NHS Blood and Transplant

BBTS 2019

Genotyping the haemoglobinopathy patient population in England

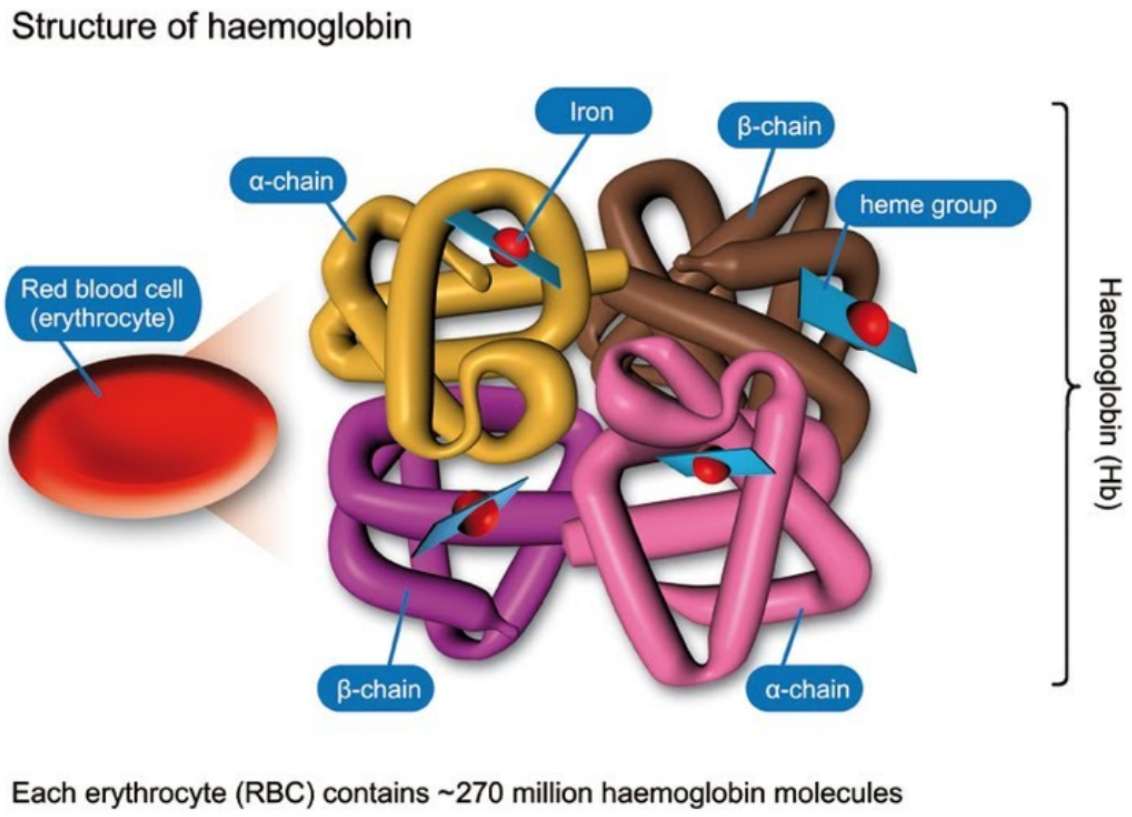
Karen DeSay

Outline

Update on data analysis from NHSBT haemoglobinopathy genotyping service

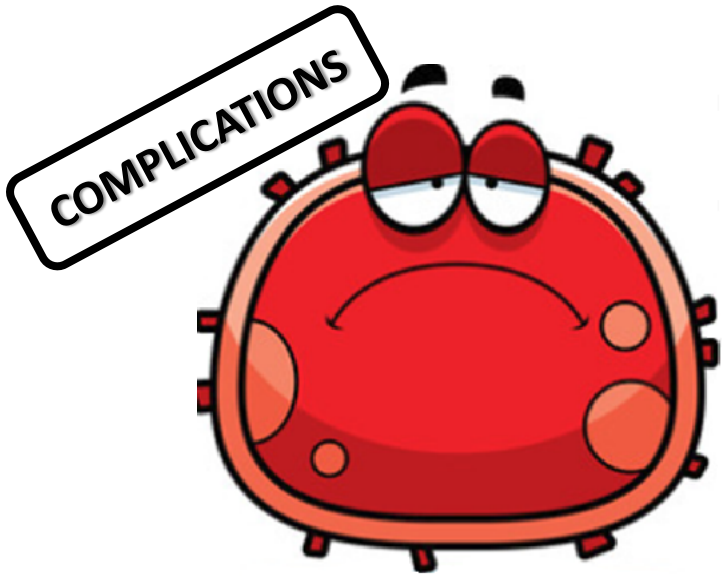
Evidence to support transfusion of haemoglobinopathy patients in the UK

Haemoglobinopathies



- In UK, most common is SCD
- Seen in BME population
- Range of clinical effects
- Transfusion therapy key treatment

Challenges of transfusion therapy in the HGP population

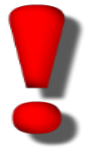


↑ Risk

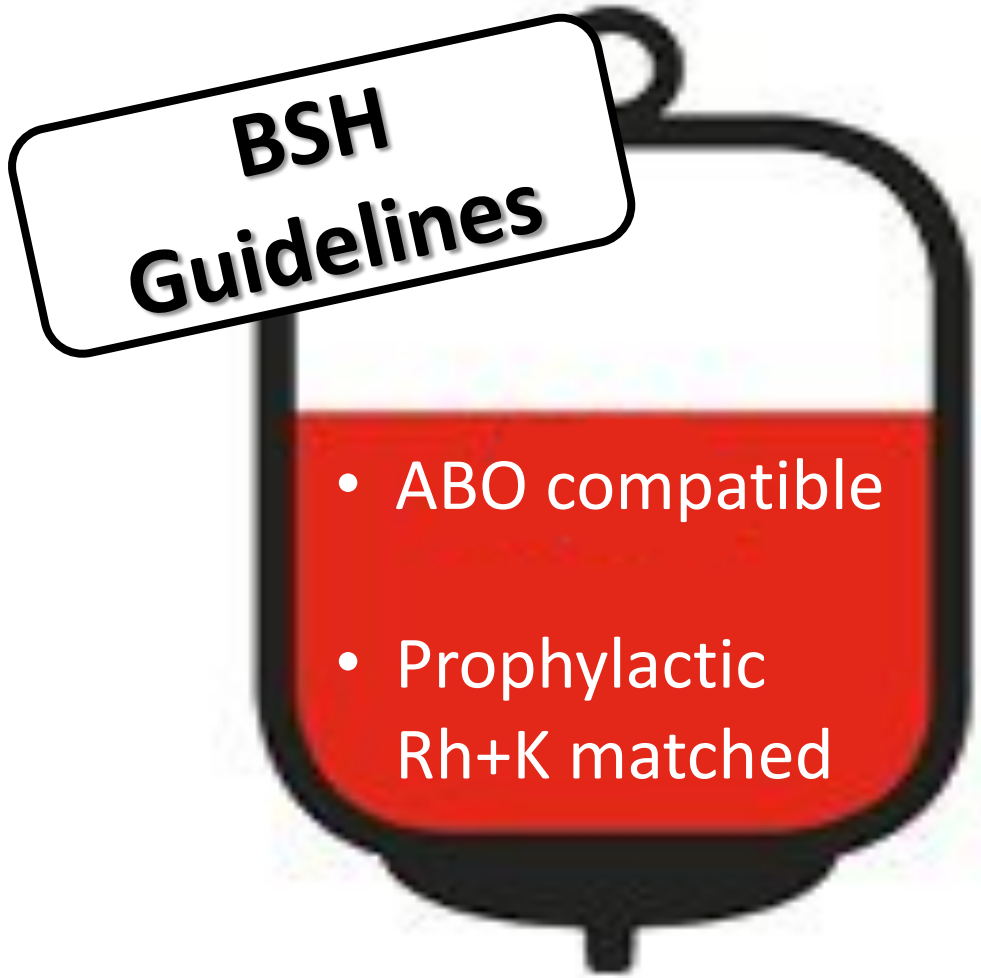
Alloimmunisation
Haemolytic transfusion reactions
(can include hyperhaemolysis)
Autoimmune haemolytic anaemia

Optimum survival of donated RBCs

“Untransfusable” patients
8-10 alloantibodies
Require rare frozen units (if available)



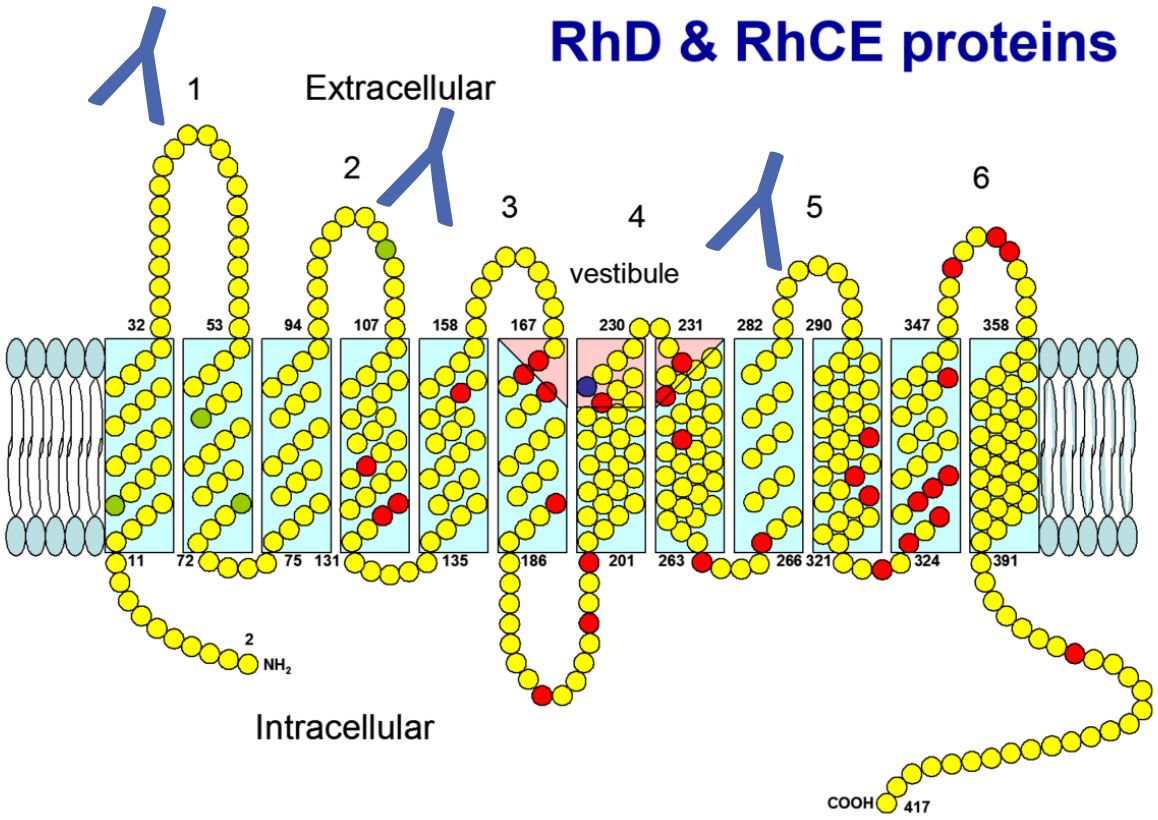
Reducing risk of alloimmunisation
Optimising RBC survival



<u>Globally reported</u>

Rh alloimmunisation despite Rh matching by serological methods

Why Rh alloimmunisation despite matching?



- Non Standard Rh antibodies (NSRH) e.g. e variant with allo anti-e
- Number of patients with NSRH in UK unknown
- Collective knowledge of clinical significance of NSRH is limited

Why genotyping over serology?

Majority of donors from Caucasian population

Majority of HGP patients from Black Minority Ethnic (BME) population

Different frequencies of RBC antigens in different ethnic populations

Cell	Rh	Rh						MNSs				P1	Lu		Kell			Le		Fy		Jk	
		D	C	E	c	e	C^w	M	N	S	s		a	b	K	k	Kp^a	a	b	a	b	a	b
1	$R_1^wR_1$	+	+	0	0	+	+	+	0	+	0	0	0	+	0	+	0	+	0	+	0	+	0
2	R_1R_1	+	+	0	0	+	0	+	0	0	+	2	0	+	+	0	0	0	+	+	0	0	+
3	R_2R_2	+	0	+	+	0	0	0	+	0	+	3	0	+	0	+	0	0	+	0	+	0	+
4	r'r	0	+	0	+	+	0	0	+	+	0	0	+	+	0	+	0	+	0	0	0	0	+
5	r''r	0	0	+	+	+	0	0	+	+	+	3	0	+	0	+	0	0	+	+	0	+	0
6	rr	0	0	0	+	+	0	+	0	+	0	1	0	+	0	+	0	+	0	0	+	+	+
7	rr	0	0	0	+	+	0	0	+	0	+	0	0	+	+	+	0	0	+	0	+	+	0
8	rr	0	0	0	+	+	0	+	+	0	+	0	0	+	0	+	+	+	0	+	0	0	+
9	rr	0	0	0	+	+	0	+	0	+	+	1	0	+	0	+	+	0	+	+	0	+	0
10	rr	0	0	0	+	+	0	+	0	+	0	4	0	+	+	+	0	0	+	0	+	0	+
Auto																							

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for antigens of

ɔing difficult to do at

Antigram showing 9 major blood group systems and used to identify antibodies in patient plasma

Study aims

1

Prevalence of selected Rh variants in HGP patients in England

2

Prevalence of immunisation in blood recipients with Rh variants

3

The burden of morbidity due to Rh variants

NHSBT genotyping service (overview)

IBGRL Haemoglobinopathy genotyping panel

- In-house selected Rh variants - designed with clinicians
- Algorithm to translate genotype to predicted phenotype
- Offered to all HGP patients in England

  Expected ~11,000, study – 4,204

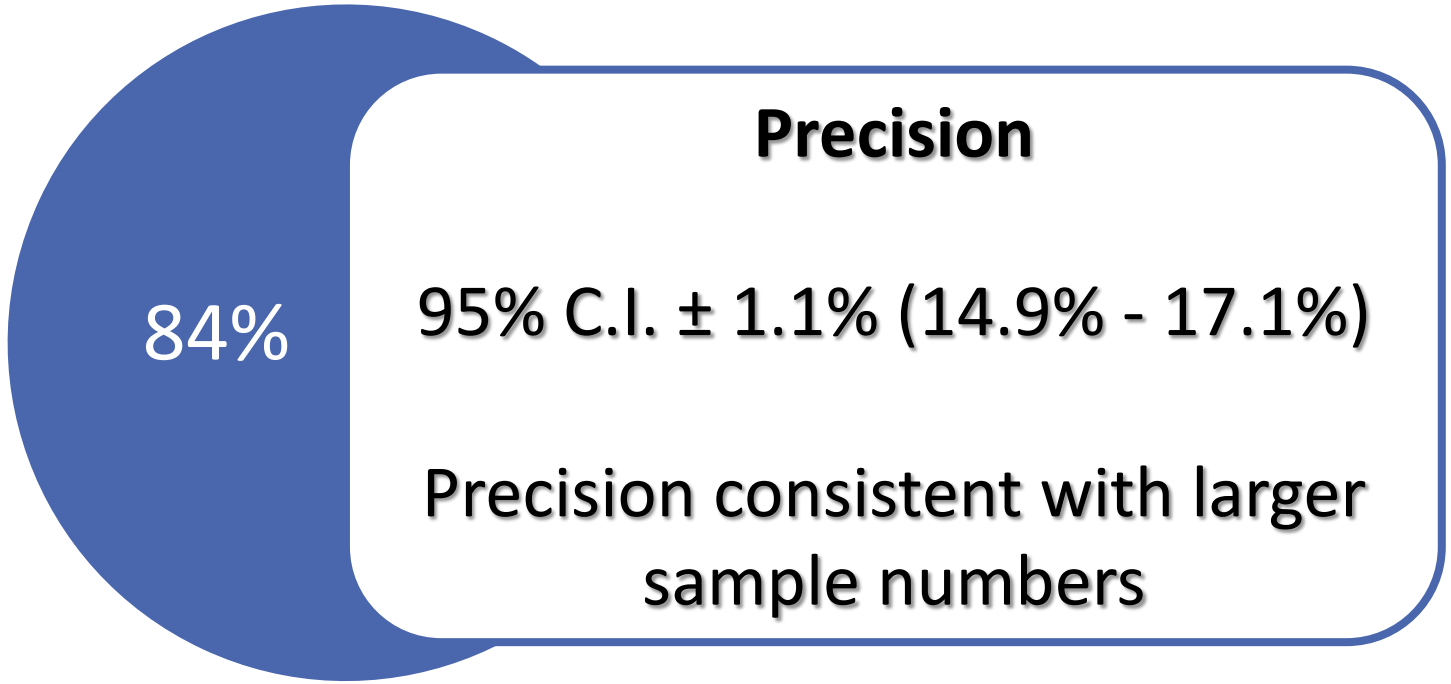
Data analysis

- Analyse data from HGP genotyping service
- Immunisation data collected from:
  - Surveys (hospital immunisation data)
  - Hematos (NHSBT LIMS)

Large dataset, national representation

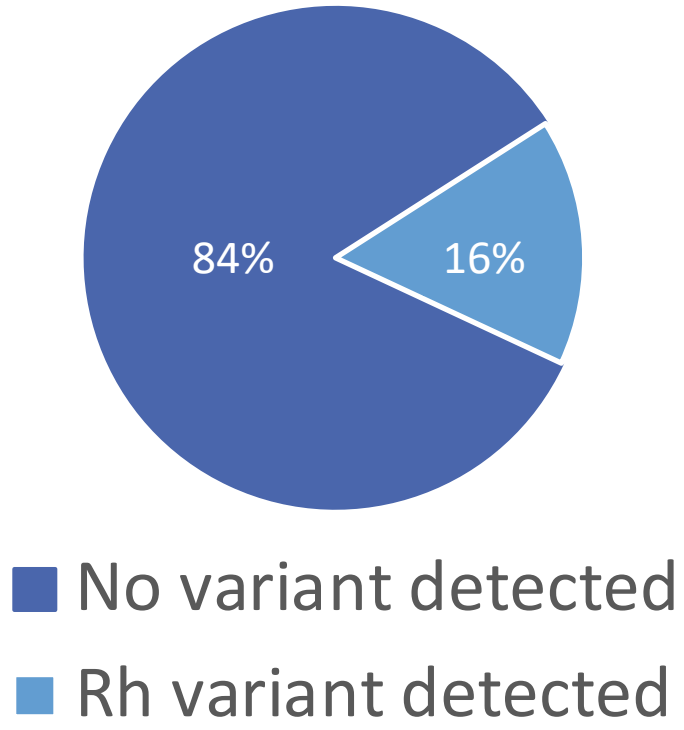
Result : Prevalence of selected Rh variant phenotypes

Prevalence Rh variants in total population (n = 4,204)

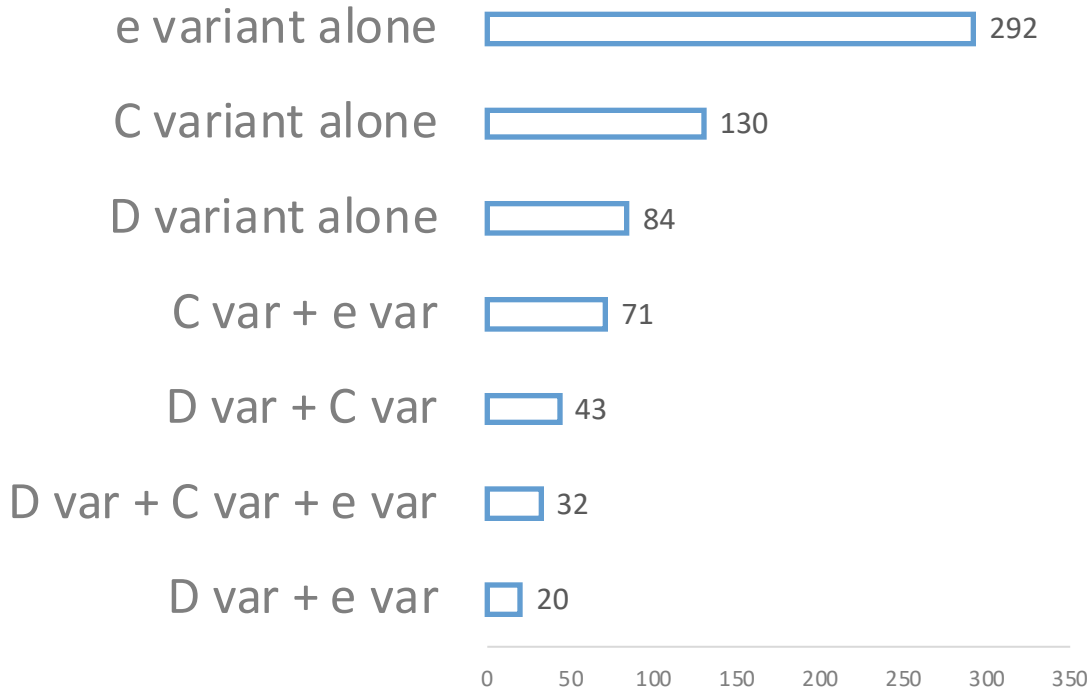


Result : Prevalence of selected Rh variant phenotypes

Prevalence Rh variants in total population (n = 4,204)



Predicted Rh variant phenotype (n = 672)



2

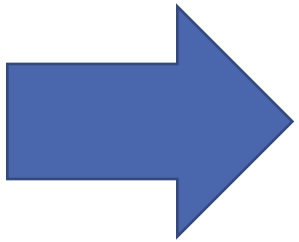
Prevalence of immunisation in blood recipients with Rh variants

Hospital survey (n= 672)

1. History of transfusion (Y/N)
2. History of antibodies? (Y/N)
3. Antibody specificity

Survey results

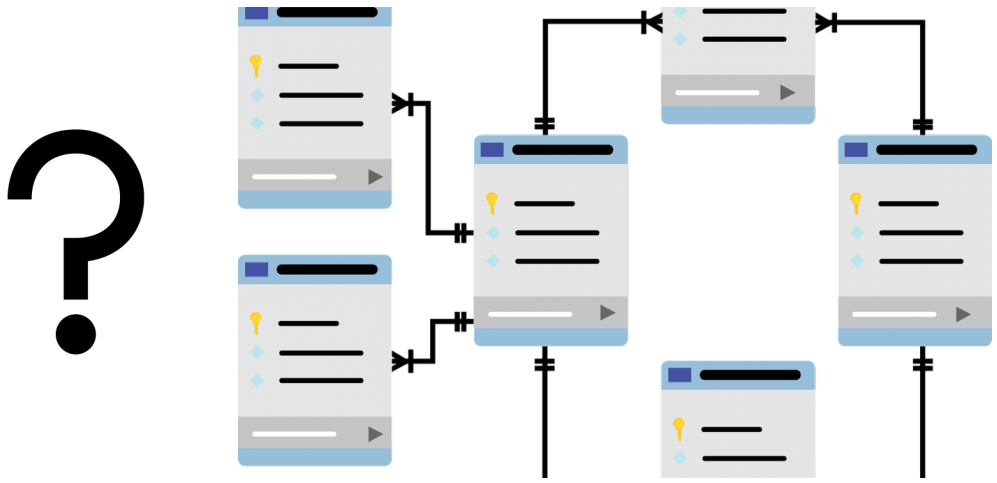
672 predicted Rh variant patients



575 returned surveys

Response rate = 86%

NHSBT LIMS (Hematos) data query (n= 672)



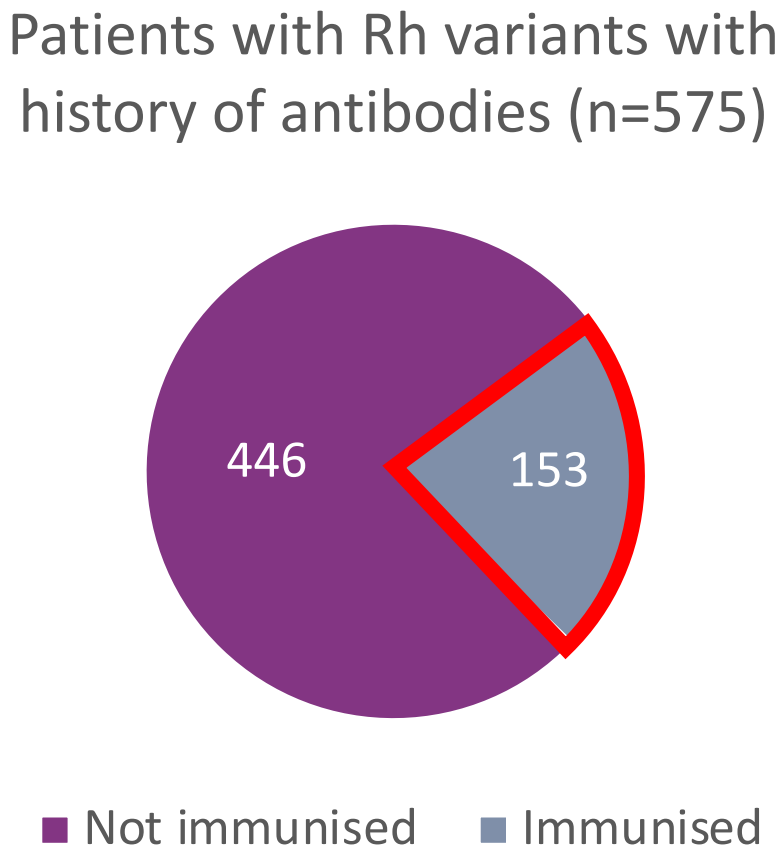
1. History of transfusion (Y/N)

2. History of antibodies? (Y/N)

3. Antibody specificity

Immunisation data: Combination of individual hospital & national LIMS results

Results: overall prevalence of immunisation

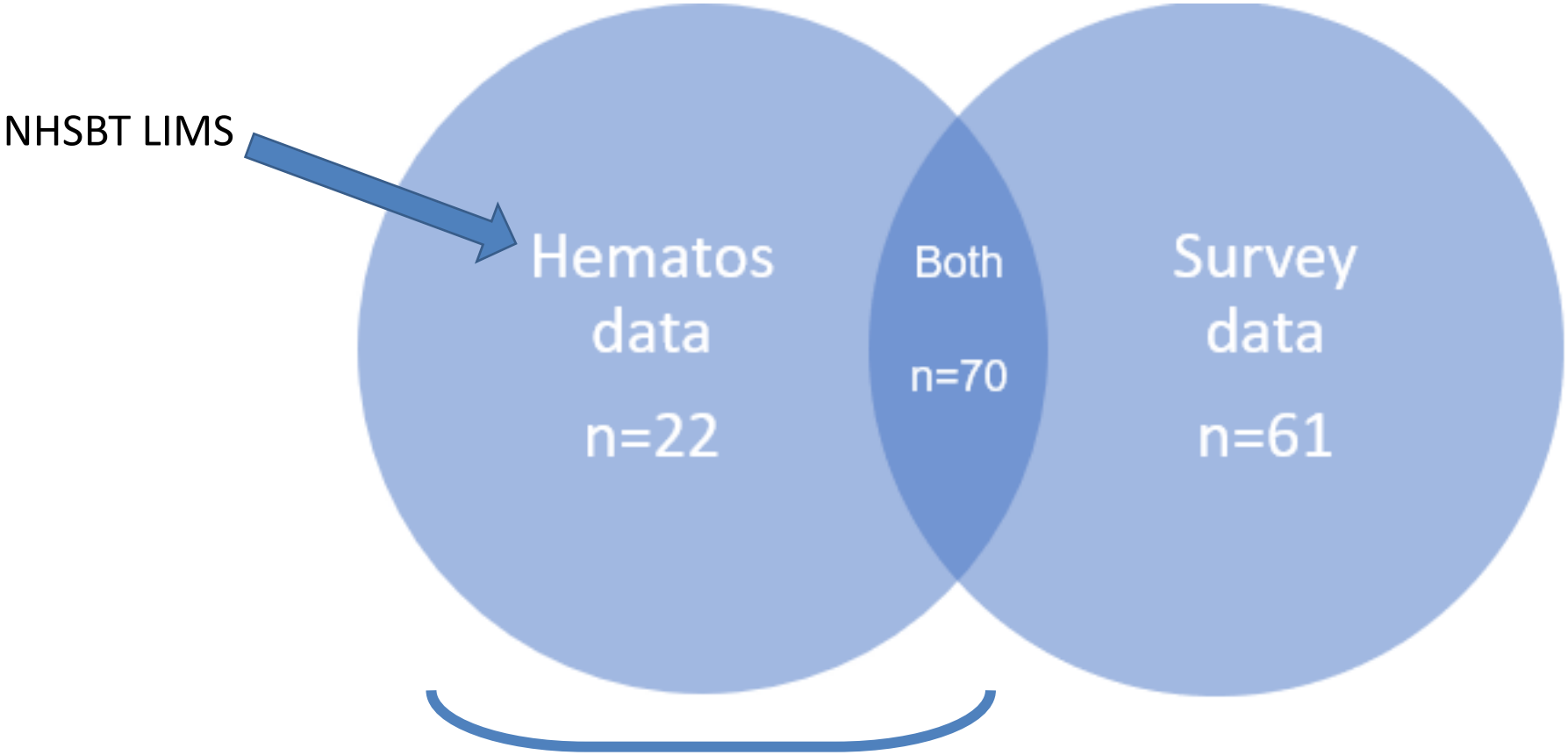


- 26.61% immunisation
  (95% C.I. 23 – 30%)

Note:

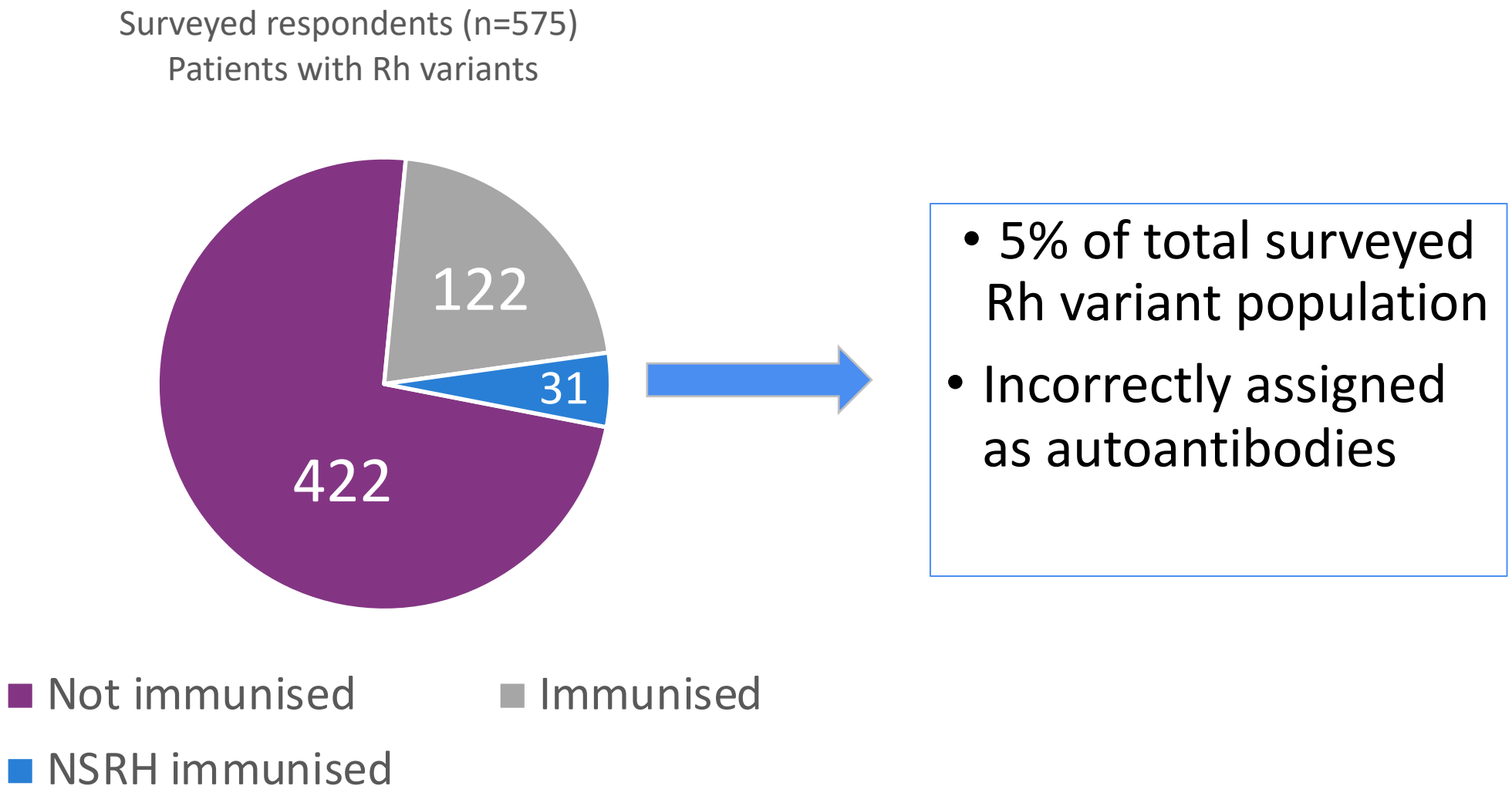
- Includes reported auto and allo specificity.
- Both clinically significant and not clinically significant e.g. anti-CR1 antibodies included

Combined national and individual hospital antibody data (n=575)



60% all antibodies confirmed by NHSBT

Patients with non standard Rh antibodies (NSRH)



- 5% of total surveyed Rh variant population
- Incorrectly assigned as autoantibodies

3

The burden of morbidity due to Rh variants

Survey 2: Clinical follow up (n=31)

1. History of pregnancy (Y/N)

2. Length of hospital transfusion record in months

3. Number of RBC units ever transfused at hospital

3. History of:

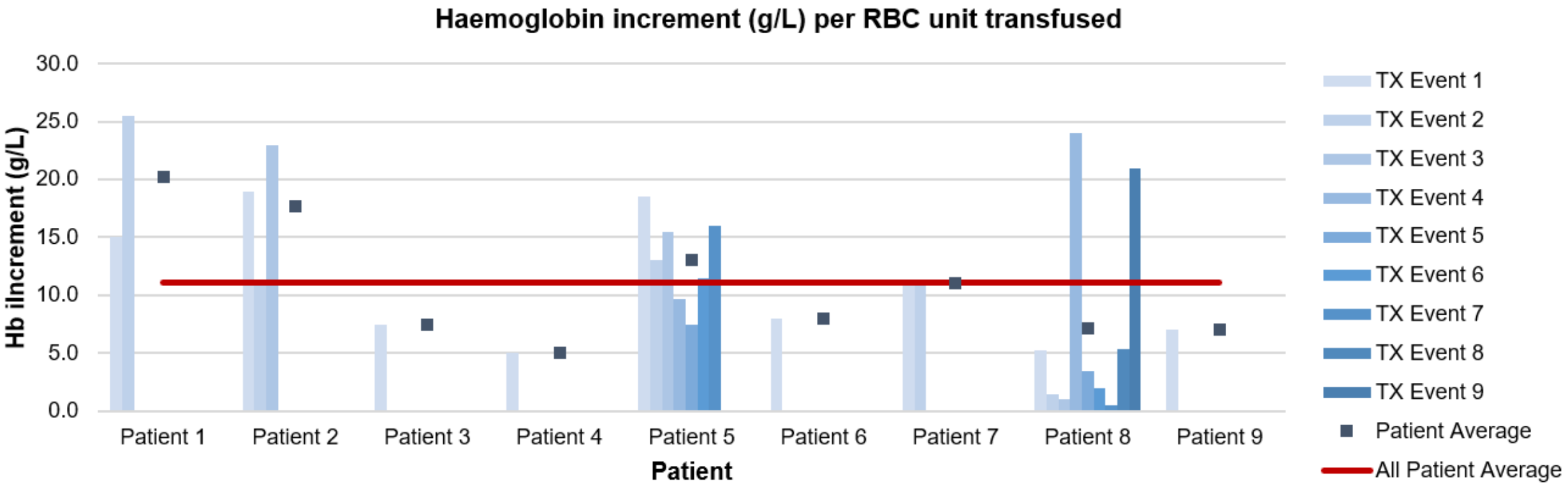
- Transfusion reactions
- Delayed haemolysis
- Hyperhaemolysis
- Poor Hb increment (where possible, please provide pre and post transfusion Hb values)

Results: Survey 2 response

31 patients has 33 NSRH antibodies. Transfused 1,737 RBC units as a group

Parameter (n = responses to question)	Range
Sex (n=31)	63% F : 36% M
Age (n=31)	4-64
Length of transfusion history (n=29)	16-351 months
Number RBC units transfused (n=29)	0-351 RBC units
Evidence of transfusion reactions (n=27)	2
Evidence of poor Hb increment (n=23)	All achieved clinically useful increments

In the presence of additional antibodies

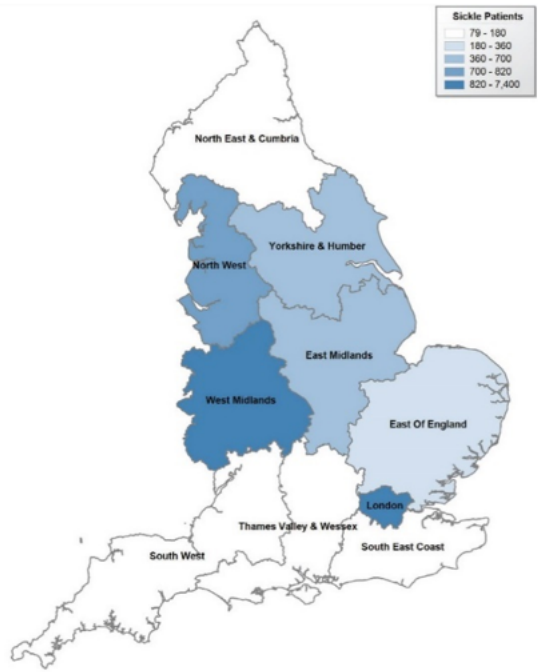


Clinical summary: many patients with Rh variants transfused incompatible blood achieve clinically useful increments

Small cohort (incomplete data), however no clinical suspicion of suboptimal Hb increment

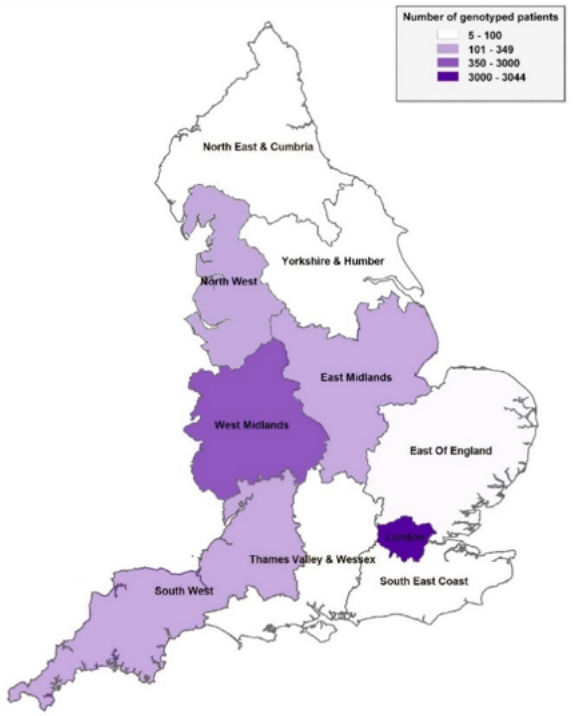
Comparison of population and survey respondent demographic

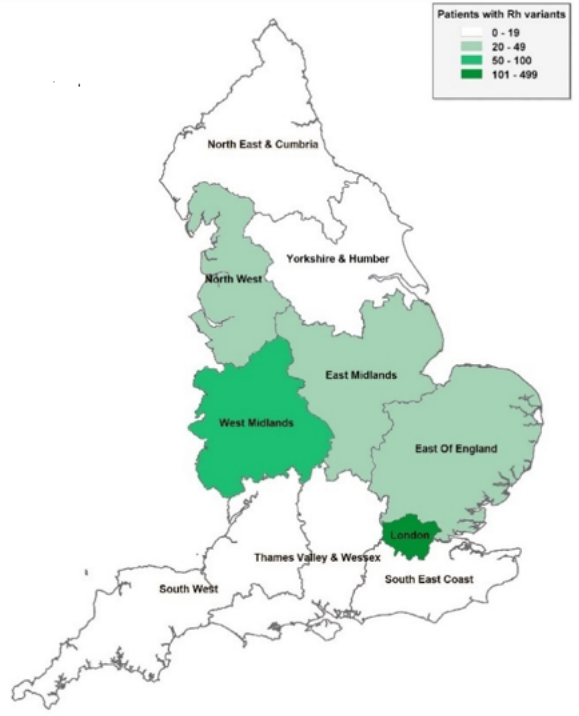
SCD population demographic



Region	No. Patients	Region	No. Patients
London	7,277	East of England	216
West Midlands	921	Thames Valley & Wessex	176
North West	721	South East Coast	119
Yorkshire & Humber	692	South West	98
East Midlands	557	North East & Cumbria	79

Respondent demographic





Region	Number of unique patients genotyped
London	3044
West Midlands	377
East Midlands	292
North West	142
South West	109
East England	82
North East & Cumbria	71
Yorkshire & Humber	49
Thames Valley & Wessex	32
South East Coast	5
Total	4203

Region	Number of unique patients with Rh variants
London	499
West Midlands	50
East Midlands	41
North West	28
East England	20
North East & Cumbria	12
South West	11
Yorkshire & Humber	8
Thames Valley & Wessex	3
South East Coast	0
Total	672

Sequencing variant = variant antigen?

- Genotyping panels can detect sequence variants which may not be associated with serologically defined variants
- Good comparison of NHSBT SNV frequencies with gnomAD data (database of large-scale sequencing projects)
- Predict *clinically significant* variant phenotype

Limiting factors to a genotype matching programme

DONORS

COST

LOGISTICS & TECHNOLOGY

T.A.T

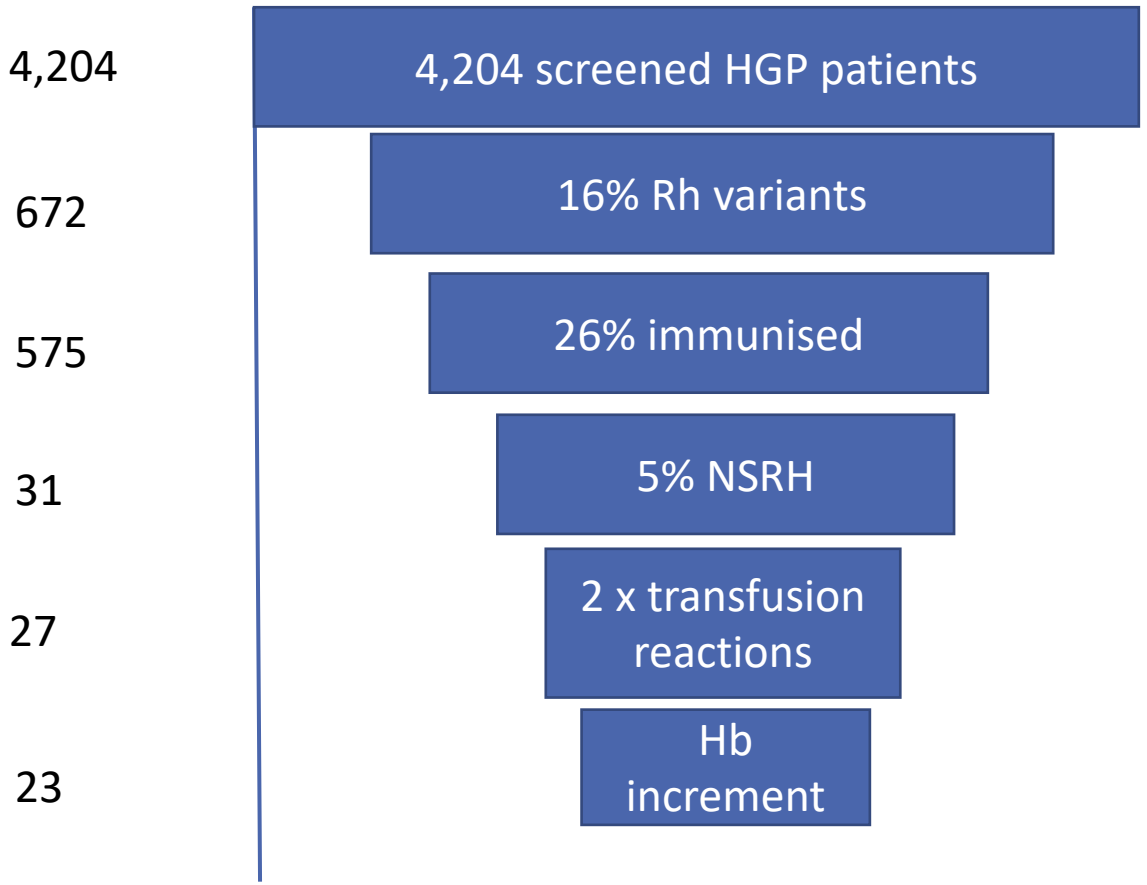
Should we genotype match patients?

Benefits

- Improved management and utilisation of the existing inventory of blood from BME donors
- Increase antigen-negative inventories and identifying rare donors
- Prevention and early intervention avoid problems and costs associated with multiple alloantibodies
- Matching for blood group systems outside Rh e.g. MNS, FY

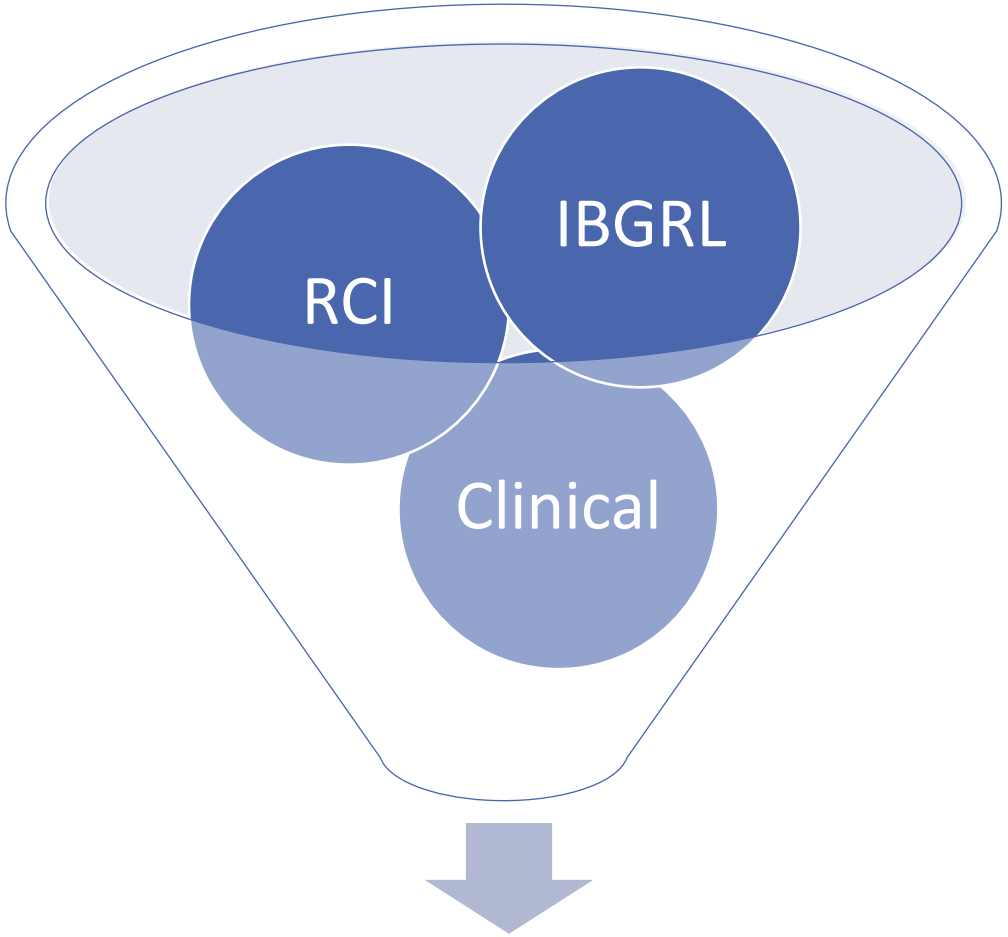
Is the cost in proportion to the medical benefit?

Summary and conclusion



- **Small group of NSRH patients**
- **No definitive correlation between NSRH to poor clinical outcome**
- **Inform matching strategies**

Thank you



- NHS staff: Hospitals BMS and transfusion practitioners

HGP genotyping initiative

Potential matching strategies

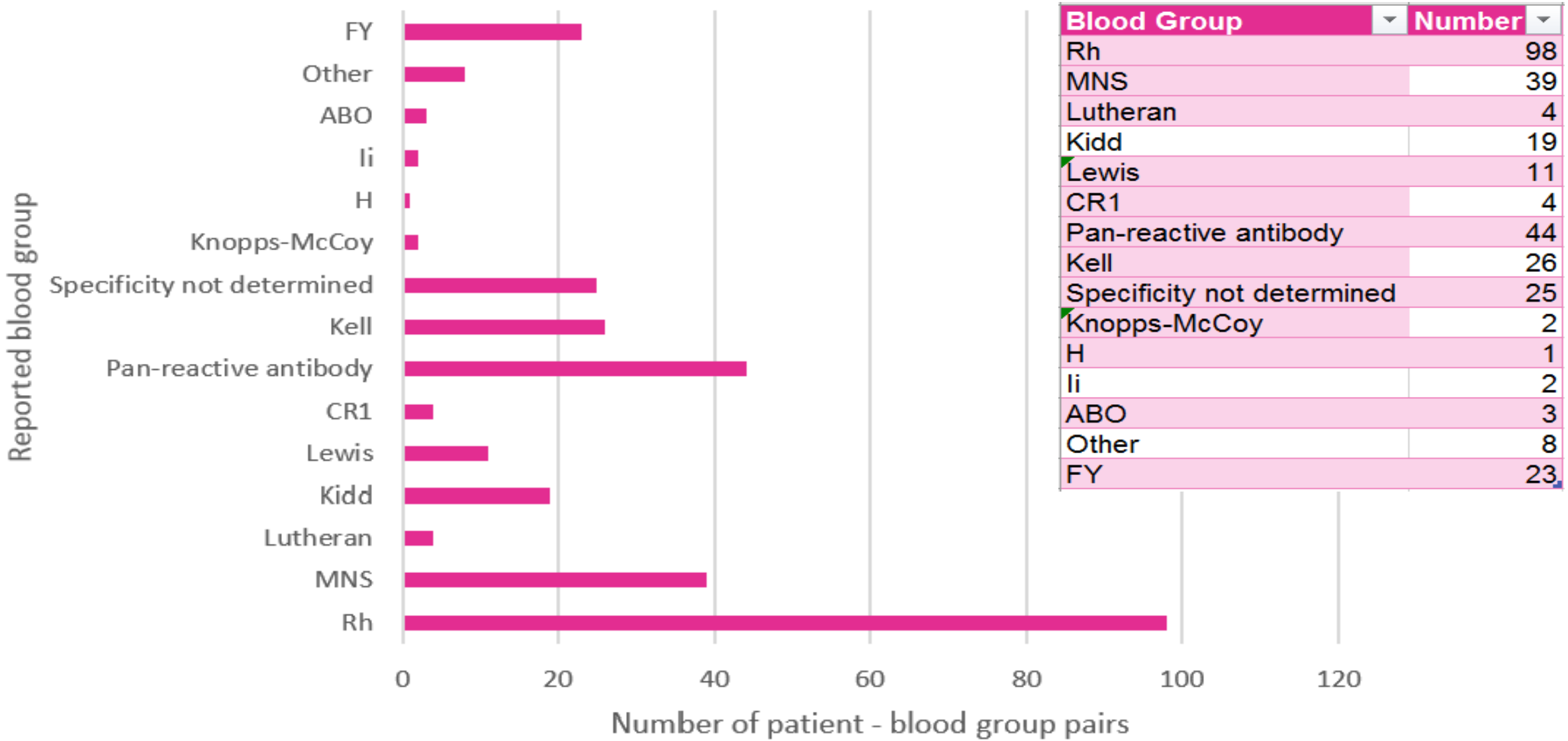
- Provide genotype matching for everyone – not cost effective
- Prioritised for paediatric patients or patients who have formed one antibody
- Patient with haemoglobinopathies or heavily alloimmunised patients
- Alloimmunised patients with clinical evidence of DHTR/ poor haemoglobin increment

Antibody detected	Phenotype (Serological)	Predicted Phenotype (Genotype)	Classification	Transfuse	Possible outcomes if NOT genotype matched
Anti C	Rh C positive	C positive	Auto antibody	C positive	N/A
Anti C	Rh C positive	C variant	Allo antibody (NSRH)	C negative	Poor Hb increment Delayed HTR etc

In a BAME patient,

BMS: Don’t assign Rh auto antibody status just because the person appears to be antigen positive

Clinical care: Be alert for patients not incrementing as expected with auto anti-Rh on their report



Blood Group	Number
Rh	98
MNS	39
Lutheran	4
Kidd	19
Lewis	11
CR1	4
Pan-reactive antibody	44
Kell	26
Specificity not determined	25
Knopps-McCoy	2
H	1
Ii	2
ABO	3
Other	8
FY	23

Result validation

Reference SNP cluster ID	NHSBT HGP genotype population		gnomAD population		Difference between African population in gnomAD and NHSBT HGP population
	Wildtype	Variant	Variant (all ethnicities)	Variant (African population)	
RHD455 (rs17418085)	0.982105	0.017895	0.00676	0.06097	3.4 times greater
RHD667 (rs1053356)	0.966207	0.033793	0.01255	0.1078	3.19 times greater
RHDEX5 (rs148014996)	0.9622195	0.0377805	0.004387	0.04266	1.13 times greater
RHCE712 (rs144163296)	0.992109	0.007891	0.00122	0.01092	1.38 times greater
RHCE667 (rs147357308)	0.9928724	0.0071276	0.001467	0.01282	1.79 times greater
RHCE733 (rs1053361)	0.7955302	0.2044698	0.02427	0.2312	1.13 times greater
RHCE1006 (rs116261244)	0.9623247	0.0376753	0.003758	0.0398	1.1 times greater

Result validation

Reference SNP cluster ID	Difference: SNP frequency African population in gnomAD and NHSBT HGP population
RHD455 (rs17418085)	3.4 times greater
RHD667 (rs1053356)	3.19 times greater
RHDEX5 (rs148014996)	1.13 times greater
RHCE712 (rs144163296)	1.38 times greater
RHCE667 (rs147357308)	1.79 times greater
RHCE733 (rs1053361)	1.13 times greater
RHCE1006 (rs116261244)	1.1 times greater

- Specifically designed to detect SNVs of clinical significance whereas gnomAD detects sequence variants which may or may not be associated with serologically defined variants
- The NHSBT HGP genotyping panel might therefore be a better predictor of clinically significant variant phenotype

Impact on product selection

Predicted phenotype	Potential Ab	Product advice **without** Ab	Product advice **with** Ab
D+	Auto/allo anti-D	D+	D–
D^{var}	Anti-D	D– *	D–
D+ E+ e^{var}	Anti- hr^S/-hr^B	e–	e– (D+ E+)
D+ E– e^{var}	Anti- E, anti-hr^s/hr^b	E–	1. E– 2. E– and IVIG cover 3. If unacceptable haemolysis D+ E+ e–
D– E– e^{var}	Anti-D, anti-E, anti-hr^s/hr^b	D– E–	1. D– E– 2. D– E– and IVIG cover 3. If unacceptable haemolysis r''r''
D+ C^{var} c+	Anti-C	C–	C–
D– C^{var} c+	Anti-D, anti-C	D– C–	D– C–
D^{var} C^{var} e^{var} E–	Anti-D, anti-C, anti-hr^s/hr^b, anti-E	D– C– e+ E–	1. D– C– e+ E– 2. e+ IVIG cover 3. If unacceptable haemolysis r''r''
D^{var} C^{var} e^{var} E+	Anti-D, Anti-C, anti-anti-hr^s/hr^b	D– C– e+ E-	1. D– C– e+ E– 2. E- + IVIG cover 3. If unacceptable haemolysis r''r''

* If there is a history of D+ transfusion, without production of anti-D, D+ may be considered.

Matching strategy – what do we need to get there?

- The development of data handling protocols so results are available via PULSE (
- Operational, medical and scientific competencies to support any future adoption of genotyping for all blood donors
- charged hospitals, would they be willing to pay?