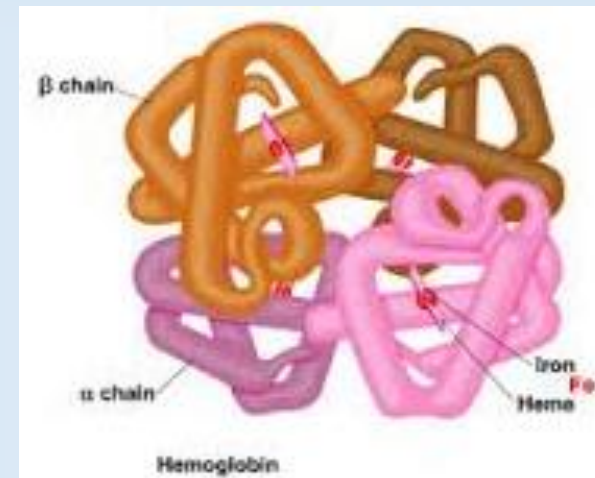


# Update on Thalassaemia and Sickle Cell Disease

Dr Jacquie Taylor

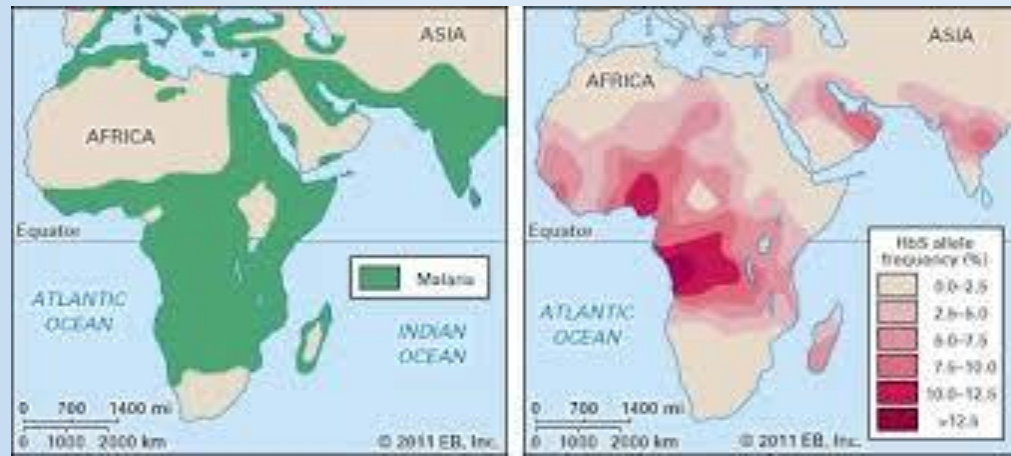
Haematology Advanced Trainee

Mater Hospital Brisbane



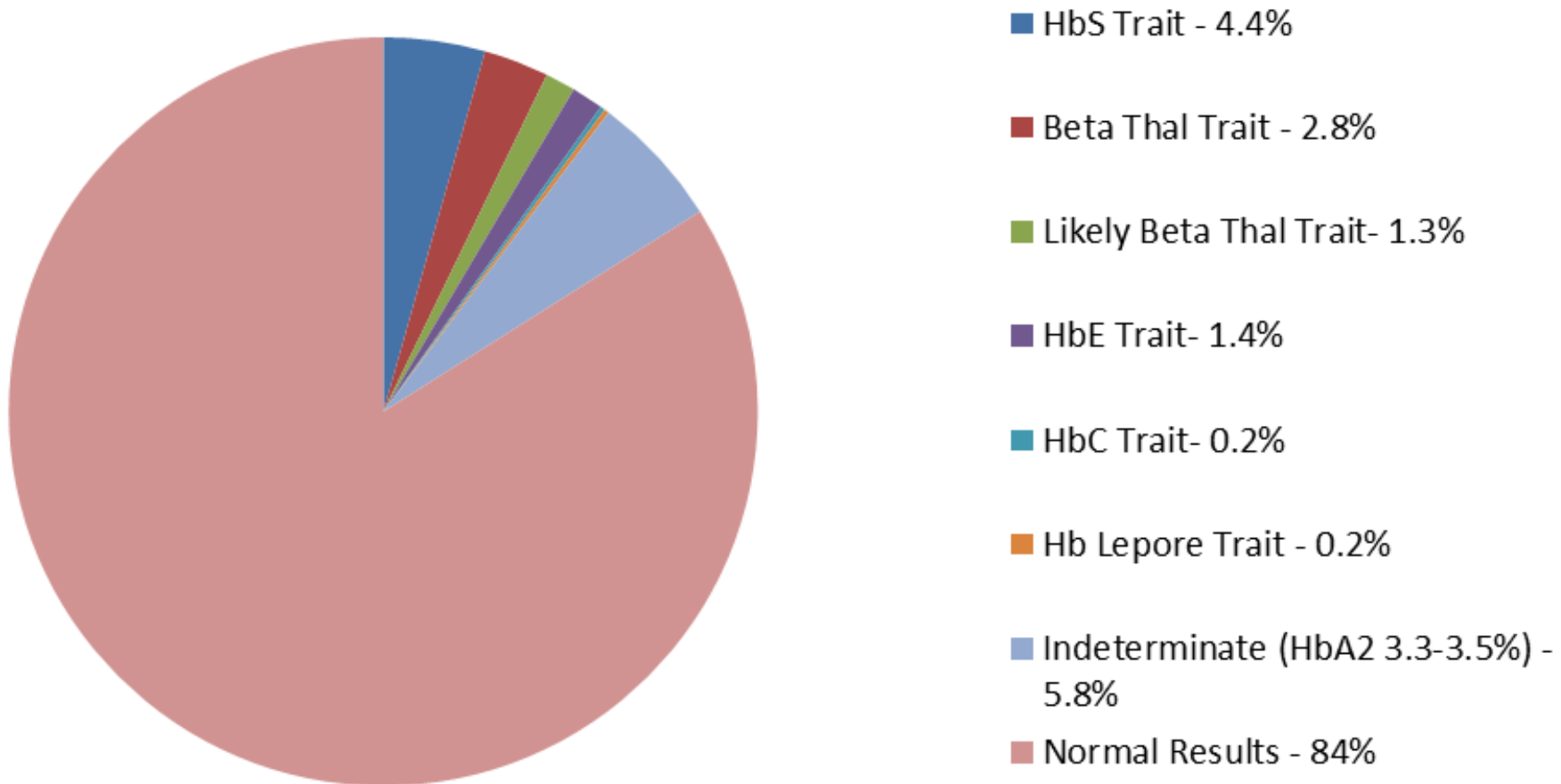
# Haemoglobinopathies

- Global Health problem
- Traditionally disorders found in malaria endemic regions
- But global Migration → changing distribution of genes
- Incidence in Australia traditionally low but will mimic immigration patterns
- Previous migrants from Mediterranean and South East Asia → introduced more thalassemia carriers
- Anecdotal current increase in Sickle Cell disease
- Carrier state asymptomatic
- Difficult to monitor prevalence



# Queensland Refugee Population

- Clinical Audit - 1460 individuals HbEPP results
- 2009-2012



# Clinically Significant Haemoglobinopathies

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Haemoglobin Bart's hydrops fetalis

$\beta$  thalassaemia major and intermedia including that resulting from  $\beta$  thalassaemia/haemoglobin E compound heterozygosity

Sickle cell disease

- Sickle cell anaemia

- Sickle cell/haemoglobin C disease

- Sickle cell/ $\beta$  thalassaemia

- Sickle cell/ $\delta\beta$  thalassaemia

- Sickle cell/haemoglobin Lepore

- Sickle cell/haemoglobin D-Punjab

- Sickle cell/haemoglobin O-Arab

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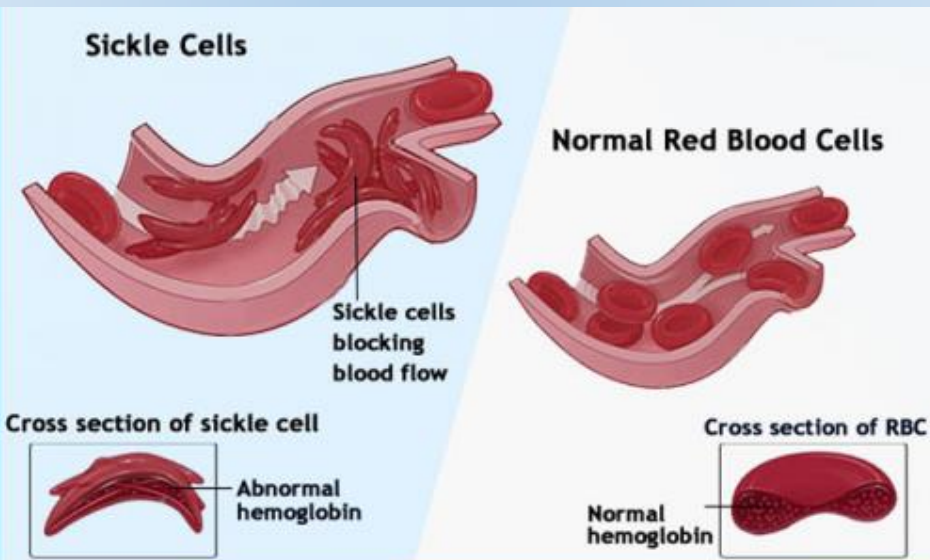
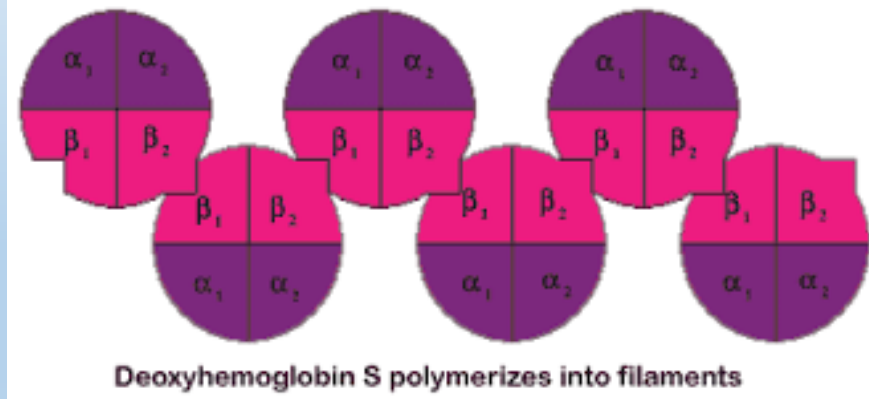
# Tonight's Talk

- Common Hb disorders
  - Sickle cell disease & Compound heterozygote disease
  - Beta thalassaemia
  - Alpha thalassaemia
- Inheritance and risk assessment for pregnancies
- Screening – Who/When
- Diagnostic testing
- Clinical presentation
- Management

# Sickle Cell Disease

# Sickle Cell Disease

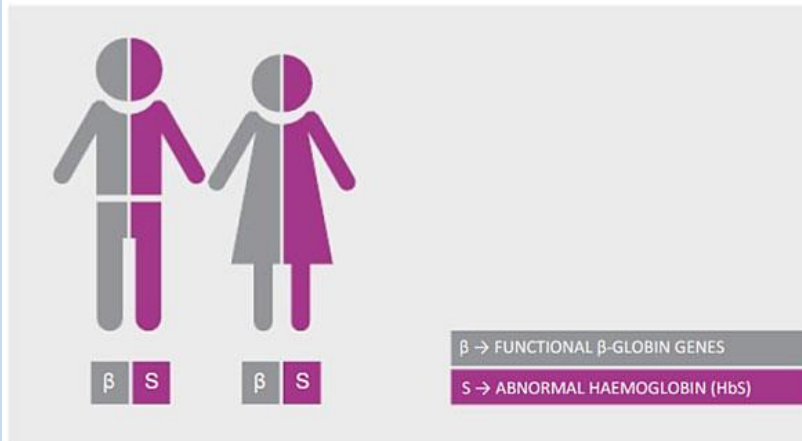
- Inherited group of disorders
- Characterised by severe pain crisis due to vasoocclusive phenomena and haemolytic anaemia.
- Mutation in beta globin gene → HbS
- HbS polymerises to filaments when deoxygenated
- Symptomatic due to homozygous or compound heterozygous state



Disease	Clinical severity	S (%)
SS	Usually marked	[mt]90
$s\beta^0$	Marked to moderate	[mt]80
$s\beta^+$	Mild to moderate	[mt]60
SC	Mild to moderate	50
$S^-$ HPFH‡	Asymptomatic	[lt]70

# Sickle Cell Disease inheritance

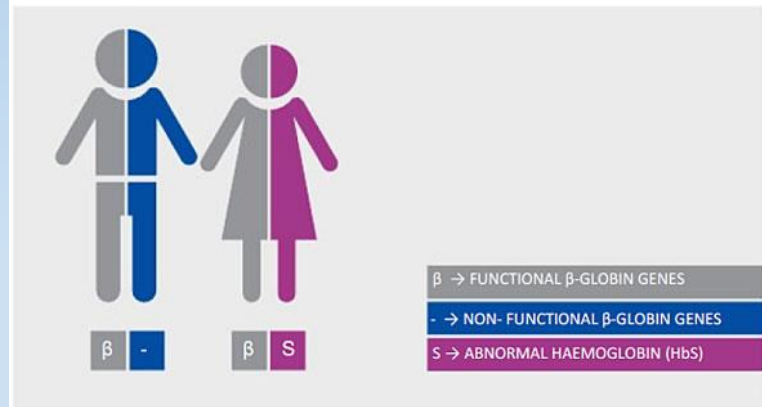
BOTH PARENTS ARE CARRIERS OF HAEMOGLOBIN S (HbS)



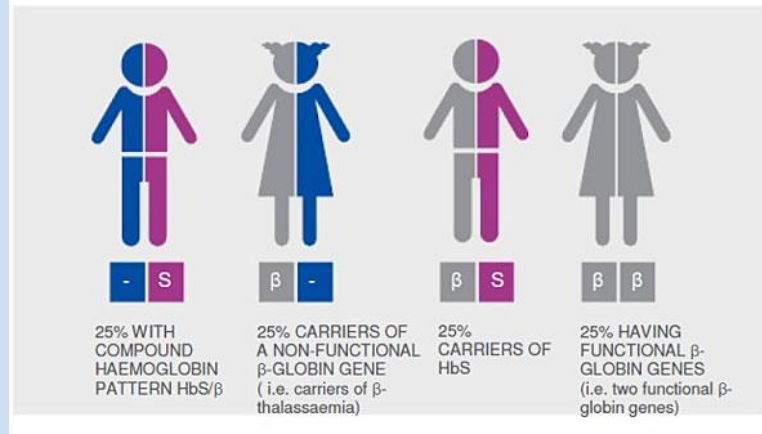
FOR EVERY PREGNANCY THE CHANCES ARE:



ONE PARENT IS A CARRIER OF HAEMOGLOBIN S (HbS) AND THE OTHER IS A CARRIER OF  $\beta$ -THALASSAEMIA



FOR EVERY PREGNANCY THE CHANCES ARE:



# Screening – who to test

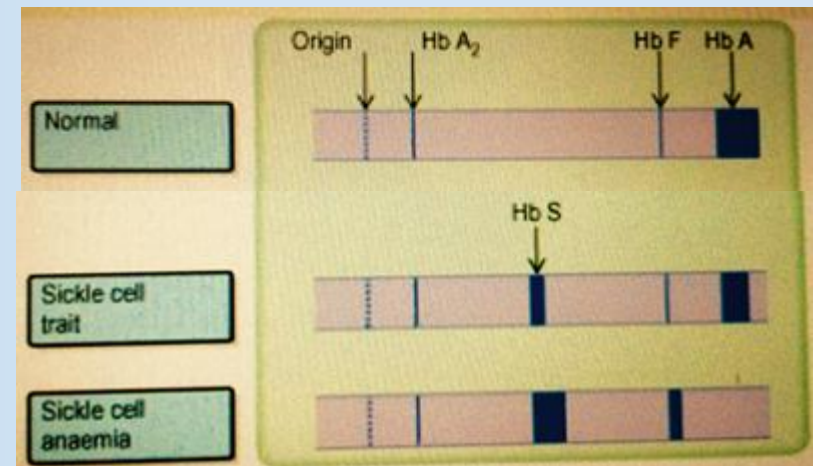
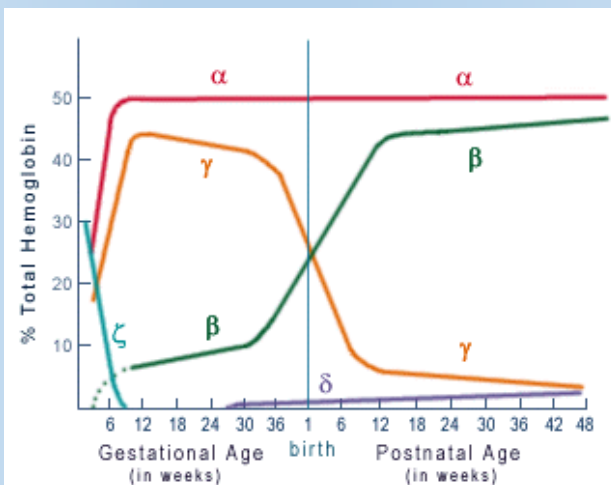
- Family history
- Ethnicity
  - Up to 1:5 carrier rate in Africa
  - HbS gene most prevalent in persons of African, Arabian, and Asian-Indian ancestry
- Unexplained anaemia
- +/- signs of haemolysis - ↑LDH, ↑bili, ↑retics  
↓haptoglobin
- May have normal FBC

NOTE: Sickle cell disease does not cause a microcytosis unless coexistent thalassaemia trait

# Diagnosis – sickle Hb

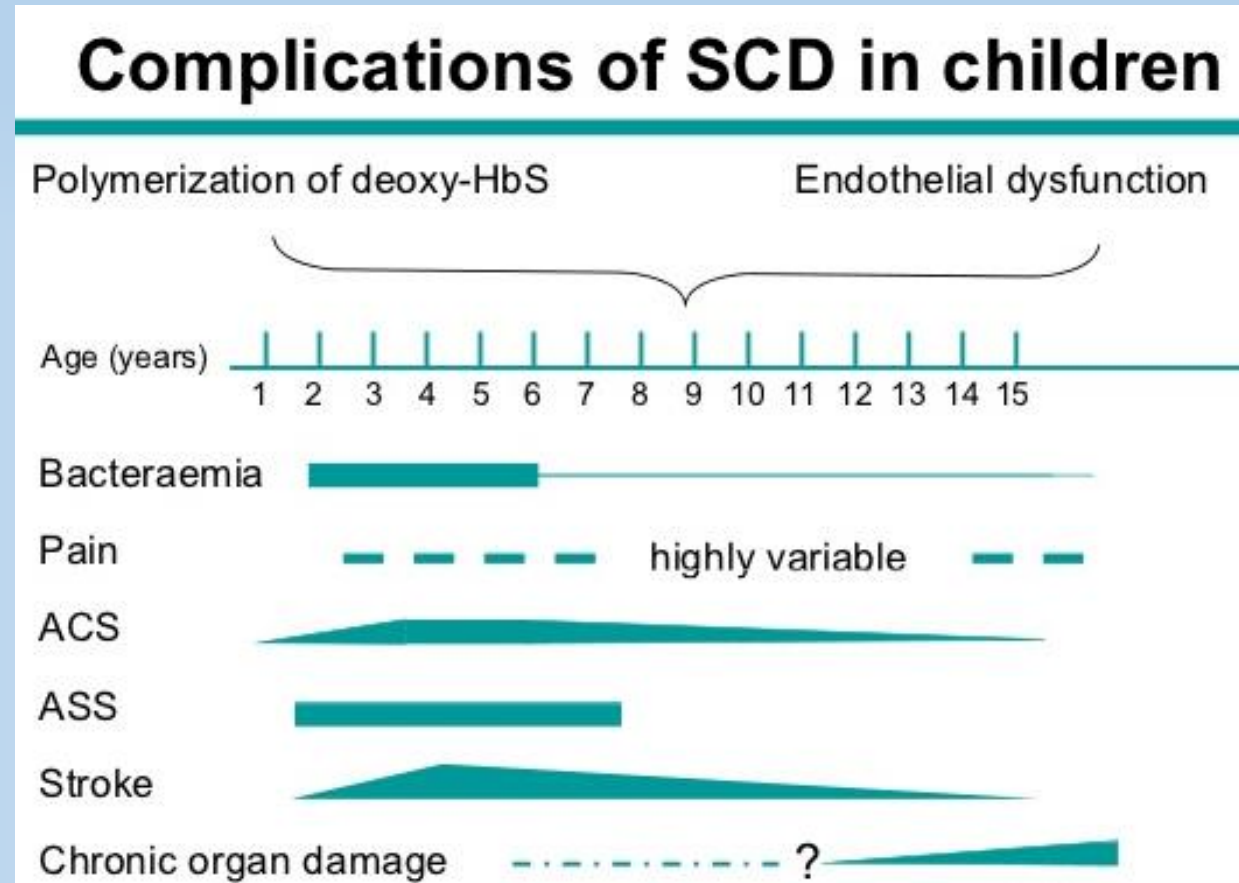
- Haemoglobin electrophoresis (HbEPP)
- Parents – if both carriers refer for Genetic counselling, also if carriers of other beta globin mutations or deletions
- Normal Adult
  - HbA →  $\alpha_2\beta_2$  = 95-98% of all haemoglobin
  - HbF →  $\alpha_2\gamma_2$  = <1%
  - HbA2 →  $\alpha_2\delta_2$  = 2-3.5%
  - HbS →  $\alpha_2S_2$  = 0%

HbEpp	
Hb A2	3.0
Hb F	<2.0
Hb S	<b>36.7H</b>
HbH Bodies	Not Tested
Alkaline Gel	Abnormal ban
Acid Gel	Abnormal ban
09P792599 07/12/09 13:50	
Comment: Sickle Cell trait.	



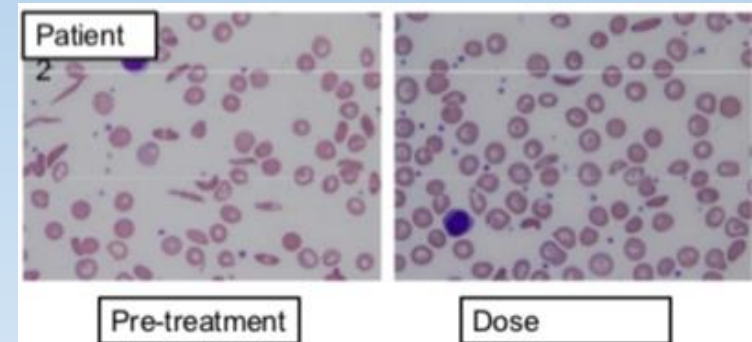
# Sickle cell disease presentation

- Asymptomatic at birth
- First presentation may be with life threatening event
- Overwhelming sepsis
- Pain crisis
- Acute chest syndrome
- Acute Splenic sequestration
- Stroke



# Treatment of sickle cell disease

- Vaccinations – functionally asplenic – [spleen.org.au](http://spleen.org.au)
  - Pneumococcal
  - Haemophilis influenzae
  - Meningococcal
- Prophylactic penicillin
  - Daily amoxicillin until at least age 5yrs
  - Emergency supply of Augmentin
- Avoid triggers to pain crises
  - Avoid dehydration, extremes of temperature, Hypoxia (smoking, altitude, intensive exercise), infections
- Hydroxyurea
  - ↑increases HbF, increases NO → improved survival, decreased frequency of pain crisis
- Folate



# Asplenia/Hyposplenism – Paediatric Guidelines

## Age 0 to 18 years

Vaccine Type	Pneumococcal Vaccines*		Meningococcal Vaccines		Haemophilus influenzae type b (Hib) Vaccine	Influenza Vaccine
	Pneumococcal Conjugate Vaccine 13vPCV	Pneumococcal Polysaccharide Vaccine 23vPPV	Meningococcal Quadrivalent Conjugate Vaccine 4vMenCV ACWY	Meningococcal B Recombinant Multicomponent Vaccine MenBV		
Brands	Prevenar13	Pneumovax23*	Menveo# Menactra Nimenrix††	Bexsero	InfanrixHexa Menitorix	Variable
< 2 years of age	Primary course as per <a href="#">NIP</a>  1 additional dose at ≥12months of age	1 dose at 4-5 years of age	<b>Menveo#</b>  <b>&gt;6 weeks to ≤6 months</b> 3 doses (8 weeks apart) 4 <sup>th</sup> dose at 12 months of age  <b>7 to ≤24months</b> 2 doses (8 weeks apart)	<b>Note: Requires prophylactic paracetamol‡‡</b>  <b>&gt;6weeks to ≤6 months</b> 3 doses (8 weeks apart) 4 <sup>th</sup> dose at 12months of age  <b>7 to ≤12months</b> 2 doses (8 weeks apart) 3 <sup>rd</sup> dose at 12months (or 8 weeks post previous dose, whichever is later)  <b>&gt;13 to ≤ 24 months</b> 2 doses (8 weeks apart)	Primary course as per <a href="#">NIP</a>	<b>&gt;6months to &lt; 9 years of age</b>  2 doses [4 weeks apart in first year of vaccination if < 9 years]  Recommend seasonal influenza vaccine <b>Every year (one dose)</b>
2-5 years of age	Primary course as per <a href="#">NIP</a>  1 additional dose at ≥12months of age	1 dose at 4-5 years of age	2 doses (8 weeks apart)	2 doses (8 weeks apart)	Primary course as per <a href="#">NIP</a>	See <a href="#">ATAGI guidelines</a> annually
>5 years of age	1 dose (if no previous doses as > 12 months at age)	1 dose (if no previous doses)	2 doses (8 weeks apart)	2 doses (8 weeks apart) *	1 dose (if <b>no</b> previous doses of Hib-containing vaccine)	
Boosters	Nil required	Booster 5 years post 1 <sup>st</sup> dose	Booster 3 years post primary course. Review ongoing boosters every 5 years	Booster requirements currently unknown, review every 5 years.	Nil required	Annual

- Additional IMMUNISATIONS for people with Asplenia or Hyposplenism
- NIP – national immunization program

# Beta Thalassaemia

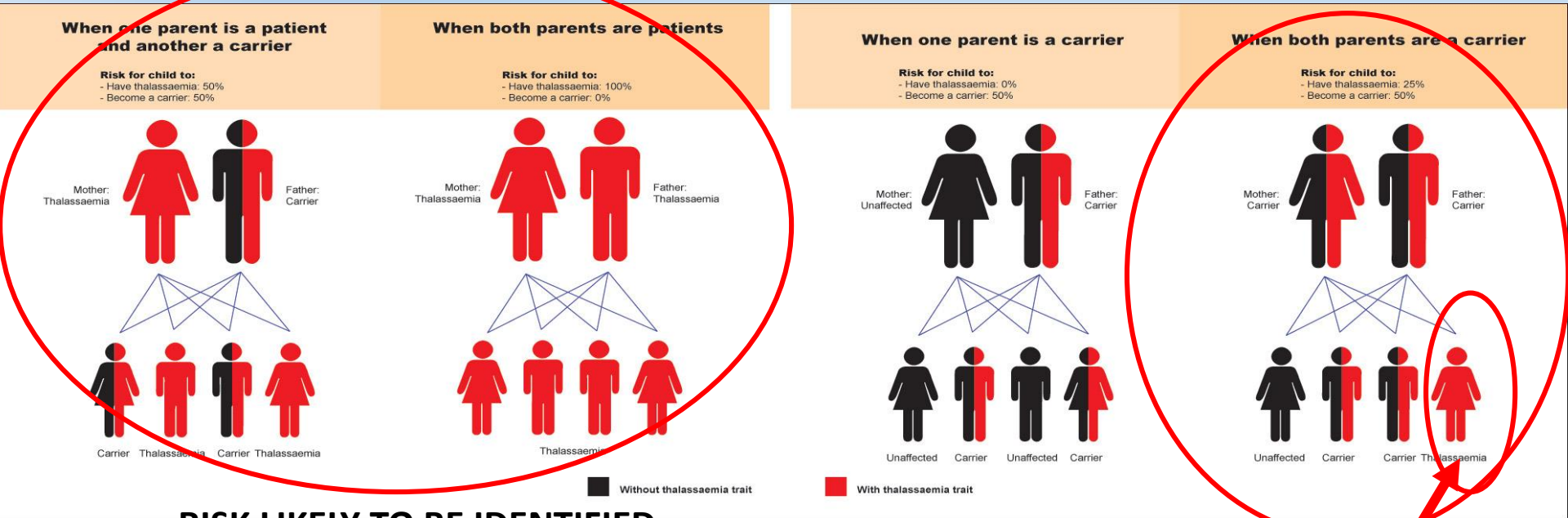
# Beta thalassaemia inheritance

- One Beta Globin Gene, two copies

$\beta^0\beta^0$  – BT major     $\beta\beta^0$  – BT trait

$\beta^0\beta^+$  or  $\beta^+\beta^+$  BT intermedia

**MOST LIKELY CASE TO BE MISSED DUE TO LACK OF SCREENING AND BOTH PARENTS ASYMPTOMATIC CARRIERS**



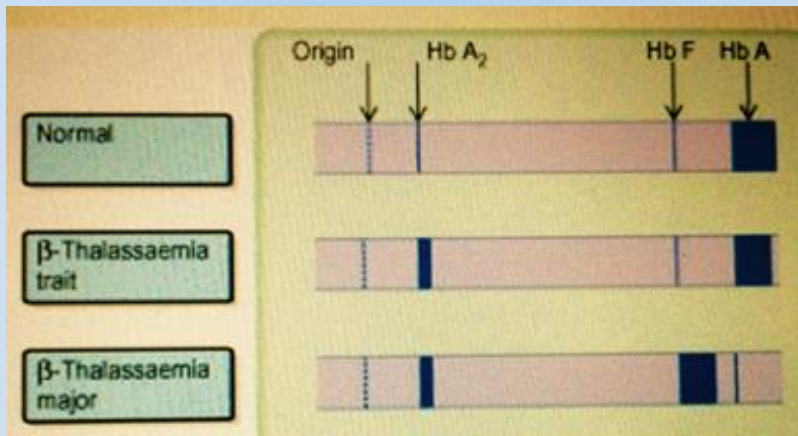
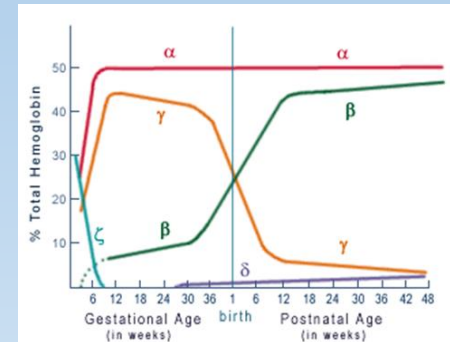
**RISK LIKELY TO BE IDENTIFIED EARLY AS AT LEAST ONE PARENT HAS BETA THAL MAJOR**

**Beta Thalassaemia Major**

# Beta Thalassaemia Trait

- When to suspect
  - Microcytic, hypochromic anaemia in Iron replete patient
  - Family history
  - Ethnicity
- How to test
  - Haemoglobin EPP – Haemoglobin studies
  - Raised HbA2 >3.5% is diagnostic beta trait
- Who/when to test
  - diagnosis microcytosis – to avoid erroneous iron prescription
  - Planning pregnancies – to determine risk of beta thal major
  - Family history of beta thal or sickle cell or HbC/HbE

HbEpp	HbS/beta thal
Hb A2	5.0H
Hb F	13.9H
Hb S	71.5H



## HAEMOGLOBINOPATHY STUDIES

-- Haemoglobin	98 g/L	(115-160)
Red Cell Count	4.8 x10 <sup>12</sup> /L	(3.6-5.2)
- Haematocrit	0.30	(0.33-0.46)
--- Mean Cell Volume	62 fL	(80-98)
--- Mean Cell Haemoglobin	20 pg	(27-35)

Haemoglobin H bodies Negative

### Haemoglobin Electrophoresis

++ Haemoglobin A v2	5.2 %	(2.0-3.4)
+ Haemoglobin F	3.6 %	(< 1.1)

Alkaline EPP Result No abnormal band detected.

HPLC Result No abnormal peak detected.

### Comment:

High A2 type thalassaemia (beta-thalassaemia minor)

# Beta thalassaemia intermedia

- “highly diverse” group of beta thalassaemia
- red cells survival sufficiently short-lived to cause anaemia but without patients requiring regular blood transfusions
- Mutation → reduction but not absence of beta globin production
- Beta plus syndromes
- Present later in childhood



# Beta Thalassaemia Major



- Severe haemoglobinopathy - Transfusion Dependent
- Ideally risk of an child being born affected by Beta thal major should be predicted prenatally
- Couples at risk of a affected child should be referred for genetic counselling preconception
- If already pregnant
  - Assess risk – test both parents
  - If both parents carriers – 25% risk with every pregnancy
- Is early termination of pregnancy an option – gestation?
  - And would the couple consider it if diagnosis was confirmed
  - Yes – then CVS (10-14weeks) and beta gene testing
  - No – await birth
- Diagnostic test after birth
  - Gene test, HbEPP less accurate in neonates as HbA very small amounts at birth
- But there is no routine maternal or newborn screening in Australia
- So ..... when will these kids present

# Presentation of Beta thal Major

- Healthy at birth
- Signs and symptoms by 6 to 12 months of age
  - pallor, irritability, growth retardation, abdominal swelling due to hepatosplenomegaly, and jaundice
  - severe hemolytic anemia with markedly abnormal hypochromic, microcytic red cells
- If left untreated – bony abnormalities due to extramedullary haematopoiesis – chipmunk facies
- Diagnosis
  - Confirmed by HbEPP –
  - absence or severely reduced HbA
  - only HbF and HbA2 present



# Management of Beta thal Major

- Transfusion
  - stops marrow expansion – bony deformities, improves growth
- Iron Chelation
  - Critical to improved survival
- If had splenectomy – (minority)
  - Vaccinations
  - Prophylactic antibiotics

## Complications of beta Thal major

- Osteoporosis, Extramedullary hematopoiesis, Hypogonadism, Cholelithiasis, Thrombosis, Pulmonary hypertension, Abnormal liver function, Leg ulcers, Hypothyroidism, Heart failure, Diabetes mellitus

Endocrinologist, cardiologist, ophthalmologist involved

# Alpha Thalassaemia

# Alpha thalassaemia

- When to suspect
  - Microcytic, hypochromic anaemia in Iron replete patient
  - And beta thalassaemia has been excluded (Normal HbEPP)
  - Or family history
- Who/when to test
  - Planning pregnancies - Most important time to test is to predict risk of hydrops fetalis
  - Symptomatic/abnormal RBC indices
  - Deletions of 1 gene (silent/alpha thal minima) or 2 gene (alpha thal minor/trait) cannot be excluded based on normal FBC indices
- Alpha gene test is not covered by medicare - cost \$70-100
- Test cost covered by Mater Pathology for patients that are referred from public specialist outpatients or antenatal clinic

# Risk of alpha thalassaemia major

## Assess Risk - Parents Genotypes

- Need to inherit two mutated alpha genes from each parent
- Two asymptomatic carriers of 2 gene deletions can cause hydrops fetalis in offspring
  - Only if on same chromosome ie Cis --/ $\alpha\alpha$
  - Cis deletion more common if Asian descent
  - (Trans deletion  $\alpha$ -/ $\alpha$ - more likely African descent)

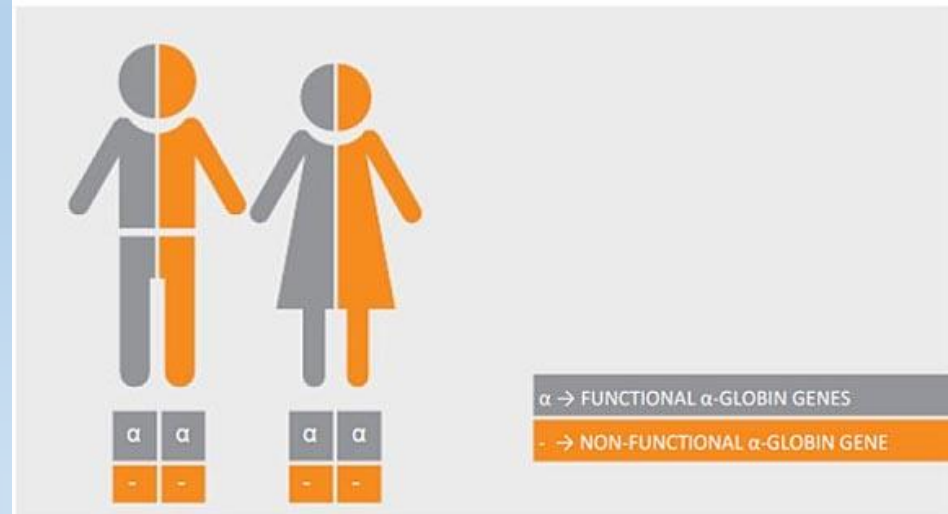
## Alpha Thalassaemia Major/ HbBarts/ Hydrops fetalis

- Deletion of all 4 alpha globin genes --/--
  - Incompatible with extra uterine life
  - Unable to form any Fetal or Adult haemoglobin
  - Causes hydrops fetalis
  - Associated with increased maternal morbidity and mortality
- If risk of hydrops based on parents genotypes then couple should be offered, preconception counselling, early pregnancy diagnosis and therapeutic termination of pregnancy

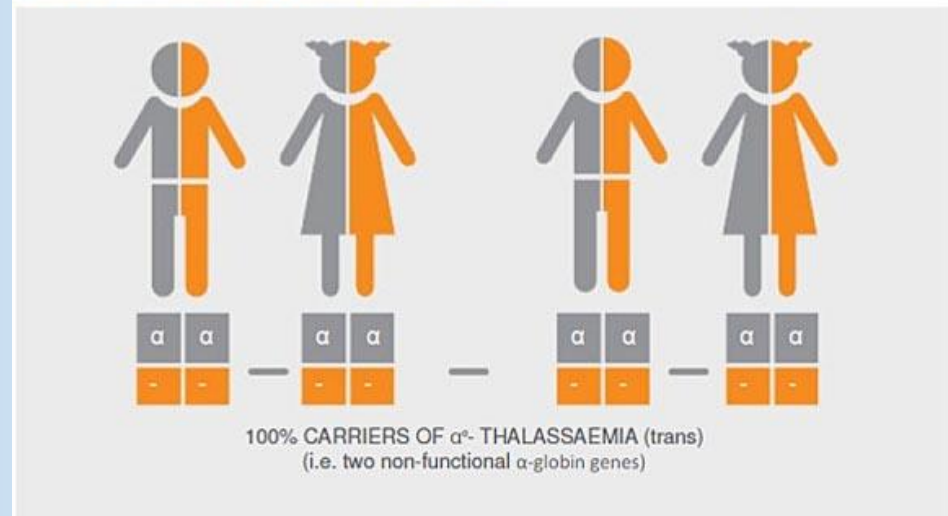
# Alpha Thal inheritance/risk

- Both parents carriers of 2 gene deletions
- but deletions are on different chromosomes
- “Trans” deletion
- NO RISK OF HYDROPS
- All offspring carriers

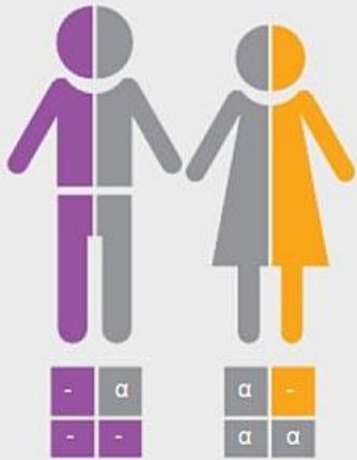
BOTH PARENTS ARE CARRIERS OF  $\alpha^0$ -THALASSAEMIA  
THALASSAEMIA GENES ON DIFFERENT CHROMOSOMES (trans)



FOR EVERY PREGNANCY THE CHANCES ARE:



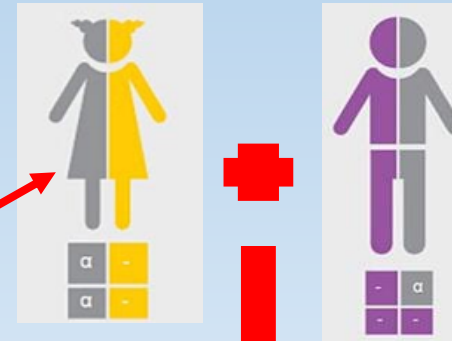
ONE PARENT WITH HbH DISEASE (3 NON-FUNCTIONAL  $\alpha$ -GLOBIN GENES)  
AND THE OTHER A SILENT CARRIER OF  
 $\alpha$ -THALASSAEMIA ( $\alpha^+$ -THAL) (1 NON-FUNCTIONAL  $\alpha$ -GLOBIN GENE)



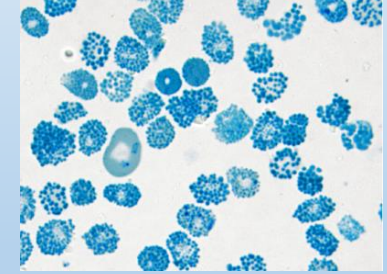
FOR EVERY PREGNANCY THE CHANCES ARE:



# “cis” deletion



25% or 1/4 risk of hydrops in offspring



# HbH disease

Not considered critical to diagnose before birth but can cause clinically significant disease

- $\alpha$ -/-- deletions of 3 of the 4  $\alpha$ -globin genes
- Excess beta globin chains form  $\beta_4$  tetramers called HbH
- Diagnosis – Alpha gene testing
- Variable phenotype
  - Haemolytic anaemia during gestation
  - Symptomatic at birth - Jaundice and anaemic
  - Stigmata of chronic haemolytic anaemia,
    - hepatosplenomegaly,
    - $\uparrow$ indirect hyperbilirubinemia,  $\uparrow$  LDH,  $\downarrow$  haptoglobin,
    - leg ulcers,
    - osteopenia,
    - premature biliary tract disease (pigmented gall stones)
- Usually not transfusion dependent
  - May require transfusions during times of increased stress (inter-current illness, pregnancy, oxidative medications)
- Prone to iron accumulation due to ineffective erythropoiesis

# HbH disease - Management

- Key Management

- Monitor Haemoglobin if increased symptoms of anaemia
  - Refer for transfusion if required
- Folate supplementation during haemolysis exacerbations
- Avoid additional iron unless proven deficiency ferritin <20
- Chelation considered if evidence of iron loading

- Preconception counselling

- Partner of any patient with HbH planning children should have genetic test done.
- 25% Risk of hydrops if partner has 2 gene deletion on one chromosome (cis deletion)

### 1. Assess risk before 10 weeks' gestation

One of:

- High-risk ethnicity\*
- Unexplained microcytosis/hypochromia (MCV,  $\leq 80$ fL or MCH,  $\leq 27$ pg)
- Family history or biological parent with known haemoglobinopathy†
- Unexplained anaemia

### 2. Request on pregnant mother‡

- FBC (haemoglobin level, MCV, MCH)
- Ferritin test
- Haemoglobinopathy screening tests

AND document:

- Gestation, ethnicity and indication for testing

Haemoglobinopathy unlikely

No further action

Haemoglobinopathy† confirmed  
or not excluded in mother

### 3. Test father‡

- FBC (haemoglobin level, MCV, MCH)
- Ferritin test
- Haemoglobinopathy screening tests

AND document:

- Ethnicity, partner name and date of birth

If both parents are  
haemoglobinopathy carriers

### 4. Arrange urgently

- Genetic counselling and molecular testing for mother and/or father
- AND document and communicate
- Gestation, ethnicity, indication for testing, details of biological parents

If only one parent is a  
haemoglobinopathy carrier

No further action§

# Key points

- FBC indices
  - Thalassaemias – microcytosis
  - Sickle cell anaemia – Not microcytic
- Presentation
  - Alpha thal major – in gestation
  - Beta thal and beta Variants – after birth (>6months)
- Diagnosis
  - Beta (thal/sickle/HbC/HbE/HbD/HbO) → HbEPP
  - Alpha thalassaemia -> gene testing
- All haemoglobinopathies → iron overload, avoid supplements unless deficient
- Pre-pregnancy screening ideally