

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*The α -Thalassemias

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THE THALASSEMIAS ARE THE MOST COMMON HUMAN MONOGENIC DIS-EASES.¹ These inherited disorders of hemoglobin synthesis are characterized by a reduced production of globin chains of hemoglobin.² Worldwide, the most important forms are the α - and β -thalassemias, which affect production of the α -globin and β -globin chains, respectively. Although β -thalassemia is the more clinically significant form,³ α -thalassemia occurs at a high frequency across the tropical belt, almost reaching fixation (a term in population genetics denoting that a mutant allele of a particular gene has become the only allele expressed in the population — i.e., that it has reached a frequency of 100%) in parts of southern Asia. It has been estimated that about 5% of the population worldwide carry an α -thalassemia variant.⁴⁻⁷

There is growing evidence that the health and economic burden of the thalassemias is increasing owing to population growth and epidemiologic transition in tropical regions⁸ and to human migrations in other parts of the world.⁹⁻¹² (Epidemiologic transition refers to a change in patterns of population age distributions, mortality, fertility, life expectancy, and causes of death, usually reflected by a shift from deaths caused by infectious diseases to deaths caused by chronic and degenerative diseases.) Population growth leads to an absolute increase in the number of births affected. Epidemiologic transition improves the diagnosis of hemoglobinopathies and the survival of affected persons, increasing the incidence of the disorders. Population migrations, although not always leading to an increase in global prevalence, contribute to the spreading of hemoglobinopathies and thus increase the number of countries that require the implementation of specific interventions to educate larger populations, diagnose the disorders, and counsel affected patients and that must account for these interventions in their health budget.

Although our epidemiologic knowledge of the distribution, prevalence, genetic diversity, and health burden of both α -thalassemia and β -thalassemia is limited and largely outdated, gaps are more pronounced in the case of α -thalassemia. This relative lack of a strong evidence base is likely to contribute to the low priority of this disorder on many public health agendas. Existing reviews focus mainly on molecular and clinical aspects of α -thalassemia.¹³⁻¹⁶ Our aim in this article is to provide a contemporary summary of our epidemiologic knowledge of α -thalassemia and to discuss the various challenges faced by the medical and public health communities in light of recent findings on the severity and genetics of this inherited disorder.

CLINICAL RELEVANCE

Normal adult hemoglobin consists of pairs of α and β chains ($\alpha_2\beta_2$), and fetal hemoglobin has two α chains and two γ chains ($\alpha_2\gamma_2$). The genes for the α chains and γ chains are duplicated ($\alpha\alpha/\alpha\alpha$, $\gamma\gamma/\gamma\gamma$), whereas the β chains are encoded by a single gene locus (β/β). In the fetus, defective production of α chains is reflected by the presence of excess γ chains, which form γ_4 tetramers, called hemoglobin

Bart's; in adults, excess β chains form β_4 tetramers, called hemoglobin H (HbH). Because of their very high oxygen affinity, both tetramers cannot transport oxygen, and, in the case of HbH, its instability leads to the production of inclusion bodies in the red cells and a variable degree of hemolytic anemia.

More than 100 genetic forms of α -thalassemia have thus far been identified,¹⁷ with phenotypes ranging from asymptomatic to lethal. Despite this complexity, the severity of this disorder is usually well correlated with the number of non-functional copies of the α -globin genes (Fig. 1). On the basis of the numbers of α -globin genes lost by deletion or totally or partially inactivated by point mutations, the α -thalassemias are classified into two main subgroups: α^+ -thalassemia (formerly called α -thalassemia 2), in which one pair of the genes is deleted or inactivated by a point mutation ($-\alpha/\alpha\alpha$ or $\alpha\alpha^{ND}/\alpha\alpha$, with ND denoting nondeletion), and α^0 -thalassemia (formerly called α -thalassemia 1), in which both pairs of α -globin genes on the same chromosome are deleted ($---/\alpha\alpha$).

Clinically relevant forms of α -thalassemia usually involve α^0 -thalassemia, either coinherited with α^+ -thalassemia ($-\alpha/---$ or $\alpha\alpha^{ND}/---$) and resulting in hemoglobin Bart's hydrops fetalis ($---/---$), which is lethal in utero or soon after birth. Affected embryos succumb to severe hypoxia either early in gestation (e.g., in the case of $---^{FIL}/---^{FIL}$ [with FIL referring to a deletion that causes α^0 -thalassemia and that is prevalent among Filipinos]) or during the third trimester (e.g., in the case of $---^{SEA}/---^{SEA}$ [with SEA referring to a deletion that causes α^0 -thalassemia and that is prevalent among persons from Southeast Asia]).¹⁸

A few children with hemoglobin Bart's hydrops fetalis who received an intrauterine transfusion or a transfusion immediately after delivery have survived to 5 years of age. These children require regular transfusions and, when appropriate, iron-chelation therapy; they usually have serious clinical complications, congenital anomalies, and delays in cognitive and motor functions.⁹ The hemoglobin Bart's hydrops fetalis syndrome is often accompanied by a variety of congenital malformations and maternal complications, including severe anemia of pregnancy, preeclampsia, polyhydramnios, and extreme difficulty in

delivery of both the fetus and the hugely enlarged placenta.^{18,19} Although these complications have been well documented, there are very limited data regarding the frequency of maternal deaths, particularly in the developing countries in which this condition is so common.

HbH disease is often considered to be a relatively mild disorder. Studies have nevertheless highlighted clinically severe phenotypes, notably in nondeletional variants of the disease.²⁰⁻²² In fact, HbH disease is characterized by a wide range of phenotypic characteristics. The form that results from deletions ($-\alpha/---$) usually follows a relatively mild course, with moderate anemia and splenomegaly. Aside from episodes of intercurrent infection, this form of HbH disease does not require blood transfusions. However, the variety that results from the interactions of a nondeletional α -globin gene mutation together with α^0 -thalassemia ($\alpha\alpha^{ND}/---$) follows a much more severe course. This is particularly

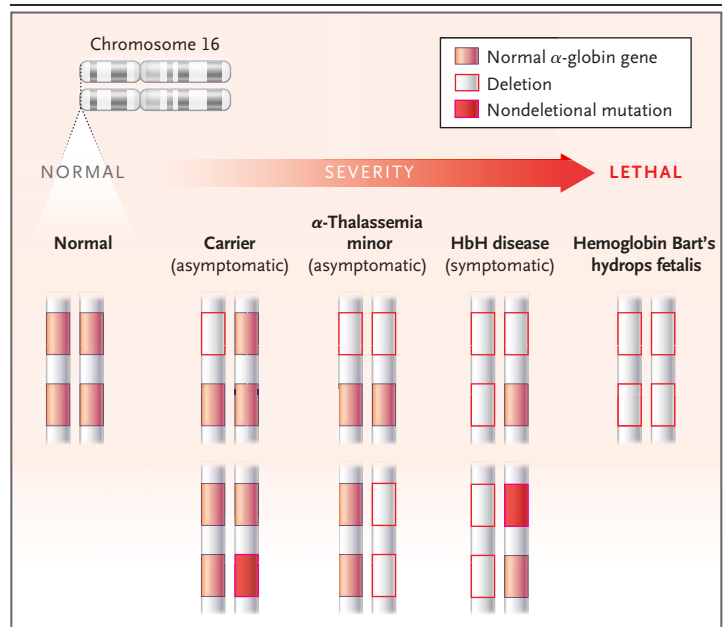


Figure 1. Phenotype-Genotype Relationship in α -Thalassemia.

In rare cases, hemoglobin H (HbH) disease or hemoglobin Bart's hydrops fetalis can result from homozygosity for nondeletional forms of α -thalassemia. Although HbH disease is usually symptomatic, some patients, particularly those with deletional variants of α -thalassemia, are asymptomatic. Furthermore, three α -globin gene deletions involving severe nondeletional mutations (e.g., hemoglobin Constant Spring) can also cause the hemoglobin Bart's hydrops fetalis syndrome. With regard to the lethality of hemoglobin Bart's hydrops fetalis, four α -globin gene deletions with persistence of an intact embryonic ζ -globin gene — for example, $-(\alpha)^{20,5}$ in the Mediterranean area — may be associated with neonatal survival.

true when the nondeletional mutation is the α -globin chain termination mutant hemoglobin Constant Spring, which is very common in many Asian countries. Nondeletional forms of HbH disease are characterized by severe anemia, often occurring from early life, and are associated with increasing splenomegaly, iron loading, and a variety of other clinical complications, including infections, leg ulcers, gallstones, and folic acid deficiency. Although splenectomy is often indicated, nondeletional HbH disease is associated with a particularly high rate of thrombotic complications. This observation makes the decision between splenectomy and lifelong transfusion extremely difficult.

Milder variants of α -thalassemia act as genetic modifiers of other inherited conditions, as illustrated by epistatic interactions (when one gene influences another) between α -thalassemia and β -thalassemia²³ or between α -thalassemia and hemoglobin S (sickle hemoglobin).²⁴ Triplications and quadruplications of the α -globin gene have been frequently observed in many populations, and these can interact with β -thalassemia variants to produce more severe phenotypes.^{25,26}

Finally, there are two syndromes in which α -thalassemia is associated with mental retardation (ATR syndromes).^{14,27} Details regarding these syndromes are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

DIAGNOSIS

Prenatal diagnosis is required to identify fetuses affected by hemoglobin Bart's hydrops fetalis and to reduce the risks to the mothers. The decision to consider such a diagnosis usually follows the finding of hypochromic microcytic red cells in both parents, in association with a normal hemoglobin A₂ level; this combination would rule out β -thalassemia, which usually involves an elevated hemoglobin A₂ level. Iron deficiency also has to be ruled out. When facilities for rapid DNA diagnosis are available, the hematologic examination is followed by confirmation of the presence of α^0 -thalassemia in the parents. The fetal diagnosis is usually made early in pregnancy by means of chorionic-villus sampling, although fetal anemia may also be diagnosed later during gestation by quantitation of the peak systolic velocity in the middle cerebral artery.²⁸ Various

alternative methods of preimplantation and pre-conception genetic diagnosis or prenatal diagnosis — for example, analysis of maternal blood for fetal DNA and identification of fetal cells in maternal blood by staining with antibodies against globin chains — are still at relatively early stages of study. Meanwhile, attempts at intrauterine and postnatal therapy are associated with numerous ethical challenges.²⁹

The homozygous state of α^+ -thalassemia and the heterozygous state of α^0 -thalassemia (grouped under the term “ α -thalassemia minor”) are associated with a substantial reduction in the mean corpuscular volume and mean corpuscular hemoglobin. In α^+ -thalassemia heterozygotes, the mean corpuscular volume and mean corpuscular hemoglobin are usually reduced, but there is a small overlap with normal values. Milder forms of α -thalassemia are often misdiagnosed as iron deficiency, although the exact frequency of misdiagnosis is unknown.³⁰ Ultimately, the diagnosis of a particular variant of α -thalassemia can be confirmed only at the DNA level.

In the pregenomic era, the frequency of α -thalassemia was assessed according to the presence of hemoglobin Bart's in cord blood. The detection of hemoglobin Bart's in newborns indicates that one or more of the four α -globin genes are dysfunctional, causing α -thalassemia. Although the level of hemoglobin Bart's at birth was initially thought to be a sensitive indicator of the presence of α -thalassemia and to correlate well with its severity, later DNA-based studies showed that this diagnostic method fails to detect a substantial number of α^+ -thalassemia heterozygotes and therefore underestimates the frequency of α -thalassemia.¹⁸ It is now well established that diagnosis of α -thalassemia on the basis of hemoglobin Bart's alone is not reliable and does not allow identification of the genotypes. This method is nevertheless still widely used in low- and middle-income countries because it is relatively straightforward and much cheaper than DNA analysis.

GEOGRAPHIC DISTRIBUTION

Evidence that α -thalassemia is highly protective against severe malaria is well established.⁵ As a result of this selective advantage, heterozygous α -thalassemia has reached high frequencies throughout all tropical and subtropical regions,

including most of Southeast Asia, the Mediterranean area, the Indian subcontinent, the Middle East, and Africa. Common α^0 -thalassemia variants, predominantly the ---^{SEA} mutation in Southeast Asia and the ---^{MED} mutation in the Mediterranean, have reached frequencies of approximately 5%. Although there are at least seven deletional forms of α^+ -thalassemia, as shown in Figure 2A, the $\text{---}\alpha^{3.7}$ variants are the most common. Frequencies of 70% and up to 90% have been reported in Melanesia⁵ and in parts of Nepal,⁷ respectively. The mechanisms by which such frequencies close to fixation have been reached require further investigation.^{31,32} In addition to studies that have revealed negative epistasis between α^+ -thalassemia and the sickle cell trait, resulting in a reduced level of malaria protection when the two are coinherited,²⁴ mathematical models have suggested that the frequency of α^+ -thalassemia might be constrained by the presence of the sickle cell gene in Africa and the Mediterranean.^{33,34}

In conjunction with large-scale global population movements in recent decades, α -thalassemia has spread to many other parts of the world, including northern Europe and North America. This phenomenon is best illustrated by the implementation in 1998 of a universal screening program for α -thalassemia in California. After the immigration of large numbers of people from the Philippines and other Southeast Asian countries, the incidence of α -thalassemia syndromes in California between January 1998 and June 2006 was 11.1 cases per 100,000 persons screened, with 406 cases of HbH disease and 5 cases of hemoglobin Bart's hydrops fetalis.¹⁵ Because of the high frequency of α^+ -thalassemia variants worldwide (Fig. 2A), it is likely that, with admixture of local populations and immigrants, such spread will increase the incidence of HbH disease (Fig. 2C), in addition to creating a health burden in a growing number of countries or regions.

Various population surveys of hemoglobinopathies have revealed remarkable geographic heterogeneities in the prevalence of these disorders.³⁵ In the mid-1980s, Flint and colleagues observed frequencies of α^+ -thalassemia ranging from 6 to 68% across Melanesian islands.⁵ Similar heterogeneities were later described in Vanuatu.³⁶ In a recent micro-mapping survey conducted across Sri Lanka, the prevalence of α -thalassemia ranged from 2 to 20% (Weatherall DJ, et al.: unpub-

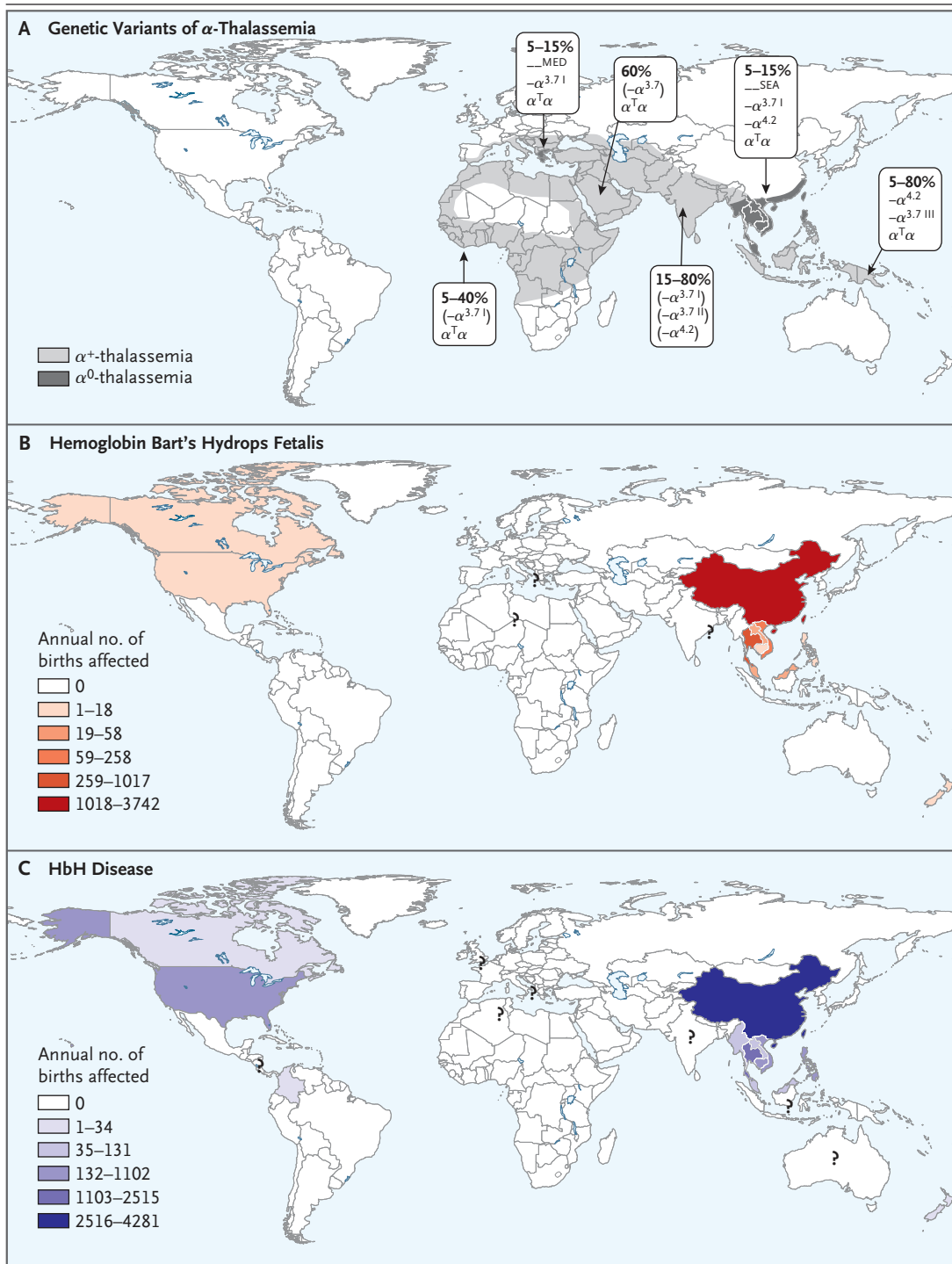
lished data). This variability is likely to be the result of a series of complex environmental factors, including the rate of malaria transmission. A better understanding of these interactions will help considerably in refining estimates of populations affected in tropical regions (Fig. 2B and 2C) and in developing policies for the diagnosis and management of α -thalassemia on the basis of characteristics of the local population. A precise quantification of the populations at risk for α -thalassemia syndromes at the national, regional, and global levels is necessary to define current and future resources required to provide accurate prenatal diagnosis of α -thalassemia variants, emergency management of pregnancies involving hemoglobin Bart's hydrops fetalis and associated maternal complications, and long-term management of HbH disease.

SCREENING

The primary objectives of thalassemia screening programs are to determine the frequency of the different genetic variants observed in the communities and to identify and inform couples who are at risk, particularly for severe forms of the disease occurring in areas of high frequency. Screening for α -thalassemia is especially helpful in preventing severe maternal complications in the case of hemoglobin Bart's hydrops fetalis and in providing accurate diagnosis in cases in which α -thalassemia is coinherited with hemoglobin S or β -thalassemia or in cases in which iron deficiency is detected. Most α -thalassemia screening surveys are conducted as part of a β -thalassemia prevention program and are therefore not adequate to determine population frequencies of α -thalassemia. The benefits of population screening should be carefully considered in any population in which α -thalassemia variants are prevalent and cases of unexplained microcytic hypochromic anemia in the absence of iron deficiency are observed.¹⁸ Major screening efforts that have been implemented in various countries and their main outcomes are summarized in the Supplementary Appendix.

HEALTH AND ECONOMIC BURDEN

Early studies of the global burden of hemoglobin disorders that evaluated the frequency of the disorders and the number of disability-adjusted life-



years (DALYs) associated with them were limited by a lack of data on α -thalassemia, particularly with regard to hemoglobin Bart's hydrops fetalis and its burden through stillbirths or deaths shortly after delivery.³⁷ The World Health Organization (WHO) does not collect data on still-

births, and the only data that were available provided an estimate of 1250 pregnancies involving homozygous α^0 -thalassemia per year in Thailand, a figure that amounts to 37,242 DALYs. In comparison, homozygous β -thalassemia and hemoglobin E β -thalassemia were estimated to result

Figure 2 (facing page). Geographic Distribution of α -Thalassemia, Hemoglobin Bart's Hydrops Fetalis, and HbH Disease.

Panel A shows a map of our current knowledge of the distribution, prevalence, and genetic diversity of α -thalassemia globally. Only the most common variants for α^+ -thalassemia ($-\alpha^{3,7}$ and $-\alpha^{4,2}$) and α^0 -thalassemia ($-\alpha^{\text{MED}}$ and $-\alpha^{\text{SEA}}$) are shown for each region. The variants that appear in parentheses in Panel A are those for which the data used to make this map are limited. The information in Panel A is based on data from Weatherall and Clegg.¹⁸ Panel B shows current estimates of the annual number of births affected by hemoglobin Bart's hydrops fetalis ($-\alpha/\alpha$), and Panel C shows births affected by HbH disease ($-\alpha/\alpha$). No difference is indicated between countries in which the disorder has not been reported and those for which no data are available. The maps in Panels B and C highlight various inconsistencies (indicated by a question mark) in current estimates, particularly in the Mediterranean area and, with regard to HbH disease, in India and western Europe. These maps also reveal the need for subnational estimates, as in the United States and China. The information in Panels B and C is based on data from Modell and Darlison.⁴

testing was cost-effective, although no published data on the cost of managing a pregnancy affected by hemoglobin Bart's hydrops fetalis were available.²⁸ Whether these results apply to countries with larger populations and lower incomes than those in Hong Kong needs to be carefully investigated.⁴⁰ The benefits of accurate diagnosis of iron deficiency and other hemoglobinopathies — hemoglobin S and β -thalassemia in particular — should also be considered. Cost-benefit analyses of β -thalassemia prevention programs in Quebec,⁴¹ Iran,⁴² Israel,^{43,44} and the United Kingdom⁴⁵ have generally confirmed the overall benefits of such programs (i.e., the costs of prevention were lower than the costs of treatment), but the studies did not include α -thalassemia. In low- and middle-income countries, the implementation of such programs could benefit from existing infrastructures (e.g., ongoing screening programs for phenylketonuria or glucose-6-phosphate dehydrogenase deficiency) or could result in an overall improvement in access to health care for local communities.⁴⁶

in a total of 53,600 DALYs in Thailand, on the basis of a life expectancy of 10 years and 30 years, respectively. These are likely to be underestimates because the mother's disability was accounted for only in the last trimester of pregnancy, without consideration of postnatal complications that can result in death, and because estimates were not calculated for HbH disease, since data were collected before it was realized that a particularly severe form of HbH disease occurs in many Asian countries. Information on the incidence of α -thalassemia was insufficient to permit calculation of the regional and global burden of disease.³⁷ Global estimations of the number of DALYs resulting from hemoglobinopathies have recently been reported in the Global Burden of Disease Study 2010, although no accurate data on the various subtypes of thalassemia have yet been added to this project.^{38,39}

To our knowledge, there has been only one study to date that has investigated the cost-benefit ratio of an α -thalassemia prevention program, whether established on its own or as part of a broad program for all the thalassemias or for genetic conditions (e.g., phenylketonuria) in general. The study, conducted in Hong Kong, concluded that universal prenatal screening for the α - and β -thalassemias with the use of DNA

MANAGEMENT

A detailed knowledge of the prevalence of α -thalassemia (including carrier status) and of its genetic diversity is essential to define policies aimed at reducing the long-term health burden of hemoglobinopathies, allowing for precise diagnosis (and therefore avoiding inaccurate and expensive investigations), establishing the real cause of microcytosis, providing adequate genetic counseling, and allocating resources to address the emergency and long-term needs of patients and their relatives in a cost-effective manner. To achieve these goals, the medical community faces several important challenges, summarized in Table 1.

Most couples at risk for conceiving fetuses with hemoglobin Bart's hydrops fetalis are not currently identified. It is therefore highly likely that current estimates represent large underestimates of stillbirths caused by this disorder.⁴ In the absence of specific treatments and a clear understanding of the underlying mechanisms responsible for the wide range of congenital abnormalities associated with this lethal disorder, screening and early prenatal diagnosis represent the only options to identify pregnancies at risk and to prevent severe maternal complications. Although termination of affected pregnancies is

Table 1. Main Challenges Associated with the Increasing Health Burden of α -Thalassemia and Recommendations for Addressing Them.

Challenge	Recommendation
Prevention of hemoglobin Bart's hydrops fetalis	Education, screening and counseling; prevention of maternal complications
Accurate diagnosis of hemoglobin H disease	Affordable DNA-screening methods
Increase in international migration	International collaborations
Geographic heterogeneities	Micro-mapping studies
Better understanding of phenotype–genotype interactions and of the role of environmental and genetic modifiers	Theoretical epidemiologic modeling alongside clinical studies
Need for reliable population estimates of affected persons	Population surveys and data sharing
Sustainable allocation of resources for the management and control of thalassemias	Greater awareness and more cost–benefit analyses

usually recommended owing to the increased risk of severe maternal and fetal complications and the psychological effects on families, cultural and religious backgrounds need to be carefully taken into account when counseling couples at risk, both in communities in which α -thalassemia has traditionally been prevalent and in those in which it has recently been introduced through migration.^{18,47} A correct diagnosis early in pregnancy is essential to avoid severe medical complications and psychological trauma. Such a diagnosis can be made reliably with relatively low costs provided that pregnant women receive regular follow-up care from medical staff familiar with this syndrome.

Recent progress in DNA testing has revealed a greater phenotypic diversity in HbH disease than previously thought.^{20,22} As noted above, non-deletional variants are usually more severe than deletional variants. It is therefore crucial to conduct DNA analyses to identify the underlying genetic variant responsible for this disorder. Gap-polymerase chain reaction (PCR) and multiplex-PCR assays allow easy screening for a range of common variants,⁴⁸ but such methods remain costly and are not widely used in low- and middle-income countries. With DNA testing methods becoming more and more affordable, it is likely that this will become a regular part of the services available for the control and management of thalassemias, particularly in Asian countries.⁴⁹ As our knowledge of the phenotype–genotype

relationship in HbH disease improves, correct genotype identification will become essential to inform parents about reproductive risks during genetic counseling and to provide appropriate care to affected patients.

With increasing population movements, the diversity of combinations of α -thalassemia variants or coinherited hemoglobinopathies will continue to increase. Although it is difficult to predict the exact phenotype of such new combinations, a detailed knowledge of the current distribution of genetic variants will at least help in defining diagnostic procedures and in assessing the potential risks. Collaborations between “source” areas (those with a high prevalence of α -thalassemia and substantial emigration) and “sink” areas (those with substantial immigration from source areas), as have developed between the Philippines and California and between Sri Lanka and the United Kingdom, certainly represent beneficial models for both sides and should be replicated more widely.^{50,51}

The health burden of α^+ -thalassemia is currently not known. Although α^+ -thalassemia variants alone do not represent a direct clinical problem, they are probably the most common genetic disorders in the world, and they represent important genetic modifiers for a range of other conditions, including malaria, sickle cell disorders, β -thalassemia, and iron deficiency. A better understanding of these interactions is crucial to provide appropriate diagnosis and treatment for affected patients but is relevant only if interventions resulting from our improved understanding are implemented in all areas in which these interactions are occurring. For example, whether epistatic interactions between the sickle cell trait and α^+ -thalassemia that have been observed in Kenya²⁴ are also occurring in Indian populations is currently not known.

Because of the remarkable geographic heterogeneities in the prevalence of α -thalassemia, interventions have to be tailored to the specific characteristics of the local population (e.g., prevalence of the disorder in the population, ethnic makeup, and consanguinity) and the local health care system.^{35,52} A better understanding of the relationship among the prevalence of α -thalassemia variants, environmental factors, and infections, combined with modern analytic and modeling methods, would support more refined estimates of affected populations. Such knowledge would also help

in the development of stratified prevention programs that focus, for example, on regions in which α^0 -thalassemia variants are the most prevalent.

CONCLUSIONS

The α -thalassemias represent a global health problem with a growing burden.¹¹ A refined knowledge of the molecular basis of α -thalassemia^{53,54} will be fully relevant from a public health perspective only if it is complemented by detailed epidemiologic data. To ensure appropriate care of patients and the sustainability of health care systems, more effort must be put into obtaining evidence-based estimates of affected populations, providing resources for the prevention, control, and management of the thalassemsias, and performing cost-effectiveness analyses.²⁸ Such goals will be achieved only through a concerted effort by the research and medical com-

munities and the support of international funding agencies to collect and share epidemiologic data.⁵⁵ The recent inclusion of hemoglobinopathies in the Global Burden of Disease Study⁵⁶ and the assessment of the burden of α -thalassemia in terms of DALYs will be meaningful only if contemporary and reliable data are available.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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