THE PREVENTION OF THALASSAEMIA REVISITED BY THALASSAEMIA INTERNATIONAL FEDERATION A HISTORICAL & ETHICAL PERSPECTIVE

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A HISTORICAL AND ETHICAL PERSPECTIVE

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INTRODUCTION

The Thalassaemia International Federation (TIF) adopts and advocates the position of the World Health Organisation (WHO) that a genetic control programme should be an intrinsic part of national healthcare systems, encompassing the components of prevention, clinical management and social care.

TIF in this chapter, revisits the thalassaemia prevention programmes, strategies, policies which exist in a selection of its member countries. It discusses their effectiveness and whether any changes in policy or public attitudes to thalassaemia prevention have occurred through the years, in view of the significant improvements in patient outcomes, public health (including prevention of communicable diseases) and healthcare systems.

An effort will be made to answer the questions:

- Have a) the improved prognosis (mainly due to the increasing use of oral chelating agents), b) the improvement of iron load monitoring [15], c) the provision of multidisciplinary care, and d) the recent availability of new innovative therapeutic and curative products [16] influenced public health decision-makers and/or the attitude of the public at large with respect to prevention of thalassaemia?
- Are public awareness, screening, genetic counselling and prenatal diagnosis still recognised and considered essential components of an effective prevention programme?
- Are these principles, and the essential elements of national coordination and funding, which aim at the reduction of birth incidence, still regarded as the main pillars of an effective prevention programme and is the possibility of an increasing birth incidence in countries where optimal care is available a real one?

Haemoglobin disorders are a group of hereditary anaemias which, without lifelong optimum care, are fatal, often in early childhood. In high prevalence regions of the world, they constitute a serious medical and public health problem. In a zone ranging from the Mediterranean basin to China, as well as Africa, these conditions are prevalent in the indigenous populations. However, migrations over the years have introduced them to many parts of the world, especially to western countries [1]. Patients receive varying levels of care, according to national policies and priorities. Optimal care is defined as the application of clinical and laboratory approaches that are validated at a given period of time, and which may change as new practices are adopted.

Over the years, advances in clinical care of thalassaemia have changed the prospect for survival and quality of life [2,3]. The accumulation of experience and knowledge, particularly in the Southern Mediterranean countries over the last 2-3 decades, have led to the publication, initially by the WHO (in 1993) and later by TIF and others, of guidelines for both management (in 1999, 2007, 2008, 2013, 2014, 2017) and prevention (2003, 2004, 2012, 2013, 2018) of thalassaemia [15, 49]. Guidelines for the prevention of thalassaemia to-date encompass the same elements as those identified in the 1970s applied mainly by the countries of the Southern Mediterranean. These used the guidance offered by the WHO and its expert medical groups that were established by the 1980s. The value of effective prevention programmes has been significantly appreciated in these countries since they have allowed, mainly through the reallocation of resources, the survival and quality of life of patients to improve. In developing countries, however, where more than 75% of the patient population is born and lives, optimum care cannot be, and is not, provided. Therefore, improving the effectiveness of prevention programmes constitutes the most important element that would contribute to great improvements, given that only a very small percentage of patients (TIF estimates this is less than 10% of the global patient community) in these countries has access to what is today referred to as optimal care.

HISTORICAL ASPECTS AND GENERAL PRINCIPLES

Steps towards better management historically date back to the 1960s when blood transfusion became increasingly used [4], and iron chelation was recognised as an essential component of treatment [5]. Over the ensuing years these basic modalities of care have been optimised and new oral iron chelating agents have been introduced. Increased survival led to the recognition of multi-organ damage due to transfusional iron overload and toxicity, and the need for a multi-disciplinary approach to clinical management. In addition, psychosocial aspects were recognised and community

support was introduced. This escalating complexity of patient care required increasing resources and demands on healthcare systems, especially noticeable in high prevalence countries. Reducing birth incidence as a means of reducing the public health impact and persuading health authorities to provide optimal care to patients as a means of ultimately saving resources, became imperative. The willingness to invest more on treatment rather than prevention was and still is, in many settings, limited by the lack of in depth knowledge by health authorities of the real needs of these conditions. In addition, perceived 'other' priorities, such as infectious diseases, have been put forward as a reason for avoiding addressing effectively the issue of congenital disorders. Over and above this, the lack of precise epidemiological data has continued to sustain the view that these are rare disorders, with a low health burden and public health significance.

The importance of comprehensive control programmes was recognized as early as the 1950s when Silvestroni and Bianco in Italy, recommended to the High Commission for Hygiene and Health in 1955 the provision of free medical care for patients and the establishment of large scale screening and preventive counselling programmes [6]. Lack of public and healthcare professional awareness was a limiting factor, along with the fact that only counselling for "at-risk" carrier couples was available at the time. However, the dreadful clinical picture experienced in these early years, the uncertain prognosis and the projection of an ever increasing number of new cases as life expectancy was improving with better care, led health authorities and medical specialists to adopt and implement a programme for the prevention of newly affected births in some high prevalence countries. This gave "at-risk" couples the option of avoiding an affected birth.

The first attempts at large scale and national prevention were adopted by some Italian provinces, Greece and Cyprus from the 1970s [7,8, 9,10]. These have served as models for other high prevalence countries, to formulate their own programmes. Later, prenatal diagnosis was introduced and became an additional choice for couples [11].

Support for these programmes also came from the WHO, which formed a Working Group in the 1980s.

In one of the WHO working group first meetings it was stated:

"a genetic control programme is an integral strategy combining the best possible patient care with prevention through carrier screening, genetic counselling and the availability of prenatal diagnosis" [12].

Further to this, a WHO Executive Board decision (EB118.R1) in May 2006, Member States are urged to "design, implement, and reinforce in a systematic and effective manner, comprehensive national, integrated programs for prevention and management of thalassaemia, including information and screening. such programs being tailored to specific socioeconomic and cultural contexts aimed at reducing incidence, morbidity and mortality".

These prevention programmes were developed in accordance with fundamental principles of genetic counselling [13,14] i.e. the autonomy of the individual or couple, the right to complete information, and strict confidentiality. Following these principles, couples were enabled to make 'informed choices' concerning marriage and reproduction, according to the information provided by the professional(s) offering counselling.

For all the above reasons, voluntary avoidance of new births affected by thalassaemia has been gradually encompassed in several national thalassaemia policies.

In this Chapter, an investigation to identify any changes that have occurred through the years, in policy or public attitudes to thalassaemia prevention given the improvement in patient outcomes seen in recent years, is undertaken. The possibility of an increase in birth incidence of affected births in countries where optimal care is available is a question to be debated. Indeed, currently, because of the implementation of complex but comprehensive clinical management, which now includes early detection and effective management of complications, patients are surviving into the 7th decade [17, 18, 19]. These good outcomes hold true however, in high income settings but are variably achieved in several middle and low income countries. The need to control birth incidence by offering a prevention programme is still, for these reasons, necessary in countries in which premature death of patients is the prominent clinical outcome.

PREVENTION PROGRAMMES

The free and informed choice of "at-risk" couples is the guiding principle of any programme of control presented to an "at-risk" population, including the provision of adequate and accurate information. Community awareness, and the quality of genetic counselling also have a significant impact on parental choices. All "at-risk" couples are presented with the same choices in premarital and preconception screening, and need the appropriate counselling in order to proceed to their own 'informed' decisions *(Table 1)*. These are significant elements affecting the choice of partner, marriage and in creating a family. Therefore, planning a service requires that these considerations are effectively addressed, in nationally coordinated, supported and funded strategies.

Risk identified	Choices
Before marriage or pregnancy	1. To avoid marrying another carrier 2. To separate from a relationship that puts their future children "at-risk" 3. To marry their chosen partner, with knowledge of the risk involved
After marriage or cohabitation	1. To proceed with a pregnancy, accepting the risk of possibly bearing an affected child 2. To avoid having children (e.g. choosing adoption) 3. To undergo prenatal diagnosis, choosing to either accept an affected child or pregnancy interruption 4. To use pre-implantation genetic diagnosis, as an alternative to prenatal diagnosis, and so avoid pregnancy interruption
When already pregnant	1. To undergo prenatal diagnosis (if in early pregnancy) 2. To accept any outcome with no further action 3. To interrupt the current pregnancy with no further action

Table 1. Choices available for couples "at-risk".

In cases where prevention policies for thalassaemia have been implemented, those which have demonstrated success and effectiveness include mainly the following key components:

- National strategy on prevention which suggests government approval, control and support
- Public awareness programme
- Screening programme to identify carriers
- Genetic counselling services
- Prenatal diagnosis as a choice for "at-risk" couples
- Preimplantation genetic diagnosis
- New emerging technologies (such as non-invasive prenatal diagnosis)

The difficult choices faced by "at-risk" couples, make the quality of information and counselling expertise provided of the utmost importance and this, unfortunately, falls below expectation in many settings [20]. Cultural differences across the world have resulted in a variety of practices, which must be taken into account [21] and understood

when ethical considerations are discussed. Consanguineous marriage is common in most countries of the Middle East, where the β-thalassaemia carrier rate is also high. Interruption of pregnancy has a variable acceptance across many cultures and individual couples may even differ among themselves. The acceptance of pre-implantation genetic diagnosis (PGD) over prenatal diagnosis and the possible interruption of pregnancy, for example, in many settings has had limited utilisation due to cost and complexity. If non-invasive pre-natal diagnosis becomes feasible it may also have a poor uptake across the world because of the continuing need for pregnancy interruption. All these factors suggest the conclusion: a single policy on prevention cannot be universally accepted in view of the diversity of cultures, services offered and the patient clinical outcomes that are experienced in various settings.

The thalassaemia patient journey in each setting is a factor that influences public responses to prevention. To date, limited information exists on the quality of care across the world, and even less on patient outcomes, including both morbidity and mortality, especially in developing countries. This requires the establishment of national patient registries [22], which in fact very few countries keep *(for more information see Chapter on Registries).*

The adoption of programmes aimed at the reduction of birth incidence cannot be an isolated policy. It must, at the same time address the unmet needs of patients, who now, with good quality care, have the chance to return any investment in their care by becoming productive members of society. When considering the reduction of new affected births as a policy, the element of autonomy of the couple is vital and is based on 'informed choice', which depends on accurate unbiased information [23]. The extent to which this is adhered to cannot be quantified when looking at an overview of national policies. The objective of such policies is not always clearly stated by health planners but ultimately they offer the chance for reduction of affected births. How this is achieved, the contribution of carrier screening, the acceptability of pregnancy interruption and other measures, will vary from country to country and from culture to culture. The efficacy of the prevention programmes is most often evaluated by the reduction of affected births and no doubt, a number of countries, mainly those with high incidence of β-thalassaemia, have already achieved a significant decrease of the birth of children with the disease. However, control of a disease is ultimately a reduction in suffering, so the improvement of the lives of affected patients and family outcomes must be the ultimate goals.

Patient care leaves much to be desired in most of the world *(for more information see other relevant Chapters).* Moreover, new therapies are emerging, which due to cost, are anticipated to only reach a minority of patients in the developing world. Moreover, universal health coverage has yet to reach most of the global population. Collectively, these facts demonstrate a picture of inequity in care. Hence, policies for the reduction of affected births cannot be considered an outdated philosophy.

PUBLIC AWARENESS

One aspect that is a major factor in any public health policy is the adequate preparation of the public through an effective education and awareness raising policy [24]. The real impact of this is difficult to adequately assess, since there may be policies and actions in place, and whether they reach the public effectively can only be assessed through questionnaires.

For example, in Oman [25] 36% of married participants in a survey who reported that they did not volunteer for a premarital test, gave ignorance as the reason, while another 13% did not know where to go for a test; among other reasons, 6% stated there was lack of knowledge of the partner's status before marriage. Most, believed that a premarital test is necessary, but 30% were not in favour of taking it even though 50% agreed that the test should be made compulsory. The situation in Oman is mirrored in other countries. In Malaysia [26], in 70% of families in which a child with thalassaemia was born, neither parent was aware of their carrier status until their child's diagnosis; while in other cases they did not receive accurate information or support for prenatal diagnosis and option for pregnancy interruption. Of the 38 parents interviewed, 20 (52.6%) indicated that they would terminate an affected pregnancy. Notably, 52.2% of Muslims supported termination. Likewise, in Saudi Arabia [27], of 920 students, 445 (48%) had never heard of thalassaemia and despite the mandatory premarital testing for thalassaemia, only 50% of married students stated having heard of the disease.

This lack of awareness constitutes a lack of communication and ineffectiveness of the policies adopted (or not adopted) to reach the wider society, and are witnessed across the world. In many cultures a fear of stigmatisation (often underplayed as a factor) plays a large part in decision, as the perceived reduction of being a good choice in the marriage 'market' may be endangered. This issue is ignored in health education campaigns and will take much time, even years, to overcome in some societies [28, 29]. Lack of population awareness, cultural and religious factors, the element of stigmatisation and

marriage practices all differ widely across the world, and greatly influence the acceptance of genetic prevention. A dialogue with the public has been an essential component of programmes, such as the one practiced in Cyprus and other countries [30].

COUNSELLING

Information to the public must be supplemented by individually informing the "at-risk" couple in a session, or even better in a series of counselling sessions. To offer as many 'choices' as possible, carrier detection should occur before conception; the timing of screening is thus of great importance [29]. In areas where thalassaemia is of low prevalence, reaching out to the "at-risk" population is difficult and screening in early pregnancy has been adopted. This however limits the choices of parents to either accept an affected child or proceed to prenatal diagnosis and thereafter to possible interruption of an affected pregnancy [31]. The difficulties of conveying correct, reliable, updated and understandable information to couples was recognised early and not only in the case of haemoglobinopathy prevention [32].

One important question is the quality of counselling and who, with what qualification and/or prior training, offers the service. Rowley *et al*. [20] investigated the effects on programme efficiency, comparing if the counselling was offered by primary providers and tertiary providers. They used indicators such as (i) the proportion of β-thalassaemia births after counselling, (ii) the knowledge of both partners "at-risk" after counselling and (iii) whether the individual counselled brought his/her partner to be tested. The two groups differed only in the case of bringing the partner to be tested. The similarity in effectiveness however may be because the study was preceded by a training session, so that the primary group were made familiar with a 'counselling protocol'. In the real world, haemoglobinopathy counselling is not offered by professional tertiary, trained professionals. Especially in large, high risk populations, such counsellors are scarce and usually concerned with rare hereditary conditions while haemoglobin disorders are left to clinic doctors, nurses and laboratory personnel who know the condition, but however are not trained in counselling. In some cultures, directive counselling is the norm.

The situation in the early days of screening in Cyprus, in an analysis of the causes of 55 children born with thalassaemia despite an ongoing screening campaign, indicated that parents were not advised to go for testing (49%), or neglected to be screened (13%), or were given wrong advice (13%, usually by an obstetrician), or presented late in pregnancy (16%); 9% were screening laboratory errors [8]. This is still the situation in

many high prevalence countries across the world, where poor counselling, due to inexperience and/or lack of training is added to the challenges.

In a recent publication (2018), there were only 7,000 professional and qualified genetic counsellors globally, and of these only 350 were in the high prevalence countries (mainly in Asia); these countries include a 1.6 billion population with countless genetic conditions and with annual anticipated thalassaemia and sickle cell disease births of around 25,000 and 20,000 respectively [33]. The possibility of having professional counsellors for haemoglobinopathy prevention is therefore, very small.

Counselling services that are based on internationally accepted principles are the basis of in-depth information for the "at-risk" couples and lead to real informed choices. The global lack of trained counsellors is a major obstacle to the provision of quality counselling, albeit this does not mean that genetic counsellors should always be employed. The professionals (doctors, nurses), social workers and others who do counsel in real life should be trained before being permitted to assist people in understanding the implications of their risk for genetic diseases and presenting them with choices.

CULTURAL INFLUENCES

Most Islamic countries, particularly in the Middle East, practice mandatory premarital screening. This is, to a great extent, due to the fact that pregnancy interruption is not allowed by civil law in some countries, even though according to religious law, expressed in various theological opinions (fatwas), termination is acceptable up to the first 100-120 days of pregnancy [34]. Premarital screening, for these reasons, is conducted with the aim of limiting marriages between carriers. Marriage restriction in these countries is not, however, supported by the social norms, which include customary cousin (consanguineous) and arranged marriages. However, mandatory premarital screening has been said to promote community awareness of haemoglobinopathies, which may in the long-term increase the efficacy of the programme [35]. Nonetheless, even where premarital screening is mandatory, marriage cancellation may be not acceptable to most [36].

Consanguineous marriage is associated with a higher risk of having offspring with an autosomal recessive condition, if this is present in the family. The prevalence of congenital anomalies in the offspring of first cousin marriages (where they occur) is estimated to be 1.7 – 2.8% higher than the general population risk [37]. If evidence-based

recommendations are to be the basis of community and individual counselling, then the social factors behind these traditions must also be considered, and the benefits weighed against the risks. Culturally sensitive advice in genetic prevention is imperative and the contribution of other academic disciplines, such as sociology and anthropology, as well as legal and religious input, help provide a more tailored approach to communication between the medical specialists and the general population.

Health planners should also be aware of cultural change over time. One example is Cyprus, where premarital screening has been the choice of the services, the public and the Church, which wanted to limit the interruption of affected pregnancies by pursuing the timely detection of carrier couples. In the 21st century, civil weddings are increasing and many couples cohabit and marry after the first, or even second, pregnancy. So there are new social issues which may make premarital testing less effective as a measure, and pre-conception screening the focus of public education. Likewise, in the Middle East, cousin marriage is decreasing with recent urbanisation [38, 39, 40].

AVAILABILITY AND IMPACT OF PRENATAL DIAGNOSIS

Prenatal diagnosis leading to interruption of pregnancy is viewed with particular distaste, not only on religious grounds, but also by couples "at-risk" and families, whatever their cultural background [14]. Factors that made the interruption of pregnancy acceptable in some settings included the spectre of premature death of the child, the complexity, expense and risks of treatment, and the painful experience of a previous affected child. Modell *et al*. [41] showed that prenatal diagnosis was introduced on the basis of the collective informed choices of couples "at-risk" . In Cyprus, avoiding marriage to another carrier was rejected by 90% of the population as a means of prevention of thalassaemia, while prenatal diagnosis was immediately accepted [7]. A large majority accepted prenatal diagnosis also in Sardinia [42] and Greece [43]. The effect of prenatal testing and interruption of affected pregnancies has been a basic factor in reducing affected birth incidence in the Mediterranean countries and others, such as Iran, where all aspects of prevention (including prenatal diagnosis) are implemented leading to an over 80% reduction in birth incidence [44] This is not always acceptable in other cultures, but it is noted that without this choice, avoiding carrier marriages may also not be acceptable.

CURRENT TRENDS

These complex steps and difficult choices have led couples to question the need to avoid the birth of affected children, particularly with improved patient prognosis. This trend is currently limited but visible. Taking the example of Cyprus, where since the 1980s the birth of thalassaemia patients was reduced to 0-2 per year from an expected number of 50-70; in recent years up to 8 new cases per year have been seen (Fig.1 data from the Cyprus thalassaemia registry).

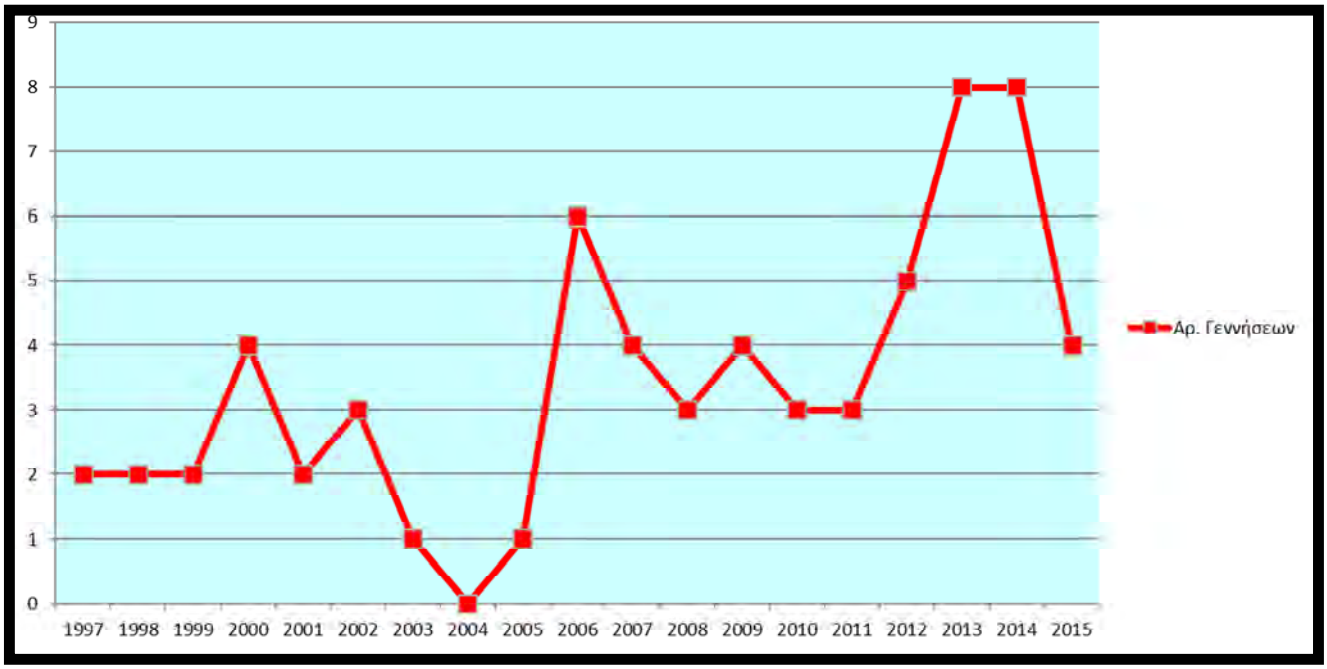

Figure 1. Annual births of babies with -thalassaemia major in Cyprus.

When asked by journalists, one Cypriot couple responded that a child with thalassaemia can live to old age, so *'we have chosen to have our baby'*. This confidence in outcomes has also been experienced in Italy; in Sicily, the residual cases *'were because of a conscious choice by expectant parents in relation to improved life expectancy as well as improved quality of life of the affected patients'* [45]. Other reasons for residual births exist of course, for example, the influx of migrant groups with cultural differences with perhaps a lack of appropriate and sufficient knowledge on the disease compared to the indigenous population, poor communication and counselling and laboratory errors [46]. In many countries ignorance, poor communication and poor laboratory standards are expected to be the more prominent reasons.

CONCLUSIONS

Almost 50 years ago programmes were initiated in high prevalence countries, mainly in the Mediterranean basin, aiming to limit new affected births. These countries had in mind the need to reallocate resources to more effectively address the increasing needs for lifelong management of patients. Over the years, these needs have been largely satisfied in these countries, and this is reflected in the results related to patient outcomes. These may indeed not have been achieved if the thalassaemia birth incidence remained unchecked.

Populations "at-risk" have made choices based on awareness programmes and the poor clinical picture, including early mortality of affected children and the difficulties faced by the families. Social determinants, such as having to still find paid blood donors or replacement donations (which remains the case in the majority of countries) and to provide medications beyond the capacity of the family income were, and still are in many countries, important factors in the acknowledging the necessity of thalassaemia prevention programmes.

Over the years, this situation has begun to change, but only in some very limited parts of the world where patient outcomes have indeed shown dramatic improvements. In many of the high prevalence countries of the world, however, conditions related to significantly improved patient outcomes have not substantially changed.

As long as the burden of care for thalassaemia patients manifests as out-of-pocket expenses for families and is not supported by healthcare systems, inequalities and poor outcomes will continue to shape the global landscape of these conditions.

The impact on the whole family in countries where universal health coverage is not effective, must not be underestimated. In a social study from a developing country (conveyed through a confidential report from the country's authorities), 42% of the surveyed families pay their own health expenses and nearly 80% are in debt. Such information on the plight of families is indeed the daily experience in the work of TIF. This is without considering other psychosocial effects, including isolation and stigmatisation. The socioeconomic consequences of chronic illnesses must always be at the forefront when health planning is being considered.

Offering people in these countries the possibility to choose and even prevent the birth of affected children, therefore remains perhaps a less painful alternative to experiencing multiple medical complications and early death. For such countries, limiting new annual

affected births remains a policy, which may be regarded as justified. The concept of eugenics, often cited as criticism of prevention of any genetic disease, cannot be sustained when the overall picture of severe and lifelong suffering is understood. When Galton first used this term [47] he had in mind the '*the improvement of the inborn qualities or stock of the human population*'. In medical genetics, the aim of hereditary disease prevention programmes is to offer and contribute to improvements in the lives of patients and their families [48].

In countries where the patient outcomes indicate the possibility of a long and good quality of life, the perspective on prevention has changed or has begun to change. Couples are now seeing adult patients, often professionals, and are asking why should their child not have the same fate? People are aware of new therapies, which may either cure or seriously reduce the need for blood transfusions and all the consequences that follow this dependency. Is the choice of 'prevention' still relevant in such settings? However, the added value of prevention cannot be ignored when weighed by policy-makers in respect to ensuring the provision of quality care to existing patients and the *competition* for medical, public health and infrastructure resources, that the steadily and exponentially increasing numbers of affected children will entail, in the absence of prevention. Indeed, the increase in patient numbers goes hand-in-hand with increasing costs for treatment, that even in the developed high Human Development Index (HDI) countries of the world may not be sustainable. Therefore, risk information and genetic counselling must still be available for people to make fully informed choices.

Public awareness policies, and their continual amendments to reflect societal perceptions, norms and other impacting factors (e.g. migration of populations) should continue to be pursued by national, regional and international professional, medical, scientific (e.g. haematology associations) organisations as well as health bodies (e.g. WHO) and patient support groups (e.g. TIF) in an effort to safeguard the welfare of patients across all countries, including importantly those where no policies are currently implemented and/or suboptimal services exist. In these cases, awareness can help in advocacy and motivational actions.

People "at-risk" of genetic diseases like thalassaemia, in whichever healthcare environment they may live, will always be faced with challenges and painful choices in their reproductive lives and the effort of every government to provide all available tools to support their decisions must continue. Their support by healthcare professionals and patient organisations at the national, regional and international level, in addition to relevant official health bodies (mainly the WHO) is imperative to ensure informed decisions are made.

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