Irish Blood Transfusion Service
Seirbhís Fuilaistriúcháin na hÉireann

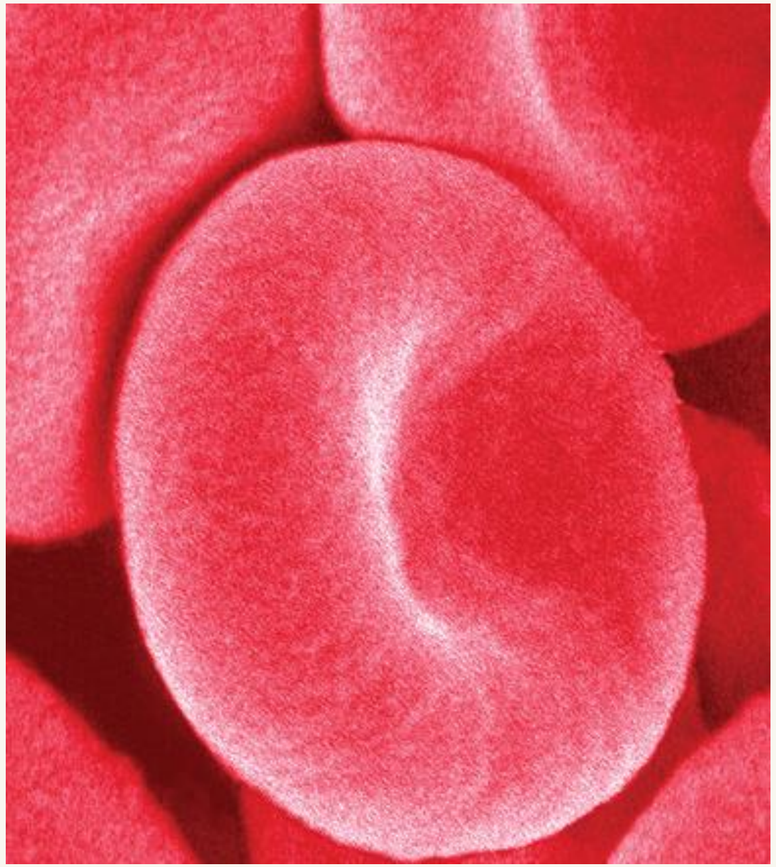
giveblood.ie

The challenge of providing appropriate red cell component support for sickle cell disease

Dr Kieran Morris

6th October 2021

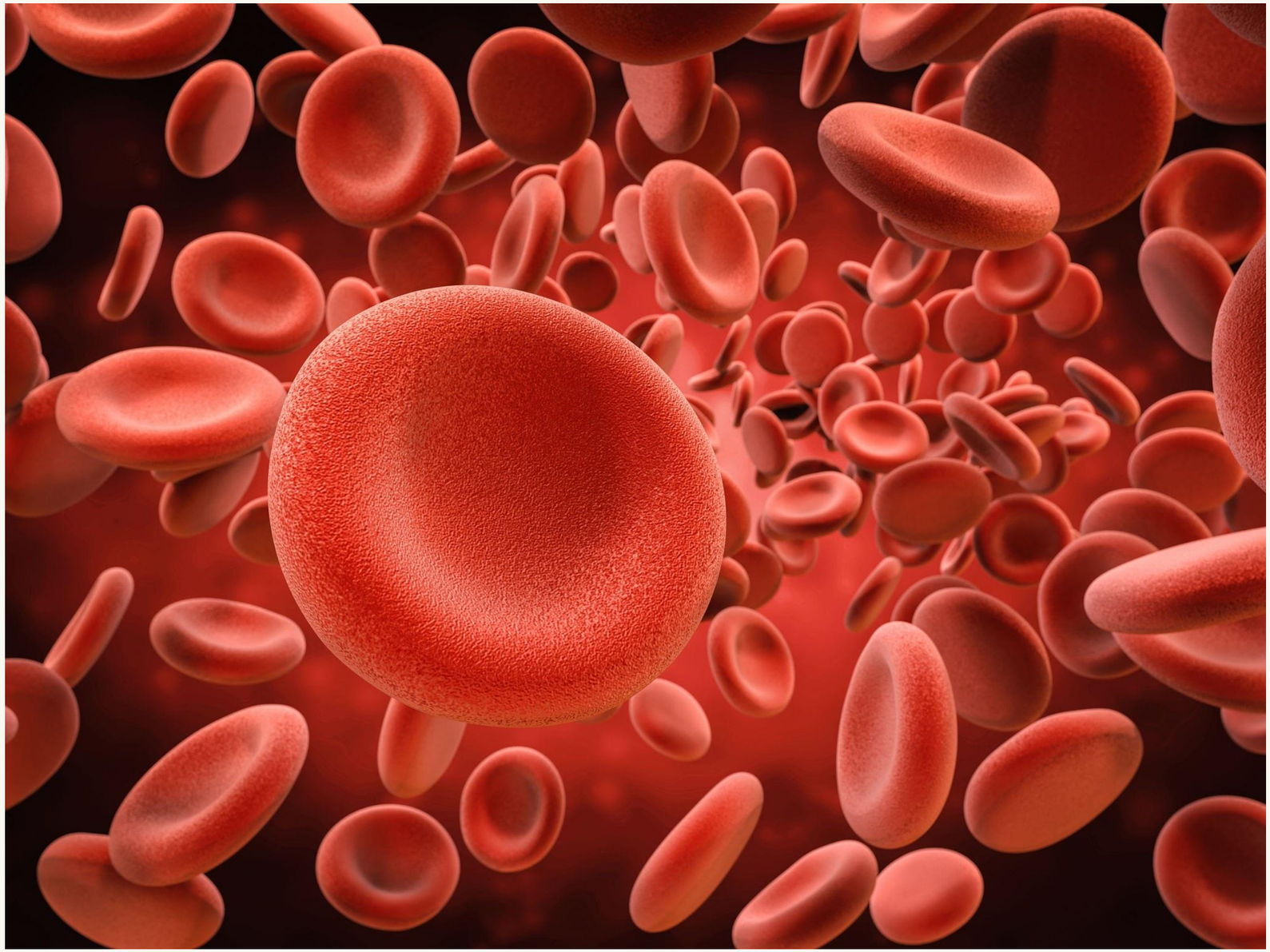

MIAI & AMA



Presentation Outline

TODAY'S TOPICS

- Normal haemoglobin (a senseless act of beauty)
- Sickle haemoglobin a survival advantage for malaria
- Adaptive responses
- Understanding sickle cell disease SSD
- The clinical presentations of SSD
- The treatment options in SSD
- The transfusion strategies in SSD simple and exchange transfusion and making a difference
- The importance of red cell antigen matching and the prevention of alloimmunistation
- The current impact of substituting O D (-) on O D (-) inventory management
- Future options for sustainability



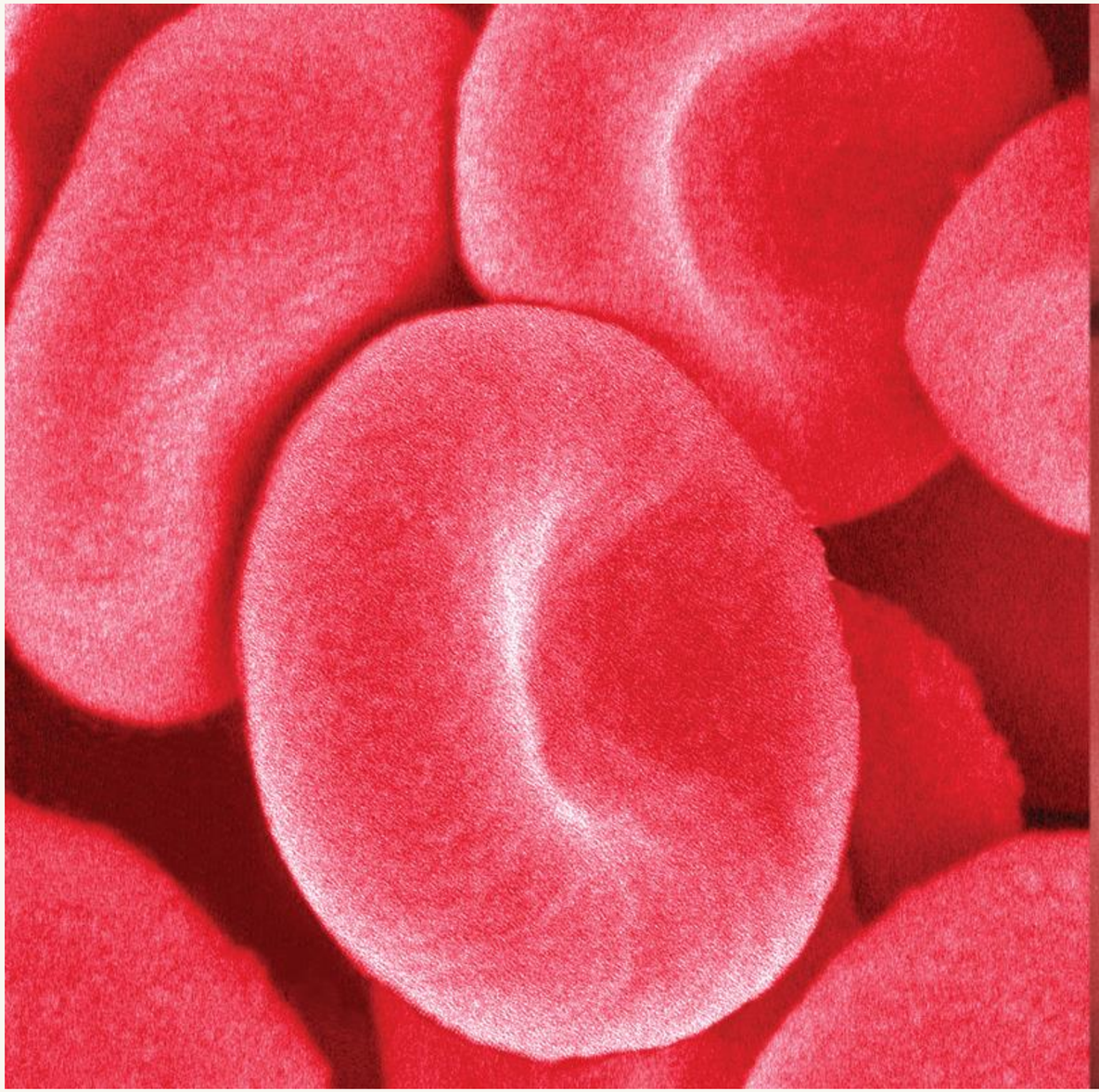
WE LOVE OUR DONORS

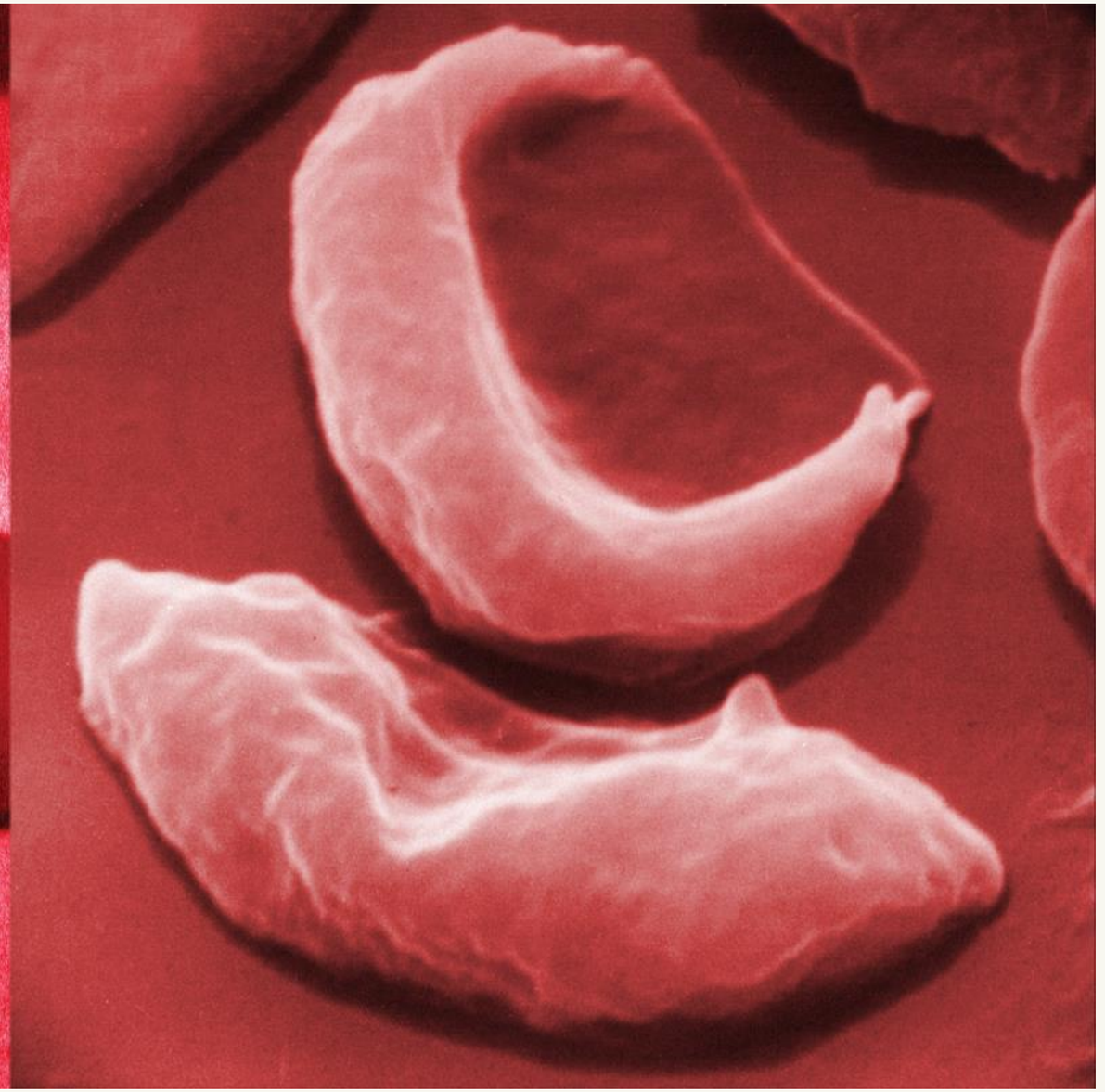
WE IMPROVE PATIENTS LIVES, TOGETHER

WE LEAD BY EXAMPLE

WE STRIVE FOR EXCELLENCE

WE ARE THE IBTS





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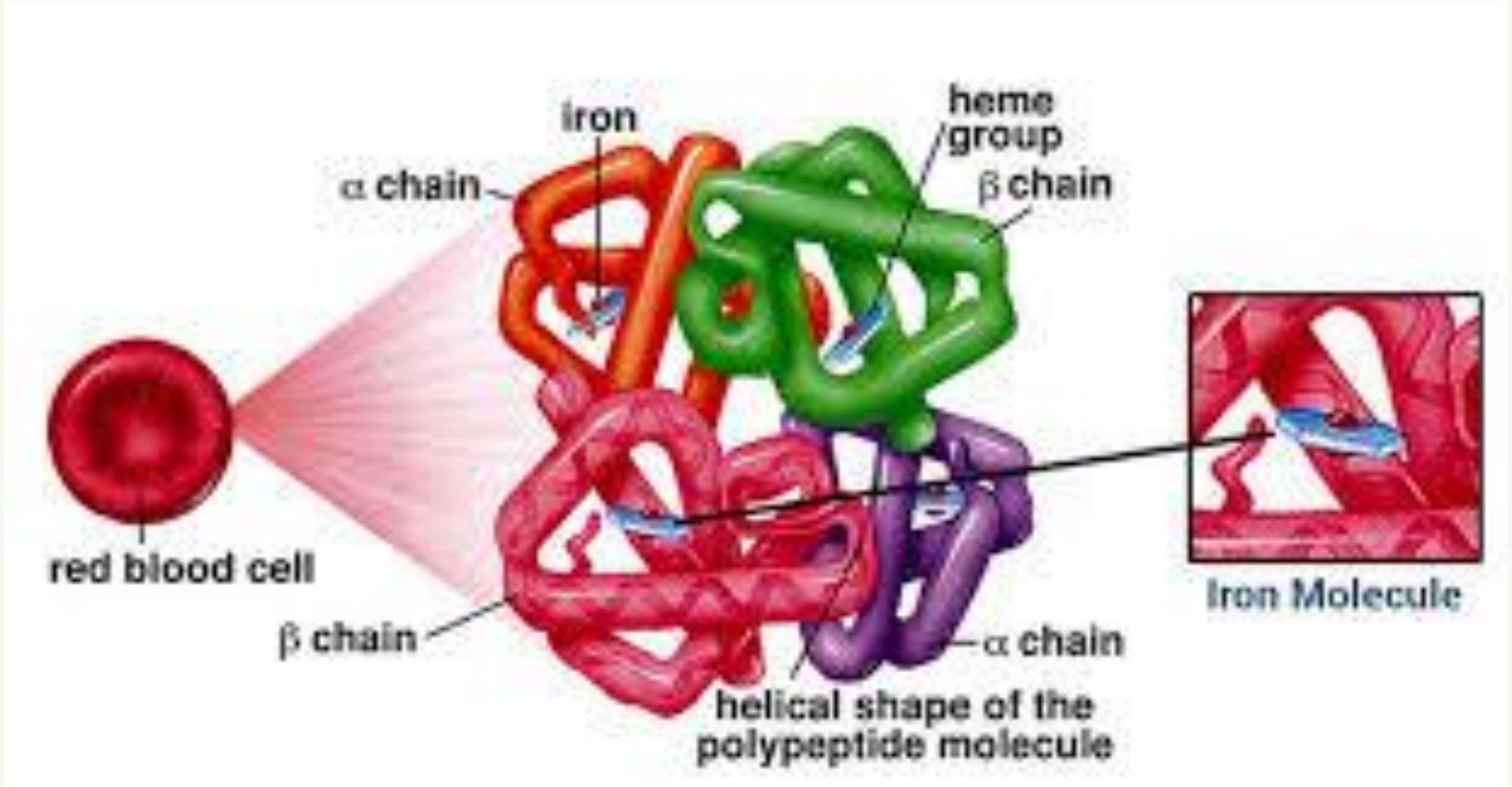
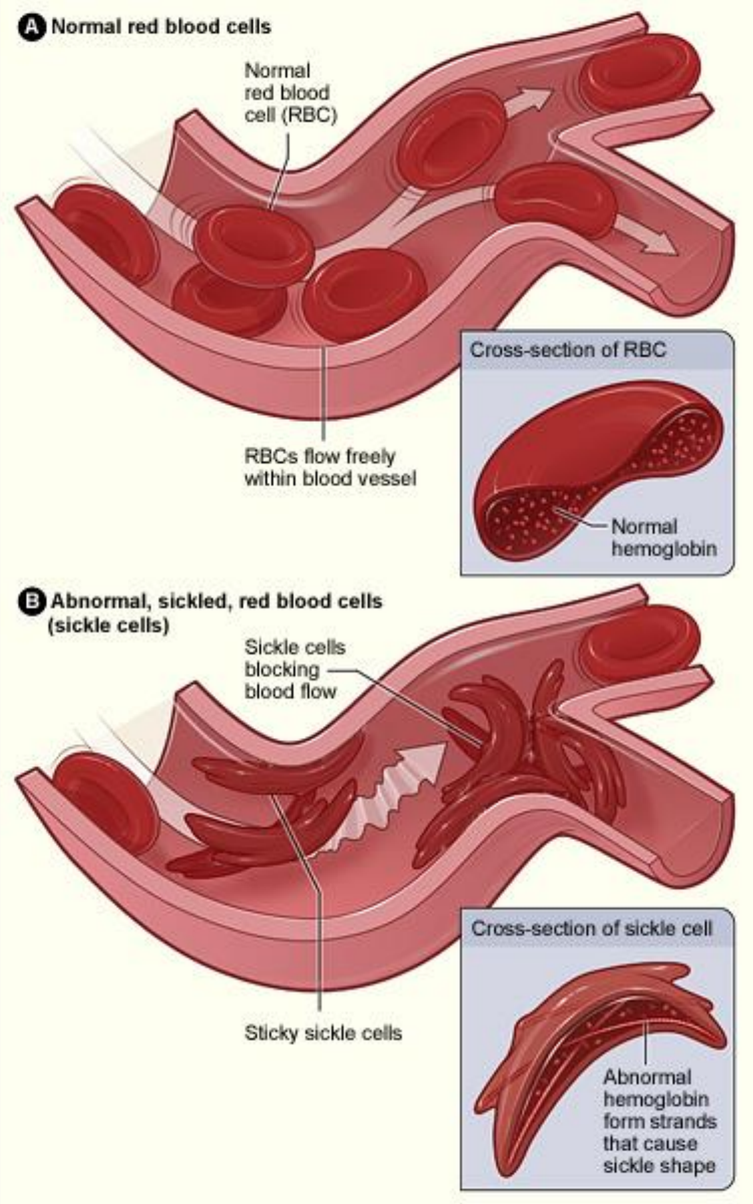
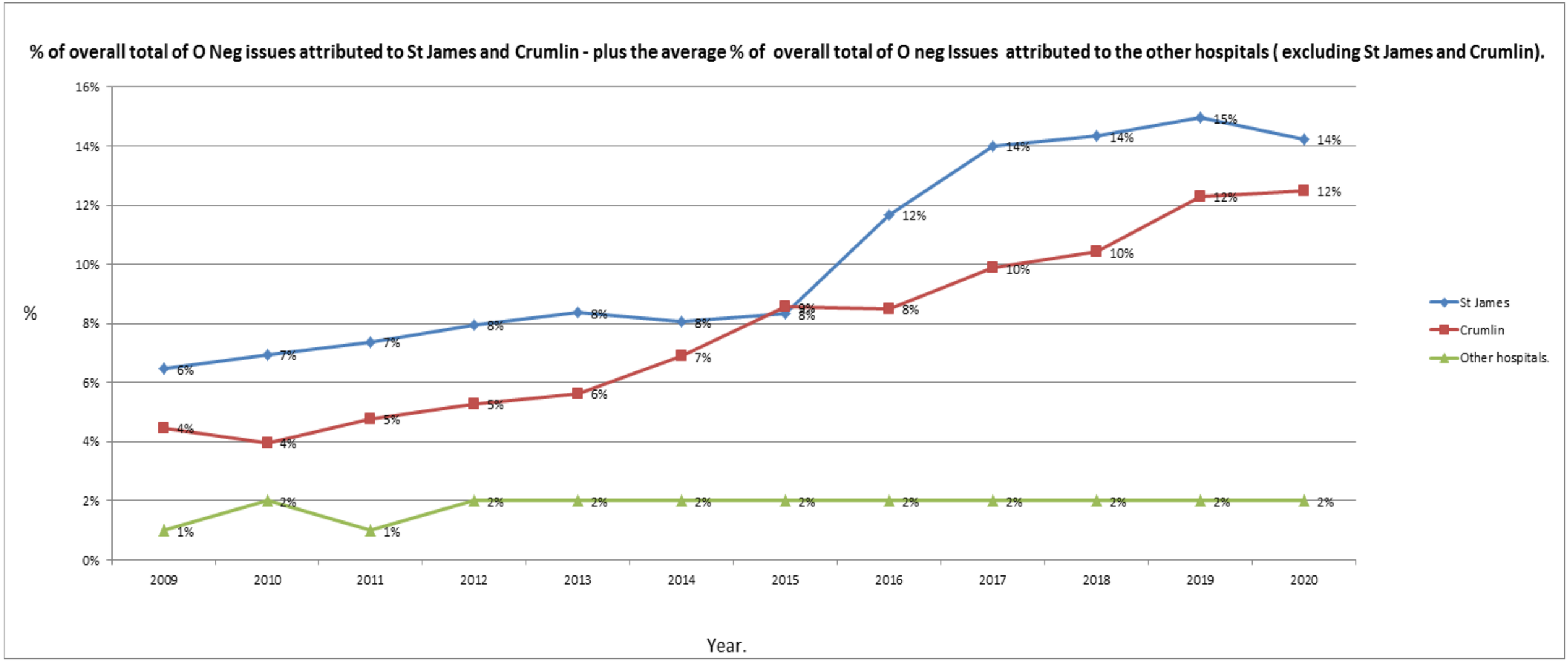

iron
heme group
α chain
β chain
red blood cell
β chain
α chain
helical shape of the polypeptide molecule
Iron Molecule

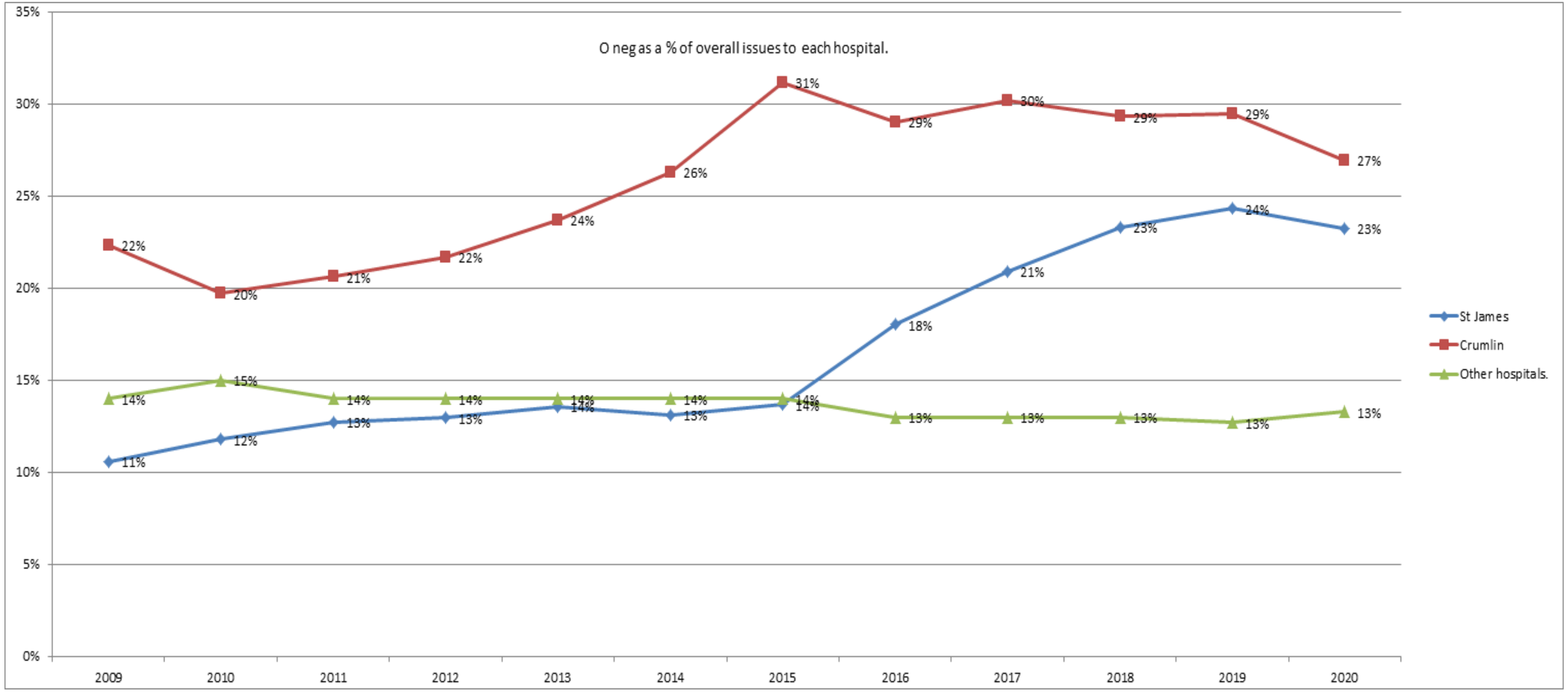


Ireland the changing demographic	
Census 2001	80% born in Ireland living in Ireland 14% GB 2% US and 4% Canada Australasia and EU
1991	Foreign born residents = 7%
2016	Foreign born residents = 17% 13% population had non Irish nationalities (children of returned Irish emigrants)

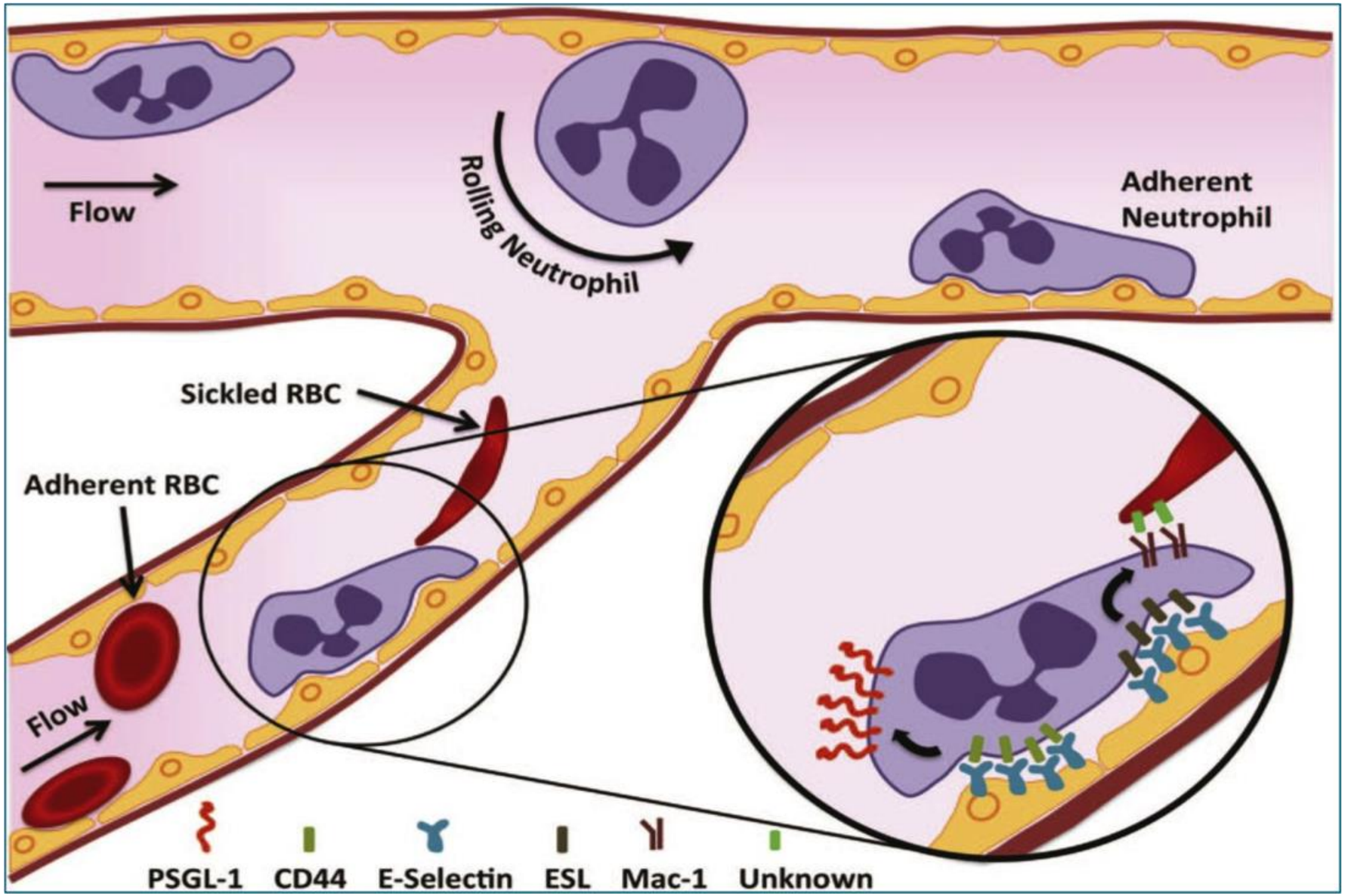
Issues trends

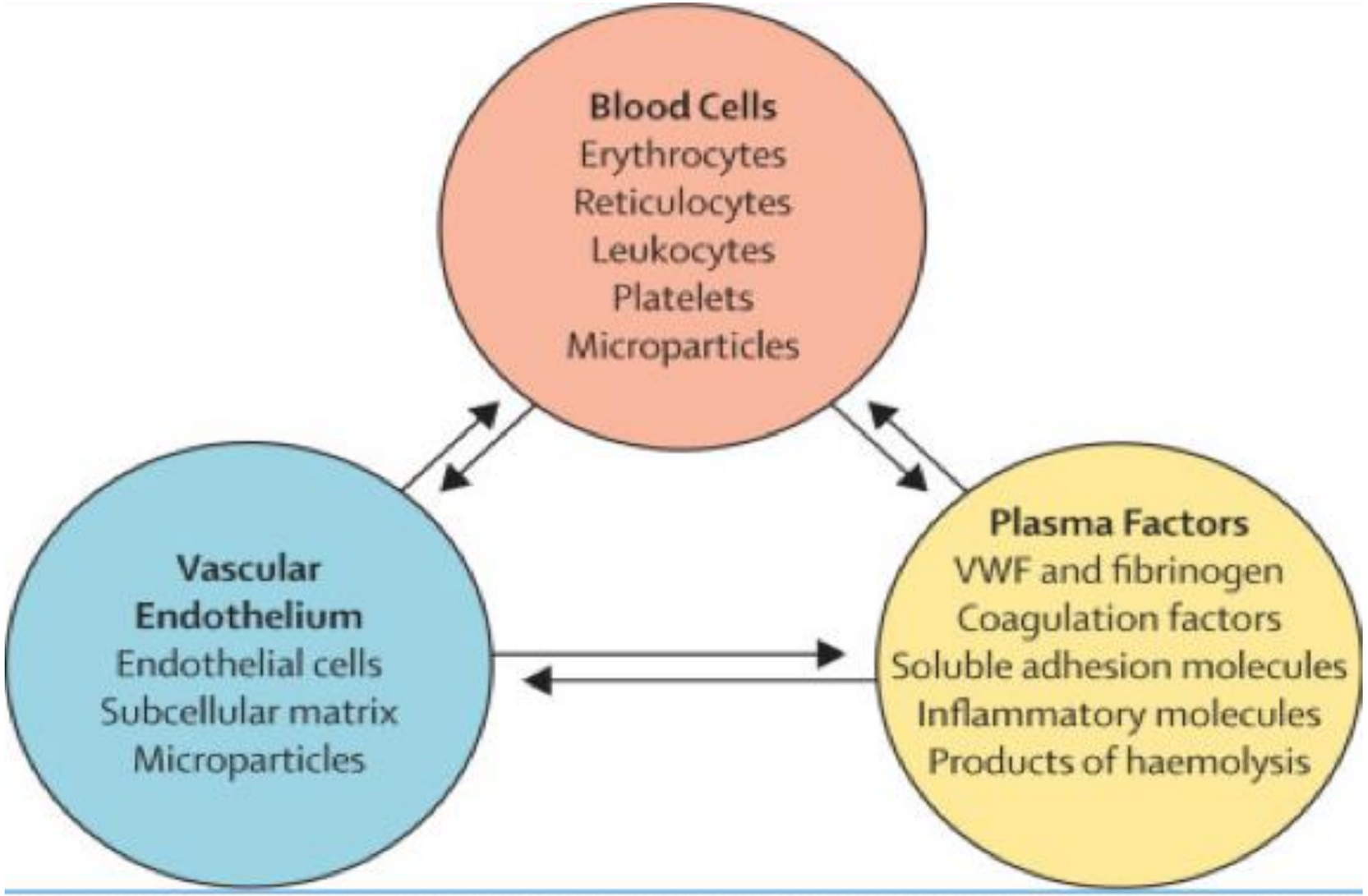


Issues trends



What is sickle cell disease?


Flow
Rolling Neutrophil
Adherent Neutrophil
Sickled RBC
Adherent RBC
Flow
PSGL-1
CD44
E-Selectin
ESL
Mac-1
Unknown


Blood Cells
Erythrocytes
Reticulocytes
Leukocytes
Platelets
Microparticles
Vascular Endothelium
Endothelial cells
Subcellular matrix
Microparticles
Plasma Factors
VWF and fibrinogen
Coagulation factors
Soluble adhesion molecules
Inflammatory molecules
Products of haemolysis

Brain
Silent Stroke

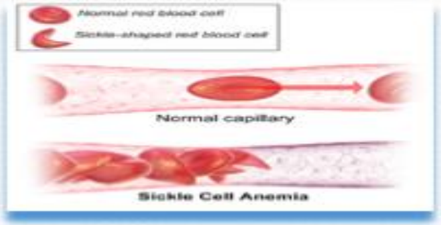
Acute Organ Failure

Liver & Spleen sequestration

SMALL VESSEL OBSTRUCTION

Lungs
Acute Chest Syndrome

Kidney
Glomerulopathy
Papillary necrosis



Bone
Infarction & Pain

LARGE VESSEL OBSTRUCTION

Pulmonary Fibrosis

Brain
CoW stenosis and/or elastic degeneration

Intimal hyperplasia

Lungs
PA thrombosis & narrowing

Heart
Intramyocardial arteriosclerosis

Ischaemic & haemorrhagic stroke

LV fibrosis & failure

Pulmonary HTN
Cor pulmonale

Pathophysiology
The vessel blockage is responsible for vasoocclusion
This impairs blood flow and prevents effective delivery of oxygen to the tissues
This is the underlying cause for painful crises (acute) and chronic damage to potentially every organ in the body
Brain damage is stroke and disability
Acute chest syndrome leads to pulmonary fibrosis and hypertension
Kidney damage leads to renal failure
Splenic infarction leads to hyposplenism (non functioning spleen) and life long susceptibility to infection and sepsis
Avascular (no blood supply) necrosis of the hips and chronic leg ulceration (reduced blood flow) are common complications
There are increased risks for pregnancy and child birth

Clinical course and survival
Significant morbidity and mortality
Variable in severity and onset of acute and chronic complications is unpredictable
This uncertainty is increasingly recognised as having adverse psychological consequences and social disruption for the patient and family
As recently as 1970s patient not expected to survive to adulthood (UK)
2020…99% children survive to adulthood (Ireland)
Median survival for sickle cell anaemia (UK) mid forties
Irish sickle cell anaemia population not matured
NCEPOD (2008) listed stroke disease, multi-organ failure and acute chest syndrome as most common causes of death

Aim of transfusion therapy and choice of modalities	Comment
Increase oxygen carrying capacity	Sickle cell anaemia patients typically have a haemoglobin 6.0-8.0 g/dl Simple additive transfusion (top up) (2-3 units) is indicated when the primary reason for acute transfusion is severe anaemia
Decrease haemoglobin S percentage	Target reduction is < 30% and this will decrease vaso occlusion Exchange transfusion is deployed (remove patient blood replace with donor blood) (3-6 units)
Long term automated transfusion programmes for control of haemoglobin S percentage (prevention of stroke disease)	Automated exchange transfusion every four weeks (8-10 units)

Selection of blood and component	Comment
ABO compatible	
D Cc Ee K compatible	This is to prevent the formation of red cell antibodies and has been recommended since 2004
Allo immunised (formed red cell antibodies)	Red cells negative for corresponding antigens
Perform extended phenotype as a base line	C c E e K k Jka Jkb Fya Fyb M N S s (U)
Perform genotype	This is important because of variant expression of CcEe in African ancestry and non ethnically matched donors will alloimmunise
Hyper haemolytic transfusion reactions	Poorly understood serious complication of red cell transfusion….the patient will haemolyse transfused and own red blood cells and antibody may not be detected on testing

Common Antigens		% in Caucasian Donors	% in African – American recipients
Rh	D	85	92
	C	**68**	**27**
	E	**29**	**20**
	‘c	80	96
	‘e	98	98
KEL	**K**	**9**	**2**
FY	**Fy^a**	**66**	**10**
	Fy^b	**83**	**23**
JK	Jk^a	77	92
	Jk^b	74	49
MNS	**S**	51	31
	s	89	93

Red cell antigen		Percentage Irish blood donors	Percentage African ancestry recipients
Rh	D	85	92
	C	**68**	**27**
	E	**29**	**20**
	C	80	96
	E	98	98
	K	09	02
Fy	**Fy^a**	**66**	**10**
	Fy^b	**83**	**23**
Jk	Jk^a	77	92
	Jk^b	74	49
	S	51	31
MNS	s	89	93

Request blood for exchange transfusion acute chest syndrome (14 units)	IBTS response
O cDe/cde	O cDe/cde(2) O cde/cde (12)
Less than five days from date of collection	
Request for chronic transfusion programme three patients (two brothers and one cousin in kinship travel to OLCHC from rural Ireland)	
B cDe/cde (12) B cDe/cde (11) B cde/cde (07)	B cde/cde (12) B cde/cde (11) B cde/cde (07)
Less than seven days from date of collection	Note issuable stock index for B D(-) is 10 i.e. this represents three days supply

Hospital blood bank	Percentage O D (-)	Comment
SJH	23.0	Sickle cell anaemia (adults) and allogeneic stem cell transplant centre
OLCHC	30.0	Sickle cell anaemia cohort (paediatric)
NMH	40.0	Maternity cohort
SVUH	09.9	Exemplar best practice (hepatobiliary service , vascular repair surgery, haematology oncology and major trauma centre)

Case study

- 23-year-old female gender, avascular necrosis, total hip replacement
- Group O R_0r Fy(a-) Jk(b-) S(-) M(-) x 12 red cell components
- Surgical mishap vascular tear

Red cell importation event D(-) 01 July 2021

Blood group	Patient characteristic	Clinical diagnosis	Number of red cell components
O D(-)	Female gender, potentially child-bearing	Severe postpartum haemorrhage	14
O D(-)	Female gender, potentially child-bearing	Vascular repair surgery (arterial tear)	14
O D(-)	Female gender, potentially child-bearing	Orthotic liver transplant	18

Case study (3)

Calendar year	SCD patients on transfusion programmes	SCD patients on exchange programmes	Number of red cell components transfused (per month)	Requested (cDe) haplotype (per month)
2018	86	15	401	146
2019	93	17	418	192
2020	94	20	507	182

Annual increase 15-21% recurring

Note 41% molecular genotype D variant (transfusion protocol O-)

Haemoglobinopathy Schedule for St.James & Our Ladys Childrens Hospital Crumlin (Ro and rr orders)

Month : **October**

Orders in black = SJH
Orders in green = Crumlin

Monday	Tuesday	Wednesday	Thursday 1st	Friday 2nd
			7 O Ro 7 O rr	14 O Ro
Monday 5th	**Tuesday 6th**	**Wednesday 7th**	**Thursday 8th**	**Friday 9th**
	1 A Ro 8 ORo 11 A rr	3 ORo 8 B Ro 10 B rr 11 A Ro	4 ORo 6 O rr	12 O Ro 18 O Ro 13 B Ro
Monday 12th	**Tuesday 13th**	**Wednesday 14th**	**Thursday 15th**	**Friday 16th**
2 O Ro 7 O rr S-Fya- 12 B rr	1 B Ro 11 B Ro 8 A Ro	14 A Ro	7 B Ro 7 B Ro	7 O rr 8 O Ro 13 B Ro
Monday 19th	**Tuesday 20th**	**Wednesday 21st**	**Thursday 22nd**	**Friday 23rd**
2 O rr 10 B rr	2 B rr 6 A rr	9 O rr	5 ORo 7 ORo	8 A Ro
Monday 26th	**Tuesday 27th**	**Wednesday 28th**	**Thursday 29th**	**Friday 30th**
	9 ORo 10 B rr 11 A rr	7 O rr 11 A Ro	7 O Ro 9 A Ro	2 O Ro

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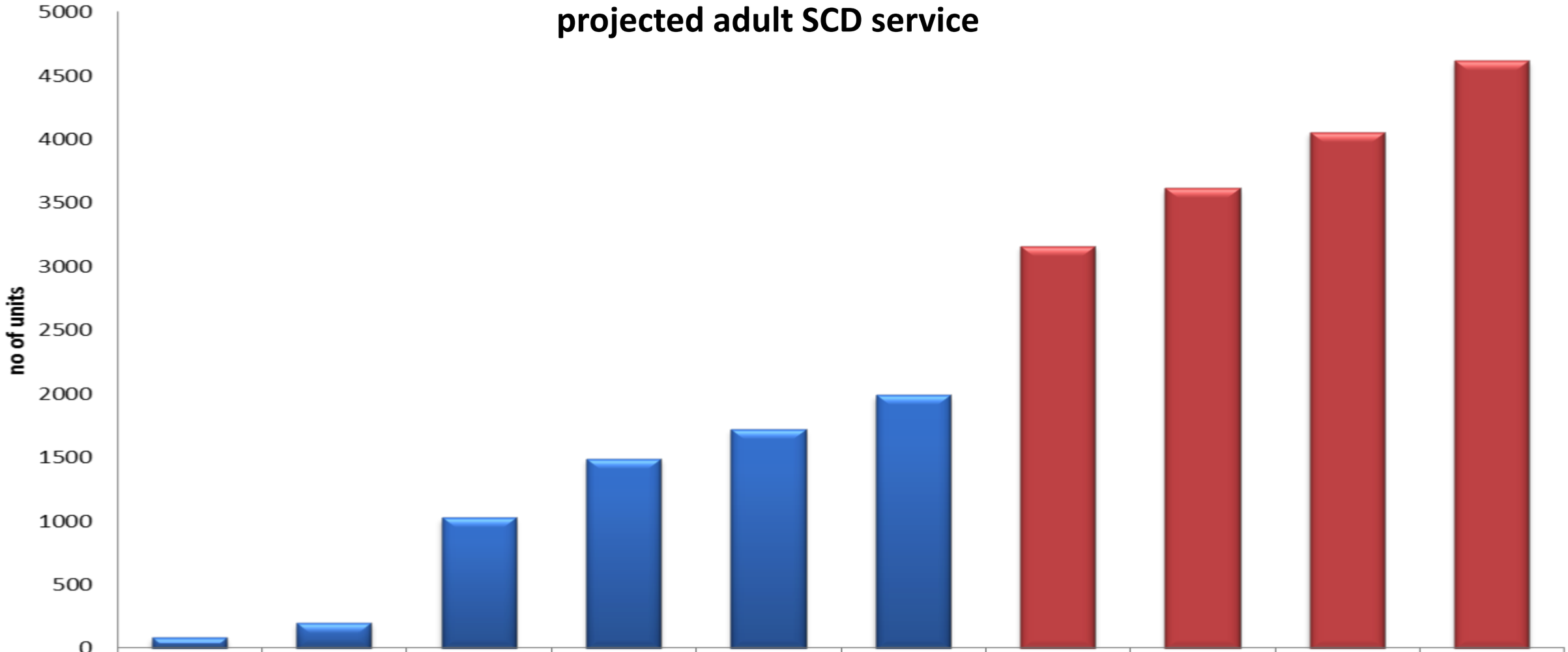
Type	Number	% of order	% in population
R0	228	66.1%	1.25%
rr	117	33.9%	16.66%
Total	345	100%	17.91%

SJH sickle service projected demand for red cell components	Number of red cell components
2019	1991 (actual)
2020	3160
2021	3615
2022	4057
2023	4616

Number of red cell components transfused and projected adult SCD service



	2014	2015	2016	2017	2018	2019	2020	2021	2022	2022
RCC	85	203	1026	1490	1722	1991	3160	3615	4057	4616

Special requirements	Comment
Hb S negative blood	Sickle trait blood Hb AS will potentially aggravates crisis
Fresh blood	Improves oxygen delivery and clinical response, requirement varies and relative
Antigen matched blood	Register antibody status Match for C D E K

Transfusion risks
Alloimmunisation
Delayed haemolytic transfusion reactions
Iron overload
Hyper haemolytic syndrome
Lack of blood availability in medical emergencies
Hyper viscosity

Alloimmunisation
47% of SSD have at least one red cell antibody
Risk per red cell component transfused = 3.1%
Anti K E C Jk account for 80%
17% have > 4 red cell antibodies
10% have positive DAT (autoantibodies)
Attributable to genetic differences in red cell antigens expressed in donor and recipient populations
Prophylactic matching E C K reduces alloimmunisation rate from 3% to 0.5% per red cell component in children

Alloimmunisation

- Up to 48% in patients with SCD[1]

- C, E, K, Fy^a, Jk^b ,S higher incidence than Caucasians
  - 2/3 Antibodies anti C, E, K
  - C,E, K matching
    - Reduced rate of allo-immunisation from 1.7-3.9 AB/100 units transfused to 0.26-0.5.

- Racially matched units
  - Reduced anti Jk, Fy and S antibodies
  - Rh allo-immunisation rate remains high

[1]*Zalpuri S, Zwaginga et al. Vox Sang. 2012 Feb ;102(2):144-49*

Red cell antigen	Gene frequency in Caucasians	Gene frequency in African Americans
Ro (Dce)	0.04	0.44
K1	0.09	0.02
Jka	0.77	0.09
Fy(a-b-)	<0.01	0.68

High prevalence of red cell alloimmunisation in SCD despite ethnic matching donors
African American donors matched for D C E K (n=182 patients)
58% chronic and 15% episodic transfused patients alloimmunised
45% chronic and 12% episodic transfused patients Rh immunised
N=146 red cell antibodies, 91 unexplained Rh (28% associated haemolytic transfusion reactions)
High resolution genotyping confirmed variant alleles in 87%
Adapted protocols C- to C + patient variant C; D - to patient D+ genotype predict partial D….downside is disparate Jk^b Fy^a S in Caucasian D- donor
There is a need for clinical trials

Action	Comment
Recruitment and retention of African ancestry donors	Clinicians must act as advocates Patients and their families are captive audience
	Bespoke recruitment campaign with targeted messaging (medical team to script message as appropriate)
Implement malaria antibody screening	Validated test and method
Confirm eligibility rules, procedures and systems	Has been the biggest delay to date
Sickle haemoglobin test	Implemented
Ethnic matching	R0 supply increased, D (-) supply conserved Opportunity for prospective randomised clinical trials of molecular genotyped donors and patients

Calendar year	Blood group O Ro	Blood group B Ro
2021	800	200
2022	1600	400
2023	2400	600


BELFAST
OFFICIAL TRAILER

What we have achieved

- Engagement clinicians
- Engagement advocacy groups
- Validation malaria antibody assay
- IT link secure
- Pilot exercise deferred

Barriers to completion

Factor	Comment
Cultural barriers to donation	Fear, mistrust and suspicion
Discriminatory question “Have you had sex with someone from sub-Saharan Africa?”	Fair Assessment of Individual Risk (FAIR) Effectively a permanent exclusion
Sample only no donation	23% return
Risk assessment	Initial test reactive repeat in duplicate, individual donation PCR, surface antigen and anti-hepatitis core antibody Default repeat test next donation (malaria) every time

What needs to happen next

- Confirm eligibility rules
- Resource plan
- Information and awareness campaign
- Special invitation bleed/clinic model
- Targets and timelines defined
- Pilot clinic (proof of concept)
- Implementation plan

Connections that count

Diversity

Inclusion

Equality

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