IMPROVING DIAGNOSIS, REDUCING MISDIAGNOSIS – THE CASE OF THALASSAEMIA

Dr Androulla Eleftheriou

Executive Director, Thalassaemia International Federation
President, Cyprus Alliance for Rare Disorders
Member of the Board of Directors of the International Alliance for Patient Organizations (IAPO)

Thursday 23 May 2019
Universal Health Coverage: Including Rare Diseases to leave no-one behind
Informal Side Event, 72nd World Health Assembly

THALASSAEMIA INTERNATIONAL FEDERATION

THALASSAEMIA INTERNATIONAL FEDERATION

Thalassaemia International Federation (TIF)

Established in 1986 as a

- Non-profit
- Non-governmental
- Patient/parent-driven

5 Founding Members from National Patient Associations of Cyprus, Italy, Greece, USA, UK – the first members

6 Medical Advisors forming the Scientific Advisory Panel

Supported by the World Health Organisation

Mission: Development and implementation of national disease – specific control programmes within national healthcare systems based on universal coverage

In 1986

Vision: Equal and timely access to quality health, social and other care for all patients with thalassaemia globally, in a truly patient-centred healthcare setting

Values:

- Patient-centredness
- Strong patients' voice
- Health and social equity
- Accountability
- Independence
- Transparency
- Ethos

Statements by TIF President, Mr Panos Englezos

1996: TO ACHIEVE ITS MISSION TIF IS FIGHTING FOR:

(i) POLITICAL RECOGNITION OF THE DISEASE BURDEN, NATIONAL/INTERNATIONAL LEVEL

(ii) POLITICAL COMMITMENT TO BUILD AND SUSTAIN NATIONAL CONTROL PROGRAMMES

2003: TIF NEEDS TO ACHIEVE: (1) POLITICAL COMMITMENT AT THE NATIONAL, REGIONAL, INTERNATIONAL LEVEL

- INCREASE OF GOVERNMENT HEALTH EXPENDITURE
- PROVISION OF FULL COVERAGE/REIMBURSEMENT FOR CHRONIC DISEASES

(2) NEED TO PRIORITISE Hb DISORDERS ON WHO'S PROGRAMMES:

- NON-COMMUNICABLE DISEASES (NCDs) (WHA61.14)
- BIRTH DEFECTS (WHA63.17)

(3) NEED TO MONITOR IMPLEMENTATION OF WHO RESOLUTIONS:

- SPECIFIC: EB118.R1 (THALASSAEMIA) & WHA59.R20 (SICKLE CELL ANAEMIA)
- NON-SPECIFIC: WHA63.12 (AVAILABILITY, SAFETY, AND QUALITY OF BLOOD PRODUCTS); WHA63.18 (VIRAL HEPATITIS); WHA65.19 (COUNTERFEIT/SPURIOUS MEDICINES)

THALASSAEMIA INTERNATIONAL FEDERATION

Thalassaemia International Federation (TIF)

227 National Patient Associations in **61** countries

216 Medical Advisors

63 Patient volunteers

Wide Network of Collaborators:

- **8** Medical, Scientific & Academic bodies, associations & societies
- **16** Patient NGOs at European & International levels
- **36** Industry organisations / companies

Mis … n of
na … es
wi
ur

Vi … alth, social and other care
fo … a truly patient-centred
he

Va
- …
- … ncy
- …
- …
- …

Mission

Vision

Values

Remain the same….

In 2019

*Working in official relations with the **World Health Organization (WHO)** since 1996*

*In special consultative status with the **United Nations Economic and Social Council (ECOSOC)** since 2017*

*Official Partners of the **European Commission** in the field of Health since 2018*

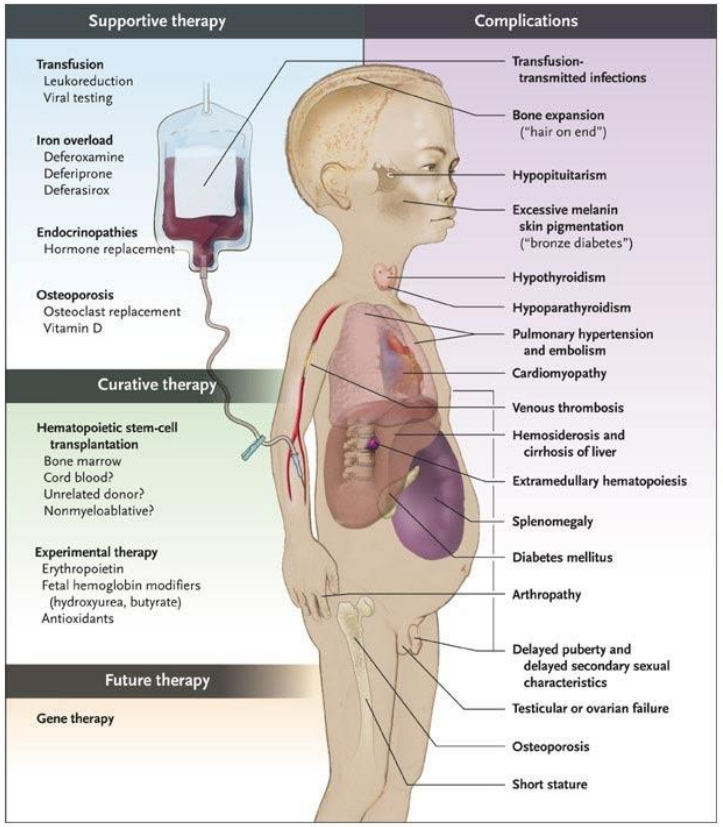
TIF Members Global Representation

EURO	Albania, Azerbaijan, Belgium, Bulgaria, Cyprus, France, Germany, Greece, Ireland, Israel, Italy, Luxembourg, Malta, Netherlands, Portugal, Romania, Spain, Turkey, UK
AMRO	Argentina, Canada, Trinidad & Tobago, USA
EMRO	Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Morocco, Pakistan, Palestine, Saudi Arabia, Sudan, Syria, Tunisia, UAE, Yemen
SEARO	Bangladesh, India, Indonesia, Maldives, Nepal, Sri Lanka, Thailand
WPRO	Australia, Cambodia, China PDR (including Hong Kong SAR of China and Taiwan Province of China), Malaysia, Philippines, Singapore, Vietnam
AFRO	Algeria, Mauritius, South Africa

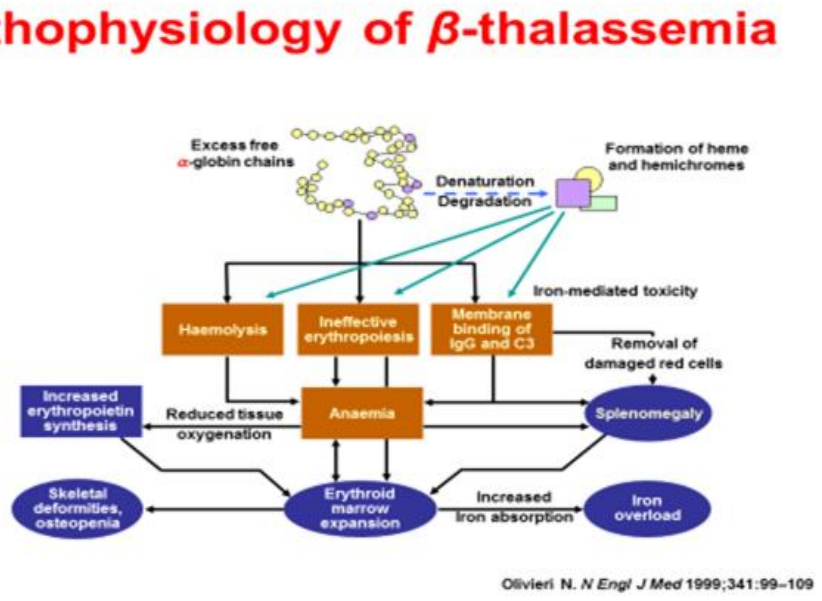
Thalassaemia: A polyorganic disease

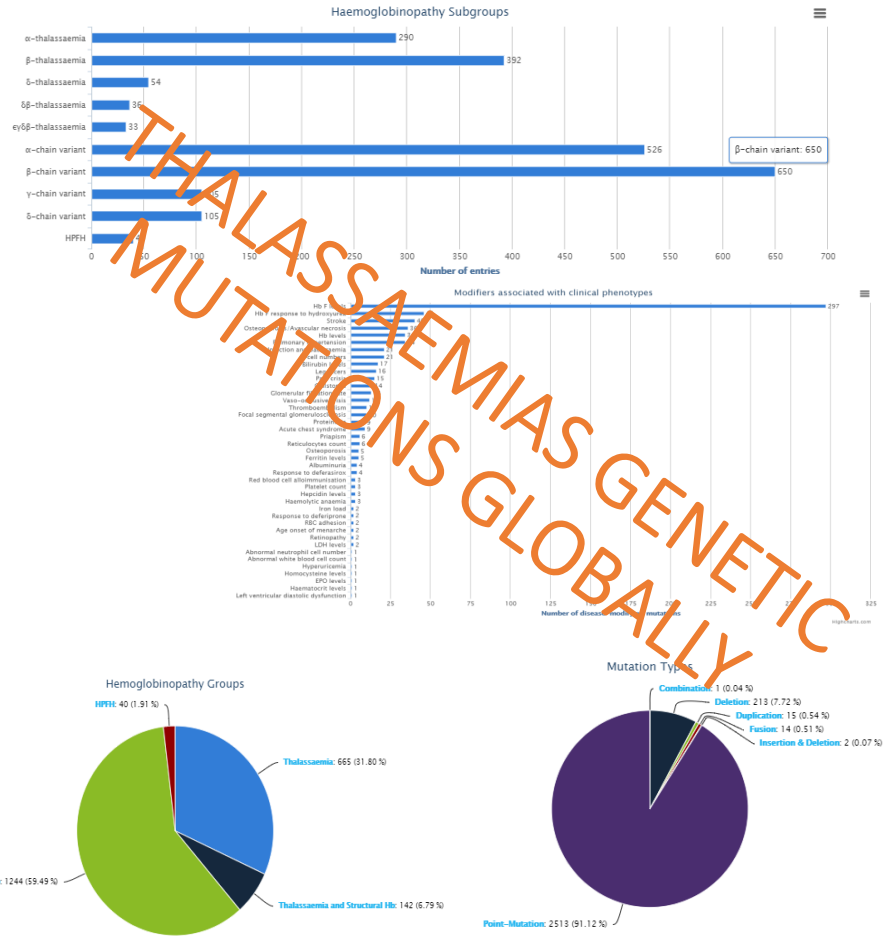
Thalassaemia is no longer a fatal disease of childhood, but this is not the case globally.

Medical /public health impact



Source: New England Journal of Medicine





THALASSAEMIAS GENETIC MUTATIONS GLOBALLY

From the ITHAnet Portal. Available at http://www.ithanet.eu

THALASSAEMIA INTERNATIONAL FEDERATION

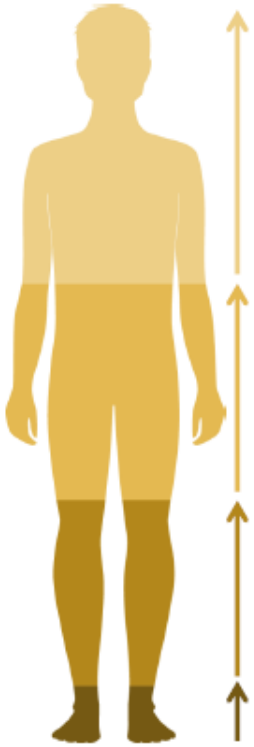
Consequences of Un-diagnosis / Misdiagnosis / Late Diagnosis

NTDT patients may develop iron overload if untreated

NTDT patients develop iron overload primarily due to increased gastrointestinal iron absorption[1,2]

β-thalassaemia intermedia patients have been shown to develop severe iron overload in the liver if left untreated[3,4]

Liver iron concentration (LIC) is associated with increased risk of complications in patients with β-thalassaemia intermedia[5]



9.0 mg/g dw
Osteoporosis

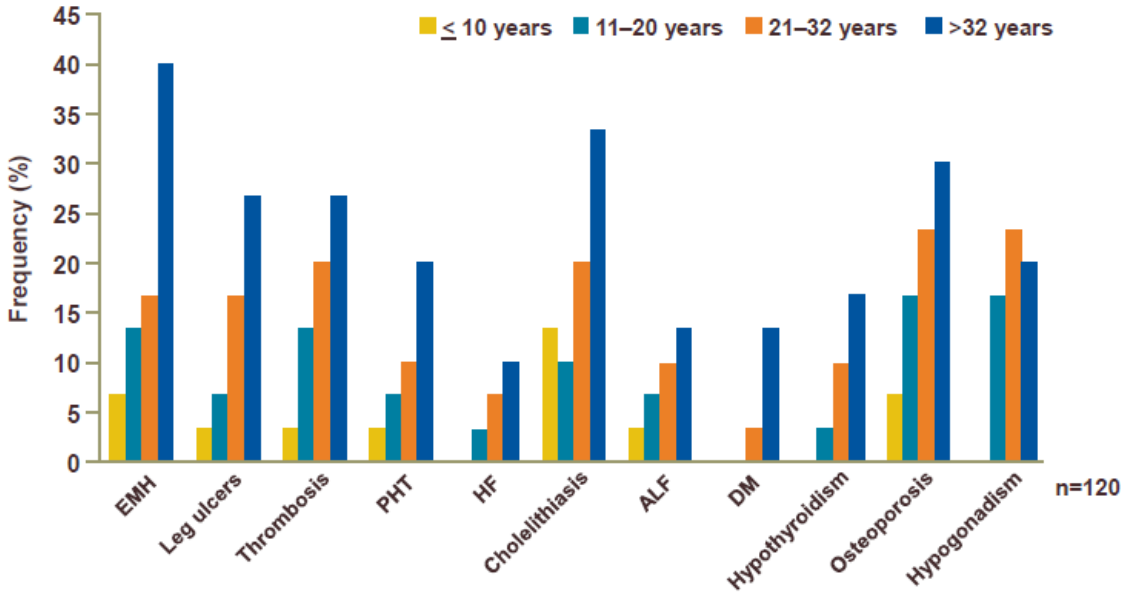
7.0 mg/g dw
Thrombosis
Vascular complications

6.0 mg/g dw
Pulmonary hypertension
Hypogonadism
Hypothyroidism
Endocrine/bone complications

1.8 mg/g dw
Normal LIC

[1]Pippard M *et al. Lancet* 1979;2:819–821; [2]Pootrakul P *et al. Birth Defects Orig Artic Ser* 1988;23(5B):3–8
[3]Taher AT *et al. Am J Hematol* 2010;85:288–290; [4]Origa R *et al. Haematologica.* 2007;92:583–588;
[5]Musallam KM *et al. Haematologica* 2011;96:1605–1612

NTDT complications increase with age if left untreated



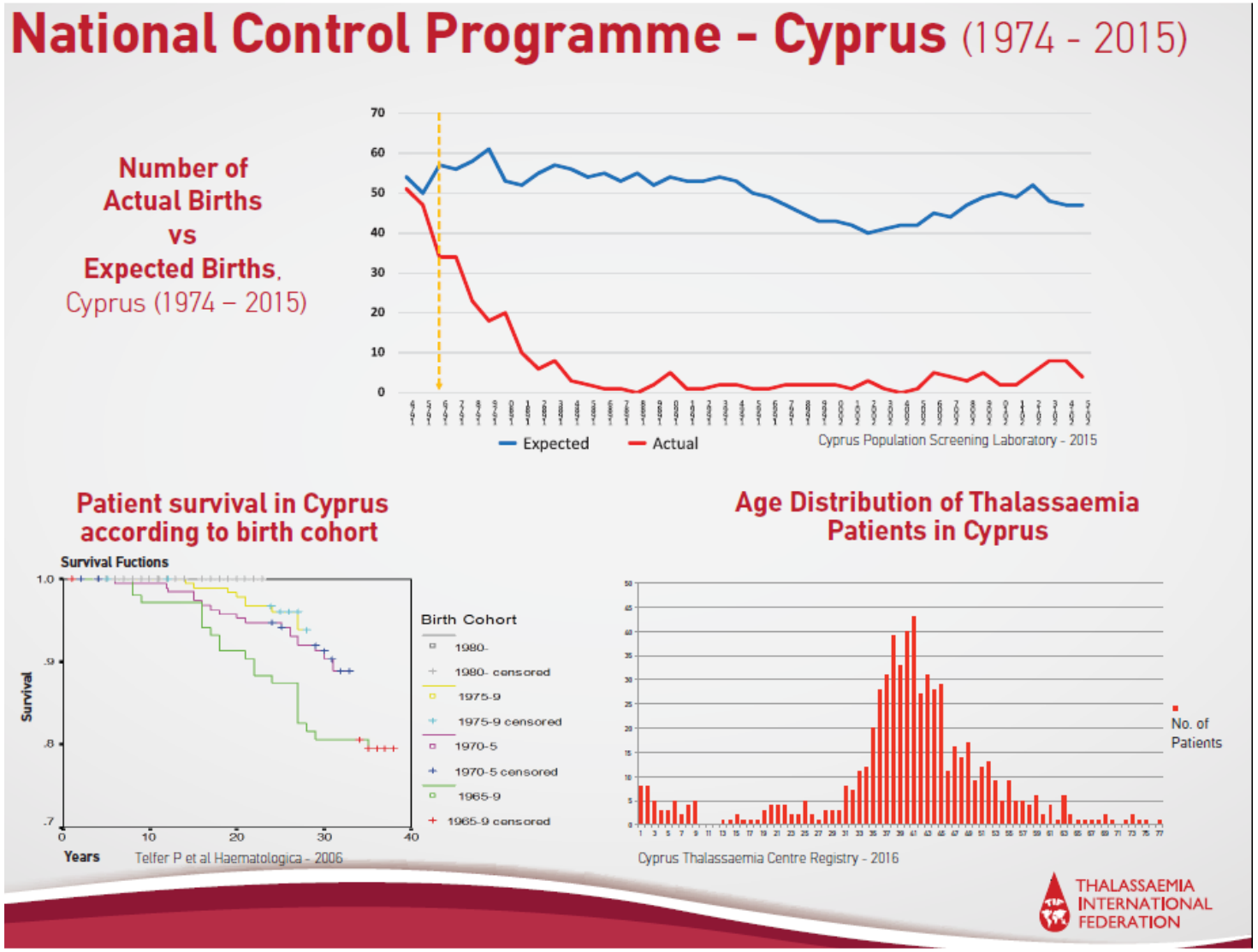
EMH, extramedullary hematopoiesis; PHT, pulmonary hypertension; HF, heart failure; ALF, abnormal liver function; DM, diabetes mellitus

Taher AT *et al. Br J Hematol* 2010;150:480–497

Pioneer success stories of the Southern Mediterranean Example: Cyprus

Cyprus, Italy, Greece: The first countries to develop disease-specific policies within their national healthcare system

Later followed by the **UK and France**



Pioneer success stories of the Southern Mediterranean Example: Greece

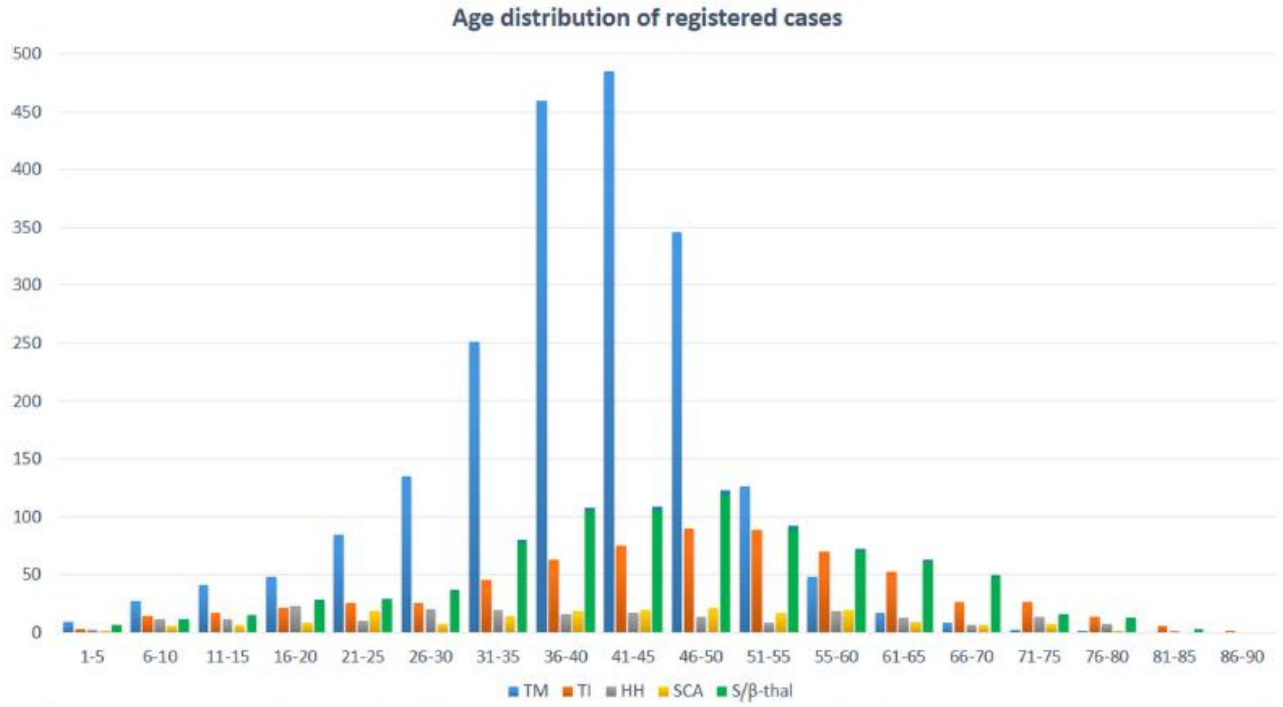
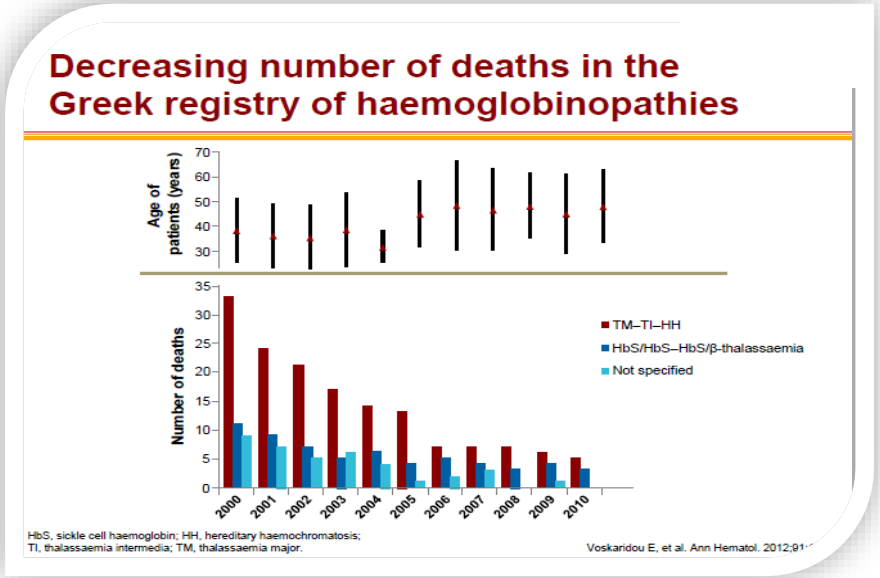
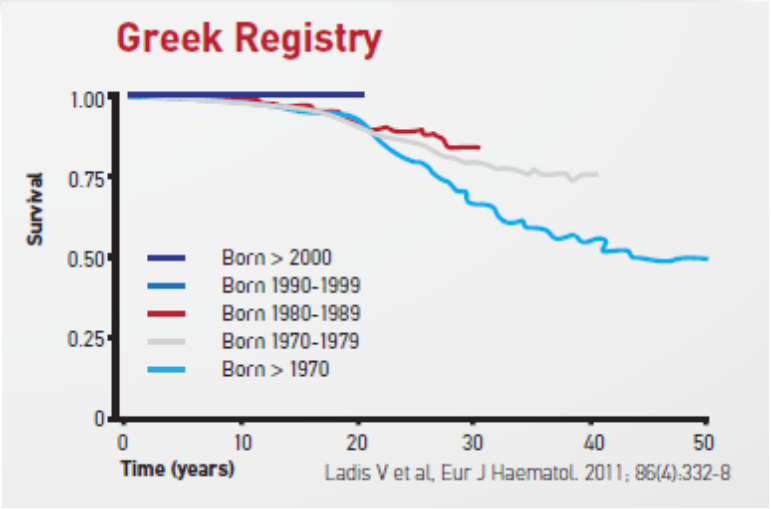


Fig. 1 Distribution of registered cases in the NRHG according to age groups. The peak of patient distribution corresponds to the age group of 36–45 years regarding TM, 46–55 years among TI, and 41–50 years among SCD patients. TM thalassemia major, TI thalassemia intermedia, HH hemoglobinopathy "H", SCA sickle cell anemia, S/β-thal double heterozygous HbS and β-thal

Source: Voskaridou E et al, 2018



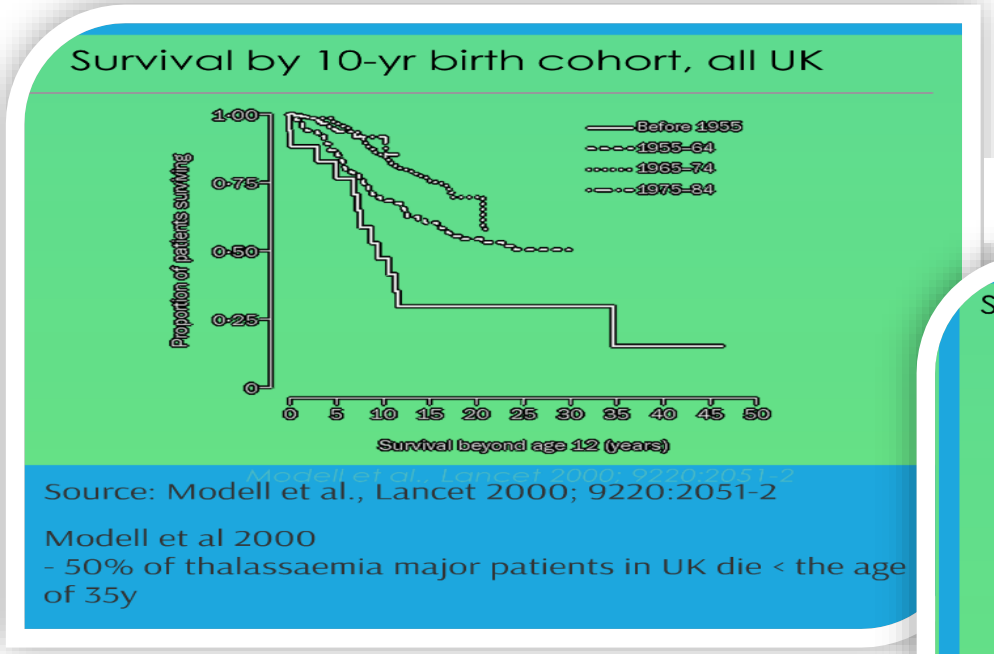


THALASSAEMIA INTERNATIONAL FEDERATION

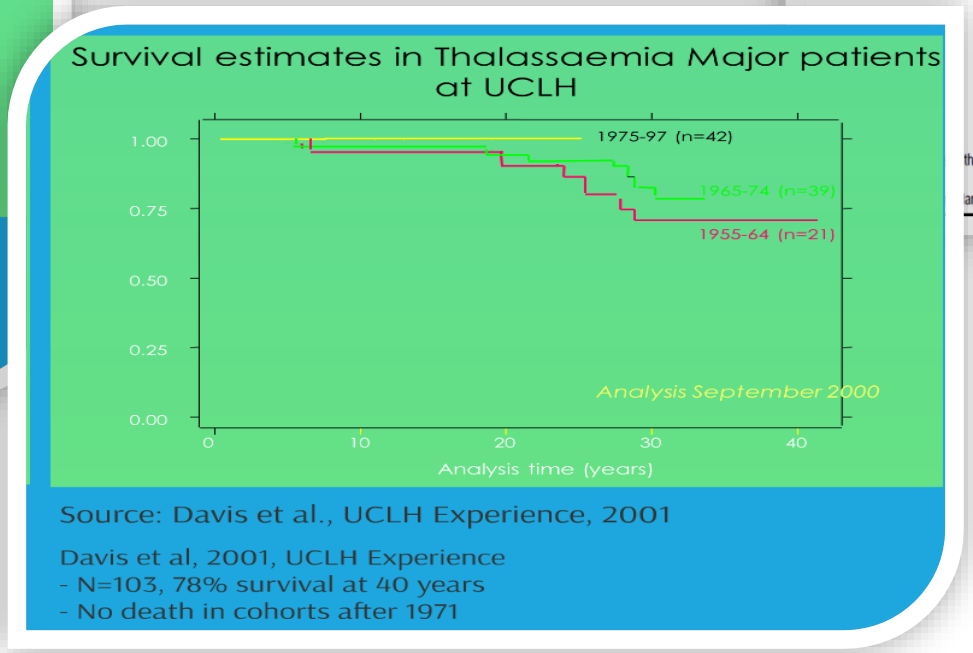
Before & After inclusion in the NHS – the example of the UK

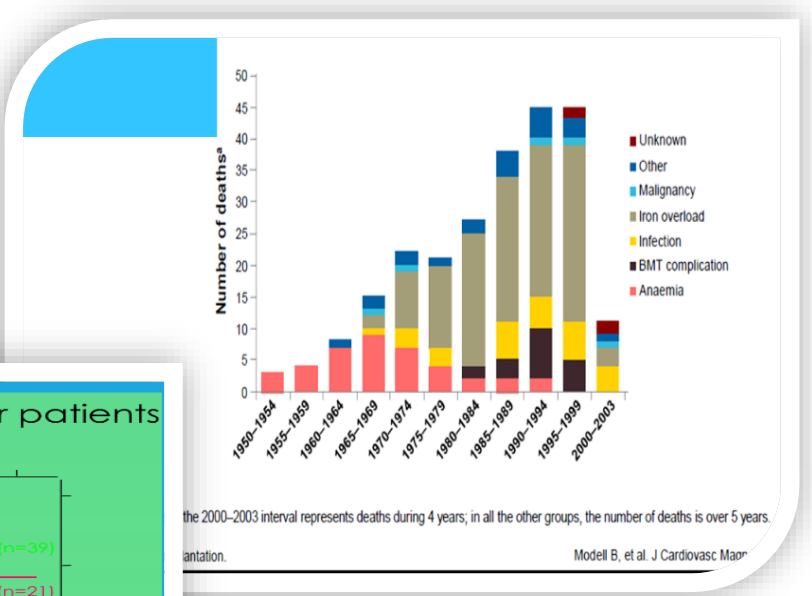
2003: Community awareness, diagnosis & Standards of Care are integrated in the NHS

Before inclusion in NHS:



After inclusion in NHS:



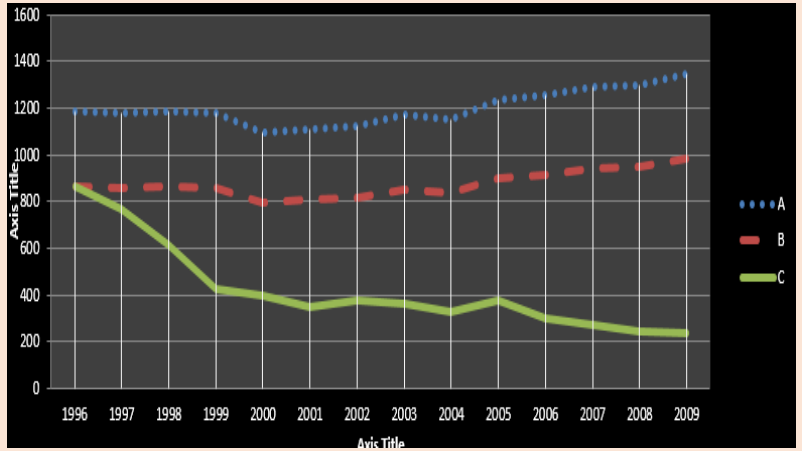


THALASSAEMIA INTERNATIONAL FEDERATION

Successful National Control Programmes: Middle East

(consequent to inclusion of control programmes in national HC system)

Iranian National Prevention Programme Results



C = Actual Births

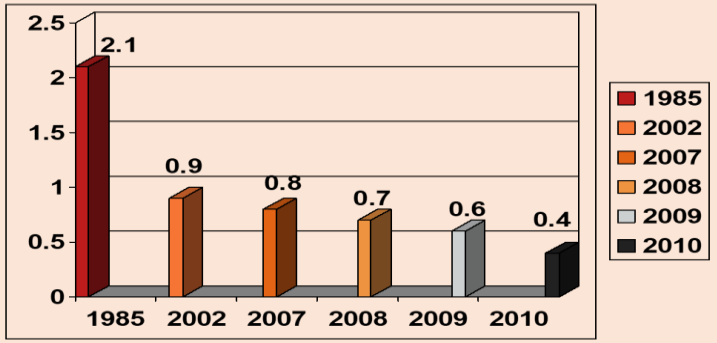
Iranian National Prevention Programme

2 *M. Hadipour Dehshal et al.* Hemoglobin, Early Online: 1–9

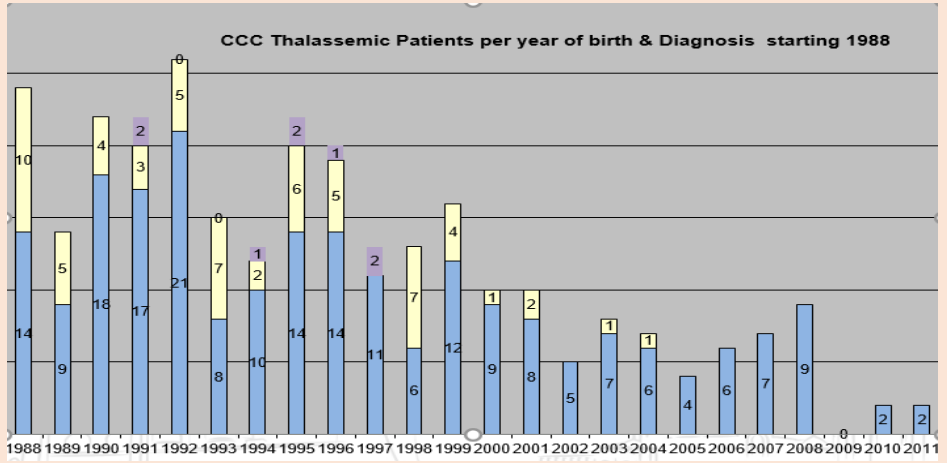
Step 1	Step 2	Step 3	Step 4
1. A couple decides to marry			
2. The couple decides to register their intent to marry at the notary office			
3. The couple undergoes compulsory thalassemia screening			
4. The male candidate is the first to undergo screening[a]	MCH >27.0 pg or MCV <80.0 fL	The couple are officially allowed to get married	
5. MCH >27.0 pg or MCV <80.0 fL			If indices are normal and Hb A_2 is <3.5%
6. The female undergoes CBC testing	MCH >27.0 pg or MCV <80.0 fL		
7. MCH >27.0 pg or MCV <80.0 fL			
8. Hb A_2 level in both male and female is evaluated	If Hb A_2 is <3.5% in either male or female		Treatment for iron deficience anemia and reevaluation of Hb A_2 and indices after 1 month
9. If Hb A_2 level is between 3.5 and 7.0% in both male and female, the next step should be taken			If indices are normal but Hb A_2 still is <3.5% in either male or female
10. The carrier couple are offered counseling by genetic advisors		If indices are abnormal but still is Hb A_2 <3.5% in either male or female	
11.			DNA analysis and globin chain synthesis studies are conducted

Figure 1. The process by which the National Thalassaemia Prevention Programme is implemented in Iran. (a) Thalassemia screening starts with the male to avoid stigmatization of the woman in a male-dominated society. MCV: mean corpuscular volume; MCH: mean corpuscular Hb.

Bahrain – Falling SCD births (1985 – 2010)



Lebanon – Declining new births (1988 – 2011)



Carrier Rates of β-thalassaemia & HbS in EMRO

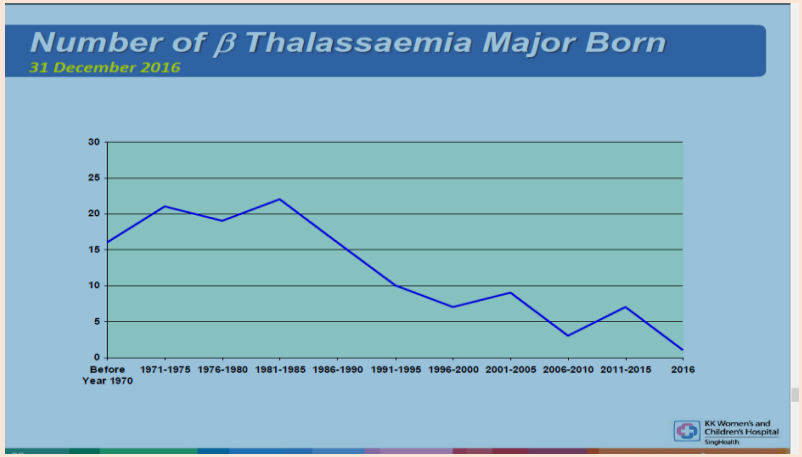
Country	B-Thal (%)	HbS (%)
Afghanistan	3	0
Bahrain	3.5	11
Egypt	5.3	0.3
Iran	4	1
Iraq	4.8	0.7
Jordan	3.5	1.5
K.S.A.	1.8	4.24
Kuwait	2.2	2
Lebanon	2.3	1.8
Libya	1.5	2
Morocco	1.67	1.78
Oman	2	6
Pakistan	5-6	1

Carrier Rates (Beta Thalassaemia) - Eastern Mediterranean Region

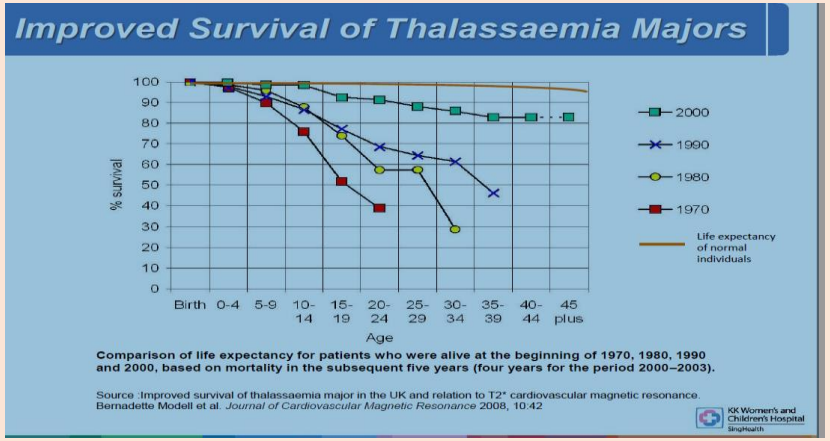
Selected EMR Countries

Successful National Control Programmes: West Pacific

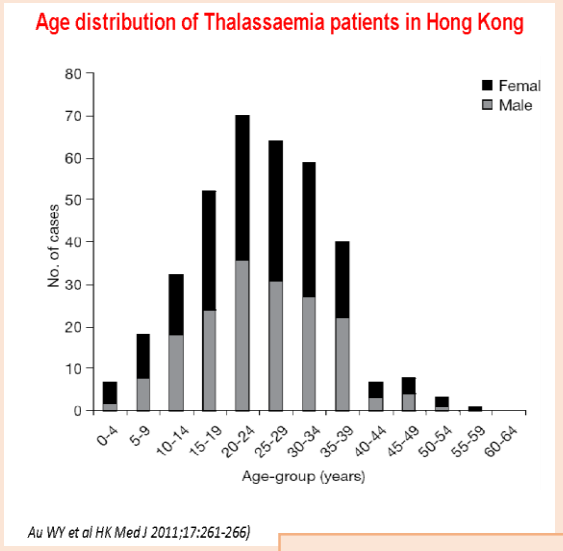
Singapore – Decrease in births (1970 – 2016)



Singapore – Increased survival (1970 – 2003)

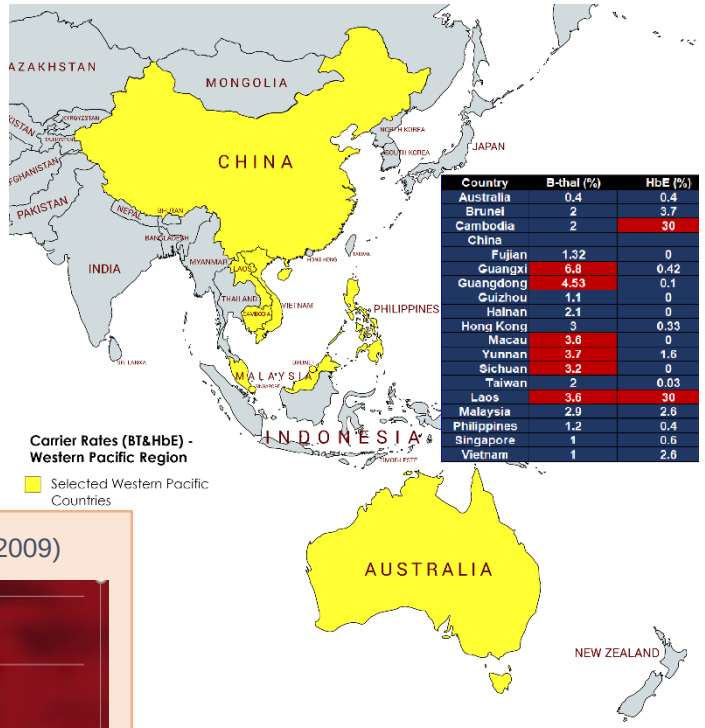


Hong Kong – Age Distribution



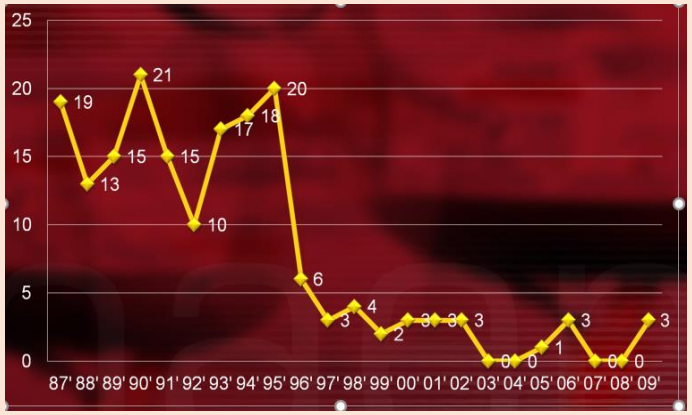
Au WY et al HK Med J 2011;17:261-266)

Carrier Rates of β-thalassaemia & HbE in WPRO



Country	B-thal (%)	HbE (%)
Australia	0.4	0.4
Brunei	2	3.7
Cambodia	2	30
China		
Fujian	1.32	0
Guangxi	6.8	0.42
Guangdong	4.53	0.1
Guizhou	1.1	0
Hainan	2.1	0
Hong Kong	3	0.33
Macau	3.6	0
Yunnan	3.7	1.6
Sichuan	3.2	0
Taiwan	2	0.03
Laos	3.6	30
Malaysia	2.9	2.6
Philippines	1.2	0.4
Singapore	1	0.6
Vietnam	1	2.6

Taiwan – Decrease in births (1987 – 2009)



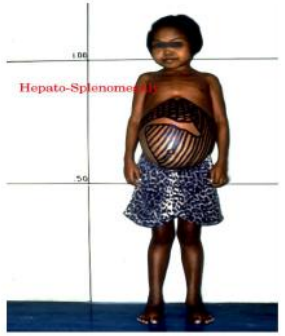
Successful National Control Programmes: South East Asia Example: Thailand

COMMON THALASSEMIC DISORDERS IN S.E. ASIA

MAHIDOL UNIVERSITY
Wisdom of the Land

Hb H Disease

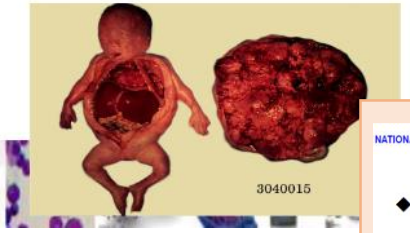
Homozygous β-Thal and β-Thal/Hb E



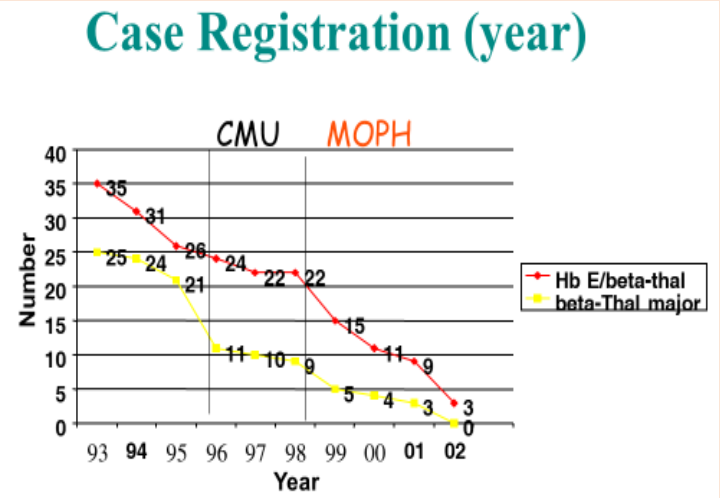
Asymptomatic Thalassemia

- α, and β-thalassemia trait
- Homozygous Hb E
- Homozygous
  Hb Constant Spring

Hb Bart's Hydrops Fetalis



Thailand – Reduction in new births (nationwide)



NATIONAL THALASSEMIA PROGRAM:

MAHIDOL UNIVERSITY
Wisdom of the Land

2000

◆Integration of thalassemia program to existing health care system

Dept of Health	Policy and education
University	R&D, Technical support
Regional Health Center	Co-ordination, Technical support
General Hospital	Complete service
District Hospital	Counseling, simple screening
Community Hospital	Counseling, transfer blood specimens

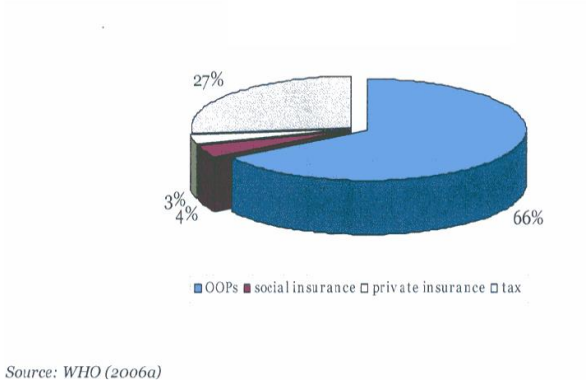
THALASSAEMIA INTERNATIONAL FEDERATION

Diagnostic challenges

1. **Huge challenges** particularly in NTDT cases

2. Contributing factors:

Comparison of total health spending in SEAR



Source: WHO (2006a)

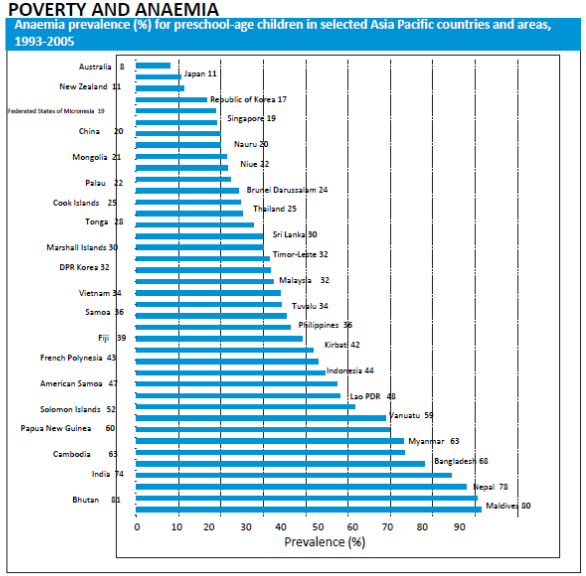
Table: Proportion of households with catastrophic health expenditure

Selected Asia Pacific countries	Percentage of households experiencing catastrophic OOP*
Viet Nam	10.45
Cambodia	5.02
Republic of Korea	1.73
Indonesia	1.26
Sri Lanka	1.25
Bangladesh	1.21
Thailand	0.80
Philippines	0.78

* Defined here as the incidence of household payments for health services exceeding 40% of net income after subsistence needs have been met.

Source: Xu K, et al. Household catastrophic health expenditure: a multi-country analysis. Lancet, 2003, 362: 111-117.

POVERTY AND ANAEMIA



Source: WHO global database on anaemia. Geneva, World Health Organization. Available from: http://www.who.int/vmnis/anaemia/en/Accessed May 2007.

3. Lack of integrated disease-specific policies within UHC healthcare system, leading to **undiagnosed / misdiagnosed cases with thalassaemia left out**

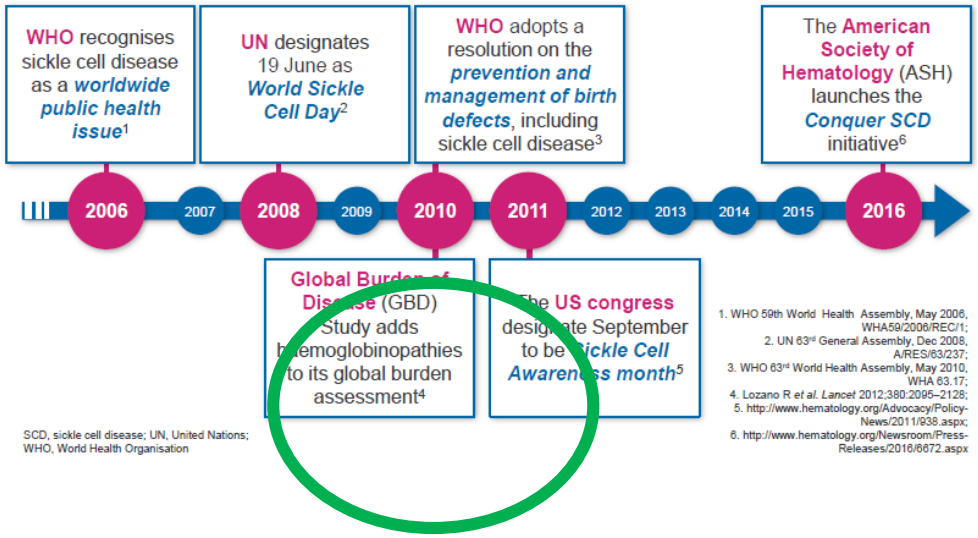
4. **High % of comorbidities** leading to **disabilities**, and **low quality of life** for patients

Considering that thalassaemia is both PREVENTABLE and TREATABLE,
this situation is UNACCEPTABLE and
a violation of basic HUMAN and PATIENTS RIGHTS
with costs to patient family, society, public health, economic development

THALASSAEMIA INTERNATIONAL FEDERATION

Burden of Disease vs Prioritisation on Health Agendas

Recognition of the burden of haemoglobinopathies

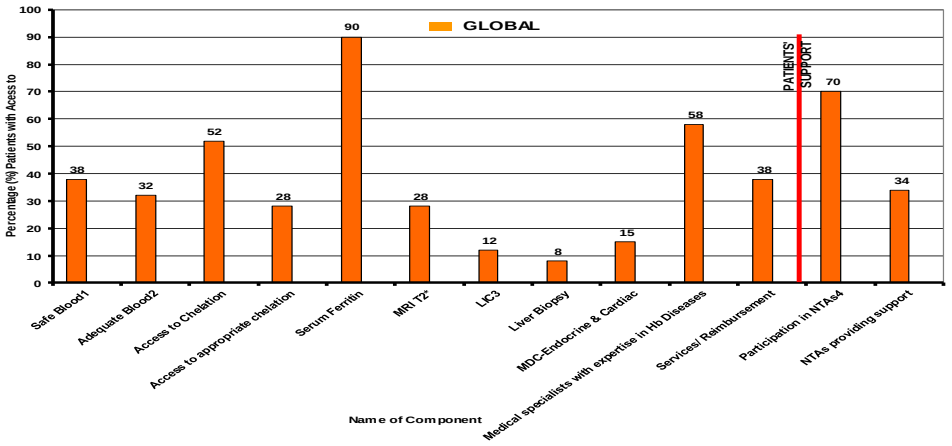


SCD, sickle cell disease; UN, United Nations; WHO, World Health Organisation

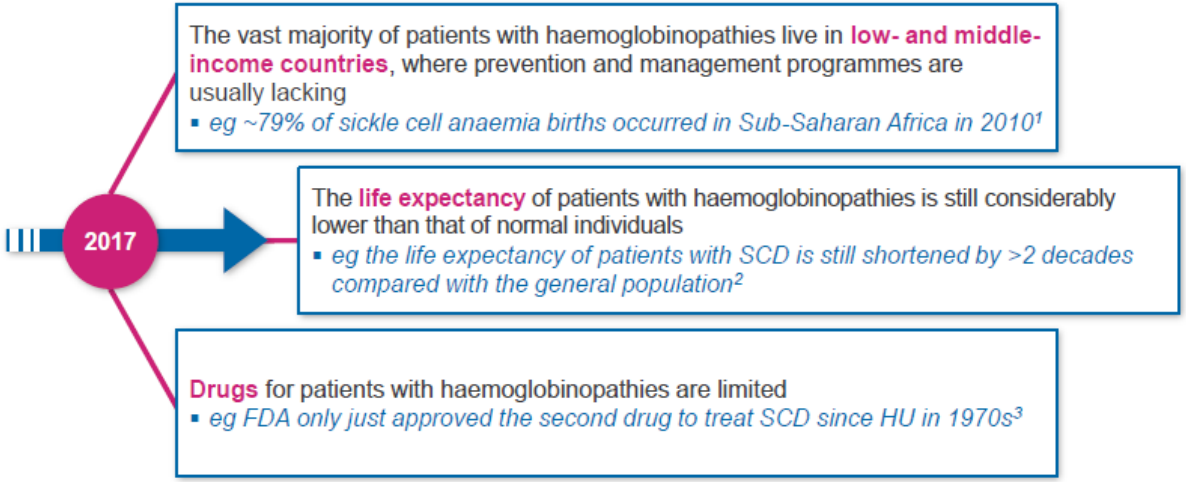
1. WHO 59th World Health Assembly, May 2006, WHA59/2006/REC/1;
2. UN 63rd General Assembly, Dec 2008, A/RES/63/237;
3. WHO 63rd World Health Assembly, May 2010, WHA 63.17;
4. Lozano R *et al. Lancet* 2012;380:2095–2128;
5. http://www.hematology.org/Advocacy/Policy-News/2011/938.aspx;
6. http://www.hematology.org/Newsroom/Press-Releases/2016/6672.aspx

Global Burden of Disease across all ages				Deaths/year
Sickle Cell Disease	1990	74th	17th (age group: 1-4 years)	28, 640 (16756-40,869)
	2010	70th		
Thalassaemias	1990	65th	24th (age group: 1-4 years)	17,860 (15071-20430)
	2010	68th		
2013/2016/ heterogeneity Burden unidentified				

GLOBAL REGIONAL & COUNTRY STATUS: Components of Management of Hb Disorders - as per TIFs 2nd Guidelines Revised Edition - 2008 & Patients' Support



But... still largely neglected disorders



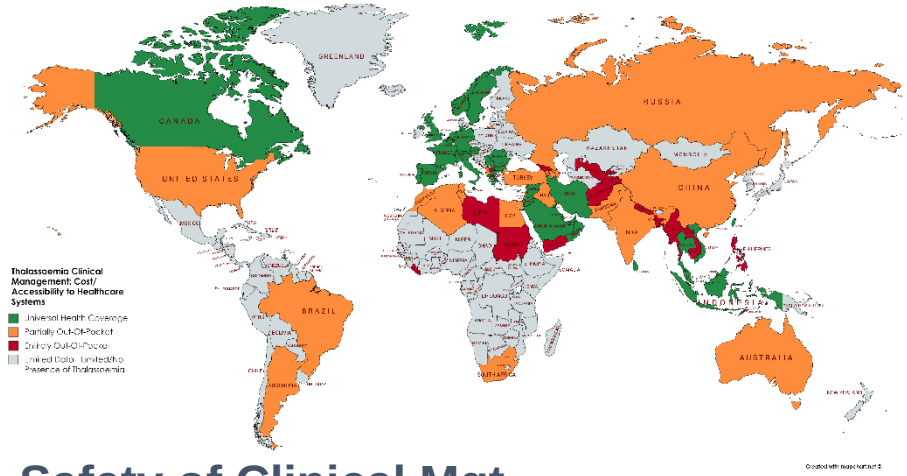
FDA, US Food & Drug Administration; HU, hydroxyurea

1. Piel F *et al. PLoS Medicine* 2013;10:e1001484;
2. Gardner K *et al. Blood* 2016;128:1436–1438;
3. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm566084.htm

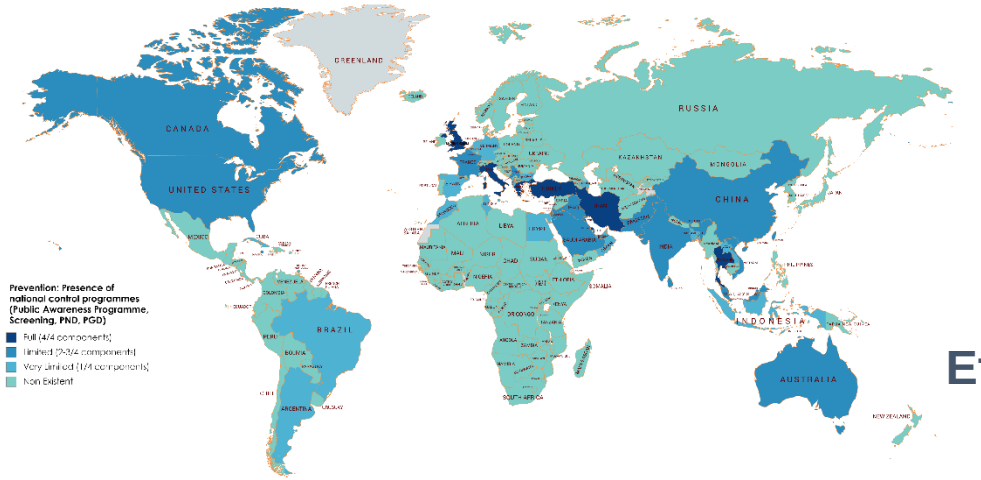
THALASSAEMIA INTERNATIONAL FEDERATION

Current Status of Prevention and Clinical Management for Thalassaemia globally

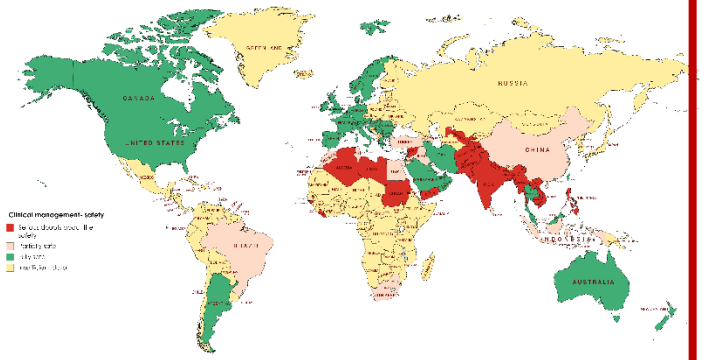
Accessibility of Clinical Mgt



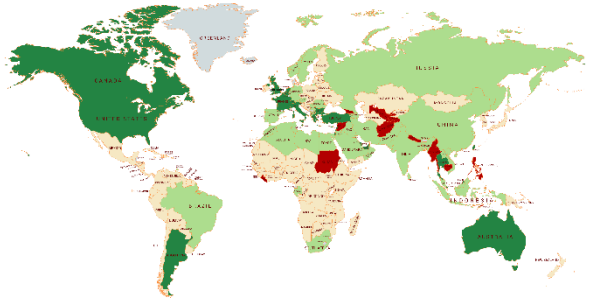
National Control Programmes Globally



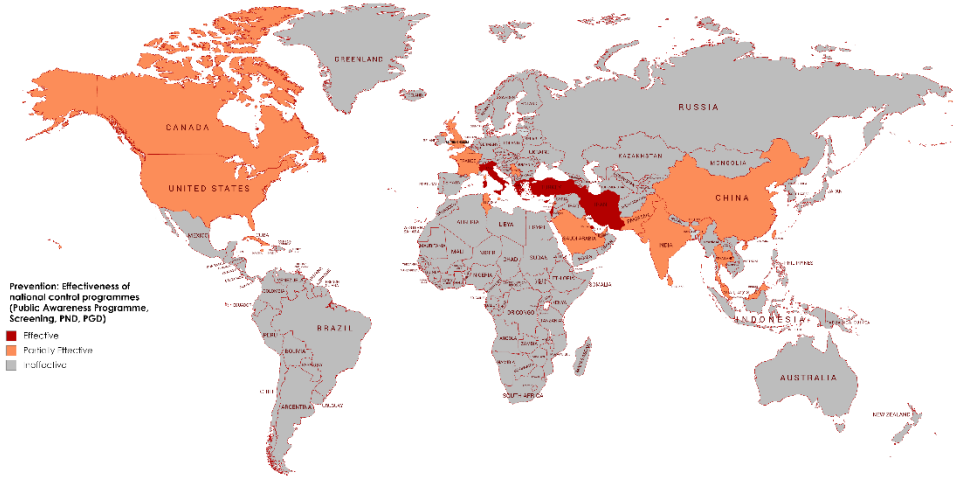
Safety of Clinical Mgt



Availability of Clinical Mgt



Effectiveness of National Control Programmes Globally



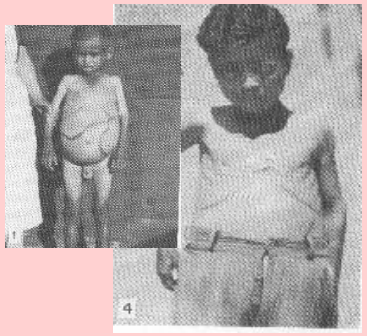
THALASSAEMIA INTERNATIONAL FEDERATION

THANK YOU FOR YOUR ATTENTION

The face of thalassaemia

Then **Now**

Facial deformities



Minimally treated patients aged 8 and 20 (Cyprus, 1940s)

Photos with permission (Modell and Berdoukas, 1984)