UK NEQAS
International Quality Expertise

Histocompatibility & Immunogenetics

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Interpretive Educational Scheme (iED)
Clinical Scenario 3/2020 – Transfusion Related Acute Lung Injury

Dispatched on 19th January 2021

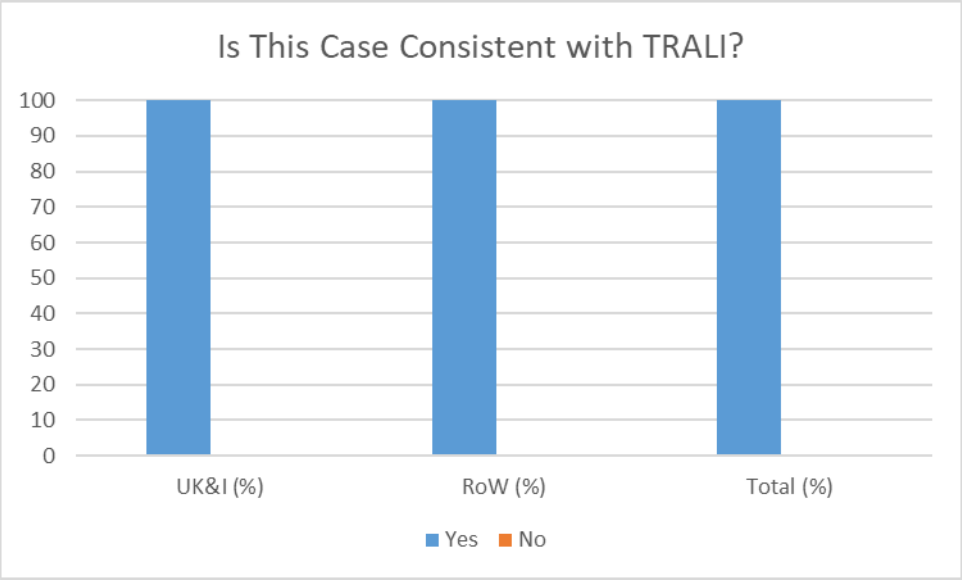
Summary of Results

A total of 33 responses were received, 16 from laboratories based in the UK and Ireland (UK&I) and 17 from Laboratories based in the rest of the world (RoW) participants.

A case was presented to the laboratory for investigation on 14/06/2020. A 69 year old white British female with Myelofibrosis was admitted with weight loss, fevers and bronchopneumonia received 2 units of red cells (Donor 1 was transfused on 13/06/2020 at 23:20-23:30 and Donor 2 was transfused on 14/06/2020 at 00:48-00:59) to treat anaemia. 15 minutes after the start of the second unit the patient became unresponsive and hypoxic. The patient required intubation, ventilation and further treatment. The patient improved and was extubated 48 hours later. The patient had bilateral infiltrates after the reaction.

1) Based on the information provided in this initial patient case report only, would you suspect this case is consistent with TRALI?

	UK&I	UK&I (%)	RoW	RoW (%)	Total	Total (%)
Yes	16	**100**	17	**100**	33	**100**
No	0	**0**	0	**0**	0	**0**



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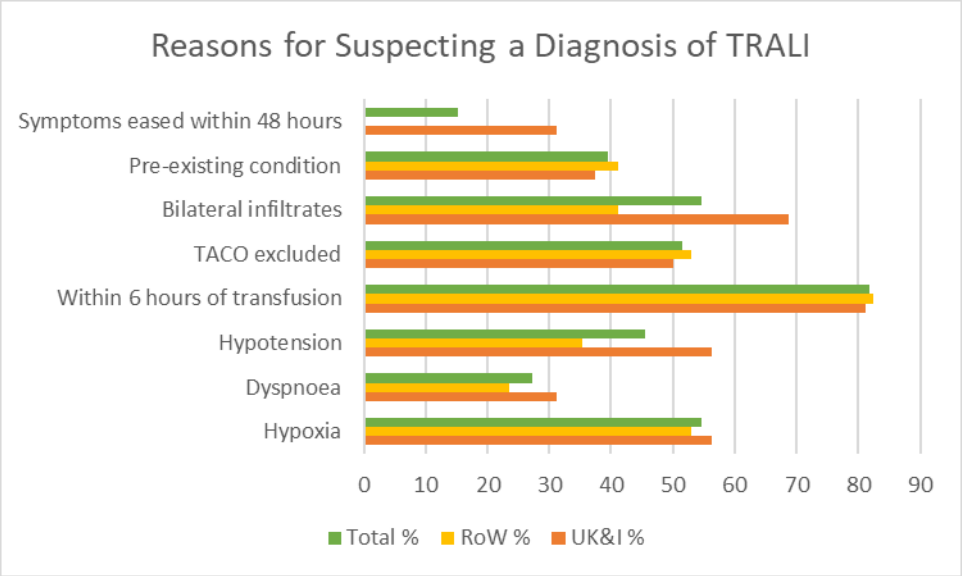
Please give reasons for your answer

Reasons	UK&I	UK&I %	RoW	RoW %	Total	Total %
Hypoxia	9	**56**	9	**53**	18	**55**
Dyspnoea	5	**31**	4	**24**	9	**27**
Hypotension	9	**56**	6	**35**	15	**45**
Within 6 hours of transfusion	13	**81**	14	**82**	27	**82**
TACO excluded	8	**50**	9	**53**	17	**52**
Bilateral infiltrates	11	**69**	7	**41**	18	**55**
Pre-existing condition	6	**38**	7	**41**	13	**39**
Symptoms eased within 48 hours	5	**31**	0	**0**	5	**15**



2) Translate the patient HLA genotype to the serological equivalent.

HLA Allele	Serological Equivalent		UK&I %	RoW %	Total %	Errors
	Split	Broad				
A*32:01:01	**A32**	**A19**	100	100	100	N/A
A*34:02:01	**A34**	**A10**	100	100	100	N/A
B*40:01:02	**B60**	**B40**	100	100	100	N/A
B*40:01:02	**B60**	**B40**	100	100	100	N/A
C*03:04:01	**Cw10**	**Cw3**	100	100	100	N/A
C*03:04:01	**Cw10**	**Cw3**	100	100	100	N/A
DRB1*04:01	**DR4**		100	100	100	N/A

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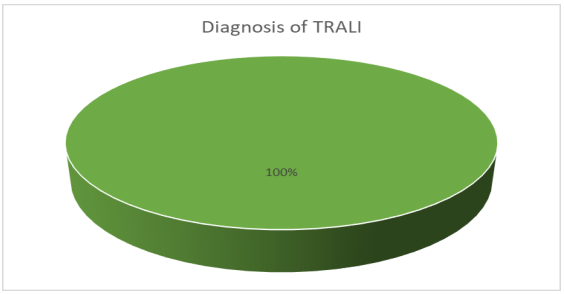
DRB1*15:01:01	**DR15**	**DR2**	100	100	100	N/A
DRB4*01:03:01	**DR53**		100	76	94	DR52 Not defined
DRB5*01:01:01	**DR51**		100	88	88	Not defined
DQB1*03:02:01	**DQ8**	**DQ3**	100	94	97	DQ7
DQB1*06:02:01	**DQ6**	**DQ1**	100	94	97	Not defined

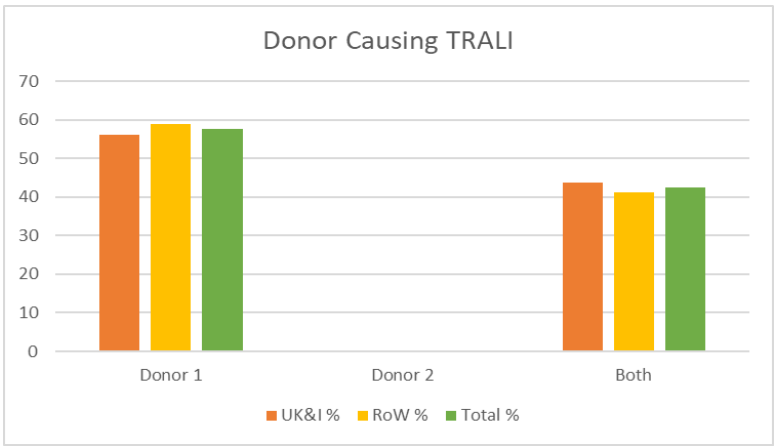
Do these results support a diagnosis of antibody mediated TRALI?

	UK&I	UK&I (%)	RoW	RoW (%)	Total	Total (%)
Yes	16	**100**	17	**100**	33	**100**
No	0	**0**	0	**0**	0	**0**



Which donor(s) are likely to be the cause?

Donor Causing TRALI	UK&I	UK&I %	RoW	RoW %	Total	Total %
Donor 1	9	**56**	10	**59**	19	**58**
Donor 2	0	**0**	0	**0**	0	**0**
Both	7	**44**	7	**41**	14	**42**



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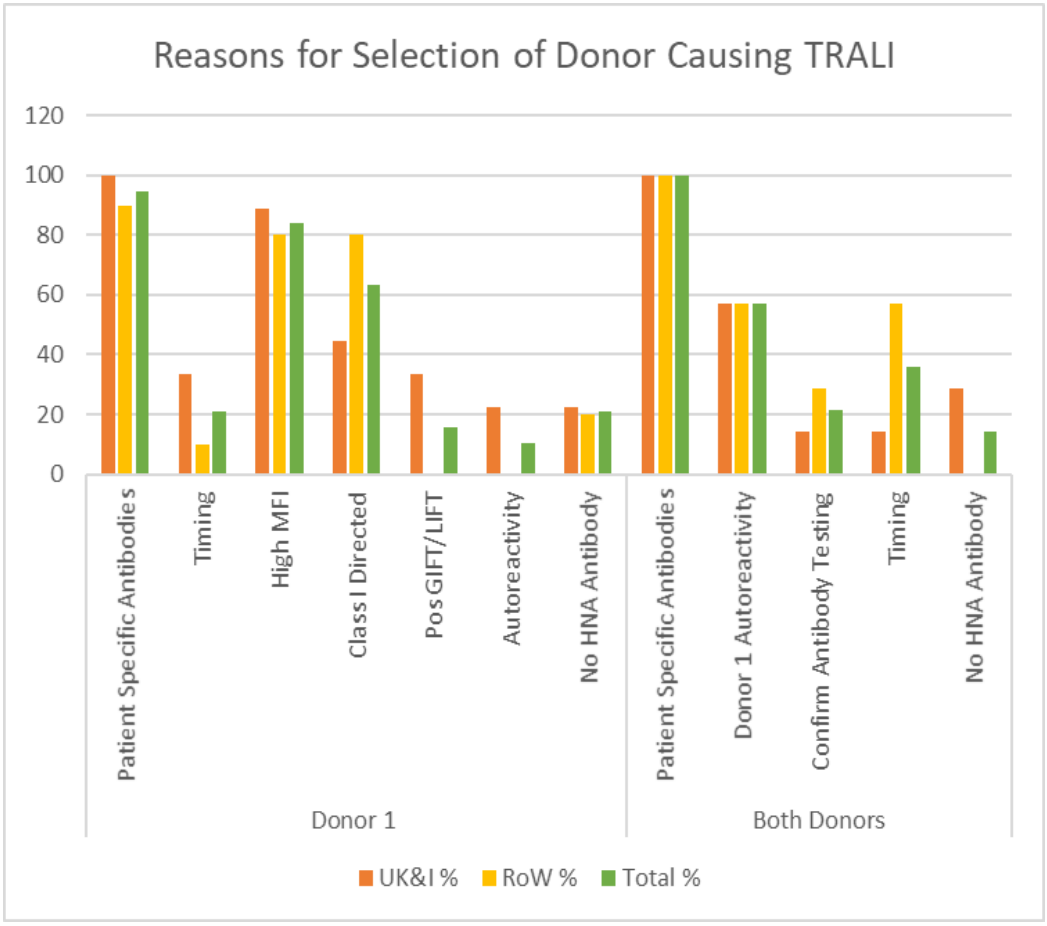
Reasons for Selecting Donor

Donor	Reasons	UK&I	UK&I %	RoW	RoW %	Total	Total %
Donor 1	Patient Specific Antibodies	9	**100**	9	**90**	18	**95**
	Timing	3	**33**	1	**10**	4	**21**
	High MFI	8	**89**	8	**80**	16	**84**
	Class I Directed	4	**44**	8	**80**	12	**63**
	Pos GIFT/LIFT	3	**33**	0	**0**	3	**16**
	Autoreactivity	2	**22**	0	**0**	2	**11**
	No HNA Antibody	2	**22**	2	**20**	4	**21**
Both Donors	Patient Specific Antibodies	7	**100**	7	**100**	14	**100**
	Donor 1 Autoreactivity	4	**57**	4	**57**	8	**57**
	Confirm Antibody Testing	1	**14**	2	**29**	3	**21**
	Timing	1	**14**	4	**57**	5	**36**
	No HNA Antibody	2	**29**	0	**0**	2	**14**



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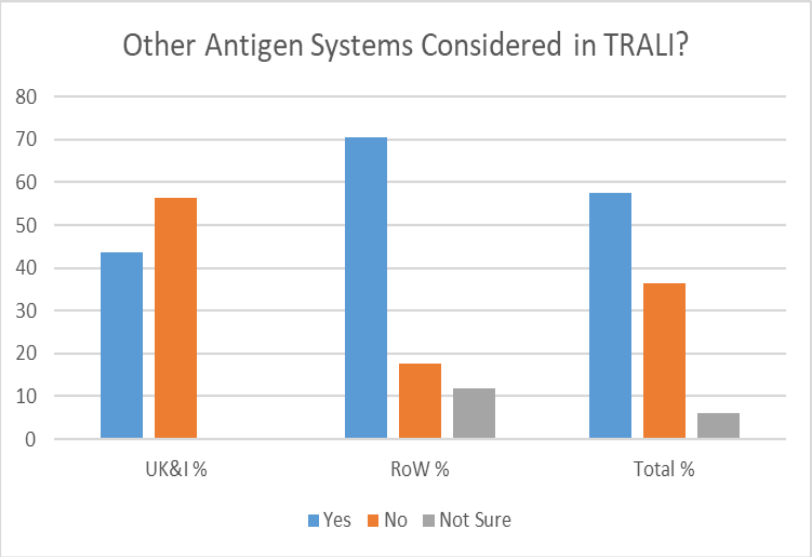
3) Do you consider any other antigen systems when considering a diagnosis of TRALI?

	UK&I	UK&I %	RoW	RoW %	Total	Total %
Yes	7	**44**	12	**71**	19	**58**
No	9	**56**	3	**18**	12	**36**
Not Sure	0	**0**	2	**12**	2	**6**



If yes please provide further details

Other Antigen Systems	UK&I	UK&I %	RoW	RoW %	Total	Total %
HNA	5	**72%**	12	**100%**	17	**90%**
HPA	1	**14%**	0	**0%**	1	**5%**
Other factors*	1	**14%**	0	**0%**	1	**5%**

*Included IgA antibodies, bacterial contamination and allergy

A second referral for a TRALI investigation is received by your laboratory. In this case, only one unit of red cells was transfused from Donor X. The patient experienced a typical TRALI-like reaction 4 hours later. Upon testing Donor X had a potential patient specific antibody to HLA-DPB1*04:01 detected at an MFI of 2564 using a One Lambda single antigen kit. No HNA antibodies were detected.

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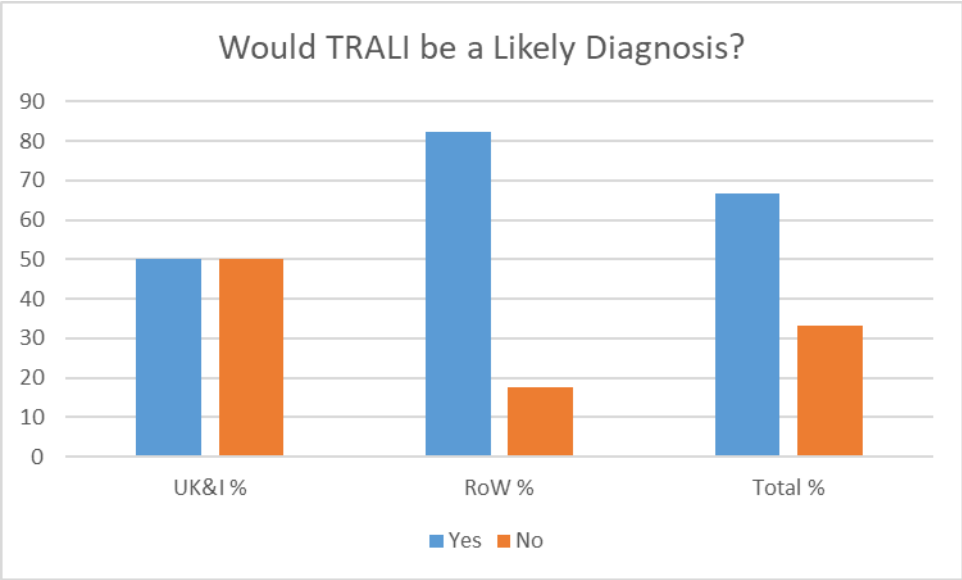
4) Do these results support a diagnosis of antibody mediated TRALI?

	UK&I	UK&I %	RoW	RoW %	Total	Total %
Yes	8	**50**	14	**82**	22	**67**
No	8	**50**	3	**18**	11	**33**



Reasons for decision

	Reasons	UK&I	UK&I %	RoW	RoW %	Total	Total %
Yes	Class II antibodies implication in TRALI	4	**50**	3	**21**	7	**32**
	Low titre antibodies can cause TRALI	1	**13**	0	**0**	1	**5**
	Patient Specific Antibody present	5	**63**	9	**64**	14	**64**
	Timing of reaction	2	**25**	3	**21**	5	**23**
	Possible dilution effect	1	**13**	0	**0**	1	**5**
	Diagnosis based on clinical symptoms	1	**13**	2	**14**	3	**14**
No	Low MFI	7	**88**	2	**67**	9	**82**
	DP low expression	3	**38**	0	**0**	3	**27**
	CII low/no expression on immune cells	2	**25**	1	**33**	3	**27**
	No documented cases of TRALI caused by DP antibodies	4	**50**	1	**33**	5	**45**
	Further testing	1	**13**	1	**33**	2	**18**

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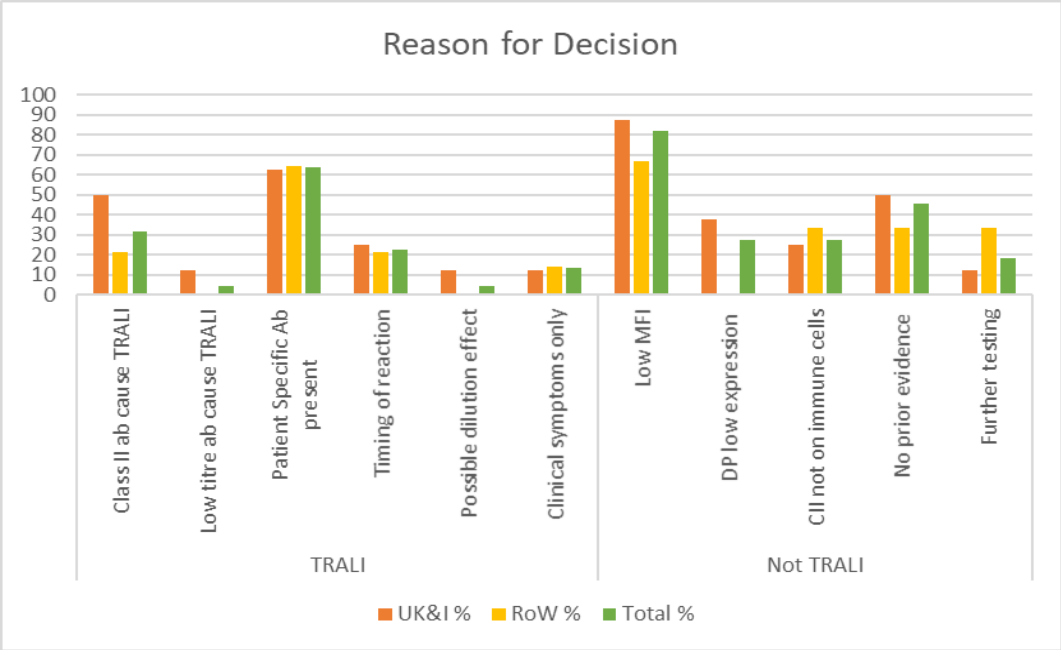

5) What advice with regards to the future blood component production would you provide to the donor management team if a donor involved in TRALI has the following antibodies:

Donor Ab	Reasons	UK&I	UK&I %	RoW	RoW %	Total	Total %
HLA	Exclude Donor (if PSA)	13	**81**	14	**82**	27	**82**
	Red Cell Donation Only (non-PSA HLA ab)	11	**69**	2	**12**	13	**39**
	Use for QA/Diagnostic Reagents	1	**6**	1	**6**	2	**6**
	Recall Products	1	**6**	2	**12**	3	**9**
HNA	Exclude Donor	14	**88**	13	**76**	27	**82**
	Red Cell Donation Only	3	**19**	2	**12**	5	**15**
	Use for QA/Diagnostic Reagents	2	**13**	1	**6**	3	**9**
	Recall Products	1	**6**	2	**12**	3	**9**
	Produce Donor Ab Card	1	**6**	0	**0**	1	**3**
HPA	Exclude Donor (if PSA)	4	**25**	7	**41**	11	**33**
	Red Cell Donation Only (no Plt Donation)	6	**38**	2	**12**	8	**24**
	Use in HPA compatible Patients Only	2	**13**	2	**12**	4	**12**
	No Issue	2	**13**	5	**29**	7	**21**
	Produce Donor Ab Card	1	**6**	0	**0**	1	**3**
	Recall Products	1	**6**	0	**0**	1	**3**
No Ab	No Action	13	**81**	6	**35**	19	**58**
	Exclude Donor	1	**6**	4	**24**	5	**15**
	Suspend Donor Pending Investigation	2	**13**	3	**18**	5	**15**

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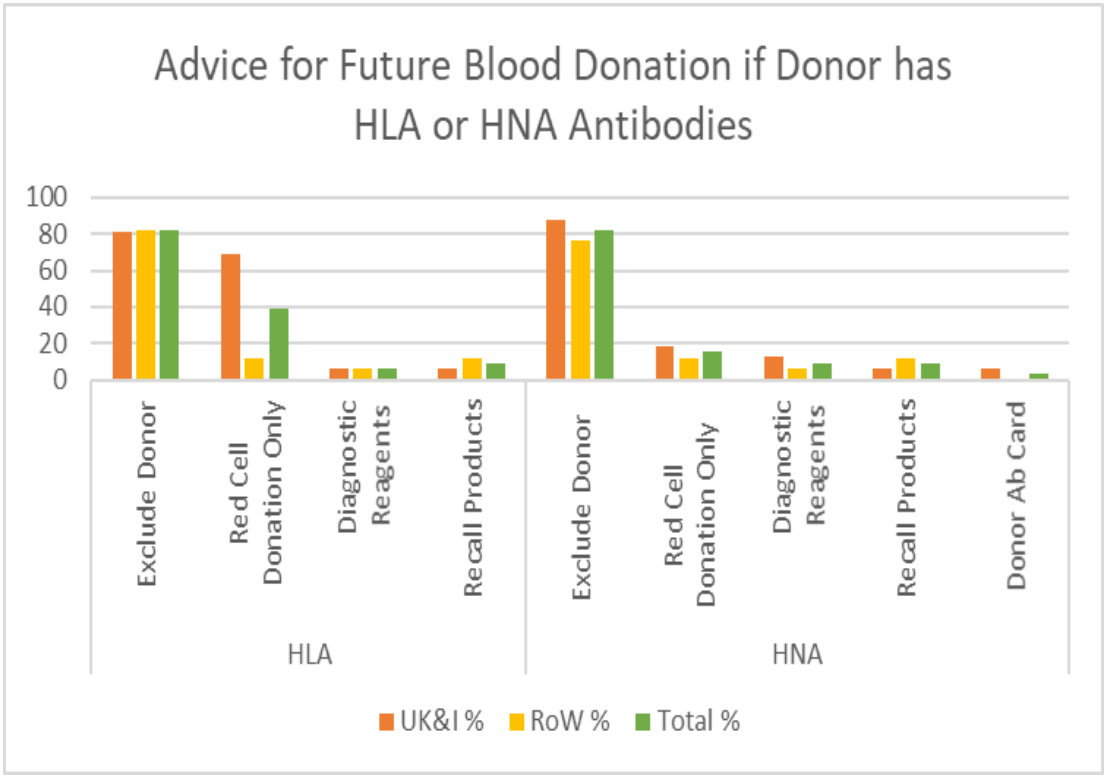

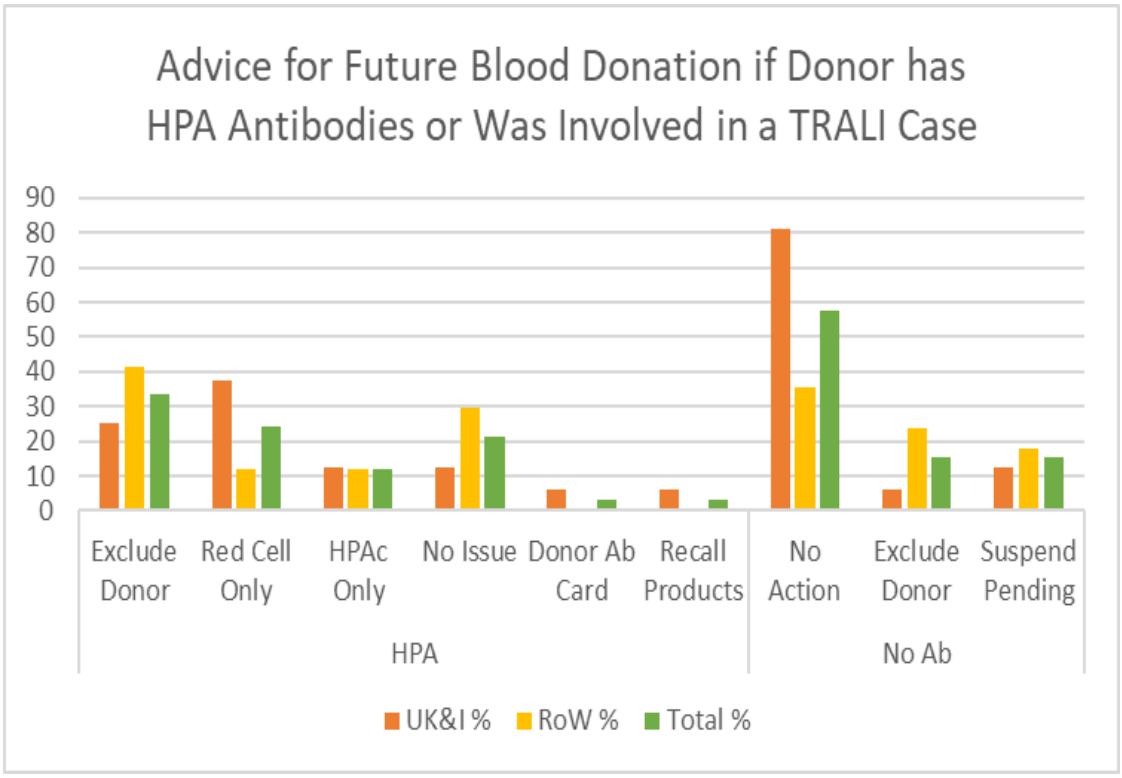

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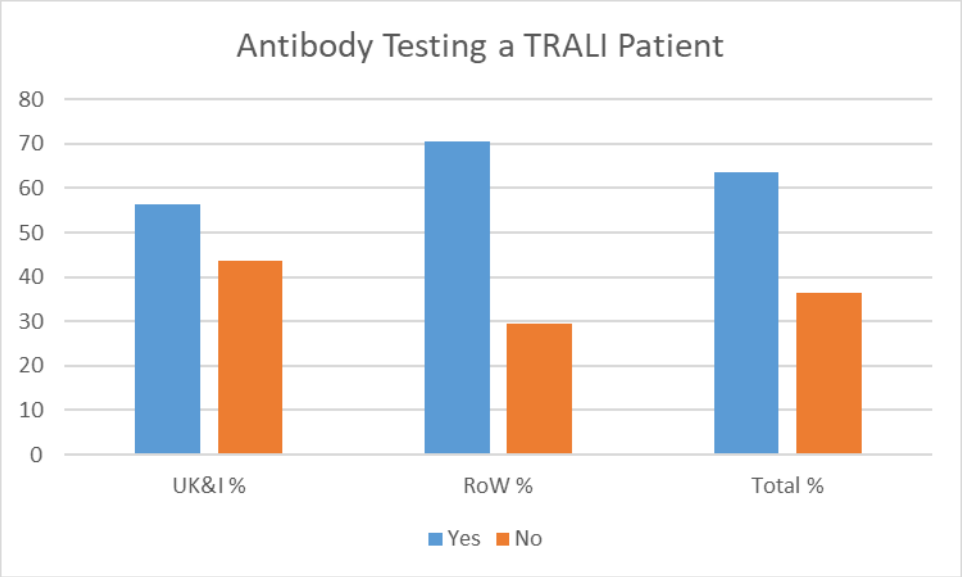
6) Would you consider antibody testing a suspected TRALI patient?

	UK&I	UK&I %	RoW	RoW %	Total	Total %
Yes	9	**56**	12	**71**	21	**64**
No	7	**44**	5	**29**	12	**36**



Most Common Reasons Given

Yes	**Investigate for HLA/HNA antibodies if indicated, e.g. if associated donors are antibody negative or antibodies are non-donor directed. Reaction of patient antibodies with donor leukocytes is feasible.**
	There is documentation of donor leukocytes reacting with recipient derived antibodies in TRALI
	In rare cases TRALI can be caused by patient antibodies. Once donors have been tested and excluded from investigation, patient antibodies can be investigated.
	Approximately 80% of TRALI cases are due to HLA/HNA antibodies in the donor, but 20% are cause unknown and could be caused by antibodies in the patient directed towards cells in the blood product, especially with granulocyte infusions.
	Cases of TRALI due to patient antibody reacting with transfused donor cells have been reported. Although UK blood products are leucodepleted they are not leucocyte free. If no donor antibodies reacting with the patient or other donor antigens are detected antibodies in the patient may be responsible for a TRALI reaction. Three cases of TRALI apparently due to patient HLA antibodies reacting with donor cells in leucodepleted products have been described. (de Clippel, Emonds and Compernolle, Transfusion, 2019, 59, 2788-2793).
	There are reports of TRALI occurring after transfusion of donor leucocytes, which have interacted with patient derived antibodies (apheresis or buffer coat granulocytes).
	Transfusion recipient data would allow assessment of the safety of blood component modifications, in addition to additional mitigation strategies.
	Some cases of TRALI (reverse/inverted TRALI) are triggered by anti-HLA or anti-HNA antibodies in the

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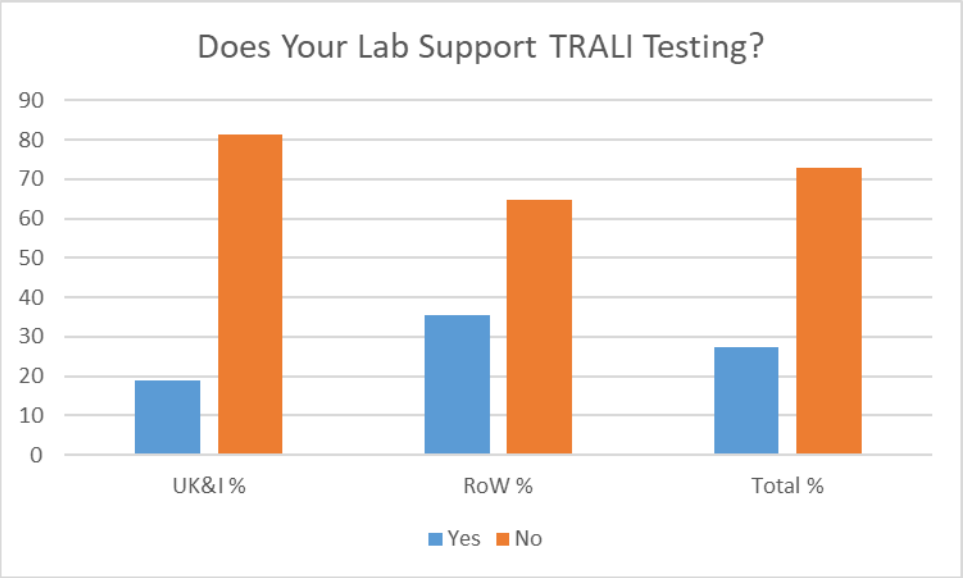
	patient's plasma.
	To support the diagnosis of TRALI and to prevent reoccurrence of TRALI in future.
No	Recipient antibodies not thought to be relevant due to low risk of passenger lymphocytes after implementation of Leucodepletion in the UK in 1999.
	Not in the Guidelines to test for antibodies in the patient.
	It could be useful to know the patients antibody profile in order to explain any further reactions while the patient is being supported in the recovery from TRALI – for instance if the patient receives further blood units and experiences a fever due to a febrile non-haemolytic transfusion reaction (FNHTR).
	Would consider if all other potential causes have been ruled out.
	No proven link between patient antibodies against donors and TRALI.
	Not unless the patient has received a granulocyte transfusion, which is exceptional.

7) Does your lab support testing for the diagnosis of TRALI?

	UK&I	UK&I %	RoW	RoW %	Total	Total %
Yes	3	**19**	6	**35**	9	**27**
No	13	**81**	11	**65**	24	**73**



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8) Any further comments?

- Additional information on the blood donors would have been useful in this case, e.g. gender, sensitising events (pregnancies). Also, storage time/age of the blood products would have been helpful.
- Answered as if the antibody and HLA types of the donors had been swapped around. Otherwise the HLA antibody profile of donor one would be invalid as would be to themselves as well.
- Q1: B60 MFI lower than "self" MFI which would call all results into question. This case is from 2019 SHOT where donor 1 had the Class II HLA. Were the units switched but not the types? Q4: Answer should be "potentially", as there is insufficient clinical and laboratory detail to make a definitive diagnosis.
- Useful to see lots of clinical information. We noticed that Donor 1 is probably the real donor 2, and vice versa, which affects what one learns from this scenario about onset of transfusion reactions.
- Using only male blood donors might mitigate the risk of TRALI. Female blood donors with pregnancy history should have HLA antibody testing performed if going to be used as plasma donors. HLA antibody testing in platelet donors. Use of PAS (platelet additive solution).
- Donor 1 has autoantibodies in the class I panel, which are not explained. To discriminate DQB and DQA antibodies in donor 2 class II panel, the results on negative beads should be provided, as well as DQA typing of the donor and patient.

Comments from NEQAS:

This scenario was based on a real-life TRALI investigation. The patient case report provided at the beginning of this scenario was reviewed by an expert panel of Anaesthetists who approved the case for laboratory investigation.

For this scenario the HLA serology raw data was swapped between the two donors resulting in high level "self" antigen reactivity in the luminex SAB results. NEQAS were hoping this unusual reactivity should have prompted a comment of concern and request for repeat samples.

Interestingly, only a total of 5 UK&I and 3 RoW based labs (8/33, 24%) commented on the usual self-reactivity seen in Donor 1, with an additional 3 UK&I and 2 RoW labs (5/33, 15%) questioning whether samples had been swapped.

One of the many purposes of performing EQA testing is to highlight potential discrepancies at the pre-analytical, analytical and post-analytical phases. In this scenario we were hoping labs might question, as they should in a clinical situation, where unusual results are found whether samples had been mixed up at one of the analytical phases.

The presence of HLA specific antibodies to the recipient's cognate HLA antigen/s did support a diagnosis of TRALI.

In question 4 NEQAS would recommend a crossmatch is performed between patient cells and donor serum if material is available, with a negative result indicating the HLA-DP antibody is unlikely to be clinically relevant.

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For question 5 NEQAS would recommend, in line with UK practice, that if a donor is identified as possessing HNA-3a that because of the association of this antibody with more severe cases of TRALI, the donor is excluded from donation of all blood products for clinical use.