Global Prevention and Control of Hemoglobinopathies

防控全球血红蛋白病

华大基因 BGI

WHF WORLD HEMOGLOBINOPATHY FOUNDATION

Abstract

Hemoglobinopathies are the most common monogenic hereditary diseases, affecting a large number of people around the world and causing serious consequences. Hemoglobinopathies have a clear etiology, as well as clear prevention and control methods, and there are many examples of successful prevention and control practices. Cyprus, Italy, the UK, Iran, Singapore, Guangxi (China) and many other countries and districts have successfully reduced the rate of severe hemoglobinopathies at birth with good prevention and control programs. These successes show that the prevention and control of hemoglobinopathies can be achieved in all countries, regardless of their financial status, when effective programs are implemented.

However, effective prevention and control measures have not been implemented on a large scale throughout the world. There are still 300,000 to 500,000 children born with severe hemoglobinopathies every year. This report summarizes the global hemoglobinopathy prevention and control situation, including the global disease burden, the implementation of disease prevention programs, and successful prevention experiences, as well as treatment progress. Based on our analyses, we propose that a global joint effort can realize the challenging and significant goal of fully preventing new births with severe hemoglobinopathies by 2035.

The WHO announced the elimination of smallpox in 1980 and the elimination of wild poliovirus type 3 (which causes poliomyelitis) in 2019, and in 2020 set a goal of eliminating cervical cancer by 2030. Hemoglobinopathies, which affect a similar number of people and cause as many deaths as poliomyelitis and cervical cancer, can also be prevented and clinically cured. The impact of preventing hemoglobinopathies around the world would be as great as the eradication of smallpox and poliomyelitis, and like those accomplishments, it merits a joint effort from all of us.

Contents

Figures

Tables

List of Abbreviations

EFS, event-free survival.....28

GDP, Gross Domestic Product 32

GVHD, graft versus host disease 29

HSCT, hematopoietic stem cell transplantation.....11

HLA, human leukocyte antigen 11

OS, overall survival 28

POCT, point-of-care testing.....38

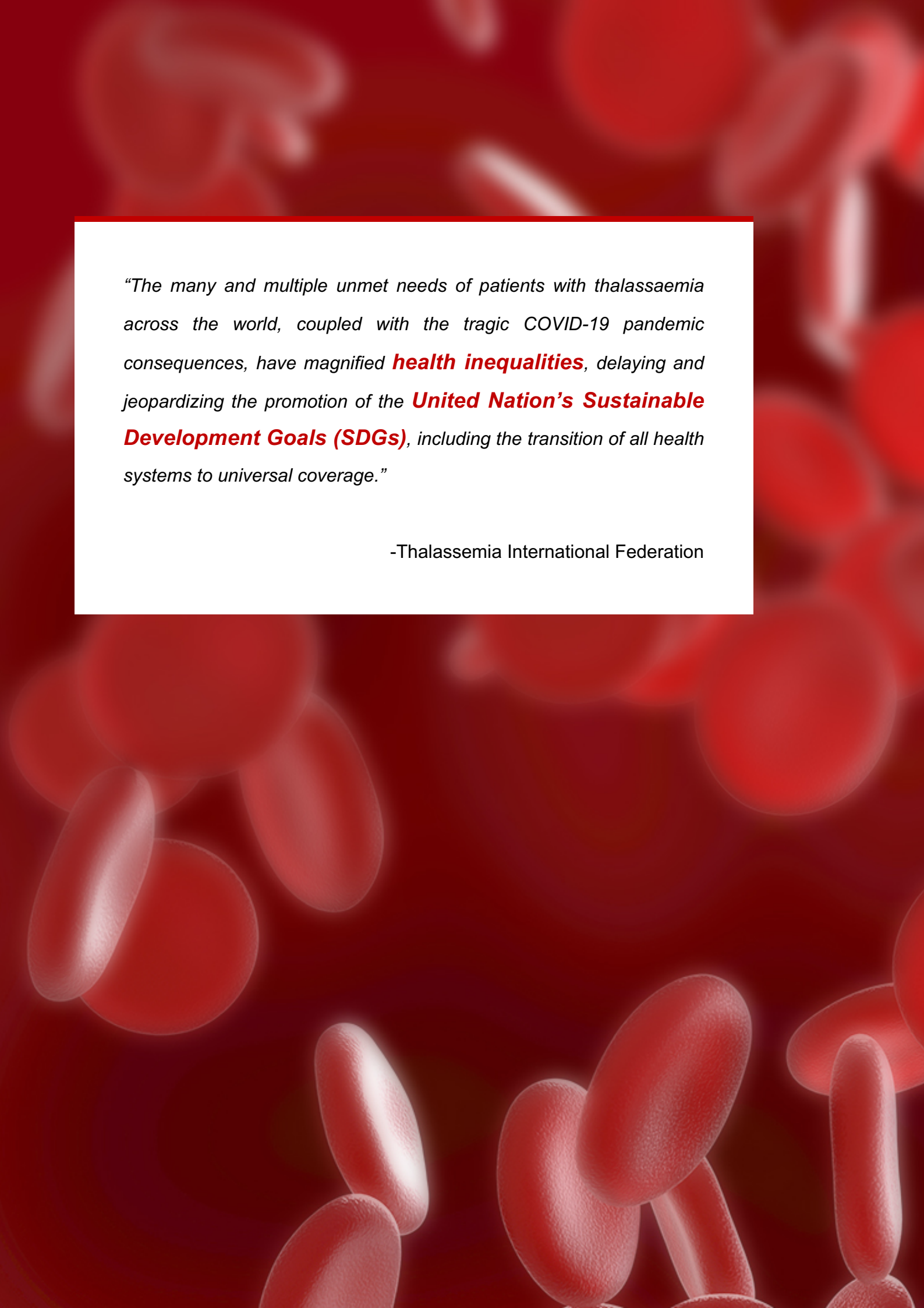
SCD, sickle cell disease 2

TSD, Tay-Sachs disease.....37

TIF, Thalassemia International Federation 2

TFS, thalassemia-free survival.....28

WHO, World Health Organization 2



"The many and multiple unmet needs of patients with thalassaemia across the world, coupled with the tragic COVID-19 pandemic consequences, have magnified ***health inequalities****, delaying and jeopardizing the promotion of the* ***United Nation's Sustainable Development Goals (SDGs)****, including the transition of all health systems to universal coverage."*

-Thalassemia International Federation

1. Background: Why is it necessary to prevent and control hemoglobinopathies globally?

Hemoglobinopathies are the most common monogenic hereditary diseases, affecting a large number of people around the world and causing serious consequences[1]. Hemoglobinopathies have a clear etiology, as well as clear prevention and control methods, and there are many examples of successful prevention and control practices. Cyprus[2], Italy[3], the UK[4], Iran[5], Singapore[6], Guangxi (China)[7] and many other countries and districts have successfully reduced the rate of severe hemoglobinopathies at birth with good prevention and control programs. These successes show that the prevention and control of hemoglobinopathies can be achieved in all countries, regardless of their financial status, when effective programs are implemented.

Hemoglobinopathies mainly consist of sickle cell disease (SCD) and thalassemia. There are other types of hemoglobinopathies such as HbE disease and HbC disease. Among newborns with hemoglobinopathies, 83 and 17% suffered from SCD and thalassemia[8], respectively (another report recorded 70 and 30% have SCD and thalassemia, respectively[9]). To highlight the importance of preventing and controlling SCD, SCD was recognized as a public health problem by the United Nations General Assembly in 2008[10]. The World Health Organization (WHO) has issued a strategy for SCD prevention in Africa in 2010[11] and summarized its implementation progress in 2020[12]. To prevent and control thalassemia, a WHO working group started laid down guidelines for the control of hemoglobin disorders in 1989[13]. The Thalassemia International Federation (TIF) published 'Prevention of Thalassemia and Other Hemoglobin Disorders', in 2003[14].

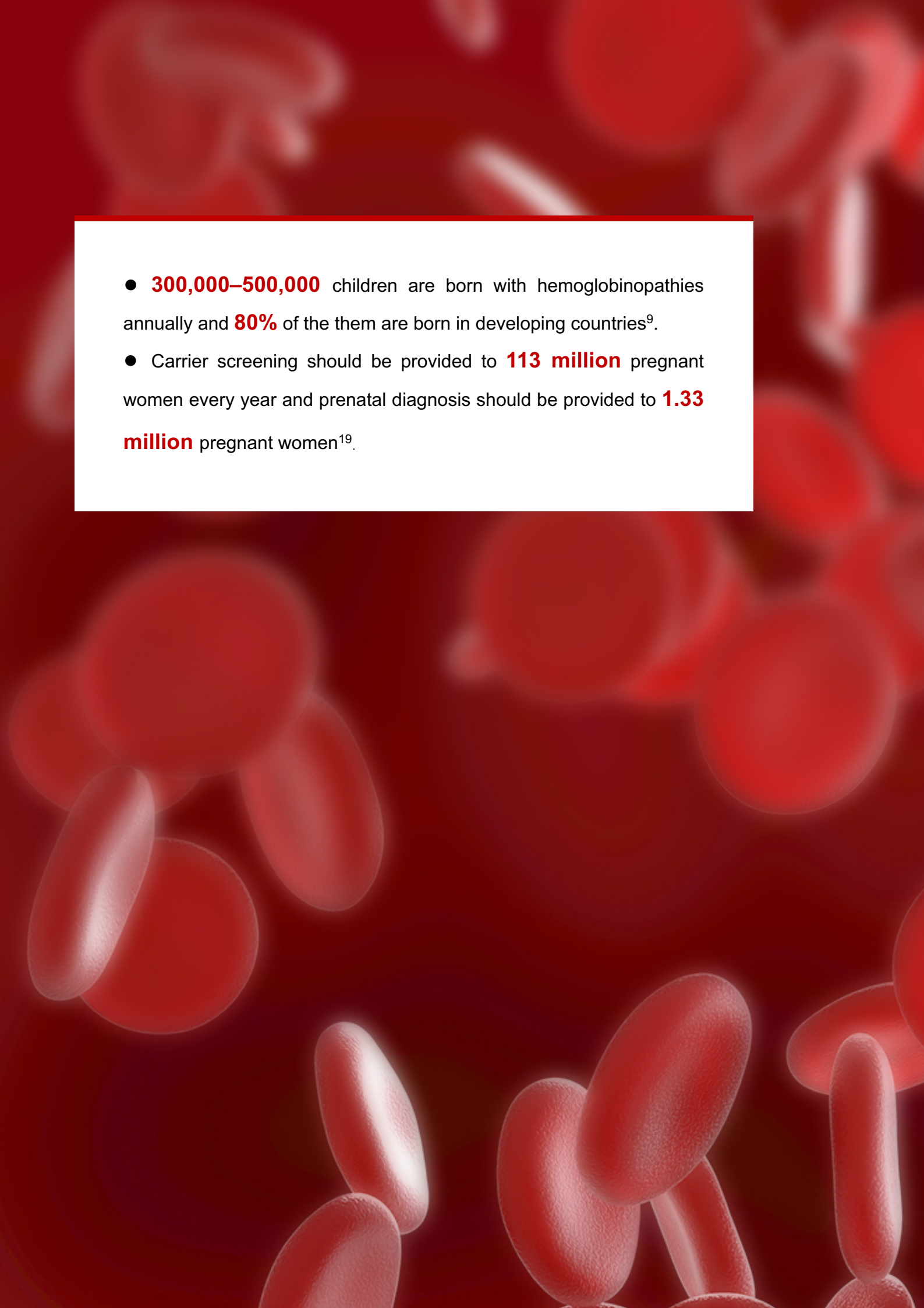
Despite these publications and calls to action, effective prevention and control measures have not been implemented on a large scale throughout the world. There are

still 300,000 to 500,000 children born with severe hemoglobinopathies every year[9]. Most patients suffering from hemoglobinopathies inhabit areas where medical resources are scarce, and so they cannot be treated effectively. The unequal distribution of medical resources has become one of the key factors hampering the global prevention and control of hemoglobinopathies. In low and middle-income countries, 50%–80% of children with SCD and 50,000 to 100,000 children with thalassemia die each year[9]. The continuing global COVID-19 pandemic has also undoubtedly exacerbated inequalities in medical resources. Therefore, the theme of this year's International Thalassemia Day (8th May 2021) is "Addressing Health Inequality Across the Global Thalassemia Community".

This report summarizes the global hemoglobinopathy prevention and control situation, including the global disease burden, the implementation of disease prevention programs, successful prevention experiences as well as treatment progress. It aims to bring more attention to these diseases around the world to accelerate the prevention and treatment of these detrimental genetic disorders. This goal is consistent with the United Nations 2030 agenda for sustainable development[15] (Table 1) and the global strategy for women, children and adolescent healthcare (2016–2030)[16].

Table 1 Hemoglobinopathy prevention assists the United Nations 2030 agenda for sustainable development[15]

Hemoglobinopathy prevention contributes to the following sustainable development goals	
Goal 1	End poverty in all its forms everywhere.
Goal 3	Ensure healthy lives and promote well-being for all at all ages **3.2** By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births **3.4** By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being
Goal 10	Reduce inequality within and among countries



- **300,000–500,000** children are born with hemoglobinopathies annually and **80%** of the them are born in developing countries[9].
- Carrier screening should be provided to **113 million** pregnant women every year and prenatal diagnosis should be provided to **1.33 million** pregnant women[19].

2. The global burden of hemoglobinopathies

2.1 The etiology and clinical manifestation of hemoglobinopathies

Hemoglobinopathies are genetic disorders caused by variants in globin genes. They mainly include SCD, thalassemia and other hemoglobinopathies. Individuals who carry only one pathogenic variant from one parent are usually healthy carriers and do not show symptoms. One must carry variations from both parents in the same gene to show symptoms of hemoglobinopathies. The clinical manifestations of SCD are chronic hemolytic anemia, small vessel occlusion, susceptibility to infection, and recurrent pain, which can all result in organ tissue damage (Figure 1)[17]. The clinical manifestations of severe thalassemia (including HbE-β thalassemia) are severe anemia, hepatosplenomegaly, and jaundice, and these are accompanied by developmental delays and other symptoms (Figure 2)[18]. Hemoglobinopathies are responsible for some of the most significant causes of early deaths worldwide[19].

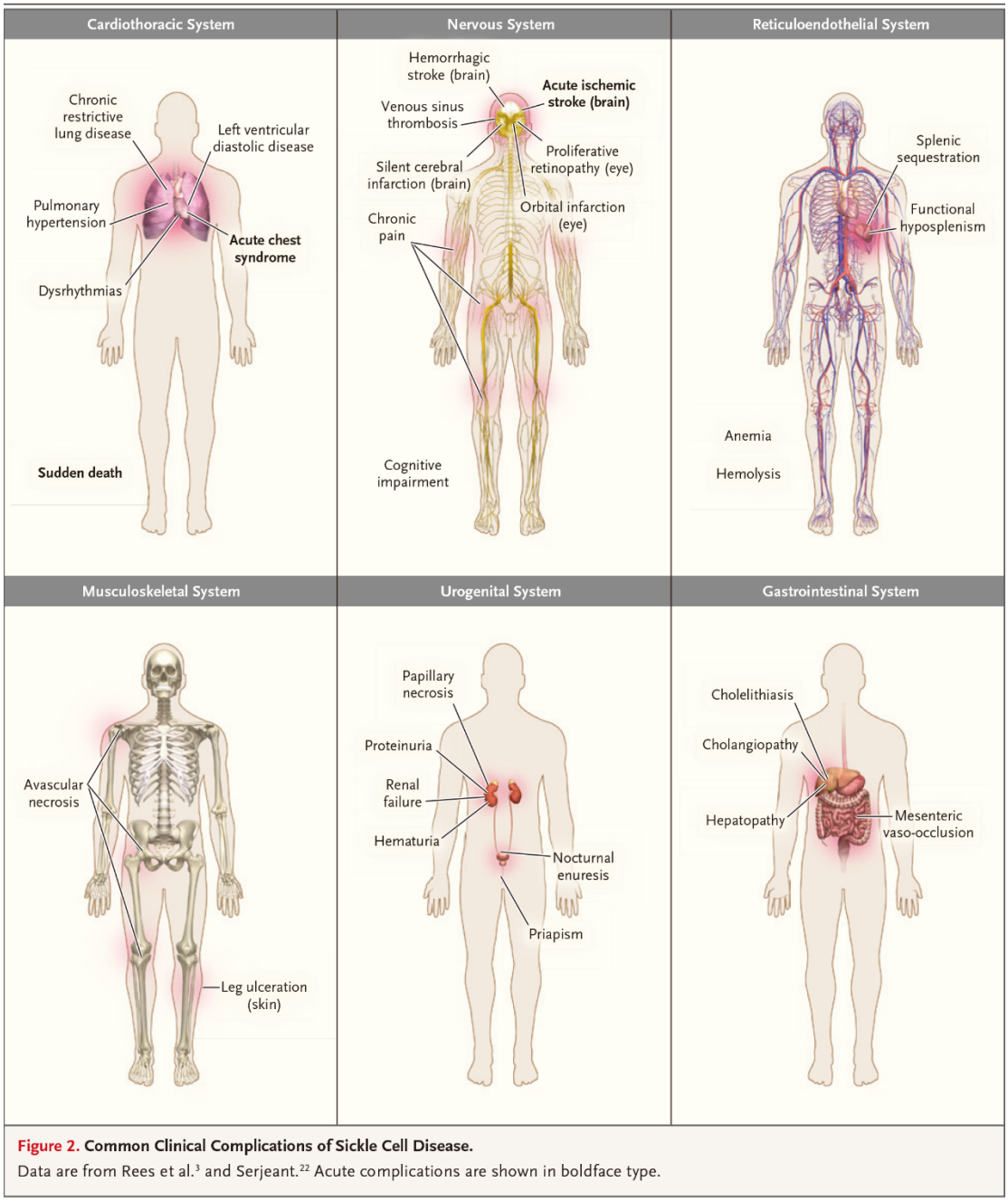


Figure 2. Common Clinical Complications of Sickle Cell Disease.
Data are from Rees et al.[3] and Serjeant.[22] Acute complications are shown in boldface type.

Figure 1 Complications of SCD (Figure 2, reference 17)

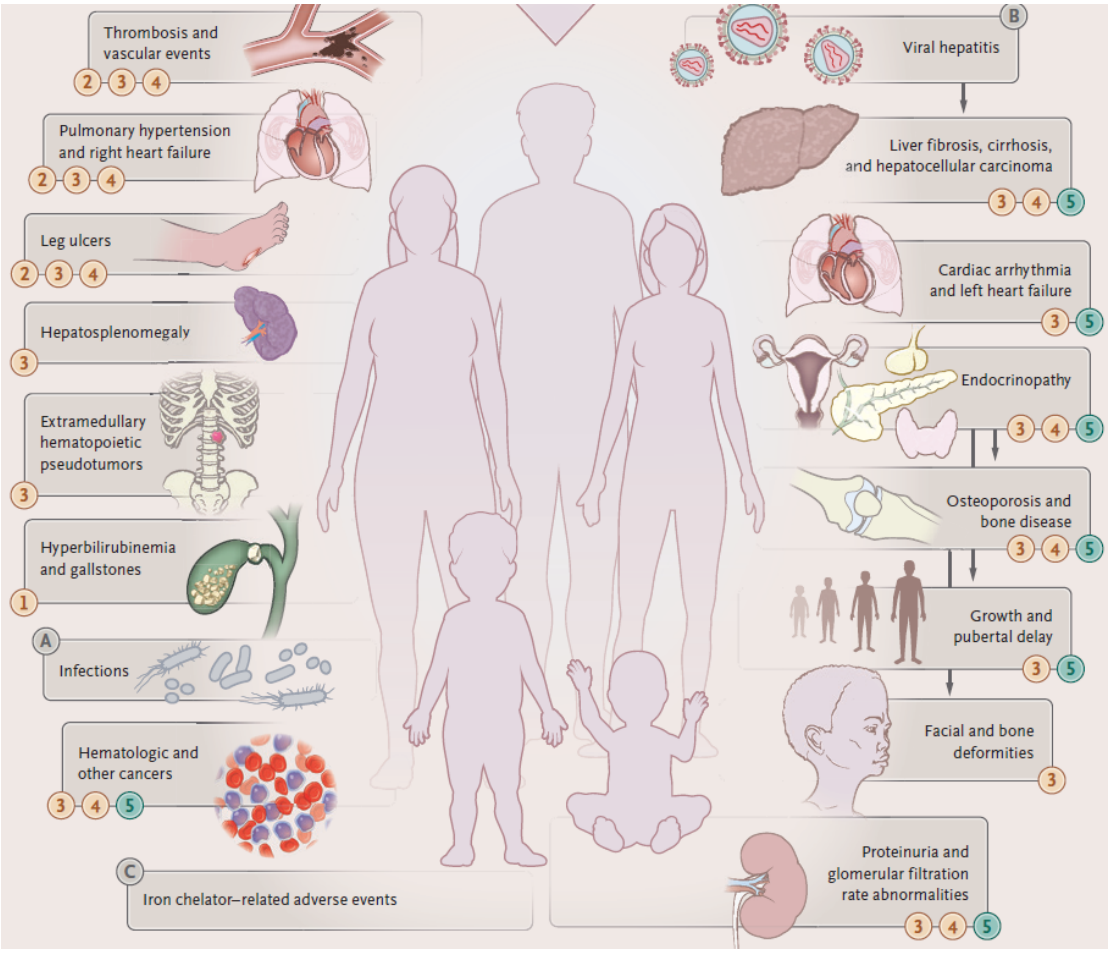


Figure 2 Complications of β-thalassemia (Figure 2, reference 18)

2.2 The global distribution of hemoglobinopathies

Around 5.2% of the global population carries an abnormal hemoglobin gene[19], and 300,000–500,000 children are born with hemoglobinopathies annually, 80% of whom are in developing countries[9]. Among newborns with hemoglobinopathy, 83% are born with SCD and 17% with thalassemia[8] (Figure 3–Figure 6). In low and middle-income countries, 50%–80% of children with SCD and 50,000 to 100,000 children with thalassemia die each year[9].

Hemoglobinopathies originated in tropical and subtropical regions of the world. Carriers of abnormal hemoglobin genes are more resistant to malaria, enabling the carrier frequency of abnormal globin genes to be increased in populations exposed to

malaria risk. Global migration then spreads these genes to other regions of the world. For example, 10% of the population of the USA belong to ethnic minorities who are at risk for hemoglobinopathies, while in north and west Europe, the proportion is 2%–9%. In some Southeast Asian countries, population migration may have increased the number of thalassemia newborns[20]. Of the world's 229 countries, 71% have a high incidence of hemoglobinopathies and these countries account for 89% of global annual births[21]. Some researchers have suggested that carrier screening should be provided to 113 million pregnant women and prenatal diagnosis should also be provided to 1.33 million pregnant women every year [19].

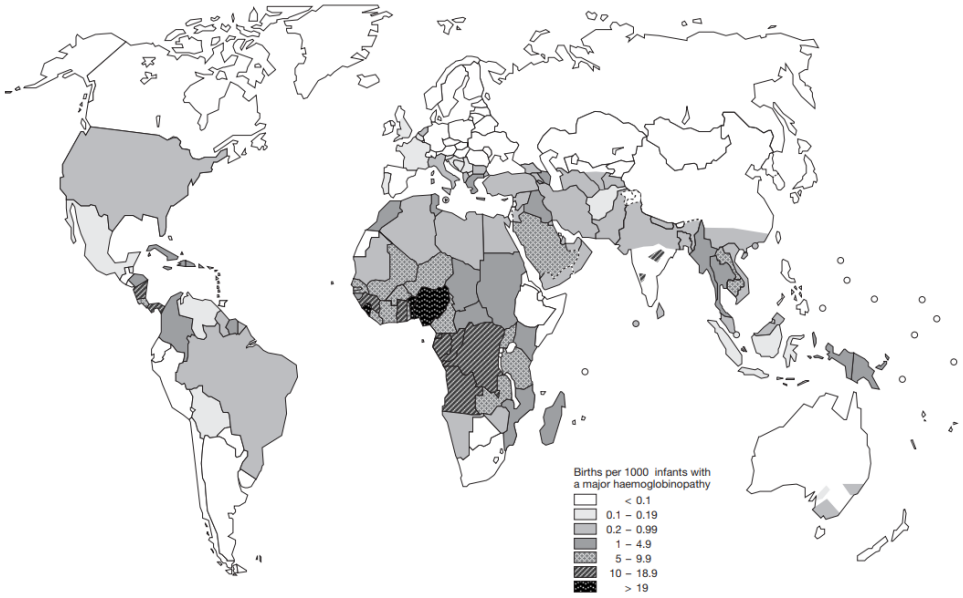


Figure 3 Global distribution of newborns with hemoglobinopathies (reference 22)

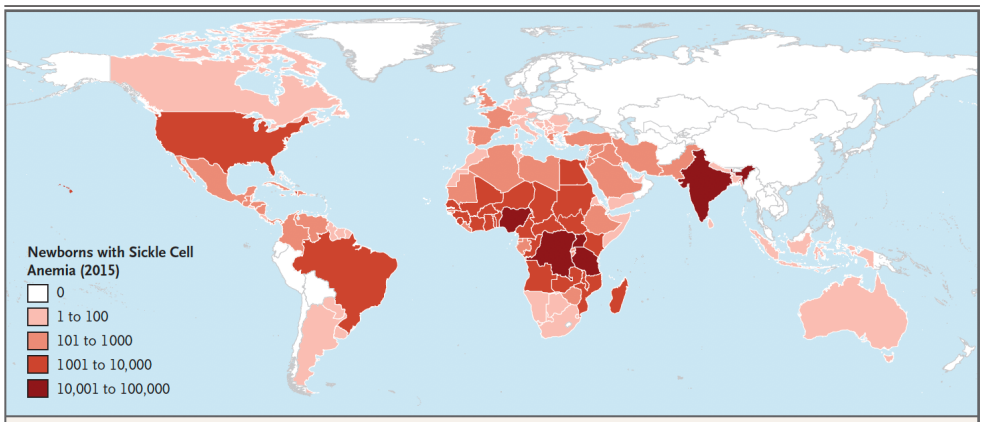


Figure 4 Global distribution of newborns with SCD (Figure 1, reference 17)

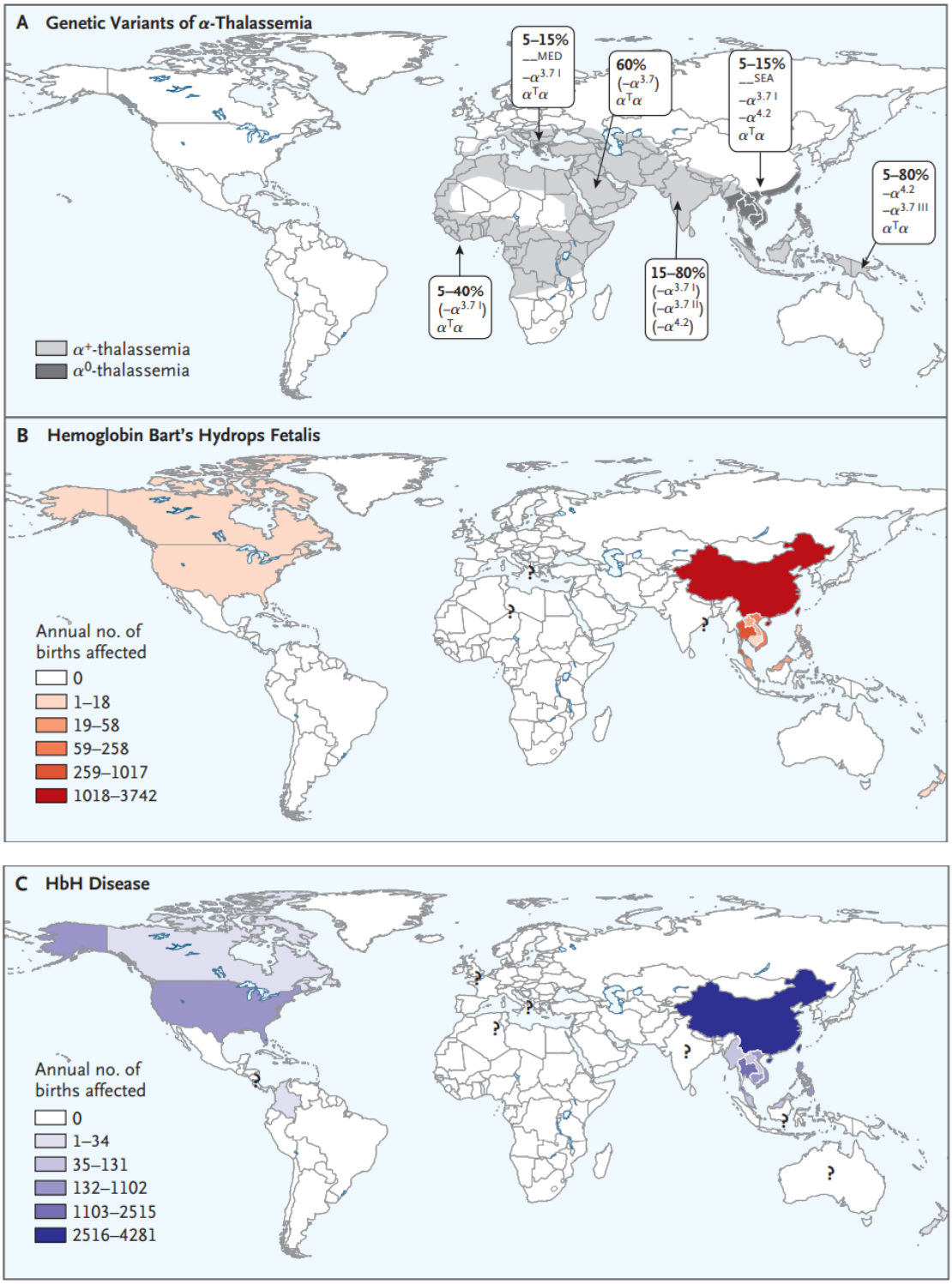


Figure 5 Global distribution of newborns with α-thalassemia (Figure 2, reference 23)

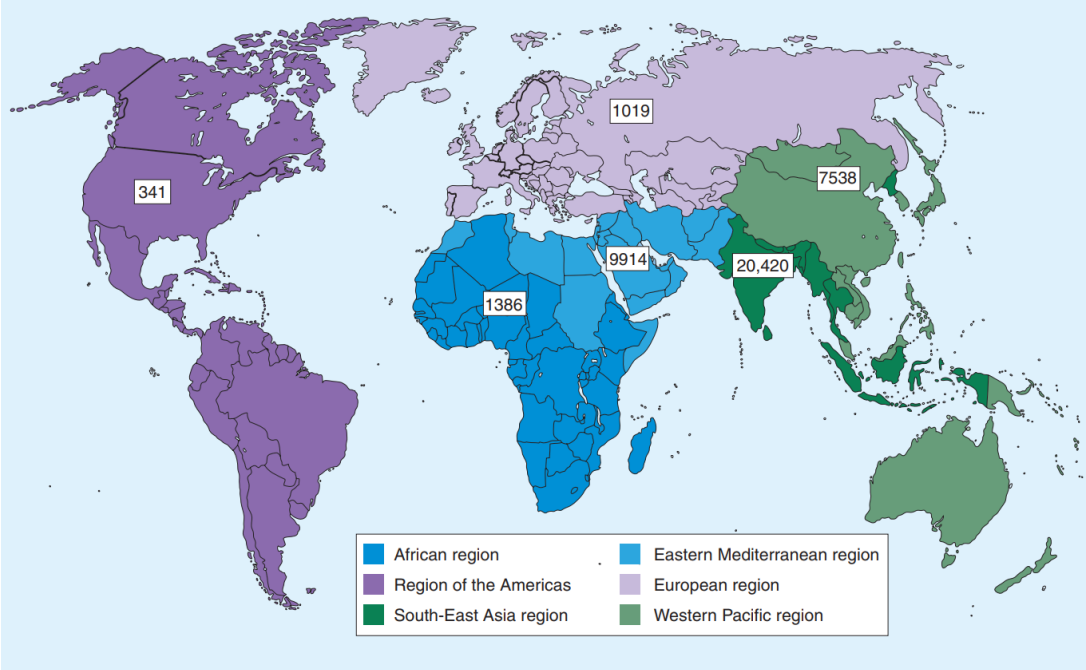


Figure 1. Estimated annual affected births of children with β-thalassemia.
These figures are from estimates calculated in [16].

Figure 6 Global distribution of newborns with β-thalassemia (Figure 1, reference 24)

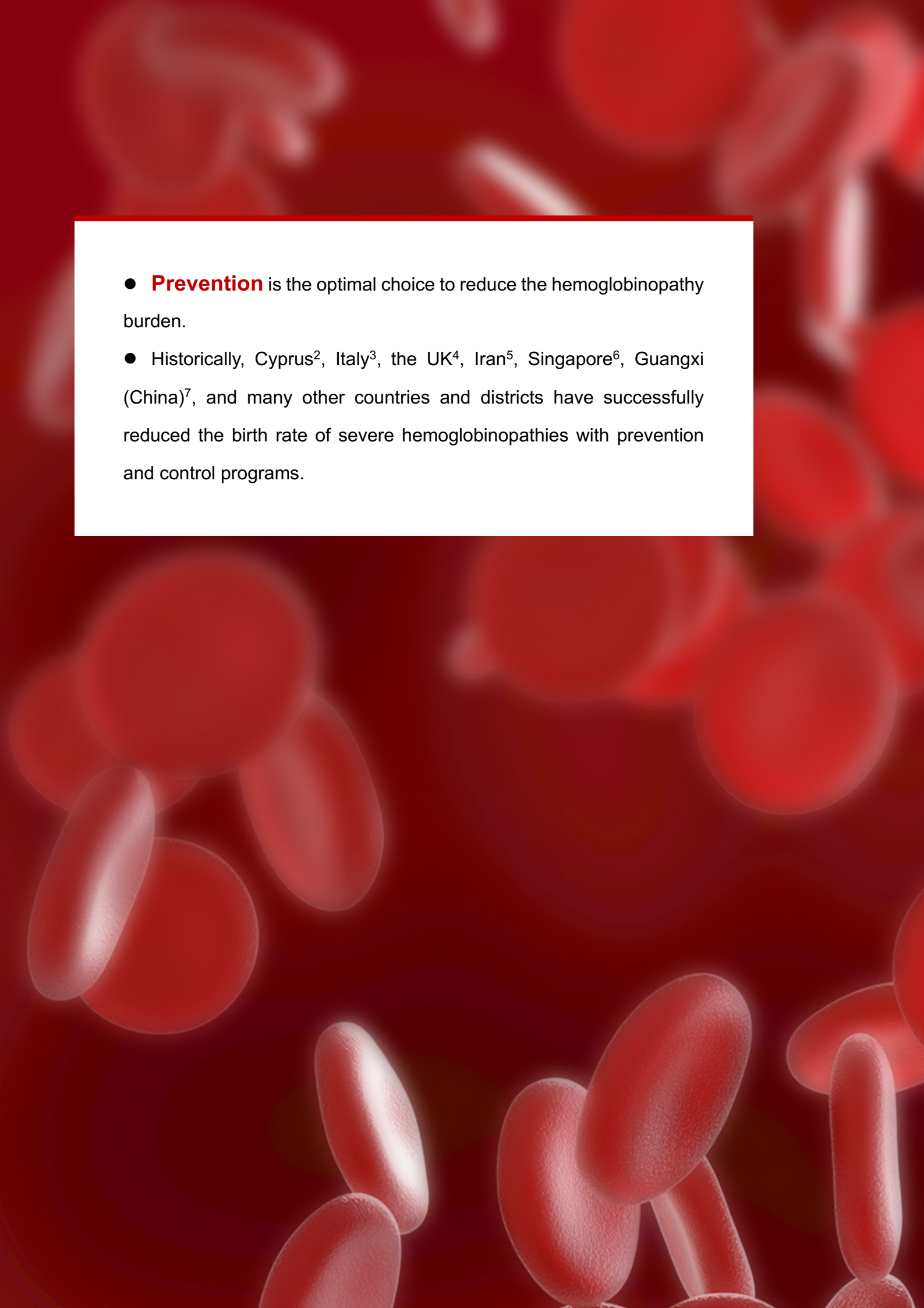
2.3 Prevention is the optimal choice to reduce the burden of hemoglobinopathies

There are 20–25 million SCD patients worldwide, and 50%–80% of SCD children in Africa would die during their first 5 years of life without effective treatment[25]. Currently, more than 90% of thalassemia children can survive to 16–20 years of age with standard treatment, and patients with optimal treatment can expect to live up to 50–60 years. However, the lifetime cost of treatment can reach up to around £800,000[26], which can be an enormous economic burden both individually and for society.

The clinical definitive treatments for hemoglobinopathies are hematopoietic stem cell transplantation (HSCT) and gene therapy. Transplanting hematopoietic stem cells from a human leukocyte antigen (HLA) matched healthy person to the patient can clinically cure the condition[27]. However, this therapy presents a risk of transplant failure

due to immunological rejection. In addition, the availability of transplants is far from sufficient to treat all patients. Recent studies have reported that gene therapy has successfully treated several hemoglobinopathy patients[28], but this approach will not be sufficient to meet the needs of all patients within a short time.

Therefore, prevention is the optimal choice in order to reduce the hemoglobinopathy burden.



- **Prevention** is the optimal choice to reduce the hemoglobinopathy burden.
- Historically, Cyprus[2], Italy[3], the UK[4], Iran[5], Singapore[6], Guangxi (China)[7], and many other countries and districts have successfully reduced the birth rate of severe hemoglobinopathies with prevention and control programs.

3. Global prevention of hemoglobinopathies

3.1 Global overview of hemoglobinopathy prevention

Prevention is the optimal choice to control hemoglobinopathies, and many studies have shown that the cost of prevention is much lower than the economic burden of the disease[29-34]. Prevention measures can vary to accommodate different countries, cultures, religions, and laws. There are three main approaches:

1) Reduce high-risk marriages through pre-marital screening to prevent the birth of affected newborns.

2) Prevent the birth of affected newborns through assisted reproductive technology and prenatal screening/diagnosis.

3) Early detection and treatment of affected newborns through neonatal screening, coupled with guidance for the next pregnancy.

Historically, Cyprus[2], Italy[3], the UK[4], Iran[5], Singapore[6], Guangxi (China)[7], and many other countries and districts have successfully reduced the birth rate of severe hemoglobinopathies with effective prevention and control programs.

Information from the WHO, national public health programs, and the academic literature was collected to summarize hemoglobinopathy prevention and control progress in different regions of the world in order to help guide the prevention of hemoglobinopathies. The prevention and control programs in several countries or regions are elaborated in detail in Table 2.

Table 2 Summary of hemoglobinopathy prevention and control effects in different countries

Country/ Region	Prevention method	Volunteer/ Compulsory	Range	Start-up time	Prevention and control outcome	Reduced neonatal morbidity	Disease	Ref
America								
Cuba	Prenatal screening	Volunteer	Nationwide	1983	Birth rate of SCD: decreased from 1/1,600 (1980s) to 1/5,000 (2018)	68%	SCD	35
Europe								
Greece	Prenatal, neonatal screening	Volunteer	Nationwide	1973	Hemoglobinopathy birth rate decreased by 90%	90%	α- thalassemia, β- thalassemia, SCD	36
UK	Prenatal, neonatal screening	Volunteer	Nationwide	2001	Hemoglobinopathy birth rate: decreased from 0.6/1,000 (2006) to 0.4/1,000 (2018)	33%	β- thalassemia, SCD	37
France	Pre-marital, neonatal screening	Volunteer	Partial areas	1978	Number of thalassemia newborns decreased from 18 (1971) to 2 (2001) (Marseille)	/	β- thalassemia, SCD	38
Spain	Neonatal screening	Compulsory	Nationwide	2003	Number of SCD newborns decreased from 42 (2007) to 5 (2015)	86%	SCD	39
Cyprus	Prenatal screening	Compulsory	Nationwide	1973	Number of neonatal patients decreased from 50-70 (1980) to 0-2 (1985)	100%	α- thalassemia, β- thalassemia	40,41
Sardinia Italy	Prenatal screening	Volunteer	Nationwide	1975	Hemoglobinopathy birth rate decreased from 1:250 (1975) to 1:4,000 (1990)	94%	β- thalassemia	42
Middle east								
Israel	Pre-marital, prenatal screening	Volunteer	Partial areas	1980	Number of β-thalassemia newborns: 22 (1987-1997) to 4 (2001-2011)	87%	β- thalassemia, SCD	34

Table 2 Summary of hemoglobinopathy prevention and control effects in different countries

Country/ Region	Prevention method	Volunteer/ Compulsory	Range	Start-up time	Prevention and control outcome	Reduced neonatal morbidity	Disease	Ref
Saudi Arabia	Pre-marital screening	Compulsory	Nationwide	2004	Rate of risk couples decreased from 2.14% (2005) to 1.13% (2009) and the marriage rate of risk couples decreased from 90% to 73%	/	β-thalassemia, SCD	43
Lebanon	Pre-marital screening	Compulsory	Nationwide	1994	Number of thalassemia newborns: 20 (1995) to 2 (2011)	90%	β- thalassemia	44
Turkey	prenatal screening	Volunteer	Partial areas	2003	Number of neonatal patients: 272 (2002) to 25 (2013)	90%	α- thalassemia, β- thalassemia, SCD	45
Iran	Pre-marital screening	Compulsory	Nationwide	1991 (Some areas), 1997 (nationwide)	Birth rate of β- thalassemia decreases 90.13% (2015)	90%	β-thalassemia	46
Asia								
Maldives	prenatal screening	Volunteer	Nationwide	1992	Predicted thalassemia newborns: 285 (1993-2007), actual newborns: 120, reduced 60%	60%	β-thalassemia, SCD	48
Singapore	prenatal screening	Volunteer	Nationwide	1997	Neonatal patients: 15-20 (1988) to 1 (2003)	92%	β-thalassemia	6
Guangxi (China)	Pre-marital, neonatal and prenatal screening	Volunteer	Autonomous region	2010	Incidence of fetal edema syndrome: 26.38/10,000 (2008) to 3.15/10,000 (2017)	88%	α-thalassemia, β-thalassemia	49

3.2 Hemoglobinopathy prevention in the Americas

Migration is responsible for the American distribution of hemoglobinopathies, which mainly consists of SCD.

The screening program for high-risk SCD couples launched in Virginia in 1970 was the world's first population screening of hemoglobinopathies[50]. In 1975, New York included SCD screening in its neonatal screening program, and in 2005 the United States included hemoglobinopathies in its national neonatal screening program[51,52]. Presently, Canada performs preconception and prenatal carrier screening program for couples from hemoglobinopathy high-risk areas[53].

National screening programs for hemoglobinopathies have also been established in several Latin American countries.

Cuba introduced a national prenatal screening program for hemoglobinopathies in 1983[54]. SCD was the most common genetic disease in Cuba, with a birth rate of 1/1,600[35] and 4,000 SCD patients nationwide in the early 1980s[55]. In 1983, Cuba initiated a national program of prenatal SCD screening and diagnosis, and termination of the pregnancy was offered to parents with affected fetuses[54]. In 1988, the coverage of prenatal screening and diagnosis in Cuba exceeded 90%. From 1995 to 2018, 98% of pregnant women in Cuba received hemoglobin electrophoresis. This program reduced 68% of the birth rate of SCD (from 1/1,600 in the 1980s to 1/5,000 in 2018) and extended the life expectancy of SCD patients by an average of 16 years[35]. Cuba's experience demonstrates that a middle-income country can successfully relieve the impact of genetic diseases by implementing a universal, public-funded primary healthcare program nationwide[35].

Brazil has the largest number of SCD patients in Latin America, with approximately 30,000 SCD patients and an annual SCD birth rate of 1/1,000[56]. In 2001, Brazil included SCD in their National Neonatal Screening Program[57]. Costa Rica is

another country that includes thalassemia and SCD screening in their National Neonatal Screening Program[58]. Colombia, Uruguay, and the Dominican Republic are undertaking pilot projects for neonatal hemoglobinopathy screening but these countries do not as yet have a national screening program[59,60]. Chile, Uruguay, Mexico, Argentina, Colombia, Paraguay, and Venezuela all have established national neonatal screening programs, but hemoglobinopathy screening is not yet included[58,60].

3.3 Hemoglobinopathy prevention in Africa

SCD accounts for the highest proportion of hemoglobinopathies in Africa. Globally, more than 400,000 children are born with SCD annually, 75% of which are in sub-Saharan Africa[61].

In 2010, a SCD strategy for the WHO African Region was proposed[11]. In 2020, the WHO reported the progress and assessment of this strategy in 26 Member States[12]. Below, we review the key points of the report.

Designated SCD units were established in all 23 Member States which had a high SCD burden. Most of the Member States (except for Burundi, Comoros, Mauritania, Senegal, and Sierra Leone) were able to integrate the strategy into their national health plans. However, the allocation of funds for this strategy varied significantly between Member States. For example, only eight Member States (Benin, Burkina Faso, Guinea, Liberia, Mali, Nigeria, Togo, and Zambia) allocated funding from their national budget for SCD health promotion, and only five Member States (Burkina Faso, Kenya, Liberia, Niger, and Nigeria) allocated funding for SCD screening. Only three Member States (Burkina Faso, Liberia, and Nigeria) allocated funding for the surveillance, monitoring and assessment of the strategy, and seven (Benin, Burkina Faso, Congo, Liberia, Mali, Nigeria, and Senegal) allocated funding for the capacity building of SCD prevention and management. Five Member States (Benin, Burkina Faso, Liberia, Mali, Togo, and Zambia) allocated funding for SCD-related research.

The purpose of this strategy was the successful implementation of nationwide SCD control programs in half of the high-burden countries. Newborn screening for SCD has been implemented in some regions of 12 Member States. Newborn screening is being performed in tertiary health facilities in most states except for Mali, the Democratic Republic of the Congo, Uganda, and Ghana. In these four states, the collection of the samples is performed by the healthcare system, and the samples are then all transported to tertiary facilities for newborn screening. To improve the early detection and control of SCD, the control program was integrated into other nationwide programs in some states. For example, the newborn SCD screening program was integrated into the HIV screening programs in Burkina Faso and Uganda. In the Democratic Republic of Congo, Gabon, Ghana, Guinea, the United Republic of Tanzania, and Uganda, the newborn SCD screening programs were integrated into the reproductive, maternal, newborn and child healthcare programs.

In summary, African countries adopt different prevention and control programs for SCD. However, due to insufficient allocation of funds by the Member States and lack of medical resources, progress in the implementation of this strategy was slow.

3.4 Hemoglobinopathy prevention in Europe

Immigration is increasing the number of hemoglobinopathy patients in Europe, especially with respect to SCD patients[62].

Europe is one of the pioneers to start hemoglobinopathy prevention and control programs. In the 1970s, Greece[63], Cyprus[64], and Sardinia (Italy)[3] implemented hemoglobinopathy prevention and control by pre-marital, pregestational, and prenatal screening. The UK was the first country in the world to introduce both prenatal and neonatal screening for hemoglobinopathies[65]. At present, France[66], Holland[67], Belgium[68], Malta[69], Portugal[70], and Spain[39,71] already conduct hemoglobinopathy screening. Although hemoglobinopathy occurs in Germany[72] and Sweden[73] as a result

of population migration, hemoglobinopathy screening programs have not been implemented in these two countries as yet.

The implementation of screening programs resulted in significant reductions in hemoglobinopathy birth rates (Table 2). The reduction in the annual rate of hemoglobinopathy in Cyprus, Sardinia (Italy), Greece, the UK, and Spain were 100%, 94%, 90%, 33%, and 86%, respectively.

The successful prevention and control experience of Cyprus has been used as a reference by many countries and regions around the world. Cyprus launched a thalassemia prevention and control program at the beginning of the 1970s. Thalassemia-related knowledge was disseminated through mass media, lectures, discussions, and school teachings. The compulsory screening was implemented nationwide through legal measures and by religious edicts[74]. In 1983, the Orthodox Archbishop of Cyprus declared that Cypriot citizens (Greek Cypriots) were required to provide a thalassemia test report before entering a church for marriage registration. Through a series of measures including carrier screening, genetic counseling, prenatal diagnosis, and pre-implantation diagnosis, remarkable prevention and control outcomes have been achieved. The thalassemia-major birth rate in Cyprus dropped from 50–70/year to 0–2/year[40,75]. In Northern Cyprus, only five babies were born with thalassemia major between 1991 and 2001[76] (Figure 7), and no babies with thalassemia were born between 2002 and 2007.

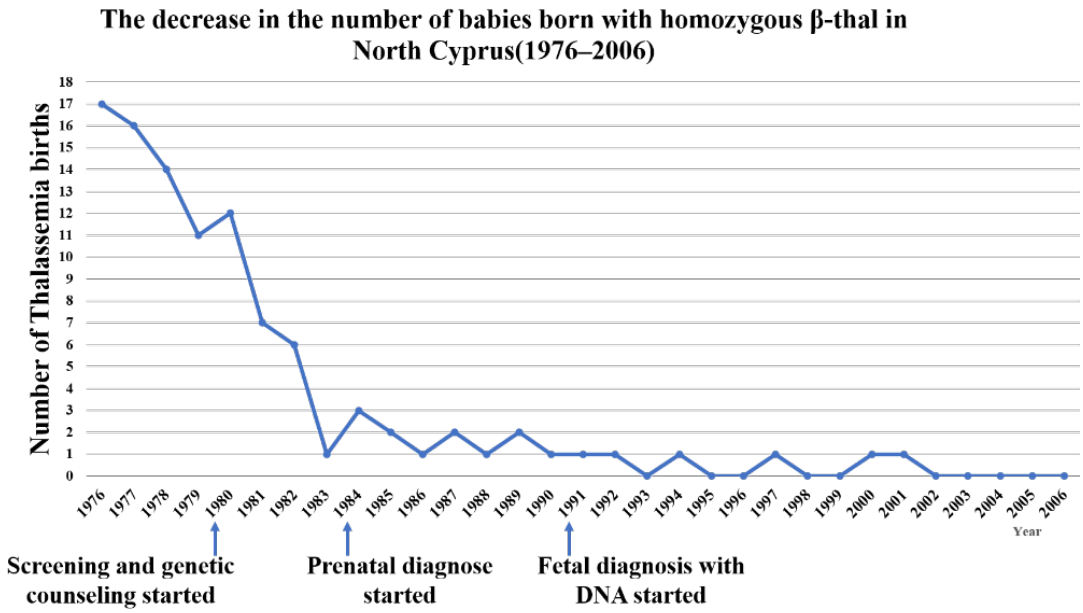


Figure 7 The number of thalassemia major births in Northern Cyprus, 1976-2006 (Figure 1, reference 76)

In the UK, hemoglobinopathy screening was introduced in some areas during the 1980s[77], and an SCD and thalassemia screening program through the National Health Service was established in 2001 and completely implemented in 2008[4]. The program consists of two parts: prenatal screening, genetic counseling and prenatal diagnosis for all pregnant women and their spouses as well as neonatal screening of all newborns[65,78]. With this program, the prenatal screening rate for SCD and thalassemia reached 99.3% in 2016–2017 financial year[79], and the neonatal screening rate reached 96.7% in 2017–2018 financial year [37]. After more than a decade of screening and prevention, the neonatal prevalence rate decreased from 0.6/1,000 (2005–2006 financial year) to 0.4/1,000 (2017–2018 financial year)[37].

In Greece, the carrier rate of β-thalassemia and SCD was about 8.0% and 1.5%[36], respectively. A national thalassemia prevention program was established in 1973, and the prenatal diagnosis was provided from 1977[80]. The prevention and control program was voluntary and free of charge. With public education through mass media, schools, and other social groups, public awareness of hemoglobinopathies was raised, and

screening services were also provided by dozens of blood transfusion organizations. More than 35,000 cases have been tested by 2011[63]. The average number of thalassemia babies born in Greece was four each year from 2003 to 2018, which represents a 90% reduction in the incidence of this disease[36].

3.5 Hemoglobinopathy prevention in the Middle East

The carrier rate of hemoglobinopathies varies greatly in the Middle East, with a carrier rate of 1–58% for α-thalassemia, 1–11% for β-thalassemia, and 0.3–30% for SCD[8]. In 1980, Israel pioneered the screening of hemoglobinopathies for at-risk groups. Over recent years, the list of countries and regions carrying out mandatory pre-marital screening and genetic counseling for hemoglobinopathies have gradually grown to include Lebanon[44], Iran[81], the Gaza Strip[82], Saudi Arabia[83], Jordan[84], and Kurdistan (Northern Iraq)[85].

In most countries and regions in the Middle East, pre-marital screening of hemoglobinopathies is mandatory. However, Turkey is an exception. Turkey provides voluntary pre-marital screening in 33 provinces in the Mediterranean and southern regions, where the incidence of hemoglobinopathies is high. Although screening is not mandatory, the proportion of people participating voluntarily greatly increased (from 30% in 2003, 81% in 2008[86], to 86% in 2013[45], resulting in a 90% reduction in the annual rate of newborns with hemoglobinopathies (272 hemoglobinopathy newborns in 2002, 23 in 2008[86], 25 in 2013[45]).

In Iran, the carrier rate of β-thalassemia is about 1.5–12%, and more than 1,000 children are born with thalassemia each year. The annual treatment cost for these children imposes a heavy burden on the national health system[87]. In 1995, Iran began to develop a nationwide thalassemia prevention program. In 1997, pre-marital thalassemia screening and genetic counseling were implemented nationwide. From 1996 to 2015, the number of children born annually with β-thalassemia decreased from

864 to 155 nationwide (Figure 8). In 2015, this program prevented the birth of 90% of children who would have had β-thalassemia[46]. This achievement was mainly attributed to the scientific prevention and control programs implemented by the Iranian government, the strengths of which presented as: 1) in order to avoid stigmatizing the female partner, the screening would first be carried out on the male member of a couple, and if he proves to be a thalassemia carrier, the female partner would then tested and 2) in 1997, a religious edict allowed abortion to become a special medical reason for terminating a pregnancy before 19 weeks if a fetus was prenatally diagnosed with β-thalassemia[88].

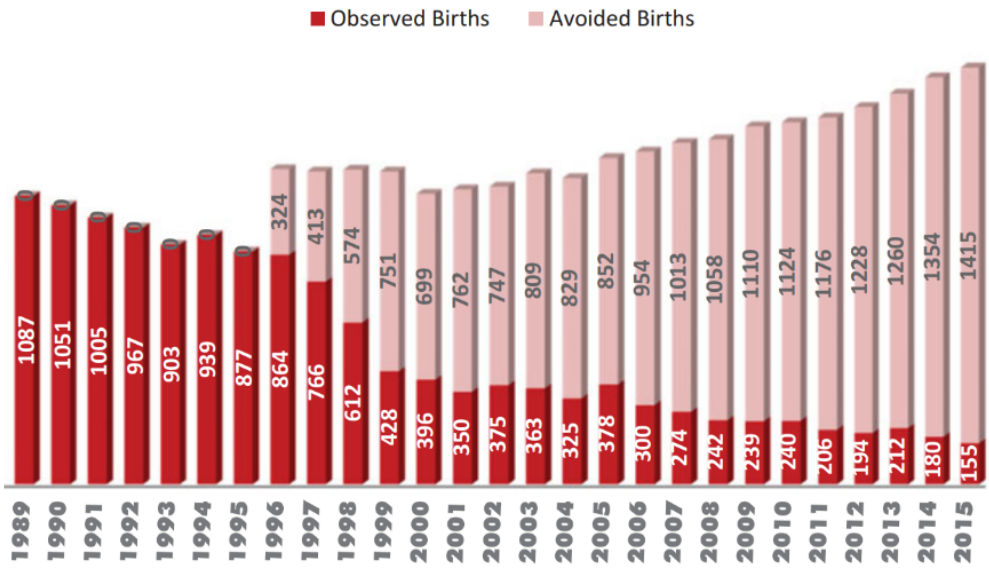


Figure 8 The number of β-thalassemia major births in Iran, 1989-2015 (Figure 1, reference 46)

The implementation of pre-marital screening in most Middle East countries and regions reduced the proportion of couples in which both partners were at-risk. For example, the proportion of marriages between at-risk couples in Saudi Arabia dropped from 90% in 2005 to 73% in 2009, and the number of couples with both partners at risk dropped from 2.14% to 1.13%[43]. In addition, in order to make the prevention of hemoglobinopathies more effective, education and screening were recommended to be

carried out earlier among school children rather than when couples were preparing for marriage in some areas[89,90].

3.6 Hemoglobinopathy prevention in Asia

High rates of thalassemia and HbE are observed in most countries in East and Southeast Asia. HbE is prevalent in Southeast Asia, with about 30 million Southeast Asians being HbE heterozygous and 1 million being HBE homozygous. India has a high incidence of both thalassemia, SCD, and HbE. However, there are almost no cases of hemoglobinopathies in Japan, South Korea, and North Korea.

Maldives[48,91] and Taiwan (China)[92] pioneered the screening of hemoglobinopathies in 1992 and 1993, respectively. National screening programs for thalassemia were also established in Sri Lanka (2006)[93], Thailand (1997)[93], Malaysia (2004)[94], Singapore (1997)[93], and the Philippines (2014)[95]. While the Philippines conducts neonatal screening, the other areas conduct the screening at the pre-marital or prenatal stages. Some states in India also deployed screening programs for hemoglobinopathies. In 2016, India's Ministry of Health & Family Welfare issued guidelines for the prevention and control of hemoglobinopathies in India[96]. High incidence rates of hemoglobinopathies also occurred in Bangladesh[97], Pakistan[98], and Nepal[8]. Despite research on the incidence of hemoglobinopathies, nationwide screening programs in these countries are still lacking. China has launched a pilot project to prevent and control thalassemia in 10 southern provinces (autonomous regions and municipalities directly under the central government)[99]. Large-scale thalassemia screening programs have been deployed in Guangdong[100], Guangxi[101], and Hainan[102].

The carrier rate of β-thalassemia in the Maldives is 16–18%, and it is one of the regions with the highest incidence of β-thalassemia in the world[91]. The first national thalassemia program in the Maldives was initiated by the Society for Health Education (SHE), a non-governmental organization, in 1992[91]. In 2012, a thalassemia prevention

law was enacted which required all the citizens of the Maldives to be tested before turning 18 years old. This test was a prerequisite for marriage. However, this rule was only fully implemented in the capital. Since the implementation of the screening program, the birth rate of children with thalassemia has dropped by over 60%[48]. However, according to a Ministry of Health report in 2013, a mean of 28 new cases was still being recorded annually over the previous decade. The rate of patients with thalassemia remains stable, and the carrier rates of β-thalassemia increased. This may be related to the high rate of marriage between relatives in Maldives[103]. Public awareness of thalassemia in the Maldives needs to be further strengthened, and more medical interventions should be provided[91].

Singapore has a carrier rate of nearly 3% for pathogenic thalassemia variants, and this poses a high risk of having children affected with severe thalassemia. In 1988, Singapore introduced a thalassemia screening program. In 1992, a national thalassemia registry was developed to provide screening, counseling, and prenatal diagnosis services for the high-risk population. In 1997, a national voluntary screening program was developed[21]. By 2003, the number of births with β-thalassemia was reduced from 15–20 cases per year to 1 case per year (Figure 9), demonstrating the successful implementation of the screening program[6,8].

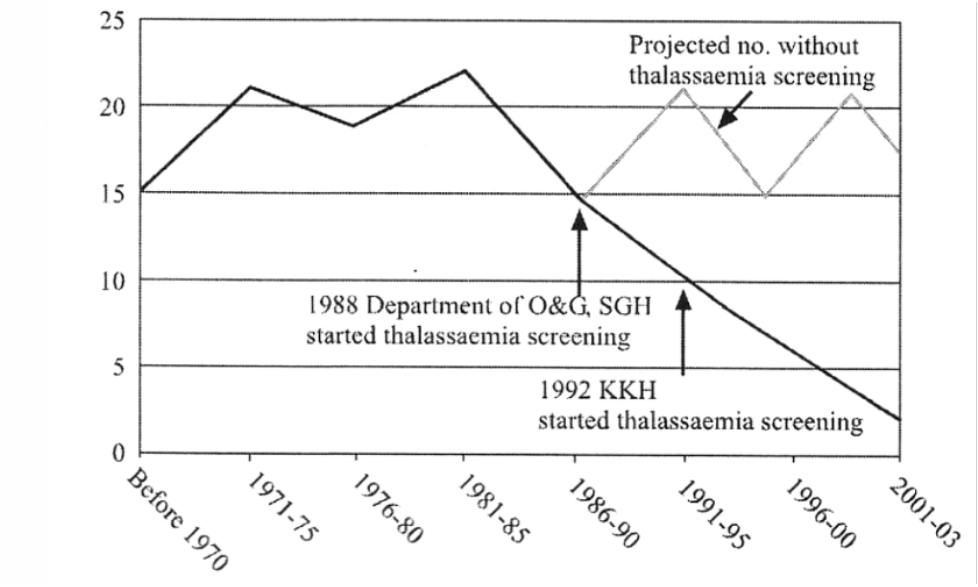
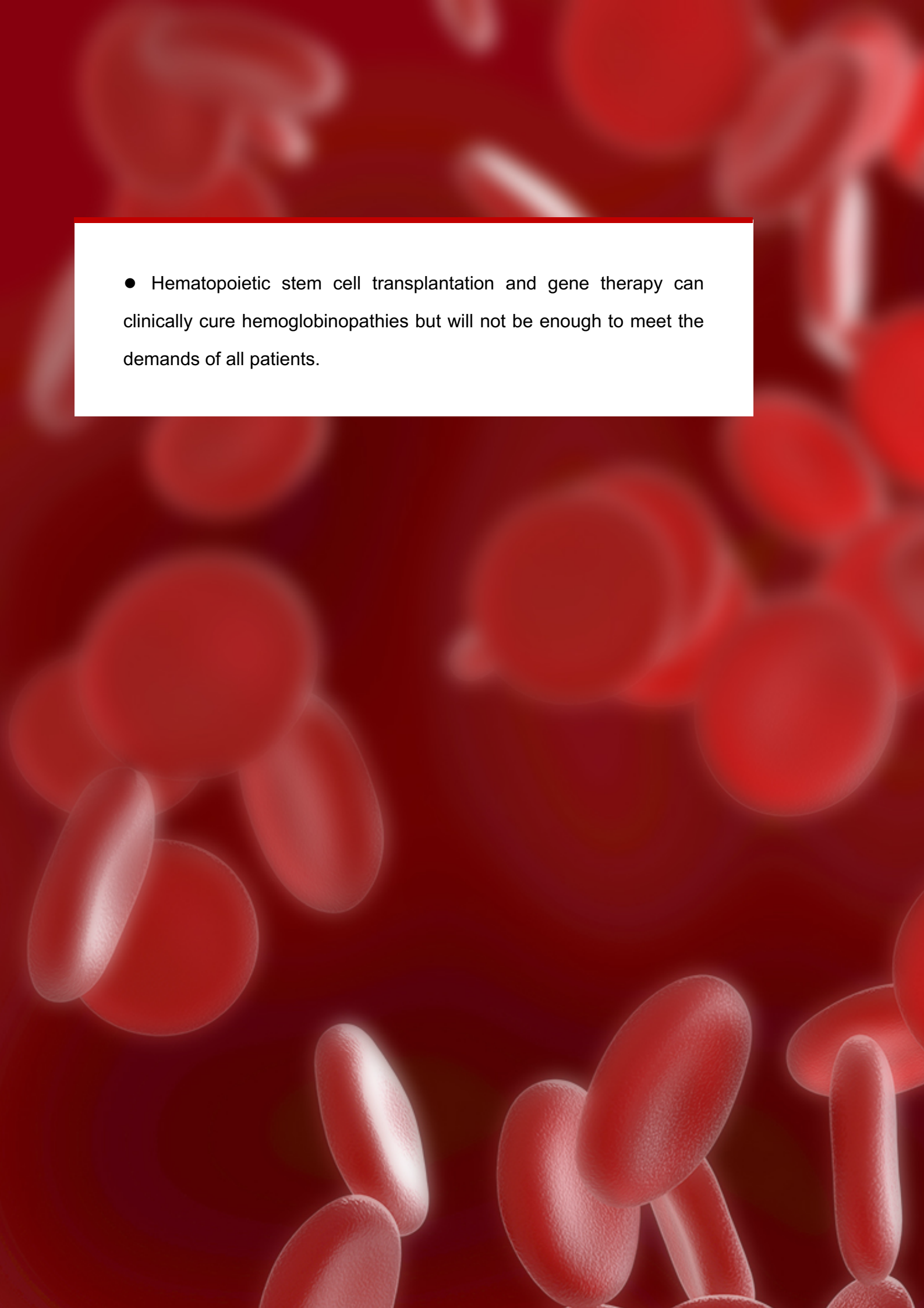


Figure 9 The number of β-thalassemia major births in Singapore, 1997-2003 (reference 6)

Thalassemia is one of the most serious genetic diseases in the Guangxi Province of China. The carrier rate in this area is as high as 24%. In order to effectively prevent and control thalassemia, the health authorities in Guangxi Province developed a thalassemia prevention program in 2010. The implementation of this program was remarkably successful. A total of 6,410,100 individuals completed pre-marital thalassemia screening, resulting in the detection of 13,775 fetuses with intermediate and severe thalassemia. Of these, 8,645 fetuses with major thalassemia received medical interventions. The percentage of fetuses undergoing medical interventions with major thalassemia increased from 65.51% in 2011 to 98.29% in 2017. In 2008, hydrops fetalis caused by thalassemia was the most common birth defect at birth (incidence rate of 26.38 per ten thousand). This dropped to the eighth most common birth defect in 2017 (incidence rate of 3.15 per ten thousand) by virtue of an 87.83% decrease in the incidence of thalassemia[7].



- Hematopoietic stem cell transplantation and gene therapy can clinically cure hemoglobinopathies but will not be enough to meet the demands of all patients.

4. Global treatment of hemoglobinopathies

4.1 Conventional therapy

There are two main types of hemoglobinopathies, thalassemia and SCD. The conventional treatment for thalassemia consists of blood transfusions and iron chelation therapy. Due to the large number of patients with SCD, providing blood transfusions for all SCD patients is difficult. Most SCD patients are treated with antibiotics and hydroxyapatite to relieve the clinical symptoms and pain, and to prevent various potential complications. With effective treatment, the lifespan of most patients can be over 50 years. However, lifetime treatment costs for each patient have been estimated to be over £800,000[26], which represents a major economic burden.

4.2 Hematopoietic stem cell transplantation

HSCT refers to the transplantation of hematopoietic stem cells from an HLA-matched healthy donor to the patient. HSCT is clinically curative for patients with transfusion-dependent β-thalassemia. In 1981, bone-marrow transplantation was used successfully for the treatment of a 14-month old child with β-thalassemia major for the first time. Since then, HSCT has been widely used in the treatment of patients with transfusion-dependent β-thalassemia. According to a 2018 report, 3,856 transfusion-dependent thalassemia and SCD patients in Europe received transplantation treatment between 2000 and 2017. The overall survival (OS) and event-free survival (EFS) for patients with SCD were 94% and 92%, and the OS and EFS for thalassemia patients were 90% and 84%, respectively[104]. In 2020, a multi-center study from China reported OS and thalassemia-free survival (TFS) rates of 94.7% and 93.3%, respectively, in 486

HSCTs[105]. Combined with previous reports, it was found that the corresponding transplant-related mortality for matched sibling donor HSCTs had dropped down to less than 5%. At present, transplantation outcomes are much improved with a long-term OS of over 90% and a TFS of over 80% being acheived[106]. HSCT from well-matched donors is limited, so in recent years, HLA-haploidentical HSCT has been widely used in the treatment of patients with major thalassemia[107]. However, a high incidence of graft failure and graft versus host disease (GVHD) may be caused by HSCT from mismatched unrelated donors. Due to the technical challenges as well as the intensive nursing requirements, together with the limited availability of transplants, the number of patients that can be treated with HSCT remains low.

4.3 Gene therapy

Gene therapy based on autologous HSCT does not have the above limitations and is a promising approach for the treatment of patients with hemoglobinopathies. Through genome editing of the patient's own hematopoietic stem cells, this method can correct and/or compensate for the malfunctioned gene. Since it is based on autologous hematopoietic stem cells, immunosuppression and GVHD can be avoided. Moreover, the transplant process and post-transplant care are less demanding. Gene therapy is currently mainly used to treat hemoglobinopathies with β globin deficiency, and these include transfusion-dependent β-thalassemia and SCD[108]. Many organizations are engaged in relevant clinical research, such as Bluebird Bio, CRISPR Therapeutic, Sangomo, CSL Behring, Orchard, Boston Children, San Raffaele University, EdiGene, BRL medicine, and BGI.

There are two main strategies being used for gene therapy of hemoglobinopathies and these are expression of vector-derived beta-globin (a vector-based gene-addition strategy) and reactivation of fetal hemoglobin by gene-editing techniques (a fetal hemoglobin reactivation strategy). The vector-based gene-addition strategy has a long

history in clinical applications and the treatment of hemoglobinopathies. It has been successfully used to treat nearly 100 patients with β-thalassemia and SCD over the last 10 years, with a success rate of over 90%[109]. So far, there have been no reports of deaths caused by anti-host immune rejection, and no carcinogenic risk was reported for this strategy[109,110]. In 2019, the first vector-based gene-addition product, Zynteglo, was approved for the treatment of patients with β-thalassemia in the European Union. In 2020, when Zynteglo was first commercially available in Germany, the price was more than €1.6 million. In 2021, Bluebird announced that it had decided to withdraw Zynteglo from the German market after failing to reach a reimbursement agreement for the drug.

The fetal hemoglobin reactivation strategy is based on the reactivation of fetal γ-globin by CRISPR-Cas9, zinc finger therapy, or TALEN. CRISPR-Cas9-based gene editing is an emerging technique enabling specific editing of the genome. The use of CRISPR-Cas9 to edit the enhancer region of BCL11 could restore the synthesis of γ-globin and reactivate the normal function of β-globin. Recently, this technique has been used in real clinical settings. In 2020, CRISPR Therapeutic reported the successful use of this technique to treat a patient with β-thalassemia and another with SCD[111]. China National Medical Products Administration approved a clinical trial of ET-01 (a product from EdiGene) in 2020[112]. BRL medicine has also initiated clinical trials[113,114].

In summary, the successful treatment of hemoglobinopathies requires the implementation of various strategies. We hope that advances in technology can further improve the treatment of hemoglobinopathy patients who underwent HSCT and gene therapy, as well as lowering the cost and improving the safety of treatment.

By **2035**, large-scale population control is expected to reduce the birth rate of children with severe hemoglobinopathies to less than **0.3 per 10,000**.

5. The goal of hemoglobinopathy prevention and control worldwide

Hemoglobinopathies can be prevented and clinically cured. For prevention and control of hemoglobinopathies worldwide, there are a few questions that need to be first considered. What should we do? What target should we aim for? When will we achieve this target? What experiences can we draw upon, and what are the challenges and opportunities ahead of us?

5.1 A large scale prevention and control program is key

Implementing a large-scale, population-level prevention, and control program is the key to the prevention of births with severe hemoglobinopathies. Our review of some programs that have been implemented shows that there is not a strong connection between a region's economic level and the successful implementation of a prevention program (Figure 10). With a (Gross Domestic Product) GDP per capita of less than 5,000 USD, Cyprus, and Iran have all successfully reduced the prevalence of affected newborns by about 90%. Today, the per capita GDP of many countries and regions exceeds this level. The key factor to prevent and control hemoglobinopathies is to integrate the prevention and control program into the national healthcare plans and to provide a conducive atmosphere for the whole society to participate in these endeavors[11].

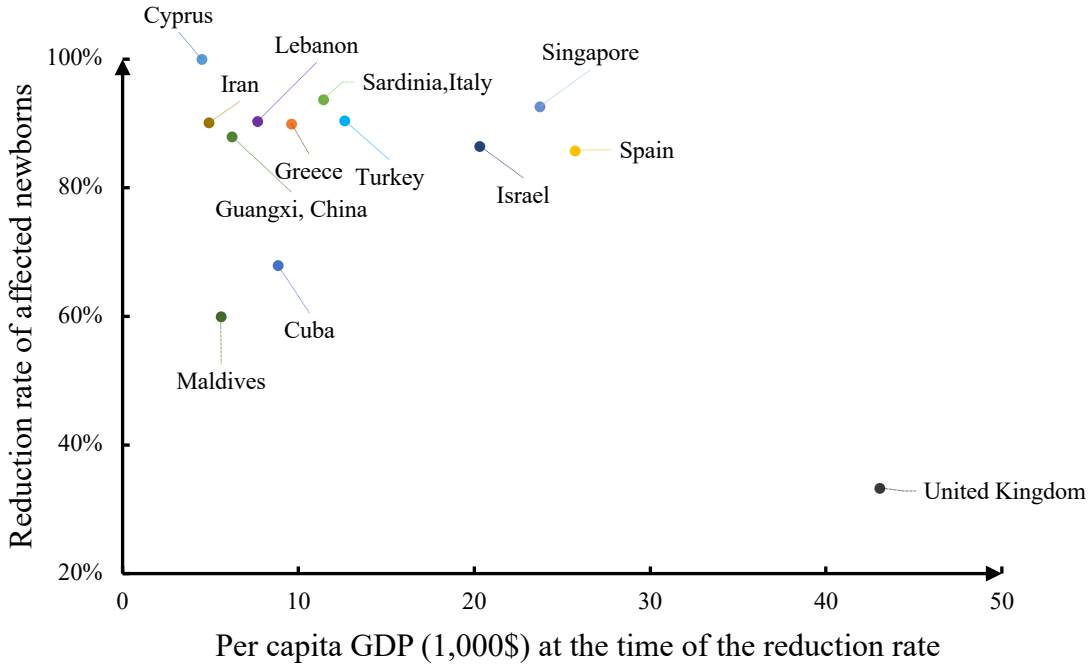


Figure 10 The reduction rate of affected newborns and per capita GDP for 14 countries and regions.

Note: Please refer to the fourth column of Table 3 for the detailed reduction rates. Per capita GDP for the 14 countries and regions was derived from reference 115.

Table 3 Results of the implementation of prevention and control programs in various countries

Countries/regions	Rate of affected newborns before the program (per ten thousand)[a]	Rate of affected newborns after the program (per ten thousand)[b]	Reduction rate of affected newborns	Program duration
Cuba	6.25	2.00	68%	35 years (1983-2018)
Greece	/	0.37	90%	17 years (1973-1990）
United Kingdom	6.00	4.00	33%	17 years (2001-2018）
Spain	0.84	0.12	86%	12 years (2003-2015）
Cyprus	45.12	0.00	100%	12 years (1973-1985）
Sardinia, Italy	40.00	2.50	94%	15 years (1975-1990）
Israel	0.23	0.03	87%	21 years (1980-2001）
Lebanon	2.27	0.22	90%	17 years (1994-2011）
Turkey	2.01	0.19	90%	10 years (2003-2013）
Iran	/	1.03	90%	24 years (1991-2015）
Maldives	/	/	60%	15 years (1992-2007）
Singapore	2.89	0.21	92%	15 years (1988-2003）
Guangxi, China	26.38 (fetal hydrops)	3.15 (fetal hydrops)	88%	9 years (2008-2017）

[a、b] Rate of affected newborns = The number of affected newborns / The number of newborns. The number of affected newborns was derived from table Table 2. The number of newborns was derived from Our World in Data [116].

In addition, the cost of implementing a prevention and control program is much lower than that of treating patients who would develop hemoglobinopathies[29-34]. As mentioned above, globally implementing prevention and control programs for hemoglobinopathies via national healthcare plans is a sensible economic strategy and provides high returns on the initial investment made.

5.2 Aim for a birth rate of affected children of less than 0.3 per 10,000

There are two elements involved in the implementation of prevention and control strategies for hemoglobinopathies worldwide: firstly, the prevention of births with severe hemoglobinopathies and secondly, the successful treatment of all existing patients with hemoglobinopathies.

The prevention of births with severe hemoglobinopathies is a key factor for the successful prevention and control of hemoglobinopathies worldwide. The rate of affected newborns is less than 0.3 per 10,000 in Cyprus, Spain, Israel, Lebanon, Turkey, and Singapore. Although the prevalence of affected newborns in Greece and Sardinia has been reduced by more than 90%, it is still above 1 per 10,000 (Table 3). The implementation of a prevention and control program greatly reduced the rate of affected children in the Guangxi Province of China. In 2018, a new program was initiated to achieve a birth rate of fewer than 0.3 children with severe thalassemia per 10,000 births in Guangxi Province[7]. Due to different cultural and religious practices and other factors in different regions, the decision of how to handle potential births of affected children can vary greatly. Each country should understand the benefits of implementing a prevention program and then establish one based on its own national conditions.

The second element is the successful treatment of all transfusion-dependent hemoglobinopathies. HSCT and gene therapy can provide a clinical cure for existing patients and affected fetuses. However, HSCT faces the problem that only a small number of patients can receive transplants in time. The lack of suitable donors and the shortage of transplant facilities can cause patients to miss the optimal age for transplantation. Gene therapy uses self-modified hematopoietic stem cells and therefore does not require a donor and has few limitations in terms of transplantation age.

However, as this technology is still in its initial stages, its long-term safety and effectiveness still need to be evaluated.

5.3 Aim for success by 2035

It took between 10 and 17 years (12 years for Cyprus, 17 years for Greece, 15 years for Italy Sardinia, 17 years for Lebanon, 15 years for Singapore, 10 years for Turkey, and 12 years for Spain) for 7 countries/regions to reduce the prevalence of affected newborns by about 90% (Table 3). The birth rate of affected children has been reduced to less than 0.3 per 10,000 in Cyprus, Spain, Lebanon, Turkey, and Singapore. If this is taken as the target for the successful prevention of newborns with severe hemoglobinopathies, we believe that countries could reach this goal in around 15 years. This time period is challenging but achievable although it will require a joint effort from everyone involved.

The WHO plays a pivotal role in global public health prevention and control. The eradication of smallpox and poliomyelitis greatly depends on efforts from the WHO. In 2020, the elimination of cervical cancer was stated as a clear goal by the WHO[117]. If the prevention of newborns with severe hemoglobinopathies was to be included in the work goals of the WHO, this would provide a strong impetus for the prevention of hemoglobinopathies, and more countries would integrate the prevention programs into their national healthcare plans before 2025. Within 10 years of implementation, the percentage of participants in prevention and control programs could exceed 90% in most countries and regions, making it possible to achieve the goal of preventing births with hemoglobinopathies by 2035.

The successful treatment of all existing patients with hemoglobinopathies is heavily reliant on advances in treatment technologies. At present, the number of clinically cured patients is still very small. A report from China showed that only 5.7% of patients with thalassemia had undergone transplantation treatment. The conditions

of only 19% of the remaining patients were suitable for transplantation[118]. We hope that advances in technology can help further improve the treatment of patients with hemoglobinopathies.

5.4 Experiences we can draw upon as well as challenges and opportunities ahead

From the successful prevention and control of hemoglobinopathies in Cyprus and some other countries, we can see that there are key factors for the successful implementation of the program, including public health education, large-scale screening, and diagnosis as well as genetic counseling[87]. There are also some differences between the countries and regions which have successfully implemented a prevention program. Different countries and regions may choose different screening methods, including school, pre-marital, prenatal, and newborn screening regimens. The impact of religious beliefs and legal systems (for instance, the legality of abortions in a particular country) can also be significant factors. The screening can be mandatory or voluntary. The program can be successfully implemented in both developed and developing countries. Thus, every country can find a model that can be used as a reference to develop its own prevention and control programs.

One worthwhile comparison is the prevention and control of Tay-Sachs disease (TSD) in the Jewish population. TSD is an inherited disease that causes mental retardation, blindness, paralysis, and eventually death. The disease is 90 times more common in Ashkenazi Jews than non-Jews[119]. In 1971, the Jewish community carried out TSD carrier screening through synagogues and other social organizations. By 2003, none of the ten TSD children born in North America came from Jewish families. By 2004, there was no newborn in Israel with TSD[120]. As a result of an effective prevention program, TSD was almost completely controlled within the Jewish population.

The main challenge in preventing hemoglobinopathies worldwide is dealing with SCD, which accounts for 83% of hemoglobinopathies. Most of the patients with SCD are in Africa and India, where nationwide prevention and control plans have not been established. The lack of medical facilities in these areas makes it more challenging to establish nationwide prevention and control programs.

Developments in science and technology can provide new opportunities to prevent hemoglobinopathies worldwide. For example, firstly, the internet makes the knowledge required for successful prevention and control more accessible to the general public and secondly, advances in technology make the detection of hemoglobinopathies more convenient and faster. In addition, point-of-care testing (POCT) is a convenient strategy which requires no professional training. Using POCT to detect SCD is more suitable for low- and middle-income countries[121]. Genetic screening based on massively parallel sequencing is high-throughput[122,123] and thus suitable for large-scale population screening. A recent study in Yunnan, China showed that the input/output ratio when using this type of screening technology was as high as 1:5.21[124]. Preimplantation genetic diagnosis technology provides an option for couples who do not want to terminate a pregnancy and want a healthy baby. We envisage that advances in technology and clinical applications will help to achieve the prevention of hemoglobinopathies worldwide.

SCD and thalassemia were first named in 1910 and 1925, respectively[125,126]. At the end of the last century, there was no newborn baby with severe thalassemia in Cyprus[40]. However, today there are 300,000–500,000 affected children born yearly worldwide[9]. All the world's population share the same fate. Hemoglobinopathies can be prevented and clinically cured. This should not be done in only a few areas but should be accomplished globally.

The WHO announced that both smallpox and wild poliovirus type 3 (poliomyelitis) were respectively eradicated worldwide in 1980 and 2019[127,128]. Historically, 300 million people died of smallpox. Poliomyelitis affects mainly children under 5 years of

age, and causes irreversible paralysis in 1 in 200 infections, of whom 5–10% die due to immobilization of their breathing muscles. Cases due to wild poliovirus have decreased by over 99% since 1988, from an estimated 350 000 cases then, to 33 reported cases in 2018[129]. Before the implementation of the poliomyelitis eradication program, 17,500 to 35,000 people died because of the disease every year[129].

Birth defects with a genetic etiology account for nearly 8 million babies worldwide each year[130], and up to 6% of these are born with hemoglobinopathies[9]. Diseases caused by viral infections can be eradicated or controlled by vaccines. Can disease-causing genetic defects be also prevented or controlled? Since the completion of the Human Genome Project in April 2003, improvements in the awareness of genetic technology as well as the understanding of global prevention and control programs in public health, have provided us with the chance to eliminate hemoglobinopathies. The impact of preventing hemoglobinopathies would be as great as the eradication of smallpox and poliomyelitis, and like those accomplishments, it merits a joint effort from all of us.

6. Motives and acknowledgements

For thousands of years, considerable and continuous efforts have been made in the pursuit of human health which has been greatly improved by advances in healthcare technology and public awareness of prevention and control efforts. In 1980 and 2019, the WHO declared the respective eradication of smallpox and Wild Poliovirus type 3 (poliomyelitis). In 2020, the WHO developed a global strategy to eliminate cervical cancer by 2030.

Hemoglobinopathies, which affect a similar number of people and cause as many deaths as poliomyelitis and cervical cancer, can also be prevented and clinically cured. By the end of the last century, there were no newborns with severe thalassemia in Cyprus. However, today there are still 300,000–500,000 affected children born every year in the world. Our motive in writing this report is to raise awareness regarding hemoglobinopathies around the world. We hope that hemoglobinopathy prevention and control programs can be integrated into national healthcare programs and these will act as an impetus for reducing the number of cases of hemoglobinopathies around the world.

We would like to sincerely thank all our colleagues for the valuable information in their published articles, and especially acknowledge Frédéric B. Piel, David J. Weatherall, Subarna Chakravorty, Moira C Dick, Martin H. Steinberg, David C. Rees, H.W. Goonasekera, C.S. Paththinige, V.H.W. Dissanayake for the valuable reference information in their review articles. We gratefully acknowledge Xiangmin Xu, Baosheng Zhu, Xinhua Zhang, Dongzhu Lei, Yan Chen, Sixi Liu and Lai Kuan Teh for offering valuable suggestions to improve this report. We thank our BGI colleges Yifan Bai, Yujie Hu, Ning Li, Yuehua Luo, Qian Mao, Ye Yin for their constructive work with respect to the writing and design of the manuscript. We also thank Sedeer el-Showk and Dev Sooranna for English language editing of the manuscript. We sincerely thank all colleagues around the world for their great efforts in the prevention and control

of hemoglobinopathies. We hope that this overview will help us all move forward to achieve complete eradication of hemoglobinopathies worldwide.

7. Author list

Lipei Liu, Shiping Chen, Lijie Song, Chaoyang Xie, Cheng Yang, Xiaoxiao Huo, Zhihong Qiao, Huishuang Chen, Yan Sun, Wenqian Zhang, Chao Liu, Jun Sun, Zhiyu Peng

Correspondence to:

Zhiyu Peng, Chief Product Officer, BGI Genomics Co., Ltd

Email: pengzhiyu@bgi.com

8. References

1. Piel FB. The Present and Future Global Burden of the Inherited Disorders of Hemoglobin. *Hematology/oncology clinics of North America* 2016; **30**(2): 327-41.
2. Kountouris P, Kousiappa I, Papasavva T, et al. The molecular spectrum and distribution of haemoglobinopathies in Cyprus: a 20-year retrospective study. *Scientific reports* 2016; **6**: 26371.
3. Cao A, Furbetta M, Galanello R, et al. Prevention of homozygous beta-thalassemia by carrier screening and prenatal diagnosis in Sardinia. *Am J Hum Genet* 1981; **33**(4): 592-605.
4. Weil LG, Charlton MR, Coppinger C, Daniel Y, Streetly A. Sickle cell disease and thalassaemia antenatal screening programme in England over 10 years: a review from 2007/2008 to 2016/2017. *Journal of clinical pathology* 2020; **73**(4): 183-90.
5. Rahimi Z. Genetic epidemiology, hematological and clinical features of hemoglobinopathies in Iran. *Biomed Res Int* 2013; **2013**: 803487.
6. Bioethics Advisory Committee Singapore. Genetic Testing and Genetic Research: C-6 Prenatal Genetic Screening and Testing. *https://www.bioethics-singapore.gov.sg/files/publications/reports/genetic-testing-and-genetic-research-annex-c-6.pdf*.
7. 广西壮族自治区人民政府办公厅关于印发广西严重类型地中海贫血胎儿零出生计划实施方案的通知. *广西壮族自治区人民政府公报* 2018; (14): 2-5.
8. Goonasekera HW, Paththinige CS, Dissanayake VHW. Population Screening for Hemoglobinopathies. *Annual review of genomics and human genetics* 2018; **19**: 355-80.
9. WHO TIF Meeting on the Management of Haemoglobin Disorders, World Health Organization, Thalassaemia International Federation. Management of

haemoglobin disorders: report of a joint WHO-TIF meeting, Nicosia, Cyprus, 16-18 November 2007. Geneva: World Health Organization; 2008.

10. United Nations. 63/237. Recognition of sickle-cell anaemia as a public health problem-Resolution adopted by the General Assembly on 22 December 2008.
11. Regional Committee for Africa. Sickle-Cell Disease: a strategy for the WHO African Region, 2010.
12. Regional Committee for Africa. Progress in the implementation of the African Region sickle-cell strategy 2010–2020: information document. Brazzaville: World Health Organization. Regional Office for Africa; 2020.
13. World Health Organization Working Group on Haemoglobinopathies. Guidelines for the Control of Haemoglobin Disorders. *the VIth Anual Meeting of the WHO Working Group on Haemoglobinopathies held in Sardinia* 1989.
14. Thalassaemia International Federation. Prevention of Thalassaemias and Other Haemoglobin Disorders, Vol. 1. 2003.
15. United Nations Transforming our world: The 2030 agenda for sustainable development. 2015.
16. World Health Organization. Global strategy for women's, children's and adolescents' health (2016-2030). 2016.
17. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. *New England Journal of Medicine* 2017; **376**(16): 1561-73.
18. Taher AT, Musallam KM, Cappellini MD. β-Thalassemias. *New England Journal of Medicine* 2021; **384**(8): 727-43.
19. Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bulletin of the World Health Organization* 2008; **86**(6): 480-7.
20. Angastiniotis M, Modell B, Englezos P, Boulyjenkov V. Prevention and control of haemoglobinopathies. *Bulletin of the World Health Organization* 1995; **73**(3): 375-86.

21. Chakravorty S, Dick MC. Antenatal screening for haemoglobinopathies: current status, barriers and ethics. *British journal of haematology* 2019; **187**(4): 431-40.
22. World Health Organisation. *www.who.int/genomics/public/Maphaemoglobin.pdf*
23. Piel FB, Weatherall DJ. The α-thalassemias. *The New England journal of medicine* 2014; **371**(20): 1908-16.
24. Colah R, Gorakshakar A, Nadkarni A. Global burden, distribution and prevention of β-thalassemias and hemoglobin E disorders. *Expert Rev Hematol* 2010; **3**(1): 103-17.
25. Mulumba LL, Wilson L. Sickle cell disease among children in Africa: An integrative literature review and global recommendations. *International Journal of Africa Nursing Sciences* 2015; **3**: 56-64.
26. Karnon J, Zeuner D, Brown J, Ades AE, Wonke B, Modell B. Lifetime treatment costs of β-thalassaemia major. *Clinical & Laboratory Haematology* 1999; **21**(6): 377-85.
27. Lucarelli G, Isgrò A, Sodani P, Gaziev J. Hematopoietic stem cell transplantation in thalassemia and sickle cell anemia. *Cold Spring Harb Perspect Med* 2012; **2**(5): a011825.
28. Rai P, Malik P. Gene therapy for hemoglobin disorders - a mini-review. *Journal of rare diseases research & treatment* 2016; **1**(2): 25-31.
29. Ostrowsky JT, Lippman A, Scriver CR. Cost-benefit analysis of a thalassemia disease prevention program. *American journal of public health* 1985; **75**(7): 732-6.
30. Mutar MT, Hameed MM. Thalassemia Prevention Program in Iraq: Cost Effectiveness and Applicability Assessment. 2020; **1**(1).
31. Ghotbi N, Tsukatani T. An economic review of the national screening policy to prevent thalassemia major in Iran. *Discussion Paper No562* 2002.

32. Ginsberg G, Tulchinsky T, Filon D, Goldfarb A, Abramov L, Rachmilevitz EA. Cost-benefit analysis of a national thalassaemia prevention programme in Israel. *Journal of medical screening* 1998; **5**(3): 120-6.
33. Ahmadnezhad E, Sepehrvand N, Jahani FF, et al. Evaluation and cost analysis of national health policy of thalassaemia screening in west-azerbaijan province of iran. *International journal of preventive medicine* 2012; **3**(10): 687-92.
34. Koren A, Profeta L, Zalman L, et al. Prevention of β Thalassemia in Northern Israel - a Cost-Benefit Analysis. *Mediterranean journal of hematology and infectious diseases* 2014; **6**(1): e2014012.
35. Marcheco-Teruel B. Sickle Cell Anemia in Cuba: Prevention and Management, 1982-2018. *MEDICC review* 2019; **21**(4): 34-8.
36. Theodoridou S, Prapas N, Balassopoulou A, et al. Efficacy of the National Thalassaemia and Sickle Cell Disease Prevention Programme in Northern Greece: 15-Year Experience, Practice and Policy Gaps for Natives and Migrants. *Hemoglobin* 2018; **42**(4): 257-63.
37. NHS Sickle Cell and Thalassaemia Screening Programme. NHS Sickle Cell and Thalassaemia Screening Programme Data report 2017 to 2018.
38. Lena-Russo D, Badens C, Aubinaud M, et al. Outcome of a school screening programme for carriers of haemoglobin disease. *Journal of medical screening* 2002; **9**(2): 67-9.
39. Cela E, Bellón JM, de la Cruz M, et al. National registry of hemoglobinopathies in Spain (REPHem). *Pediatric blood & cancer* 2017; **64**(7).
40. Angastiniotis M, Petrou M, Loukopoulos D, et al. The Prevention of Thalassemia Revisited: A Historical and Ethical Perspective by the Thalassemia International Federation. *Hemoglobin* 2021: 1-13.
41. Angastiniotis M, Federation TI. Thalassemia control: the example of Cyprus. *https://thalassaemia.org.cy/wp-content/uploads/2018/05/Thalassaemia-Control-in-Cyprus-Dr-Michael-Angastiniotis.pdf*

42. Cao A, Rosatelli MC, Galanello R. Control of beta-thalassaemia by carrier screening, genetic counselling and prenatal diagnosis: the Sardinian experience. *Ciba Foundation symposium* 1996; **197**: 137-51; discussion 51-5.
43. Gosadi IM. National screening programs in Saudi Arabia: Overview, outcomes, and effectiveness. *Journal of Infection and Public Health* 2019; **12**(5): 608-14.
44. Abi Saad M, Haddad AG, Alam ES, et al. Preventing thalassemia in Lebanon: successes and challenges in a developing country. *Hemoglobin* 2014; **38**(5): 308-11.
45. Canatan D, Delibas S. Report on Ten Years' Experience of Premarital Hemoglobinopathy Screening at a Center in Antalya, Southern Turkey. *Hemoglobin* 2016; **40**(4): 273-6.
46. Hadipour Dehshal M, Tabrizi Namini M, Hantoushzadeh R, Yousefi Darestani S. β-Thalassemia in Iran: Things Everyone Needs to Know About This Disease. *Hemoglobin* 2019; **43**(3): 166-73.
47. Premawardhana AP, Mudiyanse R, De Silva ST, et al. A nationwide survey of hospital-based thalassemia patients and standards of care and a preliminary assessment of the national prevention program in Sri Lanka. *PloS one* 2019; **14**(8): e0220852.
48. Firdous N, Gibbons S, Modell B. Falling prevalence of beta-thalassaemia and eradication of malaria in the Maldives. *J Community Genet* 2011; **2**(3): 173-89.
49. 中国妇幼健康事业发展报告(2019)(一). *中国妇幼卫生杂志* 2019; **10**(05): 1-8.
50. Florence N-C, Scott RB. Genetic Counseling in Sickle Cell Anemia: Experiences with Couples at Risk. *Public Health Reports (1974-)* 1988; **103**(2): 174-8.
51. Therrell BL, Adams J. Newborn screening in North America. *Journal of inherited metabolic disease* 2007; **30**(4): 447-65.
52. Newborn screening: toward a uniform screening panel and system--executive summary. *Pediatrics* 2006; **117**(5 Pt 2): S296-307.

53. Wilson RD, De Bie I, Armour CM, et al. Joint SOGC–CCMG Opinion for Reproductive Genetic Carrier Screening: An Update for All Canadian Providers of Maternity and Reproductive Healthcare in the Era of Direct-to-Consumer Testing. *Journal of Obstetrics and Gynaecology Canada* 2016; **38**(8): 742-62.e3.
54. Granda H, Gispert S, Dorticos A, et al. Cuban programme for prevention of sickle cell disease. *The Lancet* 1991; **337**(8734): 152-3.
55. Aguila JD, Zamora MC, Fernández OA, Jiménez LP, Vicente OM, Alvarez IV. Comprehensive care for patients with sickle cell disease in Cuba. *Haematologica* 2008; **93**(1): e20.
56. Huttle A, Maestre GE, Lantigua R, Green NS. Sickle cell in sickle cell disease in Latin America and the United States. *Pediatric blood & cancer* 2015; **62**(7): 1131-6.
57. de Castro Lobo CL, Ballas SK, Domingos ACB, et al. Newborn screening program for hemoglobinopathies in Rio de Janeiro, Brazil. *Pediatric blood & cancer* 2014; **61**(1): 34-9.
58. Borrajo GJ. Newborn screening in Latin America at the beginning of the 21st century. *Journal of inherited metabolic disease* 2007; **30**(4): 466-81.
59. Echeverry-Coral SJ, Colmenares-Mejía CC, Yepes-Molina ZX, Martínez-Nieto O, Isaza-Ruget MA. Hemoglobinopathy detection through an institutional neonatal screening program in Colombia. *Jornal Brasileiro de Patologia e Medicina Laboratorial* 2016; **52**: 299-306.
60. Queiruga G. Neonatal screening - its importance and impact in Latin America. *eJIFCC* 2015; **26**(4): 326-31.
61. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. *PLoS medicine* 2013; **10**(7): e1001484.

62. Modell B, Darlison M, Birgens H, et al. Epidemiology of haemoglobin disorders in Europe: an overview. *Scandinavian journal of clinical and laboratory investigation* 2007; **67**(1): 39-69.
63. Loukopoulos D. Haemoglobinopathies in Greece: prevention programme over the past 35 years. *Indian J Med Res* 2011; **134**(4): 572-6.
64. Angastiniotis MA, Hadjiminas MG. Prevention of thalassaemia in Cyprus. *Lancet (London, England)* 1981; **1**(8216): 369-71.
65. NHS Sickle Cell and Thalassaemia Screening Programme. NHS Sickle Cell and Thalassaemia Screening Programme: standards for linked Antenatal and Newborn Screening Programme.
66. Aguilar Martinez P, Angastiniotis M, Eleftheriou A, et al. Haemoglobinopathies in Europe: health & migration policy perspectives. *Orphanet journal of rare diseases* 2014; **9**: 97.
67. Health Council of the Netherlands. Preconception care: a good beginning. 2007.
68. Lê PQ, Ferster A, Dedeken L, et al. Neonatal screening improves sickle cell disease clinical outcome in Belgium. *Journal of medical screening* 2018; **25**(2): 57-63.
69. Felice A, Galdies R, Cassar W, et al. An Update of Beta-Thalassaemia Carrier Screening in Malta; 2006.
70. Martins MC, Olim G, Melo J, Magalhães HA, Rodrigues MO. Hereditary anaemias in Portugal: epidemiology, public health significance, and control. *Journal of medical genetics* 1993; **30**(3): 235-9.
71. Mañú Pereira M, Corrons JL. Neonatal haemoglobinopathy screening in Spain. *Journal of clinical pathology* 2009; **62**(1): 22-5.
72. Gramer G, Okun JG, Hoffmann GF. 23rd Annual Meeting of the German Society for Newborn Screening (Deutsche Gesellschaft für Neugeborenenscreening, DGNS). *International journal of neonatal screening* 2016; **2**(3): 7.

73. Hemminki K, Li X, Försti A, Sundquist J, Sundquist K. Thalassemia and sickle cell anemia in Swedish immigrants: Genetic diseases have become global. *SAGE open medicine* 2015; **3**: 2050312115613097.

74. Cowan RS. Moving up the slippery slope: mandated genetic screening on Cyprus. *American journal of medical genetics Part C, Seminars in medical genetics* 2009; **151c**(1): 95-103.

75. Kolnagou A, Kontoghiorghes GJ. Advances in the prevention and treatment are changing thalassemia from a fatal to a chronic disease. experience from a Cyprus model and its use as a paradigm for future applications. *Hemoglobin* 2009; **33**(5): 287-95.

76. Bozkurt G. Results from the north cyprus thalassemia prevention program. *Hemoglobin* 2007; **31**(2): 257-64.

77. Greengross P, Hickman M, Gill M, Dugan B, Davies SC. Outcomes of universal antenatal screening for haemoglobinopathies. *Journal of medical screening* 1999; **6**(1): 3-10.

78. Locock L, Kai J. Parents' experiences of universal screening for haemoglobin disorders: implications for practice in a new genetics era. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2008; **58**(548): 161-8.

79. NHS Sickle Cell and Thalassaemia Screening Programme. NHS Sickle Cell and Thalassaemia Screening Programme Data report 2016 to 2017.

80. Cousens NE, Gaff CL, Metcalfe SA, Delatycki MB. Carrier screening for beta-thalassaemia: a review of international practice. *European journal of human genetics : EJHG* 2010; **18**(10): 1077-83.

81. Samavat A, Modell B. Iranian national thalassaemia screening programme. *BMJ : British Medical Journal* 2004; **329**: 1134 - 7.

82. Tarazi I, Al Najjar E, Lulu N, Sirdah M. Obligatory premarital tests for β-thalassaemia in the Gaza Strip: evaluation and recommendations. *International journal of laboratory hematology* 2007; **29**(2): 111-8.
83. AlHamdan NA, AlMazrou YY, AlSwaidi FM, Choudhry AJ. Premarital screening for thalassemia and sickle cell disease in Saudi Arabia. *Genetics in Medicine* 2007; **9**(6): 372-7.
84. Hamamy H, Al-Hait S. Premarital Screening Program for Beta-Thalassemia in Jordan. *The Ambassadors Online Magazine* 2007; **10**(1).
85. Al-Allawi NA, Al-Doski AA, Markous RS, et al. Premarital screening for hemoglobinopathies: experience of a single center in Kurdistan, Iraq. *Public health genomics* 2015; **18**(2): 97-103.
86. Canatan D. Haemoglobinopathy prevention program in Turkey. *Thalassemia Reports* 2011; **1(s2)**: e4.
87. Thalassaemia International Federation. Prevention of Thalassaemias and other Haemoglobin Disorders, Vol 1, 2nd Edition. *Thalassemia International Federation* 2013.
88. Mahdavi SA, Jafari A, Azimi K, Dehghanizadeh N, Barzegar A. Therapeutic abortion in Iran: an epidemiologic study of legal abortion in 2 years. *BMC research notes* 2020; **13**(1): 261.
89. Hamamy HA, Al-Allawi NAS. Epidemiological profile of common haemoglobinopathies in Arab countries. *J Community Genet* 2013; **4**(2): 147-67.
90. Alkhaldi SM, Khatatbeh MM, Berggren VE, Taha HA. Knowledge and Attitudes Toward Mandatory Premarital Screening Among University Students in North Jordan. *Hemoglobin* 2016; **40**(2): 118-24.
91. Waheed F, Fisher C, Awofeso A, Stanley D. Carrier screening for beta-thalassemia in the Maldives: perceptions of parents of affected children who did not take part in screening and its consequences. *J Community Genet* 2016; **7**(3): 243-53.

92. Chern JPS, Lin K-H, Lu M-Y, et al. β-Thalassemia major births after National Screening Program in Taiwan. *Pediatric blood & cancer* 2008; **50**(1): 58-61.
93. Fucharoen S, Weatherall DJ. Progress Toward the Control and Management of the Thalassemias. *Hematology/oncology clinics of North America* 2016; **30**(2): 359-71.
94. Ngim CF, Ibrahim H, Lai NM, Ng CS. A single centre study on birth of children with transfusion-dependent thalassaemia in Malaysia and reasons for ineffective prevention. *Prenat Diagn* 2015; **35**(1): 51-9.
95. Padilla CD, Cutiongco-de la Paz EM. Genetics and genomic medicine in the Philippines. *Molecular genetics & genomic medicine* 2016; **4**(5): 494-503.
96. Ministry of Health and Family Welfare, Government of India. Prevention and Control of Hemoglobinopathies in India-Thalassemia, Sickle Cell Diseases and Other Variant Hemoglobins. 2016.
97. Hossain MS, Raheem E, Sultana TA, et al. Thalassemias in South Asia: clinical lessons learnt from Bangladesh. *Orphanet journal of rare diseases* 2017; **12**(1): 93.
98. Ansari SH, Shamsi TS, Ashraf M, et al. Molecular epidemiology of β-thalassemia in Pakistan: far reaching implications. *Int J Mol Epidemiol Genet* 2011; **2**(4): 403-8.
99. 国家卫生和计划生育委员会办公厅. 国家卫生计生委办公厅关于印发地中海贫血防控试点项目技术服务规范的通知-国卫办妇幼函【2015】873 号. 2015.
100. 广东省卫生健康委员会. 关于印发广东省地中海贫血干预项目管理方案（试行）的通知. 2012.
101. 广西壮族自治区人民政府办公厅. 广西壮族自治区地中海贫血防治计划. 2010.
102. 海南省卫生和计划生育委员会. 关于做好 2016 年国家免费孕前优生健康检查和地中海贫血筛诊项目工作的通知. 2016.

103. Mustafa I, Firdous N, Shebl FM, et al. Genetic epidemiology of beta-thalassemia in the Maldives: 23 years of a beta-thalassemia screening program. *Gene* 2020; **741**: 144544.

104. Baronciani D, Boumendil A, Dalissier A, et al. Hematopoietic Cell Transplantation in Thalassemia and Sickle Cell Disease: Report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry: 2000-2017. *Blood* 2018; **132**(Supplement 1): 168-.

105. He Y, Jiang H, Li C, et al. Long-term results of the NF-08-TM protocol in stem cell transplant for patients with thalassemia major: A multi-center large-sample study. *American journal of hematology* 2020; **95**(11): E297-E9.

106. Emanuele A, Susanne M-M, Donatella B, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. *Haematologica* 2014; **99**(5): 811-20.

107. Oevermann L, Schulte JH, Hundsdörfer P, et al. HLA-haploidentical hematopoietic stem cell transplantation in pediatric patients with hemoglobinopathies: current practice and new approaches. *Bone Marrow Transplantation* 2019; **54**(2): 743-8.

108. de Dreuzy E, Bhukhai K, Leboulch P, Payen E. Current and future alternative therapies for beta-thalassemia major. *Biomedical Journal* 2016; **39**(1): 24-38.

109. Thompson AA, Walters MC, Kwiatkowski J, et al. Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia. *The New England journal of medicine* 2018; **378**(16): 1479-93.

110. Ribeil J-A, Hacein-Bey-Abina S, Payen E, et al. Gene Therapy in a Patient with Sickle Cell Disease. *New England Journal of Medicine* 2017; **376**(9): 848-55.

111. Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia. *New England Journal of Medicine* 2020; **384**(3): 252-60.

112. 广州市南沙区商务局 政府信息公开. 国内首例！南沙明星企业博雅辑因CRISPR/Cas9 基因编辑疗法获批临床. *http://www.gzns.gov.cn/gznssw/gkmlpt/content/7/7040/post_7040939.html?jump=false#9664* 2021.

113. Wang L, Li L, Ma Y, et al. Reactivation of γ-globin expression through Cas9 or base editor to treat β-hemoglobinopathies. *Cell research* 2020; **30**(3): 276-8.

114. 药时代. 全国首例！邦耀生物攻克了β0/β0 型地贫难关，其基因编辑疗法在临床试验取得重大进展. *https://www.drugtimes.cn/2020/07/22/全国首例！邦耀生物攻克了β0-β0 型地贫难关，其基/* 2020.

115. The World Bank. World Development Indicators: GDP per capita (current US$). *https://databank.worldbank.org/reports.aspx?source=2&series=NY.GDP.PCAP.CD&country=* 2021.

116. Our World in Data. Number of births and deaths per year, World. *https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100?time=1950..2010&country=~OWID_WRL*

117. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem. 2020.

118. 北京天使妈妈慈善基金会, 中华思源工程扶贫基金会, 北京师范大学中国公益研究院. 中国地中海贫血蓝皮书——中国地中海贫血防治桩孔调查报告（2015）.

119. Kaback MM. Screening and prevention in Tay-Sachs disease: origins, update, and impact. *Advances in genetics* 2001; **44**: 253-65.

120. HAARETZ. Tay-Sachs, the Jewish Disease,' Almost Eradicated. *https://www.haaretz.com/1.4706480* 2005.

121. Nnodu OE, Sopekan A, Nnebe-Agumadu U, et al. Implementing newborn screening for sickle cell disease as part of immunisation programmes in Nigeria: a feasibility study. *The Lancet Haematology* 2020; **7**(7): e534-e40.

122. He J, Song W, Yang J, et al. Next-generation sequencing improves thalassemia carrier screening among premarital adults in a high prevalence population: the Dai nationality, China. *Genetics in medicine : official journal of the American College of Medical Genetics* 2017; **19**(9): 1022-31.
123. Shang X, Peng Z, Ye Y, et al. Rapid Targeted Next-Generation Sequencing Platform for Molecular Screening and Clinical Genotyping in Subjects with Hemoglobinopathies. *EBioMedicine* 2017; **23**: 150-9.
124. Ming H, Tao H, Jie Z. Cost-effectiveness analysis on thalassemia screening in Yunnan province. *Soft Science Of Health* 2020; **34**(5): 47-51.
125. Herrick Jb. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. *Archives of Internal Medicine* 1910; **VI**(5): 517-21.
126. Cooley TB, Lee PA. A series of cases of splenomegaly in children with anemia and peculiar bone changes. *Transactions of the American Pediatric Society* 1925; **37**: 29-30.
127. Organization WH. Smallpox. *https://www.who.int/health-topics/smallpox#tab=tab_1*
128. World Health Organization. Two out of three wild poliovirus strains eradicated. *https://wwwwhoint/news-room/feature-stories/detail/two-out-of-three-wild-poliovirus-strains-eradicated* 2019.
129. World Health Organization. Polio eradication. *https://www.who.int/news-room/facts-in-pictures/detail/polio-eradication* 2018.
130. Global Report on Birth Defects. Global Report on Birth Defects. 2006.