively, and they were reduced to 11% and 7.8% in 2007, denoting a 66% decline (Al Arrayed, unpublished report). Based on these data, 8 annual births would be expected to be affected with homozygote β-thalassaemia, while 134 would have sickle cell syndromes including S/S and S/β thalassaemia. It is noted that in this calculation we have ignored the quoted coefficient of consanguinity due to the expected continued reduction in cousin marriages.

Hence, Bahrain has a very high burden of haemoglobin disorders, but a well-structured service is being led by the Ministry of Health to deal successfully with these syndromes in terms of both prevention and clinical care [16], [17].

EGYPT

Egypt is a populous country of over 100 million people, making health issues difficult to manage. Its health expenditure/cap. is USD 112. IMR is 16/1000LBs and the under-5 mortality rate is 17.5/1000LBs. Income /cap. is low at USD 3,020, and even though healthcare for a chronic condition like thalassaemia is free-of-charge for patients under the age of 18, older patients are still not fully covered. All elements of prevention, screening, prenatal diagnosis and preimplantation genetic testing are available.

The national response is running behind the real needs, which are quite high given that various surveys have estimated the carrier rate for β-thalassaemia to be between 5.3% and 9%. However, a 2024 Ministry of Health report on a nationwide screening programme involving 1,700,000 young men and women found only 1.9% to be carriers of beta thalassaemia, which should reflect a more accurate picture. Sickle cell trait is confined to specific oases, so that in the general population the rate is about 0.3%. Based on these figures, it is expected that 0.09/1000 live births will have homozygous β-thalassaemia and 0.033/1000 live births will suffer from sickle cell syndromes. On the basis of the current population, this adds up to around 255 thalassaemia births per year and around 116 sickle cell births. Current reports from physicians and clinics (there is no national register) indicate around 10,000 patients of all ages are receiving treatment.

Alpha thalassaemia is less common in Egypt, where one study, based on neonatal samples and molecular analysis, reported that 3.1% had one α-globin gene deletion and 4.2% had two deletions (see Part 2: Alpha Thalassaemia Epidemiology) [18].

IRAN (ISLAMIC REPUBLIC OF)

Iran is another large country, where 85 million people have a large burden of thalassaemia and sickle cell disease that has resulted in the authorities applying much effort to address the issue. All health indices are improving. with the IMR at 9.8/1000LBs (17.7 in 2009) and the under-5 mortality rate at 12/1000LBs in 2025.

Assessing the disease burden has been an ongoing exercise in Iran. and the carrier rates of each administrative district have been calculated (Figure 2). The most quoted national carrier rate is 4%. Referring to the reported population of each region, the population who are carriers is calculated to be 4.56% of the total population. To be as accurate as possible of the expected births, the actual births of each region should be known so that an estimate of affected births can be calculated according to the Hardy Weinberg rule. Even so, high carrier rates in some nomadic groups are not included in the micromapping exercise. Taking the overall rate of consanguineous marriage into account, reported as 38.6% with a mean inbreeding coefficient of 0.0185, the expected thalassaemia birth rate is 0.4/1000LBs each year. The overall sickle cell carrier rate is 1%, with the highest prevalence in southwest Iran, mainly in Khuzestan province where the rate reaches 7%. Concerning sickle cell genes, a micromap of the whole country is not reported, therefore, it is difficult to estimate birth incidence of sickle cell disease (SS + S/β thalassaemia), which could be as high as 0.225/1000LBs.

According to current reports, there are 18,777 transfusion dependent patients and 2,000 non-transfusion dependent patients, along with 2,000 sickle cell patients living in the country. A national prevention policy has been implemented over the last 25 years and has limited new births (See Chapter 2 on prevention). [19], [20], [21], [22], [23]

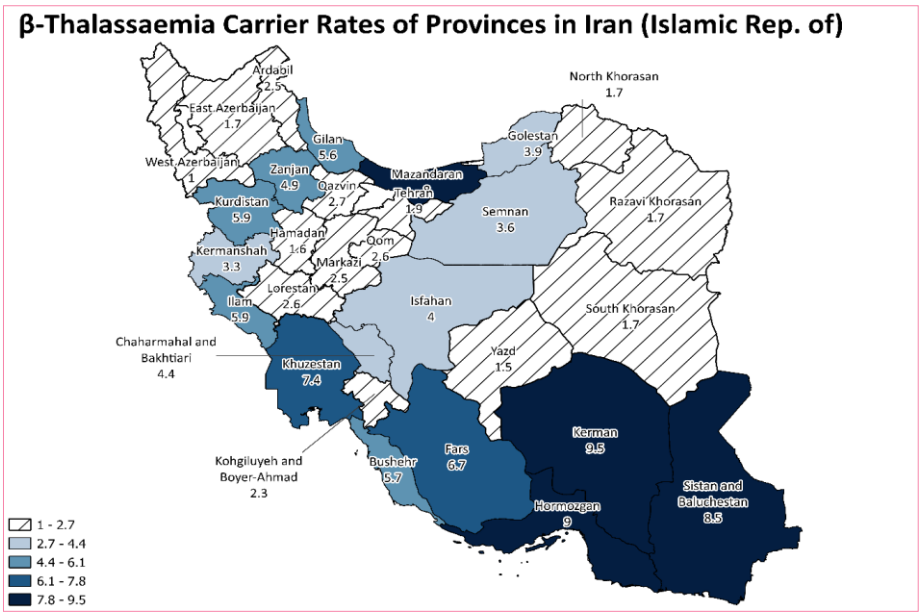


Figure 5. *Micromapping of β-thalassaemia in Iran (Source: Miri M. et al. 2013 [19])*

IRAQ

Health indicators have been improving steadily over the years. However, IMR is still high at 20/1000LBs and the under-5 mortality rate is 22.6/1000LBs. Health expenditure per capita is low at USD 254 in this oil rich country.

The haemoglobinopathy burden is considerable; the overall carrier rate for β-thalassaemia is quoted to be 4.8%, even though data from all provinces are not available. The highest carrier rate is reported from Erbil province at 6.94% (with a total population of almost 3 million), while most provinces report around 4% carriers. Sickle cell carriers are prominent in the southern governorates, mainly Basrah, where 6.5% carry the S-gene, compared to less than 1% in the northern Kurdish populations. It is expected that, each year, there will be at least 0.0313/1000LBs with β-thalassaemia syndromes and 0.123/1000 with sickle cell syndromes.

Iraq is a country with distinct populations and ethnic groups in which the epidemiology, including molecular epidemiology characterise each group. One example is the difference in the molecular characteristics of thalassaemia between Muslim Kurds and Kurdish Yazidis. Similarly, the sickle cell Benin haplotype is predominant in the north, while in Southern Iraq the Arab-Indian haplotype is predominant, similar to Eastern Arabian Peninsula. Such regional and ethnic differences must be considered when policy and strategy decisions are taken, especially concerning prevention policies.

The latest information received by TIF from Ministry of Health officials in Iraq is that there are 19,955 β-thalassaemia patients (an increase from 17,000 in 2022) and 7,800 sickle cell patients receiving treatment. There is no national registry, but these numbers were derived from the sum of local hospital registries. In the absence of systematic prevention, these figures will increase each year; the Kurdish areas alone report an increase of 50 new cases per year, yet in these areas some screening and even prenatal diagnosis are offered. According to published reports, the management of patients, who have a median age of 13 years, is suboptimal compared to Western standards (1–35 years).

JORDAN

The β-thalassaemia carrier rate in Jordan reflects those of much of the neighbouring Arab populations, with a variable rate across the country ranging from 3.04% to 3.5%. General health parameters are improving, with IMR now at 12.8/1000LBs and an under-5 mortality rate of 13.2/1000LBs. Health expenditure per capita is low at USD 295 and income per capita is USD 4,330. First-cousin marriages have declined from 28.5% (marriages conducted between 1950 and 1979) to 19.5% (marriages conducted after 1980). Sickle cell carriers were 3.17% of a newborn screening sample from north Jordan, while, in a sample 1,000 subjects, 1% were identified to be carriers, indicating a regional variation. These studies were by the same group in the north of the country, while other regions of the country have no published data. It is assumed that in Jordan at least 1.5% of the total population are carriers of AS until a nationwide survey is carried out. With these assumptions, annually, there should be 0.306/1000LBs new cases with β-thalassaemia and about 0.263/1000LBs new cases with sickle cell syndromes.

Of the number of known patients recorded, 1,450 had thalassaemia and 150 had sickle cell disorder. In a country of 10.8 million, this is a significant burden on the health services (that is exactly half of the total for Greece in both carrier rates and number of patients – see more information below) [24], [25], [26], [27], [28], [29]

Saudi Arabia

The Kingdom of Saudi Arabia is a high-income country with a GDP/capita of USD 23,139. The major haemoglobin disorder in this country is sickle cell disease. The Saudi Premarital Screening Programme estimated the prevalence of the sickle cell gene in the adult population at 4.2% for sickle-cell trait and 0.26% for SCD, with the highest prevalence noted in the eastern provinces (approximately 17% for sickle-cell trait and 1.2% for SCD). In the eastern provinces there is also a high β-thalassaemia rate, estimated at 3.4%. The distribution of the major haemoglobinopathy syndromes is accurately pictured by the premarital screening programme that has been active in the country for many years, as depicted in Table 2 below.

Prevalence rate for β-thalassemia and Sickle Cell disorders by region, in Saudi Arabia, 2011–2015.

β-thalassemia						Sickle Cell Disorder			
Regions	Population	Trait	95%CI	Disease*	95%CI	Carrier	95%CI	Disease*	95%CI
Al-Baha	29,161	13.2	11.9–14.6	0.3	0.2–0.6	34.9	32.8–37.0	2.8	2.2–3.5
Al-Jouf	29,339	2.9	2.3–3.5	0.3	0.1–0.5	2.6	2.0–3.2	1	0.7–1.4
Asir	1,65,316	6.7	6.3–7.1	0.2	0.1–0.2	42.5	41.5–43.4	7	6.6–7.4
Eastern Region	2,11,727	23.7	23.1–24.4	0.4	0.3–0.5	114.4	113.0–115.8	9.8	9.4–10.2
Hail	38,567	3.3	2.8–3.9	0.00	0.0–0.1	2.0	1.6–2.5	0.1	0.0–0.2
Jazan	72,420	32.1	30.8–33.4	0.6	0.5–0.8	135.7	133.2–138.2	6.8	6.2–7.4
Makkah	2,38,978	14.4	13.9–14.9	1.9	1.7–2.1	31.3	30.6–32	1.9	1.7–2.1
Maddinah	81,286	8.1	7.55–8.79	0.2	0.1–0.3	13.7	13–14.6	0.8	0.6–0.9
Najran	24,836	2.4	1.9–3.1	0.00	0.0–0.2	12.6	11.3–14.1	0.3	0.2–0.6
North Border	22,260	7.6	6.5–8.8	3.4	2.7–4.3	4.0	3.3–5	0.4	0.2–0.8
Qasim	70,057	4.0	3.6–4.5	0.4	0.3–0.6	2.5	2.2–2.9	0.3	0.2–0.5
Riyadh	2,00,652	7	6.6–7.4	0.2	0.2–0.3	18.1	17.6–18.7	1.1	0.9–1.2
Tabouk	45,983	6.3	5.6–7.1	0.2	0.1–0.4	27.5	26.0–29.0	1.0	0.8–1.4

95%CI = 95% confident interval.

[3] Memish ZA, Owaidah TM, Saeedi MY. Marked regional variations in the prevalence of sickle cell disease and beta-thalassemia in Saudi Arabia: findings from the premarital screening and genetic counseling program. J Epidemiol Global Health 2011;1(1):61–68. doi: 10.1016/j.jegh.2011.06.002. PubMed PMID: 23856375.

* Significant presentation among the B-thalassemia and Sickle cell disease p-value = 0.0001 [3].

Table 2. *Prevalence rate for β-thalassaemia and sickle cell disorders by region in Saudi Arabia, 2011–2015.*

These figures must be reviewed over time as new data become available; for example, a recent study from the Asir region estimates the β-thalassaemia minor prevalence at 3.57% (contrasted with 6.7% quoted in Table 2) and AS at 6.79% (contrasted with 42.5%). Similarly, a recent survey in a town in the Ar Riyad province in the centre of the country indicated a β-thalassaemia rate of 0.69% (vs. 7%) and AS 0.32% (vs. 18%).

Alpha thalassaemia is also prevalent in the Arabian peninsula even though it is less well mapped. A study of a sample from the premarital screening programme in the southwest corner of Saudi Arabia (Jazan city) found

that the carrier rate of suspected alpha thalassemia was 4.43%. This is in line with the previously reported 5.7% in the general Saudi population. There is a much higher prevalence in the eastern provinces.

Based on this information and population figures from each province (2017), the total carrier prevalence is 1.2% for β-thalassaemia and 4.66% for AS. These figures are derived mainly from the Saudi population, while non-Saudi residents affect these totals mainly in so far as β-thalassaemia is concerned, but they also introduce HbE (at a rate potentially reaching 1.9%). The expected births for thalassaemia are expected to be 130 per year while the figure is much higher for SCD at 420.

In 2004, the Health Ministry issued a Royal Decree that made premarital screening compulsory for potential partners. This programme has met with variable success because marriage cancellation has not been fully accepted (See Chapter 3 The Prevention of Thalassaemia Revisited).

In 2019, the Saudi Ministry of Health launched a national SCD registry to collect data for all SCD patients treated within its hospitals. This does not include thalassaemia patients but it recorded 26,000 sickle cell patients in the country. At a meeting in November 2022 with TIF, Saudi experts agreed that there are around 9000 thalassaemia patients but the actual number of patients with sickle cell syndromes is nearer to 90,000–100,000, if including those treated outside MoH hospitals [30], [31], [32], [33], [34], [35], [36], [37], [38].

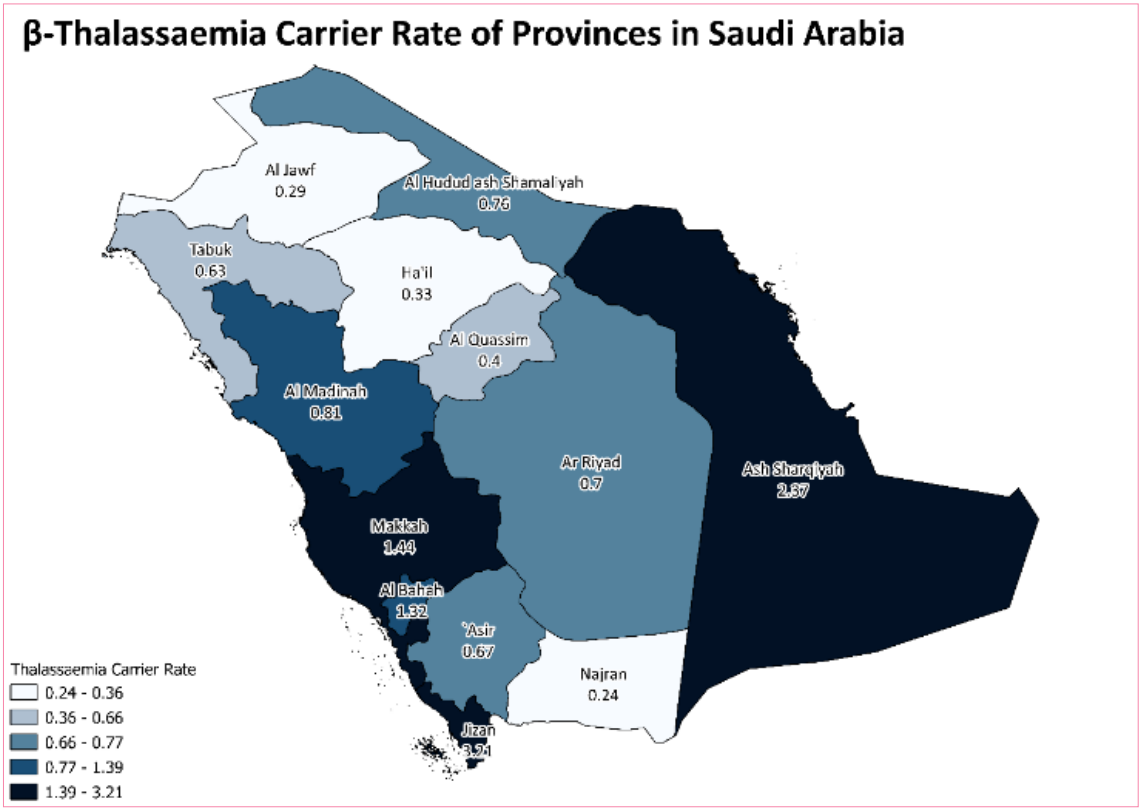


Figure 6. *Carrier rate for β-thalassaemia of provinces in Saudi Arabia.*

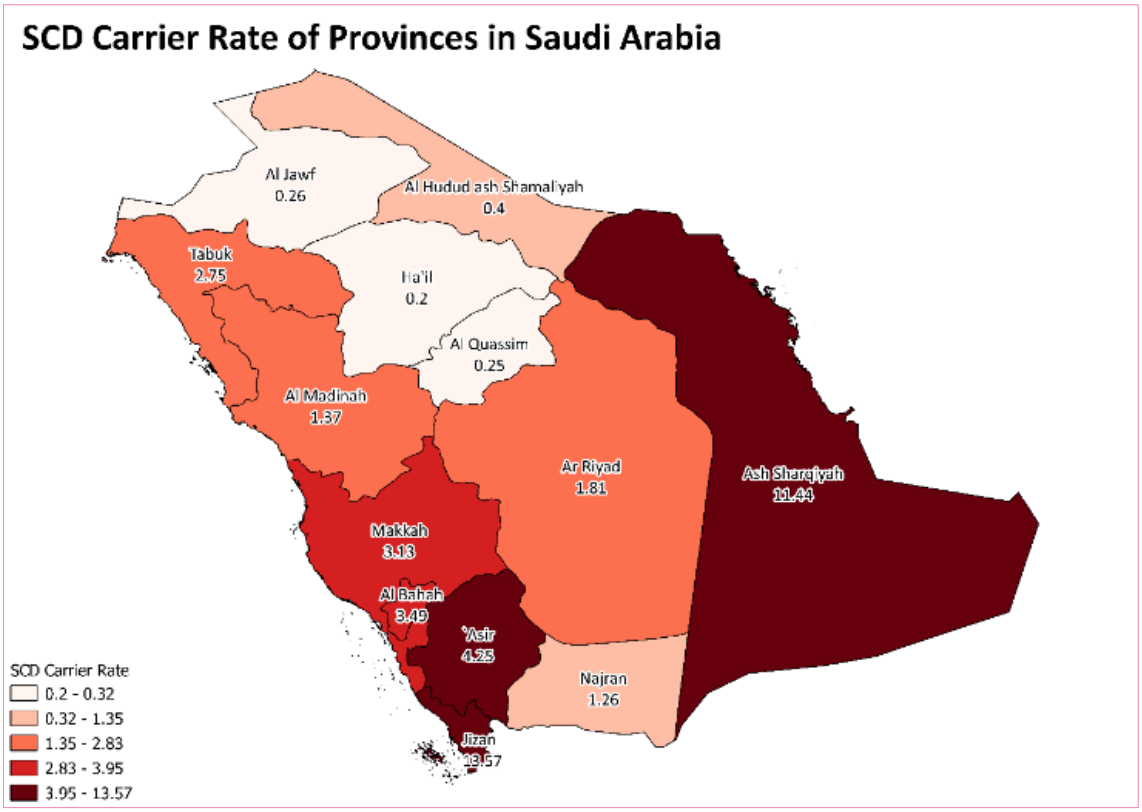


Figure 7. *Carrier rate for sickle cell disease of provinces in Saudi Arabia.*

KUWAIT

Kuwait is a petroleum-based economy and one of the richest countries in the world. Expats, however, make up around 70% of the population. Since they originate mainly from Arab and Asian countries with a high haemoglobinopathy prevalence, many have these disorders and many have actually been born in Kuwait. The quality of healthcare in Kuwait is generally high. The infant mortality ratio is currently reported as 6.8/1000LBs and the under-5 mortality rate is 8.1/1000LBs.

Concerning the epidemiology of haemoglobin disorders, much reliance is put on the data accumulated by the premarital screening programme, which was initiated in 2014 as an obligatory programme aiming to reduce "unsafe" marriages. From the first 130,000 tests (unpublished data reported by Prof. Roohaldeen), the results indicate the following:

- β- thalassaemia carriers: 2.2%
- Sickle cell carriers: 1.99%
- Other variants: 0.5%

The results of the population screening programme are regarded as more accurate because of the large sample and less likely to have selection bias. Based on these figures and according to the Hardy-Weinberg rule, the birth incidence, based on an annual birth rate of 13.77 (2019) and a total of 63,737 reported births in 2018, is presented in Table 3.

CLINICAL CATEGORY	EXPECTED NO. AFFECTED PER 1000 LIVE BIRTHS /YEAR	ANNUAL TOTAL NO. OF EXPECTED AFFECTED BIRTHS
B-THALASSAEMIA	0.112	30
HBS/S	0.082	25
HBS/B-THALASSAEMIA	0.192	30

Table 3.

This calculation has not included the consanguinity coefficient, which for Kuwait is reported to be 0.02.

The most recent publication from the premarital screening programme indicates that from 275,819 adults screened over 11 years, 2.12% had the β-thalassaemia trait and 1.81% had the sickle cell trait. These results confirm the previous report. It is also claimed that 50.4% of at-risk marriages were prevented by issuing unsafe marriage certificates.

Premarital screening has now exceeded 300,000 tests, and 218 at-risk marriages have been prevented, but the current birth incidence is unknown. A national patient registry is an urgent requirement. The estimated patient population is 475 thalassaemia patients and over 600 sickle cell patients [39].

LEBANON

Lebanon is a country with developed health services and satisfactory health indicators. IMR is currently at 8.78/1000LBs and the under-5 mortality rate is 17/1000LBs.

Screening programmes showed a carrier rate of 2.3% for β-thalassaemia in the general population. Neonatal screening of 10,095 neonates indicated 1.8% carried HbS and 0.04% HbC. Geographical clustering of sickle cell was noted in two regions: North Lebanon (50, 66%) and South Lebanon (30, 26%). Apart from regional variations, there are marked differences in the various religious groups, which are important since marriages are likely to be within each group, and cultural differences will affect people's responses to the prevention programme. These differences were identified in a study based on the population of thalassaemia patients, where 42% of patients were Shia (27% of the total national population), 36.2% were Sunni (27% of the total national population), 11.9% were Maronite (21% of the national population), 5% Orthodox Christians (8% of the national population), and 2.3% Druze (5.6% of the national population).

The latest figures from the Chronic Care Centre (CCC) report showed 375 thalassaemia patients and 387 sickle cell patients who benefit from high level clinical care and take part in clinical trials.

Lebanon hosts a refugee population originating from Syria. Around 100–125 of these refugee patients have been under the care of NGOs [40, 41, 42].

Morocco

A North African country, the Kingdom of Morocco has a population of 37,971,510. Its HDI ranking is 0.683 (in the medium category), while the IMR (2022) is 15.5/1000LBs and the under-5 mortality rate is 17.3/1000LBs. Haemoglobinopathy carriers are less prevalent in Morocco compared to other North African countries. In a survey conducted around 2011, financed by Rotary Geneva Nord, the reported carrier rate for β-thalassaemia was 1.67% and for AS was 1.76% (unpublished data). Since then there has been one reported survey in North Morocco, screening 12,000 individuals, which recorded β-thalassaemia at 0.74% and AS at 1.55%. This was a regional survey, but it does confirm the same range of prevalence. Much lower carrier rates were reported recently in around 2000 volunteer blood donors: β-thalassaemia 0.65%, sickle cell 0.1%, and HbC 0.55%.

In Morocco the consanguinity rate has fallen to 15.25% (mean inbreeding coefficient of 0.0065), but it is higher in the families of patients. A premarital programme is facilitated since all perspective couples in Morocco are obliged to visit a doctor before marriage [43].

Oman

Oman is a very high HDI ranking country with well organised health services. Current health indices indicate an infant mortality rate of 6.8/1000LBs and an under-5 mortality rate of 10.5/1000LBs. Haemoglobin disorders are prevalent in this population as demonstrated by a neonatal survey of 7,837 babies, where 5.46% were found to carry an HbS gene [50]. Micromapping of the country was conducted in 2003 by screening 6,342 children under 5 years of age. The overall findings showed: S-trait 6%, β-thalassaemia 2.1%, HbD 0.6%, HbE 0.3%, HbC 0.02%, G6PD 25% (M) and 10% (F) [51].

Region/ Population in 2017	Sickle cell trait %	β-Thalassaemia trait %
North Sharqiya (279,223)	10 (27,922 carriers)	1.1 (3,071 carriers)
South Sharqiya (312,822)	3.9 (12,200 carriers)	1.2 (3,754 carriers)
Dakhiliya (490,900)	9 (44,181 carriers)	2 (9,818 carriers)
Muscat (1,380,509)	8 (110,440 carriers)	2.8 (38,654 carriers)
South Batinah (2019 - 316,491)	7.9 (25,003 carriers)	1.5 (4,747 carriers)
North Batinah (519,660)	2.9 (15,070 carriers)	3.9 (20,267 carriers)
Musandam (31,425)	4.7 (1,477 carriers)	1.6 (503 carriers)
Dhofar (458,734)	0.2 (918 carriers)	0.2 (918 carriers)
Dhahira (224,225 in 2019)	3.9 (8,745 carriers)	1.7 (3,812 carriers)
Al Wousta (42,111)	0	0
Total Pop = 4,056,100	6.06% (245,956)	2.1% (85,544)

Table 4. *Regional micromapping in Oman*

With these carrier rates, it is expected that there will be 0.121/1000LBs (26 new cases /year at the current birth rate) with β-thalassaemia syndromes and 1.48/1000LBs with sickle cell syndromes (about 180/year at the current birth rate) each year. This calculation does not include the effect of consanguinity (coefficient 0.018).

From a TIF visit in 2019, it was noted that 591 β-thalassaemia patients were being followed in two central thalassaemia centres and some smaller centres at the periphery. Sickle cell patients are less regularly followed, and their numbers are estimated to be about 8,000.

Like all Gulf States, around 2 million (45% of the entire population) expatriates work in Oman, most of whom are from India, Pakistan, Bangladesh, Morocco, Jordan, and the Philippines – all high prevalence countries. The real numbers of haemoglobinopathy patients in the expat community is not known [44, 45].

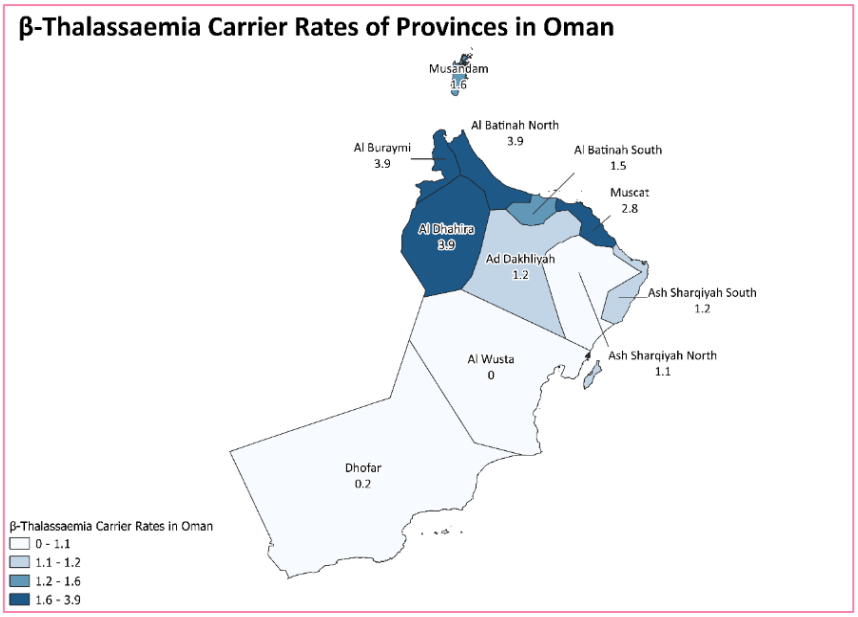


Figure 8. *Carrier rate for β-thalassaemia of provinces in Oman.*

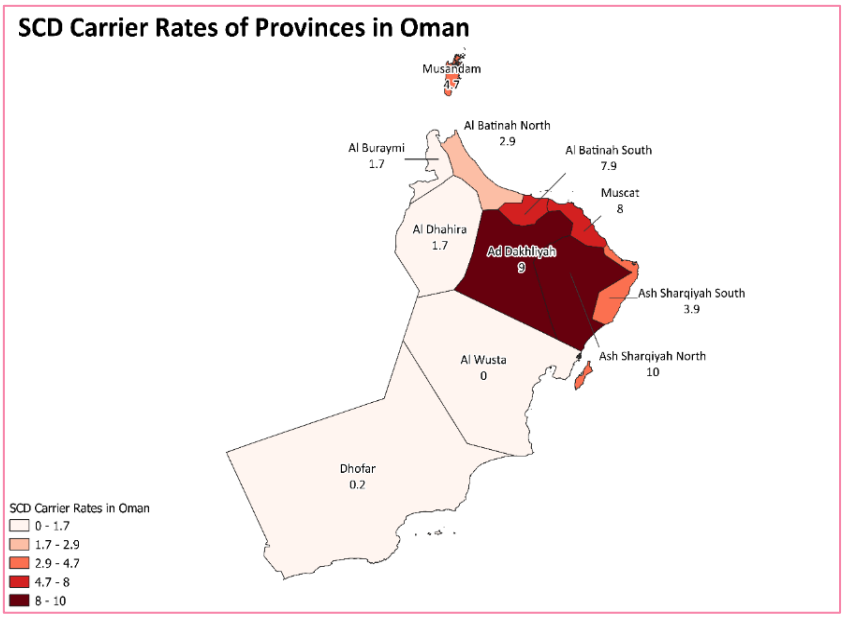


Figure 9. *Carrier rate for sickle cell disease of provinces in Oman.*

PAKISTAN

Pakistan has a very large population of 233 million, of which 60% live in the province of Punjab, which has the most organised services. Much of the population, around 60%, live in underdeveloped rural areas and health expenditure per capita is very low (USD 38.77) while income per capita is also low at USD 1824.

Concerning the epidemiology of β-thalassaemia, there are regional and tribal differences in the prevalence of carriers. Some data are available concerning these differences, which indicate that there are 10–11 million carriers, or 4.5% of the total population:

Region	Region Population	Carrier Rate (%)	Est. No. of Carriers
Punjab	100 million	4.6	4.63 million
Pathan	25 million	5.2	1.3 million
Sindhi	49.8 million	4.3	2.1 million
Beluchi	12.3	8.0	1 million
Urdu speaking	30 million	5.3	1.6 million

Table 5. *The carriers of b-thalassaemia in the provinces of Pakistan*

One study in Karachi, in the province of Sindh, involving 202,600 subjects, found the carrier rate was 5.2%. In a recent publication, the β-thalassemia trait frequency was reported to range between 5.0%–7.0%, thus, there are more than 10 million carriers in the country. Every year, around 5,000 children are diagnosed with β-thalassaemia major. Based on this data, it is expected that 0.9–1.0/1000LBs will be affected by β-thalassaemia and 0.077/1000LBs by sickle cell disease. With 6.4 million births per year in Pakistan, this means an estimated annual 6,334 affected births with thalassaemia and 490 annual affected births with sickle cell. These are approximate estimates and it should be remembered that consanguineous marriages are predominant in Pakistan. This rate is one of the highest in the world and has been relatively constant over the last decades; it was 63.0% in 1990–1991, increasing to 67.9% in 2007–2008, and it was still 63.6% in 2018.

It is difficult to estimate the actual number of patients [46, 47, 48, 49].

PALESTINE

The development of healthcare services is challenging in Palestine, with a population divided between the West Bank and Gaza, as well as political instability. This division, as well as political and social considerations, is reflected in the moderately high health indicators – IMR is 16.6/1000LBs (2019) and the under-5 mortality rate is 19.4/1000LBs.

The carrier rate for β-thalassaemia in Gaza, calculated from 21,825 samples from the premarital screening programme, has been found to be 2.6%. The prevalence of β-thalassaemia trait in the West Bank is 3.5%. The sickle cell gene is less prevalent and is reported to be 1.2% in the West Bank and 1% in Gaza.

Based on these estimates, the birth rate for β-thalassaemia patients is expected to be 0.4/1000LBs, 0.04/1000LBs for HbSS, and 0.25/1000LBs for β thalassaemia/HbS. Therefore, in accordance to the current total births, and without considering prevention, the expected annual affected births would be about 53 with thalassaemia and 39 with sickle cell disease. The most recent information (unpublished 2018) from the local patient association indicated the existence of 864 thalassaemia patients in both Gaza and the West Bank and about 200 with sickle cell disease [50], [51], [52].

According to the latest study by Aldwaik et al., the prevalence of thalassaemia was 17.4 per 100,000 population in 2018, with a total number of 847 symptomatic thalassaemia patients in both the West Bank and Gaza Strip. The age distribution of a 309 cohort of these patients was:

- 0–9 years: 20 (8.2%)
- 10–19 years: 69 (28.3%)
- 20–29 years: 110 (45.0%)
- 30–39 years: 28 (11.5%)
- ≥ 40 years: 17 (7.0%)

QATAR

A country with a well-developed economy and an income per capita of USD 65,000, Qatar also has well-developed health services. Infant mortality is at 5.3/1000 LBs and the under-5 mortality rate is 6.0/1000LBs. Carrier rates for β-thalassaemia are estimated to be 2%–3%, while the sickle cell carrier rate is 5%–6% in the indigenous population. However, 88% of residents in Qatar are foreign migrants, mainly from the Indian subcontinent. With such a large proportion of the population unstudied, the number of carriers cannot be accurately estimated and thus predictions of affected births cannot be made.

According to TIF's latest reports, 500 patients with sickle cell disease and around 160 with β-thalassaemia are being followed in the country.

TUNISIA

A country of the Mediterranean basin, Tunisia has both sickle cell and thalassaemia. β-thalassaemia carriers are reported to be 2.21% of the population, while the HbS trait is 1.89% [63, 64]. Expected annual affected births are 0.122/1000LBs for β-thalassaemia and 0.3/1000LBs for sickle cell syndromes. The latest report from local experts (unpublished) stated there were 742 thalassaemia patients and 1,526 sickle cell disease patients [53, 54, 55].

UNITED ARAB EMIRATES

A Gulf State in the high-income bracket and with a very high HDI rank, the United Arab Emirates has an income per capita at USD 43,000. This is reflected in the health indices where IMR is 4.6/1,000LBs and the under-5 mortality rate is 5.3/1,000LB.

Approximately 88% of the population are expatriates, of which almost 4 million originate from the Indian subcontinent. The burden of haemoglobin disorders is expected to be high, as shown in Table 6.

Sample type	Sample size	β-thal carriers	HbE Carriers	HbS carriers	HbC carriers	Reference
Emirati children	262	9.7%		4.6%		Miller CJ et al. 2003 [56]
UAE nationals, regional, premarital	6,420	4.73% (Hb Lepore added)	0.03%	2.9%		Belhoul et al. 2013 [57]
Regional, tribal, premarital	5,672	2.3%				Denic et al 2013. [58]
Bedouin	394	3%				Al-Dabbagh 2014 [59]
Premarital, regional	17,862	2.98%		1.05%		Salama et al. 2016 [60]
Neonatal screening nationwide	22,200		0.58%	1.5% Emirati 0.8% non-citizens	3.2%	Al Hosani et al. 2005 [61]
Neonatal screening nationwide	750,365			0.83% (overall)	0.02%	Al Hosani et al. 2014 [62]

Table 6. *Carrier rates in the United Arab Emirates*

These studies demonstrate that there is an uneven distribution of haemoglobin disorders across the Emirates. It should be noted that most of these studies refer to the indigenous population, while the migrant population may also contribute to the disease burden, since, as seen in the other Gulf States, they are mostly from the Indian subcontinent, with a high haemoglobinopathy prevalence. Since only the neonatal studies refer to the total population and not just to Emirati citizens, we can only conclude that the HbS gene is carried by around 1% of the indigenous population. The β-thalassaemia gene frequency is less clear. The premarital screening sample of nearly 18,000 individuals, however, has shown a 3% carrier rate, which is most likely to approximate the truth [68]. With these figures the expected annual births affected with β-thalassaemia syndromes would be 0.230/1000LBs and 0.175/1000LBs with sickle cell syndromes.

Reported thalassaemia patients are about 2,000, and the number of sickle cell patients is unknown [56, 57, 58, 60, 61, 62].

EUROPEAN REGION

In the Mediterranean area of Europe there is a high prevalence of carriers. In many European countries the indigenous population haemoglobinopathy genes are rare, but migrations are affecting incidence and leading to an increasing burden of these disorders.

The extent to which this is happening may challenge the robust national health services of many EU Member States. Considered under the umbrella term "rare disorders" (as defined by the European Union), this complex group of disorders is increasingly prevalent, requiring further monitoring in the years to come.

Albania

Albania is a country of just over 3 million people, which has been developing economically over the last few years. The HDI score was 0.644 (medium) in 1990 and has risen to 0.810 (high) in 2025.As expected health indices are improving and the IMR is now at 6.9/1000LBs. The under-5 mortality rate is 9.4/1000LBs.

The β-thalassaemia carrier rate is recorded as 5%, while HbS is 1.4%. It is estimated that the overall carrier frequency of both β-thalassaemia and sickle cell anaemia is about 8%. The distribution is not even; the Adriatic coast, especially the region of Lushnja, has a high prevalence of β-thalassaemia (5.2%) and HbS (3.2%). A complete nationwide survey has not been conducted to-date. Based on limited data, the birth estimate for β-thalassaemia is 0.6250/1000LBs and 0.399/1000LBs for sickle cell syndromes. According to recent figures from the patients' association, there are 356 thalassaemia patients and 174 sickle cell patients. Whereas, in the most recent virtual meeting in September 2022, the doctors reported 291 thalassaemia major (180 Tirana, 110 Lushnje, 1 Fier) and 290 sickle cell syndromes (190 Lushnje, 5 Fier, 95 Tirana) [63]

Azerbaijan

Micromapping of Azerbaijan for β-thalassaemia carriers was reported by Hajiyev at the 5th International Summer School 2008 (Figure 11). This map demonstrates the great variability in the distribution of carriers and where the hot spots are. An overall carrier rate of about 10% is estimated based on this data. Earlier studies by Kuliev suggested a 6% carrier rate. A more recent summation of the premarital screening programme (2015–2018) with 430,668 individuals tested, found 3.71% to be carriers. These are widely disparate results.

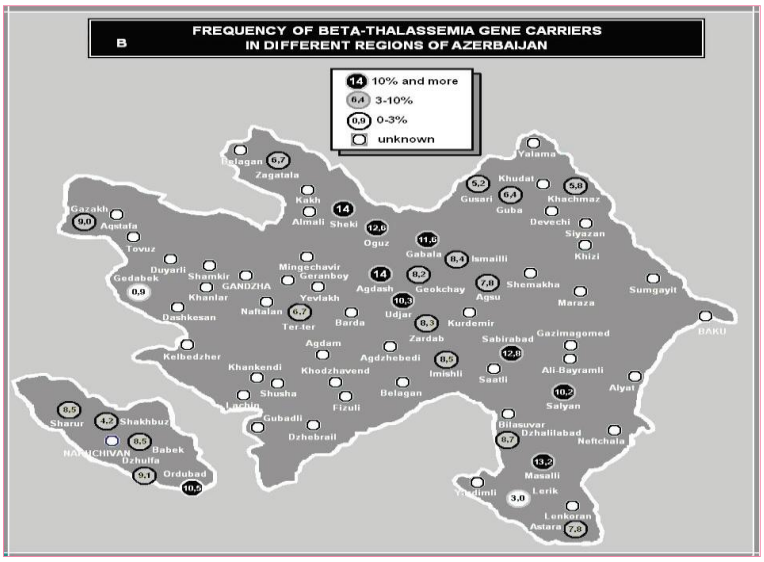


Figure 10. *Micromapping of frequency of β-thalassaemia gene carriers in different regions of Azerbaijan. (Source: Kuliev, 1994)*

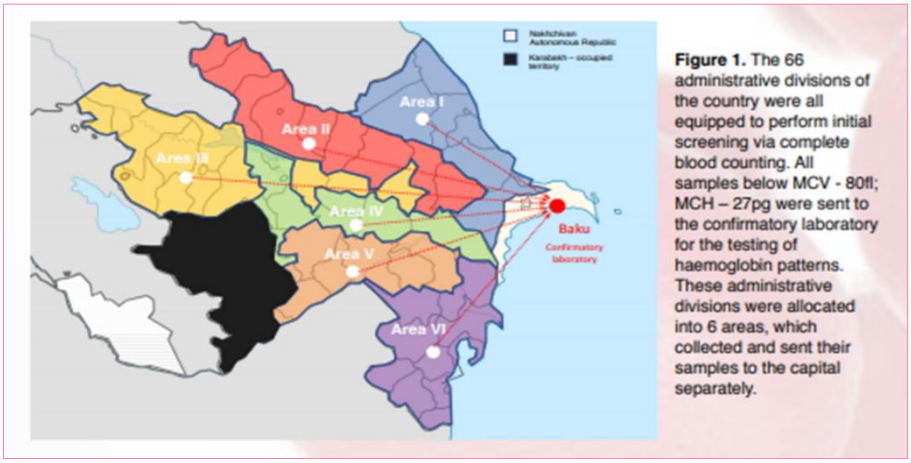


Figure 11. *Regional mapping (Source: Hajiyev, 2008 [64])*

Reports on the premarital screening programme in 2017 and 2018 were based on large population samples from all over the country, and they included molecular verification where necessary. These are likely to be the closest to the truth. 20% of marriages are consanguineous (previously reported coefficient was 0.0103), while recent urbanisation may have reduced this practice. According to the carrier rate, the expected annual birth rate for β-thalassaemia is 0.344/1000LBs and 0.164/1000LBs for sickle cell syndromes.

The total thalassaemia patients are estimated to be 1,350, while there are also around 200 sickle cell patients.

There is a steady improvement in the overall health performance in the country, as shown in the decline of the IMR from 54.6/1000LBs in 2009 to 13.3/1000LBs in 2023. Likewise, the under-5 mortality rate was 45.6 in 2007 and is now 18.6/1000 [64, 65, 66, 67].

Bulgaria

The carrier frequency of β-thalassaemia in Bulgaria has been found to be 2.5%, with no HbS in the indigenous population. As in other countries, the geographical distribution of the affected population is not even, and

according to local experts (unpublished) there is an average of 6% carriers in coastal areas. By calculation, the expected births are 0.1563/1000LBs, which roughly translates to 9–10 cases per year. There is no national registry, but an estimated total of 270–300 patients are followed in the three main centres (Sofia, Plovdiv, and Varna). Thalassaemia patients are covered by the National Health Insurance Fund [68].

Austria

Austria is a central European country with a very low carrier rate of haemoglobin disorders in the indigenous population. Recent migrations from countries of high prevalence have introduced increasing numbers of carriers and presumably patients suffering from these conditions. The carrier rate and patient prevalence for either condition (v. thalassaemia or sickle cell disease) in Austria are not known since there is no national registry. Physicians estimate around 60 patients throughout the country.

COUNTRY OF ORIGIN	IMMIGRANTS MPI DATA	CARRIER RATE (%)	EST. TOTAL NUMBER OF CARRIERS
Albania	1,834	1.4	26
Brazil	2,722	9.8	267
Greece	3,060	0.53	16
India	8,163	6	490
Iran	11,459	1	100
Iraq	3,101	1	22
Italy	26,099	2	522
Lebanon	1,147	2	23
North Africa	13,433	1.64	220
Nigeria	2,913	22	641
Other Africa	6,205	12	744
Pakistan	2,197	0.25	5
Turkey	125,026	0.44	550
TOTAL	207,359	1.75	3,626

Table 7. Origin of sickle cell carriers in Austria

A study conducted by TIF in 2015 (unpublished) noted that 3.3% of the Austrian population, i.e., 285,538, were migrants from high prevalence countries; 170,000 of these had arrived within the previous five years. This number may have increased even more during the 2016 refugee crises. It is expected that since 2010 haemoglobin disorders would have increased considerably across the country. Sickle cell is not included in the national neonatal screening programme.

Like most European countries, Austria has robust health infrastructure with an IMR of 3/1000LBs and an under-5 mortality rate of 3.5/1000LBs. Haemoglobin disorders are still very rare and treated in paediatric and adult haematology departments, mostly in Vienna. Each clinic has a small number of thalassaemia patients, with the adult clinic in Vienna having 15–20 patients (TIF visit report, 2019), and the paediatric clinic has 20.

Belgium

A neonatal screening programme for major haemoglobinopathies is applicable across Belgium. The first 10-year report of this programme was reported in 2006 indicating that 1:1,849 new-borns were identified as having sickle cell disease. Three years later (2009), this rose to 1:1,559. This did not change significantly in subsequent years, until 2017 (for both homozygotes and heterozygotes). These results are based on data from Brussels and Liege, while other regions do not participate in the neonatal screening programme.

A haemoglobinopathy patient registry is maintained in the country, according to which at the end of 2021 a total of 2,029 sickle cell disease patients were registered. Thalassaemia patients are fewer in numbers, estimated to be less than 100, and more recent data have not transpired. Survival data on sickle cell disease are reported, but there are none on thalassaemia due to the extremely confined number of patients. Belgium has robust health infrastructure with an IMR of 5.6/1000LBs and an under-5 mortality rate of 6.7/1000LBs [69, 70, 71, 72, 73].

Cyprus

A small island in the eastern corner of the Mediterranean, Cyprus has a population of 1.2 million inhabitants. Its two main ethnic communities, Greek and Turkish, have the same carrier rates for both β-thalassaemia and sickle cell disease and the same molecular distribution. The prevalence of thalassaemia is one of the highest in the world, posing a major public health challenge. More specifically, the β-thalassaemia carrier rate was estimated to be around 12%–15%, while sickle cell disease carriers are significantly less at 0.2% of the population. The α-thalassaemia carrier rate was estimated to be around 20%. With these figures, the expected β-thalassaemia birth rate is expected to be a high 5.5/1000LBs without any prevention programme.

An interesting observation is that for the more rare haemoglobin variants, including the sickle cell variant, there is a distinct geographical distribution, even on this small island. According to the parental origins of individuals carrying the sickle cell gene, HbS is mostly confined to the north and east of the island, the Hb Lepore variant is confined to one district in the south, and alpha chain variants to the north and west. These are indications of a possible founder effect for these variants. This is in contrast to the common β- and α-thalassaemia mutations, which are more evenly distributed across the island.

Another interesting observation is that the carrier rate of β-thalassaemia in the indigenous population appears to be falling following the eradication of malaria in 1948. This may be the effect of removing the selection advantage of malaria where haemoglobin disorders are concerned.

It should also be noted that Cyprus receives irregular migrants from the Middle East, which in 2021 amounted to 4% of the total population and more than 5% of the total population by the end of 2022. These may affect the prevalence of haemoglobin disorders. Also, intermarriages with northern Europeans has also reached significant proportions (having peaked at 25% of marriages in the 1990s).

A total of 1,387 patients with red cell disorders are followed at the four thalassaemia centres on the island, including 697 with β-thalassaemia major, 104 with β-thalassaemia intermedia, 475 with HbH disease, and 56 with SCD. Among 657 patients with β-thalassaemia, only 72 (11%) are aged <18 years (10.6% with TM and 14.3% with TI). The mean age of patients is 42.3 years; the aging population of patients, compared to the previous life expectancy estimations and to many other countries, reflects the quality of services offered. (The data were derived from the updated thalassaemia register and were provided by S. Christou, 2020.) [74, 75, 76].

France

France is one of the few European countries with an immigrant population that has gradually settled in the country from the 19th century onwards. However, the migrant population has increased in the country considerably in this century. The influx is generally of African population groups, and so sickle cell disease is predominant.

Neonatal screening has been gradually introduced in mainland France since 1996; testing has been performed at the national level since 2000 for all newborns that are defined as being at risk for sickle cell disease based on

their ethnic origin. As a result, by 2007, 3,890 neonates were diagnosed as having sickle cell disease. In 2016 alone, 431 children were diagnosed in France as having sickle cell disease, representing 1:771 screened babies. Of these, a birth prevalence of 1:824 was found in the Île-de-France region. This is a considerable increase compared to the 1996–2007 period; however, the extension of the neonatal screening programme to more parts of the country must be considered. Since screening is carried out by a nurse selecting at-risk pregnancies according to the origin of the parents, there is expected to be a difference according to selection. Indeed, a regional study found that selective screening leads to a carrier frequency that is twice as high in the selected population compared with the non-selected population (1.23% versus 0.62%).

The National Registry for Thalassaemia shows that there were 287 registered patients in 2008, 479 in 2010, 515 in 2012, and 635 in 2017. The sickle cell registry shows that there were 20,000 registered patients in 2016, which have risen to 28,000 in 2018 [77, 78, 79, 80, 81, 82, 83].

Germany

Populations of migrants in Germany is not a recent phenomenon. In the years following World War II, the origin of at-risk migrants was more European (Turkish, Italian, Greek, Albanian). More recently, migrants from other high prevalence countries of the Eastern Mediterranean (e.g., Afghanistan, Syria) and African regions have predominated the migratory flows to the country. Concerning the most common (parental) descent among affected patients, a study from Essen indicated that of 399 patients, 19.8% originated from Turkey, 11.8% from Syria, 5.9% from Iraq, and 21.3% from sub-Saharan Africa. Thus, haemoglobin disorders, almost invisible in the past, are now becoming the most prominent of the rare disorders in the country.

The German Central Registry for SCD and Thalassaemia officially records 600 thalassaemia patients. Sickle cell patients are reported to be 439, but 3,000 are estimated. Reports from medical advisors in Germany suggest that there may be around 1,600 thalassaemia patients. The total number of patients with sickle cell disease among migrants was estimated at 2,016 in 2007 and 3,216 in 2015, thus showing a 60% increase, which was particularly remarkable during 2014 and 2015. More than 3,000 patients with sickle cell disease are estimated to be foreign-born; the number of sickle cell disease patients of German origin (i.e., second, third, fourth generation immigrants) is not known.

In a 2014 study of newborns in Berlin, 1:129 newborns were detected with the sickle cell trait and 1: 2,434 with SCD. To-date, sickle cell disease is not one of the targeted diseases of the newborn screening programme carried out in Germany, according to the G-BA's (Federal Joint Committee) guidelines. In a recent report (2019) the prevalence of SCD was reported to be 1.96 (95% CI 1.53-2.41) per 10,000 newborns. Regions of higher prevalence include Berlin, Bremen, Hamburg, and North Rhine-Westphalia. Indeed, in 2016, of 17,000 newborns in Hamburg, 1:7 were found to carry a sickle cell gene.

The health infrastructure in this country is very advanced; examples are an IMR of 3.2/1000LBs and an under-5 mortality rate of 3.8/1000LBs [84, 85, 86, 87, 88, 89].

Greece

Greece is a country of approximately 11 million people, with a mean frequency of β-thalassaemia carriers at 7%–8% and 1% of carriers of haemoglobin S in the indigenous population [105]. This carrier rate is expected to lead to an annual affected birth rate of 1.6/1000LBs for β-thalassaemia (about 130–140 per year with an additional 20 with sickle cell disease). The geographical distribution is not homogeneous, and pockets of high prevalence have long been recognised [106]. One example is the Chalkidiki peninsula, where thalassaemia

carriers are over 10% and sickle cell carriers 4% [107]. This is a considerable burden of disease, so Greece has established a comprehensive control programme.

The healthcare system is robust, and indicators such as an IMR of 3.2/1000LBs and an under-5 mortality rate of 3.8/1000LBs are comparable to most of the EU countries.

The latest patient numbers are 3,241 for thalassaemia syndromes and 1,080 with sickle cell syndromes [10], [90], [91].

Italy

Italy is a large country in which haemoglobin disorders are prevalent in the indigenous population. There are significant regional variations in the prevalence of thalassaemia and sickle cell genes; in general, they are more frequent in the southern areas and in Sardinia. The regional differences are quite marked, with the example of Latium, where school children have been screened since 1975 and 1.8% of unselected samples have been found positive for beta globin mutations. In a similar study in Sardinia, 10.3% of school children were heterozygotes for β-thalassaemia. The carrier rate is high in the indigenous population, with an overall carrier rate of 4.3% for β-thalassaemia and 2.1% for sickle cell.

In addition, Italy is a destination country for migrants. Indeed, of a total immigrant population of 6,274,000, it is estimated that 3,622,000 (57.7%) are from countries with significant prevalence of haemoglobin disorders; 91,994 (2.5%) are expected to bear β-thalassaemia genes and 103,966 (2.9%) sickle cell genes. These migrations have been increasing in recent years. This is demonstrated by the distribution of sickle cell disease, which was once regional in this country but is now frequent in most Italian centres. In one neonatal screening programme in Ferrara, not only was AS identified but also HbC and HbE were clearly recent imports. Confirming the role of migrations in a neonatal screening programme, the family origin of neonates in two centres was found to be 65% Italians, 9% mixed couples, and 26% immigrants. Changes in regional carrier rates are evident:

- Lazio: 1.8% β-thalassaemia carriers in native population rising to 2.4% due to immigration, especially from Albania.
- Sicily: 6% β-thalassaemia carriers and 1:270 at-risk couples; around 2% HbS carriers, and 4.1% α+ carriers.
- Sardinia: 10.3% β-thalassaemia carriers, 25.6% α-thalassaemia carriers, and 0.1% HbS carriers.
- Calabria: 5.2% carriers.
- Ambruzzo (Chieti): 1.3% carriers.
- Emilia-Romagna: up to 12% β-thalassaemia carriers.

With this level of disease burden, prevention programmes for thalassaemia became inevitable.

Thalassaemia patients number around 7,200 (5,200 TM and 2,000 NTDT), distributed across the country in the following main centres:

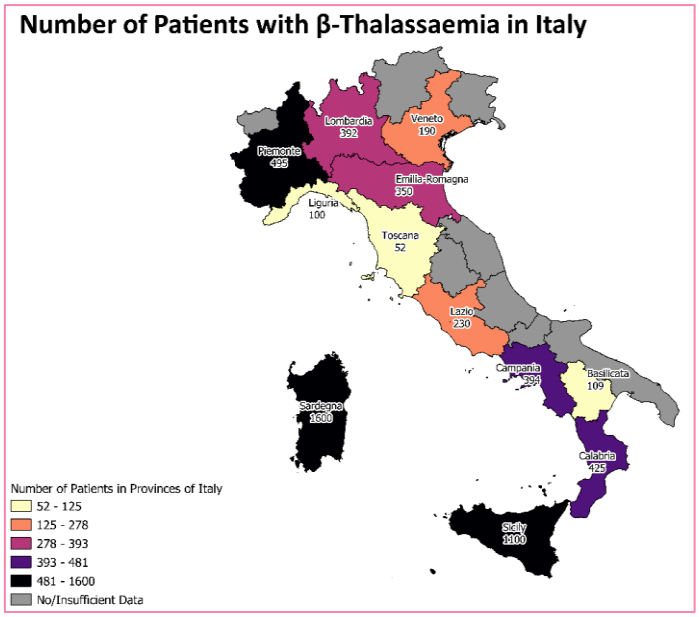


Figure 13. Number of patients with β-thalassaemia in Italy. Based on data gathered by TIF.

Total sickle cell disease cases are now estimated to be around 2,280, but this may be a rapidly changing situation in view of migrations. Interestingly in 1998, only 696 cases were reported across the country. Historically SCD in Italy was a disease limited to the population of Sicily, where the sickle cell allele frequency is between 2% and 13%. Due to migrations in the last 15 years, it is estimated that there are around 1,000–1,500 children and 2,500–3,000 adult patients.

The health system in Italy boasts excellent results in all areas. Relevant indicators are the IMR, which is now only 2.8/1000LBs, and the under-5 mortality rate, which is 3.1/1000LBs [92], [93], [94], [95], [96], [97], [98], [98], [99], [100], [101], [102]

Netherlands

Like the UK and France, the Netherlands has had a significant immigrant population for some decades, while haemogloinopathy genes are rare in the indigenous population. In a 2014 study of registered patients, 48 children (range: 36–76) per year were diagnosed with severe haemoglobinopathy. Currently 24.4% of the total Dutch population has a migration background, amounting to 2.5 million residents mainly from Turkey, Suriname, Morocco, and Asia, while another 2.0 million born in the Netherlands had one or both parents born abroad.

The current estimate of 350 β-thalassaemia patients and 2,000 SCD patients is probably an underestimate [103], [104].

Sweden

Haemoglobin disorders in Sweden are extremely rare in the indigenous populations, but increasing migration from high prevalence countries is introducing these disorders to the country in significant numbers. The total migrant population of Sweden in 2019 was reported as 2,005,000, of which 887,000 (44.2%) originated from countries with significant prevalence of haemoglobin disorders. Around 35,434 (4%) are expected to bear β-thalassaemia genes (beta + HbE) and an additional 10,928 (1.23%) sickle cell genes (HbS +HbC).

Patients with haemoglobin disorders are scattered throughout the country, and given their small local numbers, they rarely meet even if attending the same hospital. Expertise is increasing among a group of haematologists, and centres of reference are being developed in major population centres (Stockholm, Malmo/Lund, and Uppsala).

Sweden has one of the most effective health systems globally, and it is able to achieve almost unequalled health indicators such as an IMR of 2.0/1000LBs and an under-5 mortality rate of 2.6/1000LBs. Such a system is expected to have the resilience to meet new challenges.

Serbia

There has been no new work on the epidemiology of thalassaemia in Serbia since Prof. G. Efremov's work in the early 1990s. Serbia has an overall carrier rate of around 1.2%, mostly found in the south near the border with North Macedonia. This means that only a couple of new cases are born each year. Therefore, the overall thalassaemia prevalence is not known, but it is low. Sickle cell disease is also almost unknown. In Serbia, the IMR is now at 4.6/1000LBs and the under-5 mortality rate is at 5.3/1000LBs, indicating an effective health service at a good European level.

In Serbia, the migrant flow is transient and there are no reports of massive settling, thus not leading to an increase of the disease burden on health services [105].

North Macedonia

This a small country of just over 2 million people, with an emerging economy and an income per capita of USD 6,109 and an HDI of 0.759. β-thalassaemia was reported by G. Efremov in the 1990s to have a carrier rate of 2.6% and so a significant number of patients may be expected in this population. However, the exact number is not known. The health system is developing well and health indices improving: IMR is now at 5/1000LBs, and falling rapidly from being near 10/1000LBs in the not so distant past. The under-5 mortality rate is 6.1/1000LBs. This improvement in health service provision is expected to be reflected in the handling of these chronic conditions [106].

Portugal

A low frequency of haemoglobinopathy genes found in the indigenous population of Portugal leads to 0.052/1000LBs of β-thalassaemia patients and 0.113/1000LBs of sickle cell patients per year. Distribution is uneven, with the southern parts of the country having the higher prevalence. More than 500,000 immigrants have come from countries with a high prevalence of mainly sickle cell genes. The last information is of around 50 thalassaemia patients and 800 sickle cell patients, but this is probably an underestimate due to the lack of reliable data from a patient registry. The health indicators are excellent, with an IMR of 3.3/1000LBs and an under-5 mortality rate of 3.7/1000 [107], [108].

Romania

Romania has a relatively low prevalence of haemoglobinopathy genes, with about 1% carriers of β-thalassaemia and 200 patients in a country of 19 million, according to National Health Insurance data, but there is no national registry. Sickle cell genes appear to be rare or absent from this population.

Spain

Thalassaemia and sickle cell genes are rare in the indigenous population of Spain with an estimated 1.6% carrier rate for thalassaemia and 0.3% carrier rate for sickle cell disease. Migrations over the last 20 years from both Africa and South America (particularly Colombia, Dominican Republic, and Cuba) have mainly increased the presence of sickle cell disorders in the country. In 2007, a neonatal screening programme revealed a prevalence of 0.55% of HbS from 44 nationalities. A registry for sickle cell disease is maintained by the Spanish Society of Paediatric Haematology, which showed in 2009 that over the previous four years the prevalence of sickle cell disease had increased threefold. A more recent review of the national registry confirmed the continued increase in sickle cell disease while thalassaemia remains relatively static, with 1,317 patients with sickle cell disease being registered along with 214 thalassaemia patients across the country. Nonetheless, with a prevalence of approximately 1.5 cases per 100,000 people, thalassaemia and sickle cell disease are very rare diseases in Spain (0.16 thalassaemia and 1.34 sickle cell disease per 100,000 inhabitants). The increase, however, continues, and health services need to be alert to this change.

Spain, as a country with a strong health service has an IMR of 2.7/1000LBs and an under-5 mortality rate of 3.1/1000LBs [109], [110], [111], [112].

Turkey

The indigenous population of Turkey has an overall carrier rate for β-thalassaemia at 2.1%, as reported by Cavdar and Arcasoy in 1971. However, there are large regional variations which were mapped when the National Prevention programme was initiated in 2003 (see Table 8). Furthermore, many migrants from Turkey have historically settled in other European countries, however at this time, the country also hosts over 3.7 million Syrian refugees and smaller numbers of migrants from Iraq, Iran, and other countries with significant prevalence of haemoglobin disorders. These migrants are likely to be relatively transient, but in such large numbers, it is anticipated that there will be a number of affected patients needing treatment. This is already recognised among the Syrian group, especially in Eastern Turkey (Ganziatep) where the Turkish government has developed and supported services for patients.

Province	Sample	B- thal carriers	SA carriers	Reference
Adiyaman SE	1,616	1.91%	0.7%	Genc A et al., 2012[113]
Sanliurfa SE	75,924	2.44%	0.5%	Incebiyik A et al., 2014 [114]
Kayseri (Mid Anatolia)	10,261	1.71%	0	Karakukcu C et al., 2012[115]
Çanakkale (Aegean coast)	8,904	1.4%	0.06%	Uludağ A et al., 2016 [116]
Konya	72,918	2%	0.05%	Guler E et al., 2007 [117]
Kahramanmaras	48,126	2.1%	0.5%	Guler E et al., 2010 [118]
Izmir	38,554	4.95%	0.33%	Uysal A et al., 2013 [119]

PROVINCE	SAMPLE	B- THAL CARRIERS	SA CARRIERS	REFERENCE
DENIZLI	19,804	2.6%	0.11%	Keskin A et al., 2000 [120]
CUKUROVA		3.7%	10%	Cürük MA et al., 2008 [121]
ANTALYA	89,981	6.57%	0.31%	Canatan D et al., 2016 [122]

Table 8. *Micromapping Turkey*

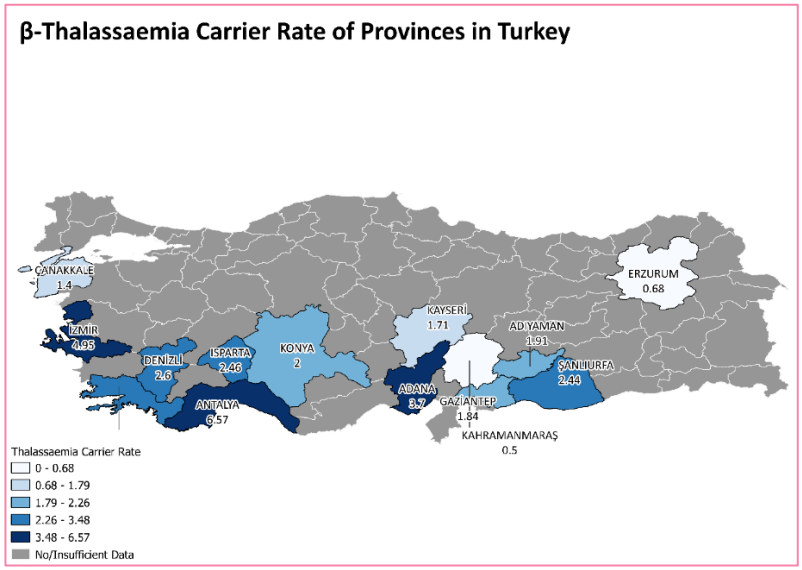


Figure 14. *β-Thalassaemia carrier rate of provinces in Turkey. Based on data gathered by TIF.*

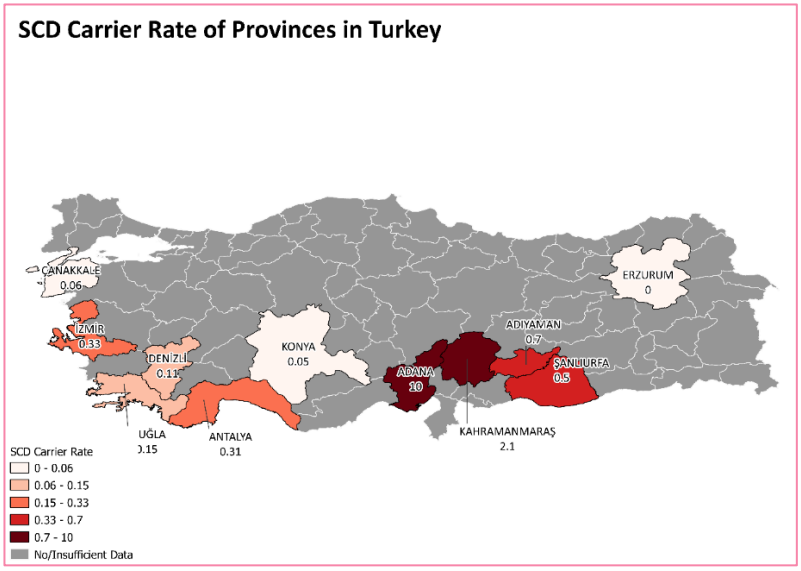


Figure 15. *SCD carrier rate of provinces in Turkey. Based on data gathered by TIF.*

These surveys indicate a high prevalence of β-thalassaemia in the Mediterranean and Aegean coastal areas and in the eastern provinces with some extension to the central provinces. The Black Sea coast and other northern provinces seem to be relatively unaffected, but a recent analysis of screening of 52,338 people in the northern region indicated a carrier rate of 1.37% and HbS of 0.04%; i.e., there is a significant prevalence of haemoglobin disorders in this region also.

The micromapping of Turkey has helped in the planning and location of services. Prevention programmes, for example, were initially concentrated in 33 provinces situated in regions of Thrace, Marmara, the Aegean, the Mediterranean and the Southeast. The distribution of β-thalassaemia alleles differs within each area with marked local variations.

The number of affected newborns reported annually was reduced from 272 in 2002 to 25 in 2010, indicating that prevention through premarital screening was considerably successful (90%). The rate of consanguineous marriages is high (21%) in communities of eastern Turkey that have a high incidence of thalassaemia.

A national registry was set up by the Turkish Society of Paediatric Haematology in 2012, and by 2015, 2,046 patients from 27 thalassaemia centres were registered. The geographical distribution, presented in Table 9, reflects the distribution of carriers.

Regions	Provices	Centres (n)	Patients (n)
Marmara	İstanbul	3	416
	Bursa	2	102
Central Anatolia	Ankara	1	36
	Kayseri	1	31
	Eskişehir	1	19
	Konya	1	54
Southeastern Anatolia	Şanlıurfa	2	187
	Diyarbakır	2	105
	Gaziantep	1	46
Aegean	İzmir	4	495
	Denizli	1	73
	Aydın	2	54
Mediterranean	Antalya	1	96
	Mersin	1	92
	Adana	1	90
	Hatay	1	49
	Isparta	1	21
Eastern Anatolia	Erzurum	1	23

More recent reports indicate a total thalassaemia population of 5,500 and a total sickle cell disease population of 4,300. IMR is also improving at 7.268/1000LBs, while the under-5 mortality rate is 9/1000LBs [113], [114], [115], [116], [117], [119], [122], [123], [124], [125].

United Kingdom

The United Kingdom, like France, is a European country whose indigenous population has a negligible haemoglobinopathy carrier rate. However, these genetic conditions have been introduced there over many decades through immigration from former colonies with high prevalence. Hence, through the consolidation of second and third generations, immigrant services have been developed, which new immigrants are able to enjoy.

In order to effectively plan and locate services where they are most needed, a knowledge of where communities settle is a necessary micromapping exercise, which was established early in the country, as shown in Figure 16.

According to the latest report, the number of patients with thalassaemia syndromes in the UK were 2,148 and those with sickle cell disease are 15,039 [126], [127].

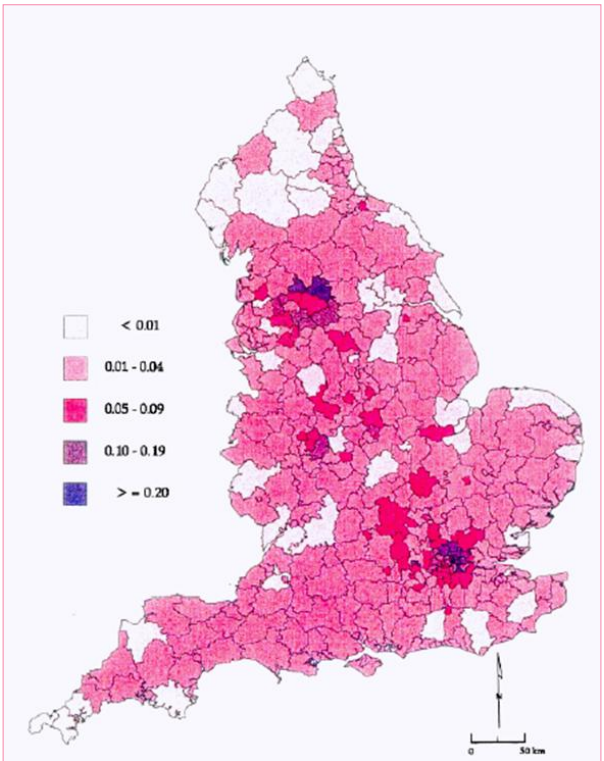


Figure 16. *The distribution of at-risk ethnic communities across England and Wales. (Source: Hickman M et al., 1999) Note: This map has not changed significantly since it was first prepared.*

AFRICAN REGION

Algeria

In Algeria, a North African country of 42 million people, the majority of the population lives in the coastal areas. A recent national survey identified 775 patients with thalassaemia major (TM: 598 cases) and thalassaemia intermedia (TI: 177 cases). This national survey is representative of 21 services (Adult clinics: 19, Paediatric clinics: 3). The current average age of TM patients is 17.90 years [range 1–44 years] and that of TI is 23 years old [range 1–61 years]. However, β-thalassaemia ranks second after sickle cell disorders in terms of patient numbers in Algeria.

The distribution of carriers across the country is variable, so that HbS ranges from 0.83% to 3.5%. HbC and other variants have also been identified. The β-thalassaemia trait is also unevenly distributed, ranging from 1.5% to 3%. Based on these estimates, it is expected that 0.1/1000LB and 0.17/1000LB newborns will be affected by β-thalassaemia and sickle cell disease, respectively.

IMR is 19.6/1000LBs and the under-5 mortality rate is 23.3/1000LBs. These indicate a continuing improvement in service provision, but the low age range of thalassaemia patients indicates that there is much yet to be done for these chronic disorders.

Mauritius

Mauritius is a small island in the Indian Ocean with a population of mixed origin; the Indian community is the largest (68%), followed by a Creole population of mostly African origin (27%). Thus, the carrier rates in each community are different: the β-thalassaemia carrier rate is estimated at 3.85% overall (4.8% in Indo-Mauritians

and 2.2% in Creoles), whereas the sickle cell carrier rate is estimated at 1.43% overall (affecting both communities in which Arab-Indian and Bantu haplotypes have been identified). Based on these carrier rates, it may be expected that 0.37/1000LBs will have β-thalassaemia and 0.28/1000LBs will have sickle cell disease. In 2022, there were 250 known thalassaemia patients and around the same number of sickle cell disease patients (exact number not recorded) [128], [129], [130], [131].

South-East Asia Region

Maldives

Maldives is an island nation consisting of 1,190 islands grouped in 26 atolls, scattered over a large geographical area. Only 201 of the islands are inhabited. Maldives has had a steady improvement in economic and social development. The HDI rank is high and health indices are improving (IMR fell to 5.0/1000LBs in 2023 from 7 in 2019, under-5 mortality is now 5.6/1000LBs, and life expectancy is 79.61 years). The β-thalassaemia carrier frequency was found to be 16.2%. In another report of 40,450 people tested, the following results were obtained:

- β-thalassaemia carriers: 18.07%
- α-thalassaemia carriers: 2.1%
- HbE carriers: 0.9%
- HbS carriers: 0.13%.

There is considerable variation in carrier rates in the different atolls, as well as the presence of HbS and HbE. In yet another study, analysis of 68,986 laboratory screening records for subjects born between 1960 and1990 showed carrier prevalence ranging from 10.1% to 28.2% by atoll.

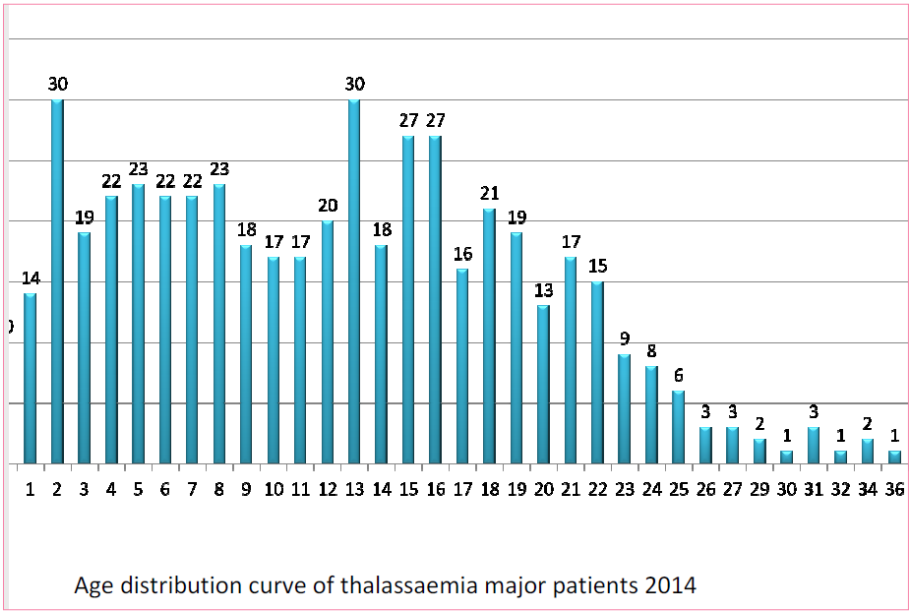


Figure 17. *Age distribution curve of β-thalassaemia patients in the Maldives, 2014*

A national registry has been kept since 1993-1994 and it has recorded 759 cases (TIF/WHO report, 2017). Of these in the 2021 report from the patient association (unpublished), 633 are currently being followed and 580 are transfusion dependent. About half of these live in the capital Male, while the other half live in other atolls. In the same report there are currently 14 patients with sickle cell disease.

The economy of the country of around 0.5 million is rising, mainly due to development of the tourist industry. By 2020 the HDI had risen to 0.740 (high level) and indices are steadily declining, such as the IMR, which is currently (2020) at 6.5/1000LBs, and the under-5 mortality rate is only 7.6/1000LBs. These figures compare favourably with those of other countries of the region.

India

India is a subcontinent of over 1.3 billion people. It is divided into 28 states and eight union territories. It has a high prevalence of all haemoglobin disorders, which are the commonest of chronic hereditary disorders, thus creating a significant burden of disease. The geographical distribution of haemoglobin disorders has been well documented, but it is still further complicated by a high prevalence in tribal groups, which are studied in many but not all areas (Table 10). There is also a variable consanguinity rate and inbreeding among the various population groups and tribes.

State	Sample size	β-thal carrier rate (%)	HbE carrier rate (%)	HbS carrier rate (%)	Reference
New Delhi	800	18.1	2.5	2.8	Rao et al., 2010 [132]
Mumbai	11,768 antenatal by OF	8.7		1.8	Colah et al., 2008 [133]
Delhi	5,408	5.47	0	0.1	Madan et al., 2010 [134]
Mumbai	5,682	2.68	0.04	0.2	Madan et al., 2010 [134]
West Bengal	10,407	5.6	5		Mukhopadhyay et al., 2015 [135]
Assam tribals	1,204	3.07	1.16	4.73	Teli et al., 2016 [136]
Maharashtra	5,172	2.1		6.4	Urade, 2013 [137]
Gujarat & Maharashtra	18,651	7.15			Colah et al., 2010 [138]
Gujarat South	32,857	4.4		1.3	Patel et al., 2012 [139]
Gujarat	4,197 students	2.6		1.4	Patel et al., 2021 [140]
Gujarat tribals	5,467 neonatal screening			12.5	Italia et al., 2014 [141]
Mumbai	18,003 neonatal screening			16.3	Colah et al., 2018 [142]
West Bengal rural	35,413	10.38	4.3	1.12	Dolai et al., 2012 [143]
Surat city	24,917	3.2		1.38	Bhukhanvala et al., 2012 [144]
Uttar Pradesh	1,000	2.8			Meena et al., 2013 [145]
Kolkata WB	20,883	4.09			Choudhuri et al., 2015 [146]
West Bengal	21,137	5.38			Bhattacharyya et al., 2016 [147]
west Bengal	28,7258	7.23	2.77		Maji et al., 2020 [148]
Madhya Pradesh tribals	3,992	1.4		10.7-15.6	Chourasia et al., 2020 [149]

Table 10. *The distribution of haemoglobinopathies in India*

Overall, it is estimated that the carrier rate in India for β-thalassaemia is 3.9%, for HbE 1%, and for HbS 3%. The incidence of βS gene varies from 0% to 40% and is particularly common among tribal groups in western India. The prevalence of β-thal trait in Central India ranged between 1.4% and 3.4%, while 0.94% β-TM was reported among the patients with anemia. In South India, the prevalence of β-thal trait was between 8.50% and 37.90% and β-TM was reported to be between 2.30% and 7.47%. Northern and Western Indian states had a higher thalassaemic burden. In Eastern India, tribal populations had a higher prevalence of β-thal trait (0.00%–30.50%), β-TM (0.36%–13.20%), and other hemoglobinopathies [Hb E (HBB: c.79G>A)/β-thal] (0.04%–15.45%) than nontribal populations.

The wide variation in so many population groups makes it difficult to estimate birth incidence, but it is near 0.58/1000LBs for the thalassaemia syndromes and 0.82/1000LBs for sickle cell syndromes. This could mean about 15,000 new births per year for each category.

Exact patient numbers are not known [132], [133], [134], [135], [136], [137], [138], [139], [140], [141], [142], [143], [144], [145], [146], [147], [148], [149], [150].

Nepal

Nepal, a country of 28 million people, is poorly developed, with a very low HDI rank (0.574) and a health expenditure per capita of only USD 48. Despite this, IMR is improving and is now at 22/1000LBs, and the under-5 mortality rate is 27.3/1000LBs. There are 125 ethnic groups, and marriage within groups and intermarriage are unusual.

It has been known for many years that haemoglobin disorders are prevalent in Nepal. Even though there have been several studies, none provide an accurate picture to describe the exact size of the problem or the disease burden.

β-Thalassaemia and sickle cell are present in the Terai regions of the country, below the altitude of 1,800m. β-thalassaemia is present from the mid-hill region and in the Terai regions from eastern to western Nepal. Sickle cell is mostly present in 5–6 districts in the far west but it is rare in other parts of the country (Table 11).

Carrier frequencies / locations are reported as follows:

- Sickle cell is characteristic of a limited region, among the Tharu of west Terai, where a carrier frequency of 5% has been described.
- β-thalassaemia is most prevalent amongst the Tharu of central Terai, in whom a range of 4%–11% has been described, but not based on unselected samples.
- HbE is found in a minority of cases, but with an unclear ethnic or geographical distribution; it is mostly in the southeast where the frequency is estimated at 0.5%–4%.
- There is need for unselected population studies and micromapping of the various haemoglobin disorders for a more accurate description of the epidemiology in Nepal.

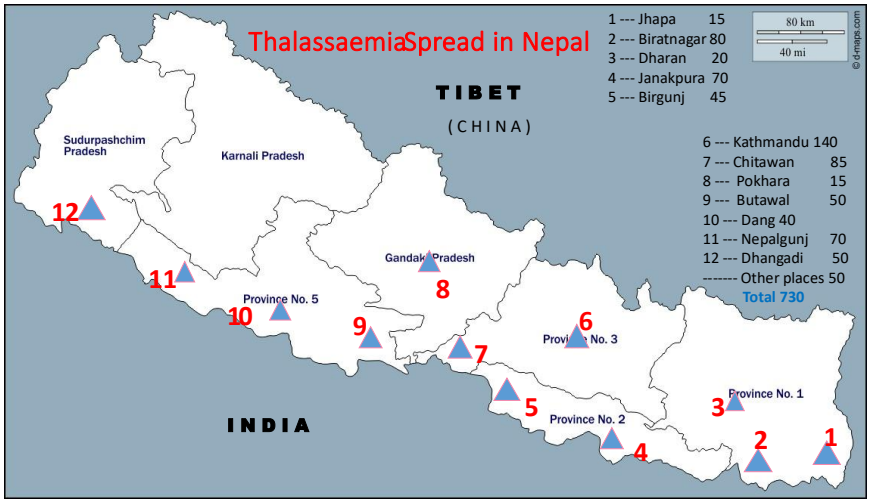
Tribal group	Region	α-thal carrier rate (%)	β-thal carrier rate (%)	HbS carrier rate (%)	HbE carrier rate (%)
Dunwars	Below 1,200m	63			3
Tamang	uplands	5			
Tamang	Kathmandu valley	8.8			
Tharu	West Terai		5.2	10	0.3
Tharu	Central Terai		4	0	
Newar (Nepami)	Kathmandu valley	20.5	0.2	0.02	0.02
Parbate (Pahari)	All over Nepal – hills below 1,800m	16.5			
Tharu Chaudhary	67-300m			Very high 16.8	
Tharu Rana				lower	
Lama				low	
Neupane				low	
Baral				low	

Notes:
Parbate (Pahari): Around 20 million, constituting 3/5ths of the Nepali population. They speak Nepali, and they are spread all over Nepal, mainly in the hills below 1,800m.
Tharu chaudhury and Tharu rana: Around 1.7 million people who live in Nepal Terai (23% of Nepal's land area at an altitude of 67–300m). Tall grasslands, scrub savannah, swamps.
Newar (Nepami): Around 1.3 million people living in the Kathmandu valley and surrounding areas. They speak Newari (a Tibetan-Burma language).
Tamang: Around 1.5 million people who also inhabit the Kathmandu valley and the surrounding hills.

Table 11. *Nepal haemoglobinopathy epidemiology*

Note: Data were collected from Nepalese sources, which give incomplete information. The purpose is to demonstrate that there is an uneven distribution both geographically and among ethnic groups. Overall prevalence cannot be derived from these figures.

The total number of thalassaemia patients in Nepal is not known, but the centre in Kathmandu registered 220 patients in 2017 and 240 in 2018, of which 140+ are regularly transfused. Around another 60 patients are followed in Janakpur, but there is no record of sickle cell patients. The Nepal Thalassaemia Society (NTS) reported in 2021 that there were 730 patients across the country (about 67% patients are from the Tarai regions and 33% from mid hill) [151], [152], [153], [154], [155], [156], [157], [158], [159], [160], [161], [162], [163], [164], [165], [166]:



Bangladesh

Bangladesh has a population of 171.5 million. Health indices are showing a steady decrease in the under-5 mortality rate, from >140/1000LBs in 1990 to about 30/1000LBs in 2020, and an IMR of 20/1000LBs in 2025.

The prevalence of both β-thalassaemia and HbE is high in all regions, and regional prevalence has been documented (see Figure 18). The overall carrier frequency for β-thalassaemia is 1%–5% (mean 3.35%) and for HbE around 6%–10%. This would result in a birth incidence of thalassaemia syndromes of 0.35/1000LBs. Among endogamous tribal groups, this rate is higher, reaching 0.6/1000LBs. It should be noted that the available data for carrier frequency has been collected from relatively small research projects.

There is no national prevention programme in Bangladesh, but recently a Thalassemia Screening and Awareness Program was launched by the Institute of Allergy and Clinical Immunology of Bangladesh (IACIB), Dhaka. A study of 989 volunteer participants indicated a carrier rate of HbE of 10.4%, β-thalassaemia 2.4%, and HbD 0.4%. These findings are similar to previous studies. Prenatal diagnosis is available in one centre in the capital city Dhaka, where over 200 cases have been performed on a private basis.

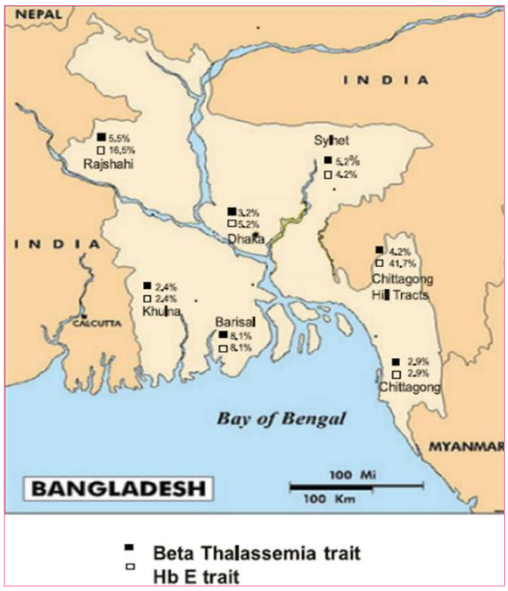


Figure 18. *Map of β-thalassaeimia trait and HbE trait (Source: Aziz et al., 2020 [171]).*

There is no national patient registry, but it is estimated that there are around 30,000–50,000 affected patients. The commonest thalassaemia syndrome, HbE/β-thalassaemia, is variable in clinical severity with about 20%–30% of patients requiring regular transfusions from early childhood (phenotypically thalassaemia major) and another 50% with moderate to severe thalassaemia intermedia (i.e., symptomatic, but requiring only occasional transfusion in childhood); the remaining 25% are mild thalassaemia intermedia and may not be diagnosed at all during childhood [167], [168], [169], [170], [171], [172], [173].

Sri Lanka

Sri Lanka is an island nation with relatively advanced health services compared to other neighbouring countries. IMR is at 6.1/1000LBs, and the under-5 mortality rate is 6.5/1000LBs. These indices are achieved despite the fact that Sri Lanka does not rank very high in the HDI category (0.782) and has a health expenditure per capita of around USD 158.

The carrier frequency of β-thalassaemia in Sri Lanka is 2.8% and approximately 2,000 patients with TDBT are being treated in thalassaemia centres across the country. There is also a carrier rate of 0.5% of HbE and rare

carriers of HbS (approximately 0.15%). The estimated birth incidence of thalassaemia syndromes is 0.18/1000LBs, and the estimated birth incidence of HbS/β-thalassaemia is 0.02/1000LBs. There is no national registry but estimates of around 2,000–3,500 thalassaemia patients live in Sri Lanka, in addition to 50 patients with SCD; these are distributed in various centres (Figure 19) but others estimate double the number [174].

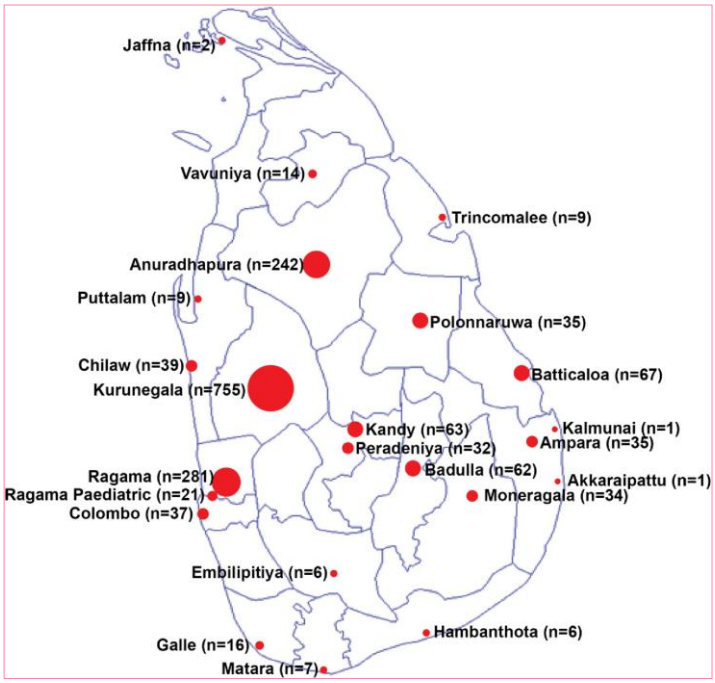


Figure 19. *Distribution of patients with thalassaeimia in Sri Lanka (Source: Premawardhena et al., 2019)*

WESTERN PACIFIC REGION

Malaysia

Malaysia is a country of 31.5 million, with developed health services shown by an IMR of 5/1000LBs and an under-5 mortality rate of 8.1/1000LBs.

The population is multiethnic, with the main groups being Malays (68.8%), Chinese (23.2%), and Indian (7%). Each group has different carrier rates for haemoglobin disorders. The carrier rate for the common thalassaemia syndromes was 6.8% (2.9% for β-thalassaemia, 2.6% for HbE). Carriers for β-thalassaemia were more common in the Chinese ethnic group (4.3%), and HbE was more common in the Malays (3.8%).

According to the 2018 report of the national registry, most patients, previously not living beyond their second decade, are now surviving beyond the fourth decade of life. As of 28 November 2018, 8,681 thalassaemia patients had been registered in the MTR. The total number of living patients in Malaysia is 7,984. Figures presented to TIF in 2023 include 5,442 TDT and 3,900 NTDT (9,554 total). These calculations suggest there may be as many as 350 births affected births per year (including HbE/ β-thalassaemia). The distribution of patients across the country is not homogeneous (Table 12). According to the report, the peak age of patients is 15–20 years, while 56.2% of patients are under the age of 20 years [175], [176].

State	No. of Patients	%
Johor	637	7.98
Kedah	694	8.69
Kelantan	486	6.09
Malacca	226	2.83
Negeri Sembilan	181	2.27
Penang	437	5.47
Perak	564	7.06
Perlis	128	1.60
Pulau Pinang	480	6.01
Sabah	1,814	22.72
Sarawak	223	2.79
Selangor	1,169	14.64
Terengganu	344	4.31
W. P. (Kuala Lumpur)	535	6.70
W. P. Labuan	25	0.31
W. P. (Putrajaya)	41	0.51
TOTAL	7,984	100

Table 12. *Number of thalassaemia patients by state & federal territory (2014–2018)*

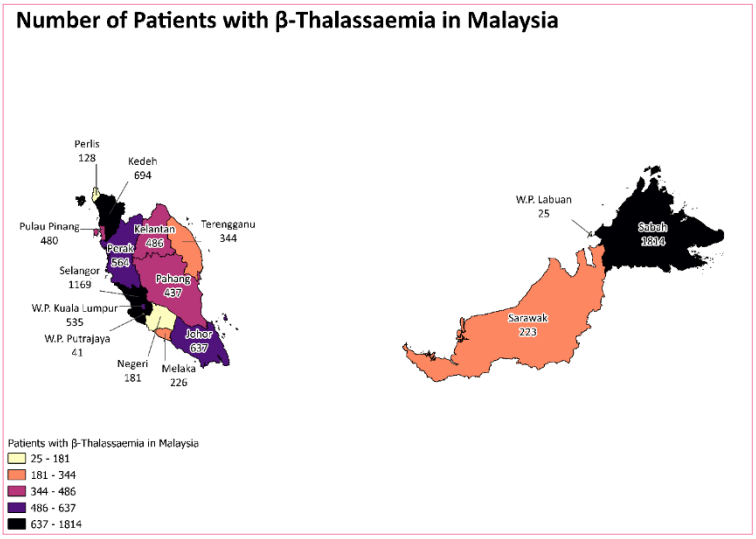


Figure 20. *Number of patients with β-thalassaemia in Malaysia.*

Thailand

A large country of 69.4 million, Thailand has a developed healthcare system with an IMR of 6.4/1000LBs and an under-5 mortality rate of 8.1/1000LBs, and these indices are continually improving. Thailand has a long history of tackling thalassaemia since its first description in the 1950s. From 1993 onwards services have been planned at the national level.

Epidemiological data are as follows:

- β-thalassaemia carriers: 3%–9%
- HbE carriers: 10%–53%
- Hb Constant Spring: 1%–8%

Considering the interactions of these various mutations and the interaction with various forms of alpha thalassaemia (in 20%–30% of cases), around 60 possible phenotypes have been identified.

As in other large populations, there are regional variations, which are important to note when planning services (see Table 13). Severe non-deletional alpha-thalassaemia mutations are responsible for the increased number of severe, even transfusion-dependent HbH disease and cases of hydrops fetalis [177], [178], [179], [180], [181].

Region	β-Thalassaemia carriers	α-Thalassaemia carriers	HbE carriers
North	9%–10%	30%	8%
East	6%	20%	30%–50%
East Central	3%	20%–25%	13%–17%
South	2%–4%	6%	9%–11%

Table 13. *Distribution of carriers across the regions of Thailand*

Cambodia

After a very difficult recent history, Cambodia now finds itself in a period of recovery. The total population is 17 million. With very limited resources, exact epidemiological data are difficult to obtain. IMR is improving over time, and in 2020 it fell to 21.9/1000LBs and to 19.3 in 2023, while the under-5 mortality rate is 24.8/1000LBs.

In a recent survey of 1,631 unrelated individuals, HbE was the most common β-globin gene mutation with a frequency ranging from 0.139 to 0.331, while the most frequent α-globin gene mutation was the $-\alpha^{3.7}$ gene frequency 0.098–0.255. β-Thalassaemia gene frequencies ranged from 0.001 to 0.003. Other alpha chain mutations include 0.008–0.011 for α-thal-1 (- -(SEA)), 0.003–0.008 for α-thal-2 -α(4.2), 0.021–0.044 for Hb Constant Spring, and 0.009–0.036 for Hb Paksé (HBA2: c.429A > T). This study confirmed the existence of severe alpha globin mutations as in other countries of the region. It also demonstrated regional variations, even though falling short of micromapping of the whole country.

A 2019 survey of 2,647 children from four provinces gave the following results:

- Normal: 45.5%
- HbE trait: 34.4%; 5% HbE homozygotes
- Alpha+: 13%; alphao: 1.5%
- HbCS: 1.25%
- HbPakse: 0.2%
- β-thalassaemia trait: 0.2%

Based on this survey, it is estimated that at least 4.5 million people are carriers, and at least 160,000 are patients. The estimated annual births of patients with serious thalassaemia disorders are about 2,500. Very similar results were reported in another survey of children of whom 23.1% had HbE trait (AE), 14.0% had α+-thalassaemia trait, 8.3% had a combination of Hb E trait with α+-thalassaemia trait, and 5.2% were homozygous for HbE (EE).

In a 2022 review, it was estimated that about 40.0% (range 30.0%–50.0%) of the population are carriers and that there are 2,240 annual births of β-thalassemia patients. Alpha thalassaemia with significant clinical consequences is also common.

Myanmar

Myanmar is a country of 53.7 million, which is still a struggling economy with a health expenditure per capita of USD 59 and a low HDI ranking (0.583). IMR is 31.8/1000LBs and the under-5 mortality rate of 40/1000LBs.

Myanmar has a high incidence of important haemoglobinopathies, with great variability in regions and among population groups. The population is composed of 135 ethnic groups, of which Kachin, Kayah, Kayin, Chin, Mon, Bamar, Rakhine and Shan are the major indigenous groups.

Overall estimates are as follows:

- α-thalassaemia:10%–56.9%
- HbE: 1%–28.3%
- β-thalassaemia: 0.54%–4.07%

Patient registries exist in tertiary care hospitals and day care centres, especially in six specialist haematology centres. According to these registries, the most frequent syndromes are HbE/β thalassaemia (46%–58%) and HbH disease (6%–37%), varying in each part of the country.

These data are derived from reports presented by physicians at the SEATHAF Conference 2018 and 2019. Published reports are on small numbers of subjects [182], [183].

Lao People's Democratic Republic

The country of Lao is home to 7.4 million people, and, like its neighbours, it is at a low level of economic and social development. Health indices are improving so that IMR is now 34.2/1000LBs, while the under-5 mortality rate 42.5 in 2023.

Epidemiological information is limited. In a study involving small numbers of Laotian pregnant women, carriers of HbE were 30.1%; 8.6% were carriers of α^0-thalassaemia while the frequency of β-thalassaemia was 2.3%. Similar findings are reported in other studies, though equally limited in sample size. In another study among 519 subjects referred for investigation, 287 (55.3%) were found to carry β-hemoglobinopathies. These included Hb E carriers (n = 135, 26%), homozygous Hb E (n = 47, 9%), β-thalassaemia carriers (n = 70, 13.5%), Hb E-β-thalassaemia (n = 25, 4.8%). There was clinical suspicion to explain the increased figures, but they indicate the range of clinically significant mutations.

A national registry is not yet established, but there are two hospital-based thalassaemia registries: at the National Children's Hospital in Vientiane and at the Luangprabang Provincial Hospital [184], [185], [186], [187].

Viet Nam

IMR is improving and is now 16/1000LBs, while the under-5 mortality rate is 19.2/1000LBs.

Viet Nam has 54 ethnic groups, and around 85% of the population (95 million) belong to the Kinh ethnic group. Regional or ethnic variations of haemoglobinopathy prevalence are expected. Overall carrier rates, based mainly on the Kinh ethnic group, are:

- HbE/thalassaemia: 3.4%
- β-thalassaemia: 1.6%

More analytically, carrier rates and expected thalassaemia in Viet Nam are presented in Table 14. The data are based on the paper by O'Riordan et al. and is supplemented by data provided by Dr Turc in a presentation at the NIHBT.

Ethnic group (% of total pop)	HbE carriers	β-thal carriers	Exp β-thal births (range)	Exp HbE/β-thal births (range)	Exp HbH births	Hydrops fetalis
Kinh (85.7%)	3.4%	1.6%	80 (50–124)	341 (257–438)	738	343
Tay (1.9%)	2.75%	7.6%	76 (41–136)	55 (29–93)	167	45
Nung (1.1%)	2%	8.1%	46 (23–87)	23 (10–44)	67	45
Dao	9.5%	0	63 (17-187)	0	0	0
S'Tieng	44.8%	0.16%	0	2 (1–4)	56	4
M'Nong (1.5%)	36.7%	0.36%	0	4 (0–12)	?	?
Thai (1.8%)	?	?25%	?	?	?	?
Rac Hay	25.8%	0.2%	0	1 (0–5)	?	?
Ede	45.8%	0.15%	1	71 (19–155)	?	?
Muong (1.5%)						
Huong (1%)						
Khmer (1.5%)						
May (1.2%)						
Total			Min 266	Min 497	Min 1,028	Min 437

***Table 14**. Carrier rates of expected thalassaemia in Viet Nam*

Similar data were obtained by other surveys in the Thua Thien Hue region, where alpha-thalassaemia carriers were found in 41.5% and β-thalassaemia carriers in 1.2% of the population studies . In the Tay ethnic minority, the prevalence of thalassaemia in 289 Tay women was 15.6% (gene frequency 0.078) for α^0-thalassaemia, 10% (gene frequency 0.050) for α+-thal, 7.3% (gene frequency 0.036) for β-thalassaemia, 2.4% (gene frequency 0.012) for Hb Constant Spring, and 1.7% (gene frequency 0.009) for HbE. This effort at micromapping Viet Nam will help in directing the planning of services.

National experts quote a rough estimate, in the absence of a national registry, of there being around 20,000 affected patients from all the major thalassaemia syndromes in the country [188], [189], [190], [191].

Indonesia

The country of Indonesia has a population of over 267 million scattered over 13,670 islands (Figure 21). This is in itself a challenge for health authorities to reach and equitably provide quality services. IMR is 16.6/1000LBs and the under-5 mortality rate is 20.6/1000LBs.

Data from the Eijkman Institute in Jakarta, which is the central laboratory for screening and prenatal diagnosis, indicate overall carrier frequencies as follows:

- β-thalassaemia: 3%–10%
- α-thalassaemia: 2.6%–11%
- HbE: 1.5%–36%

In a screening programme of the general population, between 2008 and 2017, 699 (5.8%) minor thalassaemia cases out of 12,038 were detected. These figures confirm earlier studies in which a wide variation of carrier frequencies in the regions and islands of this large country was described.

Based on these rates it is estimated that 2,500 children are born each year with β-thalassaemia, but significant thalassaemia syndromes may occur in over 6,000 newborns.

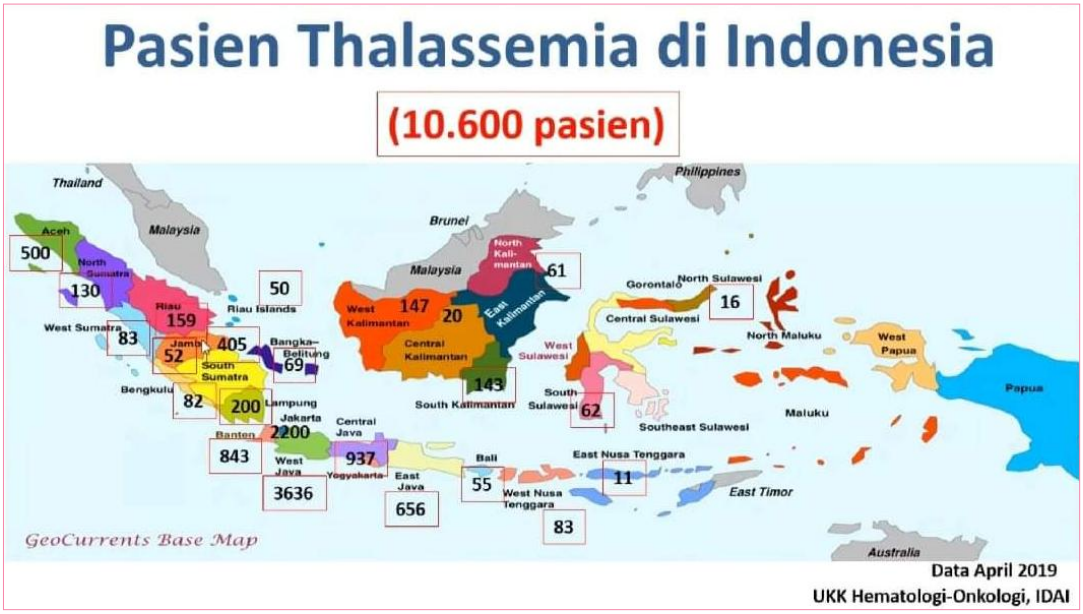


Figure 21. *Distribution of thalassaemia patients across the island and provinces of Indonesia (based on a presentation by Dr Pustika Amalia Wahidiyat in 2018. Source: Dr Pustika Amalia Wahidiyat*

More recent data, presented during a virtual meeting with TIF and a mixed group of patients and healthcare professionals, gave the registered patient population as 13,612 in 2024 [192], [193], [194].

Brunei Darussalam

With a population of just under 0.5 million, Brunei Darussalam is comprised of approximately 65% Malays, 20% Chinese and 10% indigenous tribes. It is a prosperous community in the very high HDI rank (0.838) and a health expenditure per capita of USD 671 in 2017. This is reflected in the IMR which is 7.5/1000LBs and an under-5 mortality rate of 11.4/1000LBs (comparable to neighbouring Malaysia). The presence of thalassaemia genes was reported, but this was not a random sample of the population (those referred for anaemia) [244]. The carrier rate for β-thalassaemia is estimated to be 5% and the number of patients under treatment around 200 [195], [196].

China

In China, the distribution of thalassaemia genes is very heterogeneous. The provinces most affected are in South China (See Figure 22 and Table 15).

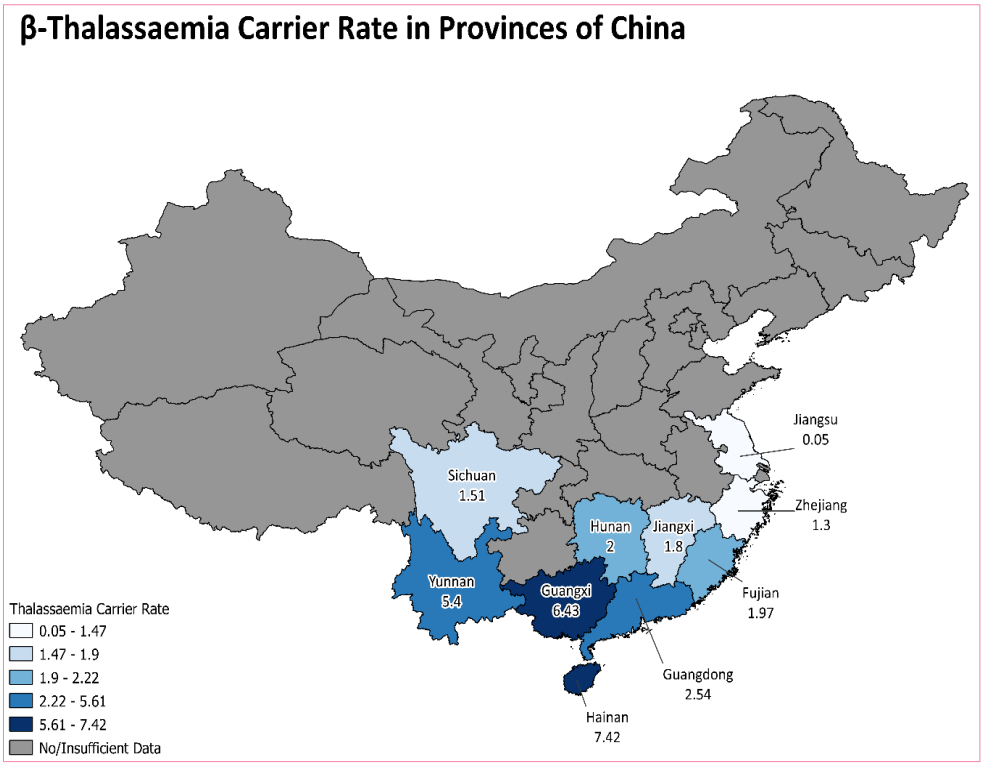


Figure 22. *β-Thalassaemia carrier rate in provinces of China, based on data gathered by TIF*

PROVINCE	TERRITORY COVERED	SAMPLE SIZE	CARRIERS A-THAL	CARRIERS B-THAL	CARRIERS HBE	REFERENCES
GUANGDONG	Sihui city	1,007cb 1,524pb	11.72%	3.87%		Tan et al., 2003 [197]
	5 regions	13,397	8.53%	2.54%		Xu et al., 2004 [198]
	Shenzhen	3,711	4.34%	1.99%		Li et al., 2006 [199]
	Shenzhen	2,028 neonatal	6.75%	2.81%		Wen et al., 2019 [200]
	Guangdong	1,888	11%	4.1%		Zhao et al., 2020 [201]
	Zhuhai city	181,483	4.5%	2.3%		Zhou et al., 2008 [202]
	Zhuhai city	141,166	5.24%	2.36%		Zhou et al., 2012 [203]
	Zhongshan city	2,055		3.56%		Zhang et al., 2010 [204]
	Chaozhou	11,450			0.1%	Lin et al., 2012 [205]
	Meizhou city	15,229	7.11%	4.13%	0.12%	Lin et al., 2013 [206]
	All 21 regions	26,534pb 14,274cb	13.3% 12.6%	4.53% 4.34%	0.07% 0.1%	Yin et al., 2014 [207]
	Antenatal screening	28,479	12.66%	4.43%		Li et al., 2014 [208]
	Guangzhou (single centre)	83,062	8.69%	3.83%		Jiang et al., 2017 [209]
	Guangzhou	137,222 couples	8.2%	3.52%		Jiang et al., 2021 [210]
	Meizhou city (Hakka people)	14,524	22%	11.6%		Zhao et al., 2018 [211]

Province	Territory covered	Sample size	Carriers a-thal	Carriers b-thal	Carriers HbE	References
	Meizhou region	22401	22.7%	11.08%		Wu et al., 2021 [212]
	Yubei (North Guangdong)	10,285	14.68%	8.08%		Ma et al., 2021 [213]
	Dongguan	19,442	8.1%	4.3%		Peng et al., 2021[214]
	Chaoshan region	6,231	4.46%	0.85%		Zheng et al., 2016 [215]
Guanxi	3 areas	2,261		5.53%	2.4%	Qiu et al., 2009 [216]
	Chongzuo city	1,097	19.87%	5.74%		Li et al., 2009 [217]
	Guilin city	1,580	3.54%	7.22%		Deng et al., 2009 [218]
	Nanning	9,952	8.5%	7.62%	0.42%	Zhang et al., 2009 [219]
	6 areas	5,789	17.55%	6.43%		Xiong et al., 2010 [220]
	Nanning		14.95%	5.65%		Chen Ping presentation 2012
	Nanning	17,555	8.1%			He et al. 2014
	Baise city	47,500	15.35%	8.72%		He et al.., 2017 [221]
	Yulin city	130,318	13.98%	6.58%		He et al., 2018 [222]
	Baise City	12,900	15%	4.8%		Pan et al., 2007 [223]
	Different regions of Guangxi	71,459	11.64%	5.88%		He S et al., 2021 [224]
Guizhou	Minority populations	3,500		5.4%		Yu et al., 2010 [225]
	Neonatal screening	18,309	8.91%	3.36%		Tan et al., 2021 [226]
Yunnan	Kunming city	1,338	3.5%	5.4%		Wen et al., 2011 [227]
	6 ethnic groups	48,973	22.6%	14.7%		Zhao et al., 2011 [228]
Sichuan	Sichuan Province	3,185	1.7%	3.2%		Wang et al., 2011 [229]
	Sichuan Province	42,155	1.83%	0.75%		Li et al., 2021 [230]
	Chengdu city	13,298	1.51%%	2.64%	0.11%	Yu et al., 2019 [231]
	Chongqing city	1,057	5.2%	1.99%		Yao et al., 2013 [232]
	Han people	1,726		1.51%		Yao et al., 2013 [233]
Fujian	9 cities	11,234cb	3.16%	1.3%		Xu et al., 2013 [234]
	9 cities	189,414	4.84%	1.97%		Huang et al., 2019 [235]
	Quanzhou city	7,082	3.21%	2.15%		Chen et al., 2018

Province	Territory covered	Sample size	Carriers a-thal	Carriers b-thal	Carriers HbE	References
	Quanzhou city	11,668	28.27%	12.06%		Zhuang et al., 2020 [236]
Jiangxi	3 regional centres	9,489	4.56%	1.8%	0.1%	Lin et al., 2014 [237]
Hainan	Li + Han	18,400	37.8%	11.3%		Yao et al., 2014 [238]
	Li ethnic	1,412	18%	3.54%		Tu et al., 2019 [239]
Jiangsu	1 region	10,297	0.25%	0.05%		Lin et al., 2013 [240]
Hunan	Changsha city	7,500	2.65%	2%		He et al., 2017 [241]
	Chenzhou city	15,807	6.31%	4.82%		Zhang et al., 2019 [242]
	Chenzhou city	11,212	5.72%	2.6%		Yang et al., 2021 [243]
Zhejiang	Huzhou city	8,578	1.01%	1.3%		Ding et al., 2016 [244]
China, Hong Kong SAR		25,834	4.4%	2.8%		Sin et al., 2000 [245]
Hubei	Wuhan	3796 (neonal screening)	38%	19.98%		Cai et al., 2021 [246]
5 Provinces	Screening	10,476	15.12	4.75		Zhao et al., 2019 [247]
4 provinces	Neonatal screening	2,258	19.64%	4.47%		Zou et al., 2022 [248]

Table15. *Epidemiological Summary of Thalassaemia in China*

Overall, the carrier rates in southern China are:

- α-thalassaemia: 1%–18%
- β-thalassaemia: 1%–8%
- HbE: 0.1%–2%

The great diversity of carriers in the various provinces, the restricted family size policy, but also the various endogamous ethnic groups make the estimation of new affected births each year a very broad approximation. Based on the regional carrier rates, it is estimated that this part of China, with around 670 million, may have 21 million β-thalassaemia carriers.

The province of Guangxi has the highest carrier rate and has been the first to respond by developing a full premarital screening programme with the availability of prenatal diagnosis.

REGION OF THE AMERICAS

This region generally has a low prevalence of thalassaemia but a high prevalence of sickle cell disease, which is particularly high because of the African origin of the populations of most countries. Since this report concentrates on countries with a significant prevalence of β-thalassaemia births (where the expected births are more than 0.1/LBs) and notes other variants in those specific countries, only a few countries in the Americas have been included as most do not meet these criteria.

Trinidad and Tobago

The people of Trinidad and Tobago are mainly of African and East Indian descent. IMR is at 15.7/1000LBs and the under-5 mortality rate is 17.5/1000LBs.

In a 2015 study of blood donors, 6.75% were found to be carriers of β-thalassaemia.

A prospective study of 1,254 cord blood samples, carried out in 1984, showed the overall incidence of haemoglobinopathy was 15.7%. More specifically, HbS was found in 9.9% of those of African descent and 1% of Indians, HbC was found in 3.1% of Africans, and 0.7% of Indians. HbE was found in 0.2% of Africans and 0.4% of Indians [249], [250], [251].

Brazil

The carrier rates are reported as sickle cell trait (2.49%), thalassemia minor (0.30%). It is estimated that there are a thousand people living in Brazil with thalassaemia major or intermedia. It is also estimated that between 60,000 to 100,000 individuals live with SCD in Brazil today. The prevalences found for sickle cell trait is according to skin colour: 4.1% among dark-skinned blacks, 3.6% among light-skinned blacks, 1.2% among whites, and 1.7% among others [252], [253], [254].

Colombia

Like all South American countries, HbS predominates in Colombia. The carrier rate for that is 10%–11% based on neonatal screening [255], [256].

Argentina

Despite the knowledge that around 50% of the population are of Italian origin and many others are of Spanish and Arab origins, the carrier frequency of either β-thalassaemia or HbS trait are not known on a population scale. No population surveys have been performed. However, a substantial number of thalassaemia patients are known to be treated in the country, but as yet there is no estimate of the total number of patients with either thalassaemia or sickle cell disease. Recently, one hospital in Argentina created a thalasseamia patients registry to gather information from all patients with transfusion-dependent thalassaemia (TDT) [https://www.garrahan.gov.ar/registrarme-talasemia].

In most Latin American countries, the β-thalassaemia carriers are estimated to be less that 1%. This is low but not negligible.

Canada

Even though carrier rates are low, less than 1%, migrations have introduced a sizable population of β-thalassaemia patients, estimated at 1,200, and sickle cell patients, estimated at 6,000. More recent migrations from Asia have also introduced alpha thalassaemia, with an increase in non-deletional variants, which may increase transfusion dependent HbH disease. Increased incidences of alpha thalassaemia will likely increase the frequency of hydrops fetalis.

USA

As in Canada, past and more recent migrations to the US have introduced haemoglobin disorders to this populous country of 342 million. The native American population is not known to have haemoglobinopathy genes and it is a minority of less than 1% of the population. The Caucasian population was originally mostly of northern European origin, but an influx of populations from Mediterranean countries during the 20th century has introduced mostly thalassaemia genes. The slave trade from West Africa during the 18th and 19th centuries, which represents 13% of the population, introduced the sickle cell genes. In recent years increasing migrations from Asia are introducing both beta and alpha thalassaemia genes.

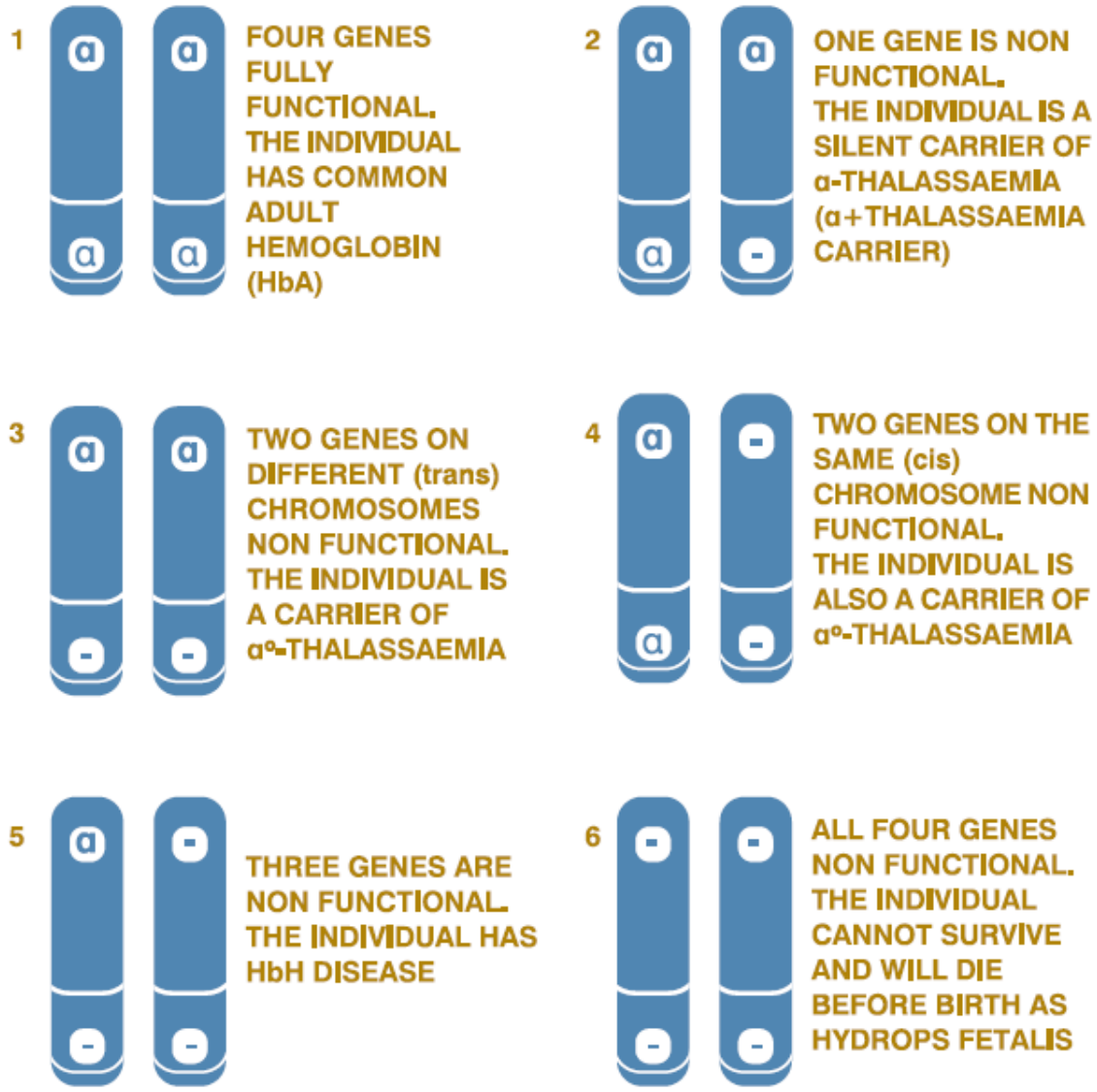
The exact carrier rate of these pathogenic genes is not known, although it is roughly estimated at 0.5% for β-thalassaemia, 0.1% for HbE, and 0.75% for HbS. According to Fu et al., (presentation at ASH 2024), an estimated prevalence of β-thalassaemia in the US in 2023 was 3,665, or equivalent to 1.07 per 100,000 persons. However, based on sensitivity analyses, the estimated prevalence was as high as 4,214 cases (1.23 per 100,000). The number of prevalent TDT cases was 2,611 and as high as 3,036 in sensitivity analyses.

Sickle cell genes are much more common because of the African American population, and it is estimated that there are 70,000-100,000 affected patients in the country.

Part 2 - Alpha Thalassaemia Epidemiology

It is estimated that 5% of the global population are carriers of α-thalassaemia. However, estimating the epidemiology only through the reported overall carrier rates is not a good indicator. Carriers can be α+ (with one of the four alpha globin genes non-functional) or α^{0} (with two alpha globin genes non-functional), and these genes may be deleted or not, with the non-deletional variants being clinically more severe. The clinically

significant phenotypes are HbH disease (reduction in three of the alpha globin genes) and alpha thalassaemia hydrops fetalis (reduction in all four alpha globin genes).



Thus, it is necessary to know the prevalence of each genotype: deletional α^{+}, α^{0} (in cis or trans), as well as the non-deletional types and variants, which can cause clinically significant conditions. For this reason, simple haematological tests based on red cell indices are insufficient, and it is necessary to have data based on molecular testing at population levels, which makes epidemiological predictions of the frequency of serious syndromes even more problematic. However, even mild deletions can complicate screening and epidemiological studies due to their interaction with both iron deficiency and β-thalassaemia. In addition, co-inheritance can modify the phenotype of β-thalassaemia and sickle cell syndromes.

Although the mutations on the alpha globin genes exist in many populations around the globe, the most severe forms are most common in the South Asian countries, especially in the Indochina peninsula. Like β-thalassaemia, α-thalassaemia has been introduced to populations where previously it was either absent or rare.

HbH disease has a wide spectrum of clinical severity. While it is considered relatively mild in the Mediterranean region, it may complicate pregnancy or other health conditions in later life. The haemoglobin level is generally

low, but it falls during infections or other illnesses. The picture is also complicated by HbH disease resulting from interactions between α^0-thalassaemia with non-deletional mutations or with abnormal haemoglobins such as Hb Constant Spring, Hb Paksé, Hb Quong Sze, and Hb Pak Num Po, and Hb Agrinion. In the more severe Asian forms, the condition may be transfusion dependent.

Due to this genotypic complexity, the epidemiology in many populations is even less clear than β-thalassaemia. Identification of α-thalassaemia carriers is suspected, in practice, while screening for β-thalassaemia. Low red blood cell indices associated with a normal HbA_2 give rise to the possibility of α-thalassaemia, but they must be differentiated from iron deficiency. Molecular studies must be considered, especially if both members of the couple present with this picture. It is particularly important to ensure that the couple is not at risk for having a pregnancy with a possible haemoglobin Bart's hydrops fetalis, since, as well as leading to foetal death, this may lead to serious maternal complications. Surveys have been conducted in many communities using the level of Hb Bart's in cord blood. Availability of intra-uterine transfusions for haemoglobin Bart's hydrops fetalis is increasing and must be regarded as a choice for couples who do not elect to terminate the pregnancy. An infant born with the condition will be transfusion-dependent and will be treated in the same clinical scheme as thalassaemia major.

In summary, the complex genotypes which result in the inheritance of the clinically significant forms of α-thalassaemia would require more detailed epidemiological studies to assess the prevalence rates of α^+, α^0, and deletional α-thalassaemia mutations, along with important variants, to predict the frequency of the various syndromes. An example of such a study was conducted in South East Asia. Accurate data, such as those attempted to be collected in the South East Asia database, are not available in many populations. The TIF database does not yet include this information even though there is recognition that HbH disease contributes to non-transfusion-dependent thalassaemia and that hydrops fetalis impacts pregnancies. Thus, this information must be recorded and presented to healthcare planners. The inclusion of α-thalassaemia and α-chain variants in neonatal screening programmes and premarital programmes is an issue that must be promoted since the burden of these conditions is significant.

United States of America

The prevalence of α-thalassaemia in the United States was underestimated in the past, but it is increasing due to recent migrations, mainly from South East Asia. A precise estimate of the total number of individuals with thalassaemia in the US is unavailable due to the lack of either a state or a national database. Ten large thalassaemia centres in the country collectively follow about 1,379 patients, while an additional 1,500 patients are estimated to receive care at other hospitals. These estimates include beta- and alpha-thalassaemia syndromes. In contrast, SCD has a prevalence of 70,000-100,000, mainly in the Afro-American population. The challenge of providing uniform and optimal clinical management in such a diluted thalassaemia population is being addressed.

Recognising that α-thalassaemia plays a significant role in the disease burden of many populations, it should also be noted that the disease burden and the public health importance of these syndromes is mostly neglected since the β-thalassaemia syndromes are generally more demanding on clinical services. In the United States, ~1 in 10,000 newborns in California have clinically significant α-thalassaemia, and the overall birth prevalence of hydrops fetalis is ~0.2 per 100,000 state births, reflecting the influx of immigrants from SE Asia to the west coast.

China

There are variations in the carrier rate of α-thalassaemia in the various provinces. For example, prenatal testing in Guangzhou identified 4.4% carriers [317]. Premarital screening in Guangdong identified 5.2%. In Guizhu province, the Buyi population has a carrier rate of 16.15% [319]. In Fujian it is 22.2%. The carrier rate of alpha-thalassaemia was 46.39% in the Li people and 10.02% in the Han people of Hainan [321]. These examples are indications of the variations in frequency of α-thalassaemia, both regional and among ethnic minority groups.

Maghreb: Despite the high frequency in many populations, alpha-thalassaemia carriers in the Maghreb region were found to be only 0.30% among 2,000 healthy blood donors in Eastern **Morocco**. Similarly in a neonatal survey from **Tunisia,** only 0.33% were found to be carriers.

A recent review of **SE Asian** countries found an overall prevalence of α-thalassaemia to be 22.6%. The highest α-thalassaemia prevalence was observed in **Vietnam** (51.5%), followed by **Cambodia** (39.5%), **Laos** (26.8%), **Thailand** (20.1%), and **Malaysia** (17.3%) [324]. As mentioned above a higher prevalence of non-deletional variants and clinically more severe HbH disease is characteristic of this region.

In the Arab world, **Saudi Arabia** has around 6% carriers, even though there are wide regional variations. In the Gulf States, a much higher prevalence is recorded of 20%–50%, in **Bahrain** it is 24.3%, and in **Oman** it is 45%.

Hb Bart's hydrops fetalis

The frequency of α^0-thal variants, such as the −−SEA genotype, reaches up to 5% in certain regions of South East Asia. This increases the chance of homozygocity or compound heterozygosity of α^0-thalassaemia and so the possibility of hydrops fetalis. This may also occur in other populations including the Mediterranean where –MED is encountered, even though it is rare, according to reports from Cyprus.

Affected foetuses with this syndrome die either in utero or soon after birth with features of nonimmune hydrops fetalis, which include severe anaemia, gross oedema, marked hepatomegaly, and a variable degree of splenomegaly due to extramedullary haematopoiesis. In addition, there is a higher incidence of maternal complications, including hypertension, proteinuria, and postpartum haemorrhage. These are indications for the termination of pregnancy when detected by prenatal diagnosis aiming to prevent complications in the mother as well as the foetus. However, early intrauterine transfusions can mitigate the anaemia and improve the survival of the foetus. When born, such an infant will be transfusion-dependent and will need lifelong treatment as thalassaemia major. Many infants may also have neurodevelopmental delay and a high rate of congenital defects. Despite these complications the survival of these infants remains a free choice of the parents where such treatments are available [43], [76], [76], [179], [203], [257], [258], [259], [260], [261], [262], [263], [264], [265], [266], [267], [268], [269], [270], [271], [272], [273], [274], [275], [276], [277], [278], [279].

DISCUSSION AND CONCLUSIONS

The epidemiology of haemoglobin disorders is the basic tool for effective healthcare development that aims to serve patients and the community. In this study the gaps in the knowledge of basic components of epidemiologic description in most populations are well demonstrated. Carrier frequencies are based on small samples, laboratory techniques are often unreliable, and patient numbers are completely unknown or roughly estimated, and even guesswork is often based on the experience of local practitioners.

The majority of patients with thalassaemia live in the developing world (Table 16), where infectious diseases have become less of a threat in recent years, but are still prominent in the public health scene. Furthermore, non-communicable diseases (NCDs) are increasing and contributing to poor health and premature death and are indeed more difficult to control. In these settings, congenital and hereditary conditions have been largely put aside. Other "priorities" are projected as major threats and childhood disorders are left to paediatricians who do what they can but are left out of healthcare planning.

COUNTRY/REGION	TOTAL PATIENT POPULATION RECORDED *	PATIENT POPULATION DENSITY AVERAGE	NEW BIRTHS ADDED ANNUALLY IF NO PREVENTION
MEDITERRANEAN EUROPE: Albania, Azerbaijan, Bulgaria, Cyprus, Greece, Italy, Romania, Turkey	19780	1: 10500 (9.5/100000 persons)	819
EUROPE WITH LOW INDIGENOUS CARRIER RATES: Austria, Belgium, Croatia, Denmark, France, Germany, Ireland, Netherlands, Portugal Spain, UK, Sweden, Switzerland	5157	1: 80000 (1.25/100000 persons)	202
ARAB NATIONS (HIGH DENSITY): Iraq, Jordan, KSA, Kuwait, Oman, Palestine, Syria, UAE, Egypt	48962	1: 4583 (1:2000-1:10000) (21.8/100000 persons)	4,687
ARAB NATIONS (MEDIUM DENSITY): Algeria, Lebanon, Qatar, Tunisia, Yemen	2786	1: 17700 (5.6/100000 persons)	532
ARAB NATIONS (LOW DENSITY): Bahrain, Morocco	1220	1: 70000 (1.43/100000 persons)	99
WESTERN ASIA: Afghanistan, Iran, Pakistan	76149	1:4000 (25/100000 persons)	8,643
INDIA SUBCONTINENT: Bangladesh, India, Maldives, Nepal, Sri Lanka	203396	1:8000 (range 1:1000 – 1:50000) 12.5/100000 persons	21,700

SOUTH EAST ASIA: Indonesia, Myanmar, Thailand, Brunei Darussalam, Laos, Malaysia, Singapore, Vietnam	146205 without considering Cambodia because of no estimates	1: 4000 (25/100000 persons)	14,052
WEST PACIFIC NATIONS: China, Philippines	300,600	China 1:5000 (21/100000) Philippines 1:20000 (5.3/100000)	1,600 min
AMERICAS AND AUSTRALIA: Australia, Brazil, Canada, Trinidad &Tobago, USA, Venezuela	9576	1:84000 (1.2/100000)	191
SOUTH AFRICA	1,000	1: 49000 (2/100000)	No data
MAURITIUS	250	1: 5000 (19/100000)	5

Table 16: *Thalassaemia patient density measures by different world regions*

** Numbers retrieved from TIF Global Thalassaemia Review (2018-2024) and [3] https://thalassaemia.org.cy/what-we-do/global-thalassaemia-review/*

The Global Burden of Disease project makes its own estimate on mortality from haemoglobin disorders, even though data are hard to come by. Do countries keep accurate death certifications? If a child dies of diarrhoeal disease, a possible underlying thalassaemia syndrome may not be diagnosed, let alone recorded!

The epidemiological landscape is changing through human intervention influenced by environmental, social, economic, and public health measures. Nevertheless, physicians trained in public health rarely "see" congenital diseases. Their training is orientated towards infectious diseases and NCDs, which can be influenced by changes in the environment and lifestyle, such as keeping clear of refined carbohydrates, alcohol, and tobacco. Keeping a child alive through targeted and expensive interventions is a luxury that few can afford.

The argument is, of course, that resources are limited. The only answer to this common position is that the decision regarding the distribution of resources in each society is the reason for inequalities in healthcare. Is the expenditure on health comparable to that for military spending? Is health high on the priority list of any society? It is true that rising costs are challenging even "prosperous" societies, but is the premature death of children an acceptable way of economic restraint?

Health planners are not always aware of the complex health issues that children and adults with these disorders have. The result is an observed low prioritisation of haemoglobin disorders to which the lack of epidemiological evidence contributes. In this respect, the Thalassaemia International Federation (TIF) has actively promoted electronic health, not only as a tool for data collection, but also as a means to better control patient management. The rarity of these disorders in some populations is another reason why electronic records and registries can help to direct policy. Such tools will enable the identification of areas where the creation of reference centres would be justified and which would support patients receiving treatment in smaller units nearer home. The development of guidelines and standards of care is also necessary so that both patients and doctors know what is expected in order to achieve the best possible outcomes. Enhancing patients' voices at all levels, from the patient/doctor encounter to the level of policymaking, will ensure that, eventually, quality care can reach all equally.

In epidemiology, patient outcomes are often poorly recorded. For some countries, measures such as the age distribution of the patient population, complications, and survival data, as well as quality of life data, are well recorded and reported. Sadly, however, these countries are a minority. For these reasons, this present study on the epidemiology of haemoglobin disorders must be regarded as a preliminary report of the continuing effort by TIF and its member patient support associations to promote the improvement of care through the collection

of information on hereditary conditions that are not so rare and affect the public health landscape of many countries.

TIF has not expressed its findings in terms of YLLs (years of life lost) or DALY's (disability adjusted life years), as is the practice of more expert epidemiological teams (e.g., Global Burden of Disease project). This is because accurate survival data that lead to such scaling have not been collected.

Service providers at both the national level and the local level should be able to estimate the burden of haemoglobin disorders in the population that they serve. In this respect TIF has created a model for such an investigation to include economic burden (See Chapter 11 Estimating the Cost of Thalassaemia Care). Epidemiological data, along with an estimation of the costs relating to the treatment of patients and the prevention of new cases are, in TIF's opinion, imperative tools that should guide policy development and ensure fair budgetary allocation for the provision of equitable care, including new innovative therapies for both thalassaemia and sickle cell disease [280], [281], [282], [283].

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