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ORIGINAL ARTICLE

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Influence of donor age, sex and ethnicity on high-titre anti-A and -B: Review of 6 million donations from two national blood providers

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Abstract

Background and Objectives: Some blood operators routinely screen blood donations for high-titre (HT) anti-A/B to reduce the risk of a haemolytic transfusion reaction due to out-of-group plasma-rich components. We assessed donor factors associated with an increased likelihood of screening positive and compared routine data between England and Australia.

Materials and Methods: Data were assessed from HT screening during 2018–2020 in Australia and 2018–2021 in England, totalling nearly 6 million blood donations. Screening was performed using a Beckman Coulter PK7300 analyser with a micro-titre plate saline direct agglutination test in both countries, although different reagent red cells were chosen. HT-positive was defined as testing positive at a titre of 128 or above.

Results: The likelihood of a donor testing HT-positive was greater for females than males, declined with age and was dependent on the ABO group. However, the proportion of donors testing HT-positive was consistently higher in Australia than in England: overall, 14% of group O donations and 5% of group A donations in England tested HT-positive, compared with 51% and 22%, respectively in Australia. English data also showed that donors from Black, Asian or mixed ethnic backgrounds were more likely to test HT-positive than White donors.

Conclusion: These data demonstrate that donor sex, age, ABO group and ethnicity affect the likelihood of testing HT-positive. Differences in testing methods likely had a significant impact on the proportion of donors testing as HT-positive or -negative rather than any differences in donor populations.

Melanie Robbins and Sian Huish contributed equally to this work and designated as co-first authors.

Keywords
blood donations, donor testing, high-titre (HT)-positive

Highlights

- Data demonstrate that donor sex, age, ABO group and ethnicity affect the likelihood of testing high-titre (HT)-positive.
- Differences in testing methods, however small, likely had a significant impact on the proportion of donors testing HT-positive.
- The likelihood of a given donor testing HT-positive or -negative tends to remain consistent over 2–3 years.

INTRODUCTION

Transfusion of ABO non-identical plasma or minor ABO-incompatible platelets (where the suspending plasma of the platelet concentrate is not compatible with the ABO group of the recipient's red cells) has been associated with increased risk of haemolytic transfusion reactions (HTRs) [1]. Therefore, the preference in many jurisdictions is to provide ABO-identical plasma-rich components [2]. However, this is not always possible in emergency situations when a patient's blood group is unknown. Moreover, transfusion of ABO-incompatible platelets may also be required to ensure the availability of platelets when needed without significant wastage of a product with a short shelf life (5–7 days in most countries). For this reason, transfusion of ABO-incompatible platelets is not an infrequent occurrence, and thus many centres have policies in place to mitigate risk to recipients. For platelets, this may include volume reduction or suspension of platelets in PAS to reduce the levels of anti-A/B, or screening of donations and selection of 'low-titre' units if ABO non-identical platelets are transfused [3]. In addition, the resurgence of interest in the transfusion of whole blood, where group O plasma may be transfused to non-O patients, also necessitates, ensuring that these units are low-titre to mitigate the risk of HTR [4].

Some blood providers routinely test either all donations, apheresis donors only or the final platelet component for high-titre (HT) anti-A/B. However, a recent international survey showed there is no international consensus regarding the HT screening methodology, with wide variation in the methods used and cut-offs regarded as HT and whether both IgM and IgG antibodies are screened for [3]. Therefore, ensuring that out-of-group plasma-rich transfusions are safe requires a careful balance between reducing risk and maintaining an adequate supply of components.

Previous small-scale studies, many performed decades ago, have identified key donor factors that may influence whether a donation tests positive for HT anti-A or -B including age and sex of the donor [5–8]. It has also been suggested that a donor's HT status may be consistent over time and questioned whether testing is needed for every donation or just once [9]. In addition, factors such as vaccination and the use of pro-biotics have been shown to increase anti-A/B titres [10], although this does not appear to be the case with more modern vaccines [11] including influenza [12]. Here we have analysed nearly 6 million test results from 2 to 3 years of data across two national providers, to assess the relationship between donor age, sex, ethnicity and likelihood of testing HT-positive for anti-A/B. Understanding these variables is key to being able to perform robust risk assessments in relation to risk-mitigation strategies for out-of-group transfusions of plasma, platelets and whole blood.

MATERIALS AND METHODS

Screening methods for anti-A and -B

England

A tube sample from the donor (EDTA plasma) is tested for HT anti-A and/or anti-B on every donation using a direct agglutination microplate method on a Beckman Coulter PK7300 analyser. Reagent red cells used are prepared in-house from A_2B donations. Random A_2B red cell concentrates ($n = 6$) are titrated against anti-A of known titre (Lorne Laboratories) and the two units with the lowest A antigen strength, which are not completely negative, are selected, pooled, aliquoted and allocated the expiry of the oldest unit used. Reagent red cells are washed and diluted to 1.4% solution in saline. Donor plasma is diluted at 1:32 ratio in 0.9% unbuffered saline, which has been validated to equate to a manual saline tube method of 128. A total of 15 µL dilute plasma and 25 µL dilute red cells were incubated at 30°C for 1 h and agglutination was assessed by digital image analysis. A positive and a negative control containing monoclonal anti-A and anti-B (ALBAcheck® BGS High Titre Controls Kit—Z257) are used for this assay, at 128 and 64 manual saline equivalents, respectively. Plasma and platelet components produced from donations that test negative using this screening method are labelled as HT negative. The choice of reagent red cell and test conditions was made to balance reducing the risk of an HTR, with the ability to supply sufficient components to meet demand. The effectiveness of testing, combined with clinical policies, is assessed by monitoring national haemovigilance data.

Australia

Screening for HT anti-A and -B was introduced in 2018 in Australia, based on the methods in England above.

A tube sample from the donor (EDTA plasma) is tested for HT anti-A and/or anti-B using a Beckman Coulter PK7300 along with the routine blood grouping (ABO and RhD) panel on every donation. Two different dilution ratios of the plasma in 0.9% unbuffered saline are tested in parallel: 1:32 (which approximates a conventional tube saline direct agglutination titre of 128, see Table S1) and 1:64 (which approximates a conventional tube saline direct agglutination titre of 256, see Table S1). The 128 titre is used to define low- and high-titre anti-A and/or anti-B. Blood components from donations that are negative at a titre of 128 are labelled as low anti-A/B. Apheresis platelet donations that test positive at a titre of 256 are further tested at a titre of 8000 to ascertain donations that may be exceptionally high for anti-A or -B (see Figure S1).

The diluted donor plasma is tested separately (using a Beckman Coulter PK7300) against a commercially available solution of 2% group A_1 or group B cells (Beckman Coulter PK System Reverse Grouping Cells—17318). The reported result is based on the combination of the results with the individual cells. Thus, in group O donations, it is possible to ascertain whether anti-A or -B or both are HT. Negative results must be obtained for both cell types for an overall negative result to be reported. Any other combination of results, including indeterminate or equivocal, is interpreted as positive. A positive and a negative control containing monoclonal anti-A and anti-B (ALBAcheck® BGS High Titre Controls Kit—Z257) are used for this assay. This negative control contains anti-A and anti-B, which may be detectable at a 1:64 dilution in manual titration (1:16 dilution in an automated system), and therefore may occasionally return a HT-positive result at a titre of 128 in some automated techniques.

DATA ANALYSIS

English data were extracted from NHSBT's PULSE database on all whole blood, apheresis platelet and plasma donations collected between 9 April 2018 and 16 May 2021, where an HT screening result was available. Indeterminate HT results were classed as positive. The donor's sex, age at donation, ethnicity (ONS 2011 Census categories) and ABO group were available.

Australian data summarizing HT results was extracted for the period 1 March 2018–31 January 2020, including donor sex, age and ABO group (but not ethnicity). This data set included all whole blood and apheresis platelet donations during the period, as well as all plasma donations from new donors or those returning after a long interval.

Subgroup-specific HT rates (% of donations screening as HT-positive) were calculated according to the following variables: donor sex and age group; donor ethnicity (England only); and month of donation. In each case, different ABO groups were treated separately.

For the English data, it was also possible to examine longitudinal patterns of HT results within donors over time. Donors with at least four clear HT screening results over a period of at least 1 year were categorized as follows: 'always negative', 'always positive', 'flipped negative to positive', 'flipped positive to negative' or 'fluctuating'. The last category contains donors whose HT status changed twice or more during the period; the two 'flipped' categories comprise donors with only a single status change. The proportion of donors in each category was calculated, with breakdowns according to ABO group, sex, age and ethnicity.

RESULTS

The basic donor characteristics of the two cohorts included in the analysis are summarized in Table 1. The proportion of male donors in the Australian cohort was slightly higher than that of England; however, the distribution of ABO group and age of donors was similar in both data sets.

The proportion of donations testing HT-positive, as defined by each country, by sex and age of donor is shown in Figure 1. For both countries, the HT positivity rate was higher in female donors than male donors, declined with donor age and was higher in group O than A donors. However, the absolute proportion of donors testing positive, as tested and defined by each country, was considerably higher in the Australian cohort compared with England. For the entire cohort of donors, including group AB, the overall rate of HT positivity was 37% in Australia and 9% for England. For group O donations, these values were 51% and 14%, and for group A donations, they were 22% and 5%, respectively. Data for group B donations are shown in Figure S2; less than 0.1% of all group B donations in England were HT-positive, compared with 17% in Australia. Data showing indeterminate results for donations in England are shown in Table S2.

The influence of ethnicity on the proportion of donors testing as HT-positive is shown in Figure 2. These data were only available for England. Donations from Black, Asian or mixed ethnicity donors showed a higher rate of HT positivity than White donors. This was true for groups O and A, and for both male and female donors, but was most noticeable where the rates of HT positivity were higher, for example, group O female donors.

Monthly longitudinal data from HT testing are shown in Figure 3. Although there was variation in the proportion of donors testing positive over time, there was no obvious seasonal variation seen in either Australia or England. However, the HT positivity rate in England showed a greater degree of variation from month to month than that observed in Australia, which was more stable.

Patterns of testing results for donors from England who had four or more screening results during the period of data collection are shown in Tables 2 and 3. For group A donors, 94% tested negative and 2% tested positive on all occasions. A further 4%–5% either fluctuated or flipped. For group O donors, these values were 82%, 6% and 12%, respectively. The proportion of donors who consistently tested negative increased with increasing age of the donor, for both group O and A donors.

DISCUSSION

Screening for HT anti-A and -B has been undertaken for many years in England but was standardized across the United Kingdom in 2008

TABLE 1 Summary of basic donor characteristics.

		Number (%) of donations from this group during the period covered	
		England	**Australia**
Sex	Female	2,271,116 (51.9%)	659,705 (43.1%)
	Male	2,107,287 (48.1%)	869,674 (56.9%)
Age group	Under 20	80,665 (1.8%)	44,896 (2.9%)
	20–29	733,442 (16.8%)	309,492 (20.2%)
	30–39	844,322 (19.3%)	300,000 (19.6%)
	40–49	847,288 (19.4%)	277,904 (18.2%)
	50–59	985,371 (22.5%)	291,922 (19.1%)
	60–69	674,268 (15.4%)	232,472 (15.2%)
	70 and over	213,047 (4.9%)	72,693 (4.8%)
ABO group	A	1,614,863 (36.9%)	546,627 (35.7%)
	AB	119,153 (2.7%)	40,779 (2.7%)
	B	466,099 (10.6%)	124,537 (8.1%)
	O	2,178,288 (49.8%)	817,436 (53.4%)
Ethnic group (England only)	Asian	114,203 (2.6%)	n/a
	Black	37,312 (0.9%)	
	Mixed/multiple	62,000 (1.4%)	
	Other	18,651 (0.4%)	
	White	4,099,380 (93.6%)	
	Unknown	46,857 (1.1%)	

Abbreviation: n/a, not applicable.

following a review of UK-wide haemovigilance data. Of the reports of haemolytic transfusion reactions to minor ABO-incompatible platelets, 17 of 23 cases occurred in the 13 years from 1996 to 2008, with only 6 of 23 occurring in the subsequent 13 years from 2009 to 2021 (Dr Helen New, personal communication, NHSBT, 2024) [13]. Current testing uses a direct saline agglutination test, which principally measures IgM antibodies, and should give a negative result at a dilution of 128 or equivalent dilution by other techniques in order to be labelled as HT negative [14]. The screening test is set up using the same automated equipment that is used for routine blood grouping of donations and applied to every donation. Therefore, it is high throughput and low cost, with England testing in excess of 1.4 million donations per year. Australia adopted a similar approach to screening donations in 2018, following reports of haemolytic transfusion reactions to out-of-group platelets [15].

In this study, we report on 2–3 years of data from routine testing of HT anti-A/B in blood donors in England and Australia. Our data demonstrate the influence of donor-related variation on the likelihood of testing HT-positive for anti-A/B using the largest cohort of data published to date. We observed a higher frequency of donors testing positive in group O donors than in group A, and in females compared with males. Our data are consistent with previous smaller studies showing higher titres of anti-A and -B in group O donors compared with groups B and A [7, 8, 16, 17]. The rate of HT positivity in group B donors was considerably lower than that in Australia. We assume this is partly due to differences in the reagent red cells used, but further study would be required to elucidate this. We also observed a higher rate of positivity in females compared with males across all age groups and all ABO groups studied. Studies from as early as the 1950s suggested that females, especially those who gave birth to group A babies, have a higher incidence of anti-A haemolysins than the rest of the donor population [18, 19]. Our data suggest that policies to use only male donors to produce fresh frozen plasma as a TRALI risk reduction strategy will also reduce, but not eliminate, the risk of transfusion of HT anti-A/B.

We observed a notable decrease in the proportion of donors testing positive for HT anti-A and -B with increasing age of the donor. The levels of anti-A/B are thought to increase from birth to reach a maximum between 5 and 10 years of age [20]. Our data are consistent with a previous study of 1000 individuals, which demonstrated that the levels of anti-A/B haemolysins decline with age, particularly in females [5]. Interestingly, the latter study showed that even in females below the age of 19, who presumably were less likely to have been pregnant than older cohorts, the levels of anti-A are higher in girls than boys. We did not observe any significant trends in our data by season, although we did observe variation over time, which may in part be caused by changes in reagent red cell batches. Early reports suggested that lower levels of anti-A/B haemolysins are observed in winter [8]. However, later studies suggest that there is little influence on seasonal variation [5, 21].

Very few studies have assessed the influence of ethnicity on anti-A/B levels. We observed a difference in the likelihood of testing HT-

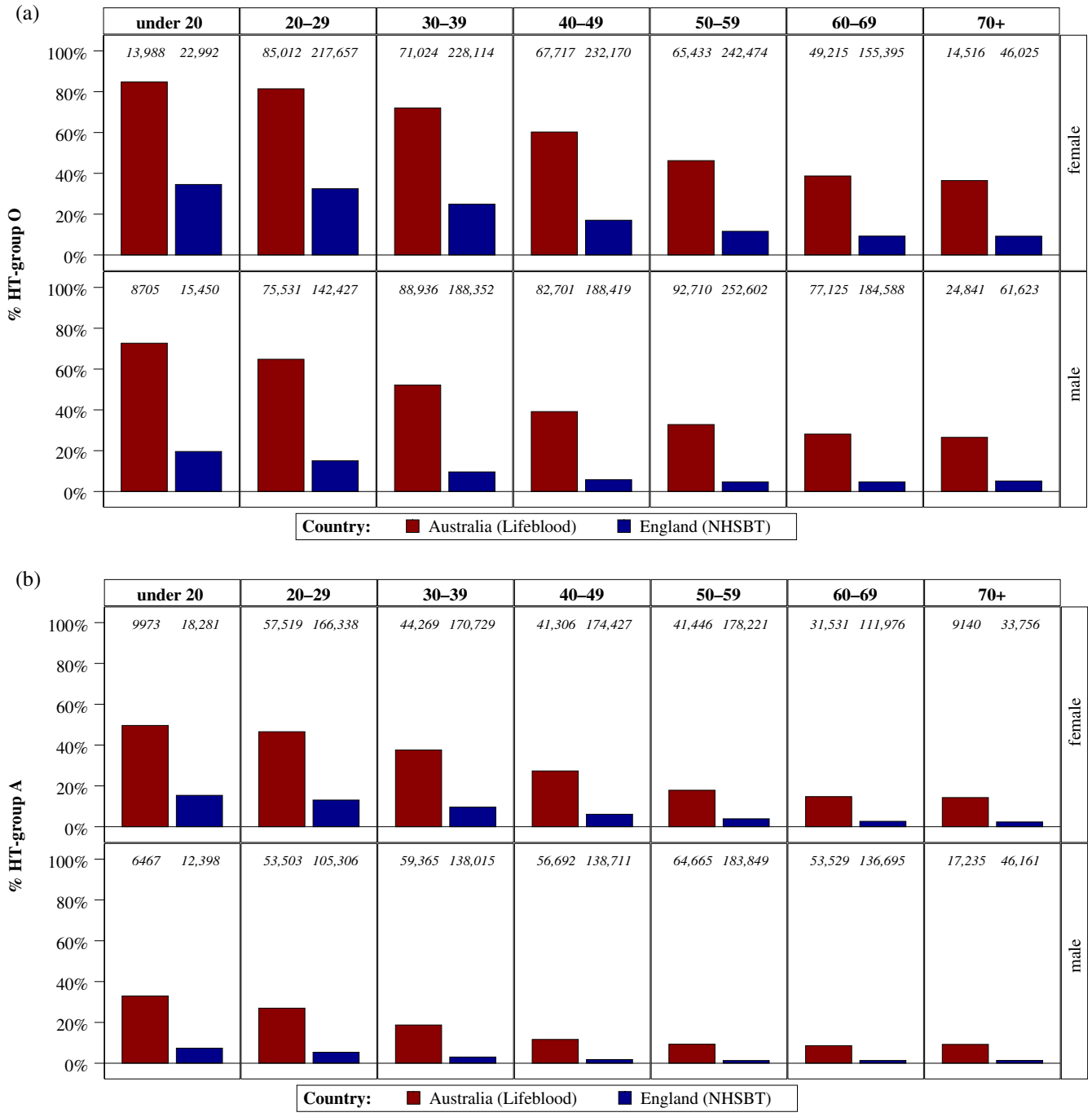

FIGURE 1 High-titre (HT) positivity rates in England and Australia by donor sex and age group (group O) (a) and (group A) (b). Number of donations tested in each subgroup shown at top of bars.

positive dependent upon ethnic background of the donor, with all other groups studied having a higher likelihood of testing positive than White donors. A previous study of 300 UK donations suggested that anti-A/B were highest in Black female donors, but this was not statistically different from the rest of the donor population [22]. In contrast, a study assessing the relative contribution of genetic factors to anti-A/B levels suggested that the levels of all ABO antibodies were higher in Black donors [23], and this has also been reported to be true for total IgG and IgM [24]. Others have postulated that this may reflect ancestral exposure to differing pathogens including parasitic infection.

We also assessed the consistency of results for a given donor over time. The majority of donors were consistently either negative or positive over the study period (3 years). However, a small subset of donors either fluctuated between positive and negative, or flipped from testing as one to the other for the rest of the study period. We assume that donors whose results fluctuated between positive and negative probably have titres of antibodies that are close to the

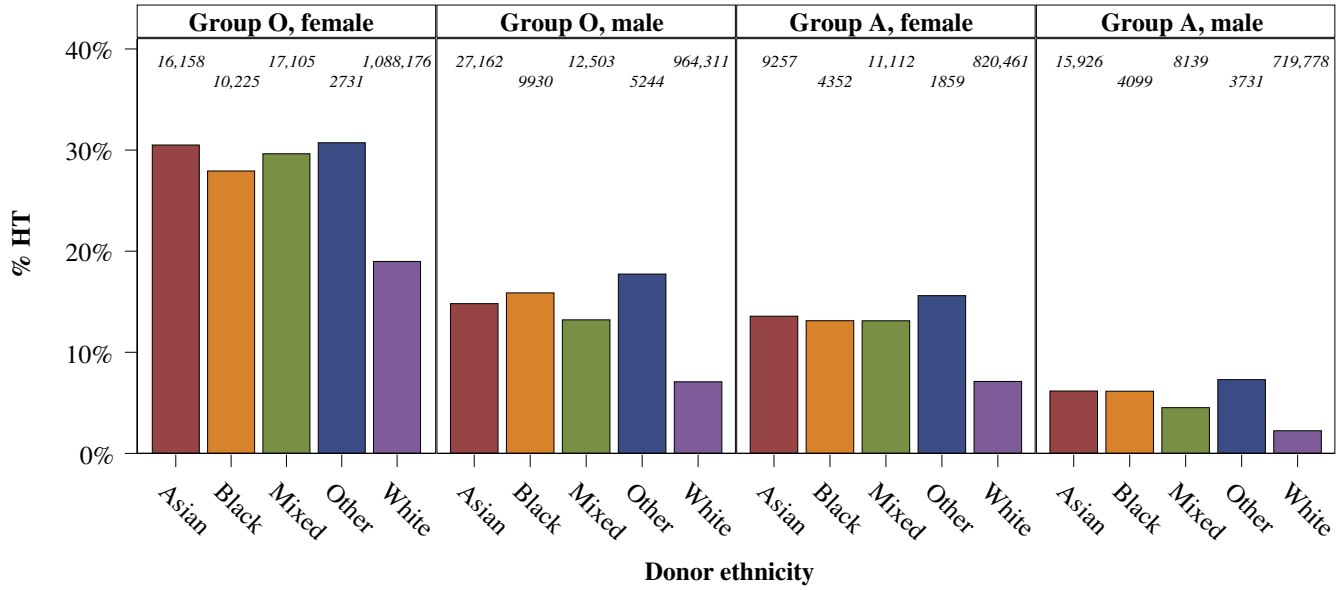

FIGURE 2 High-titre (HT) positivity rates in England by ABO group, donor sex and ethnicity. Number of donations tested in each subgroup shown at the top of bars.

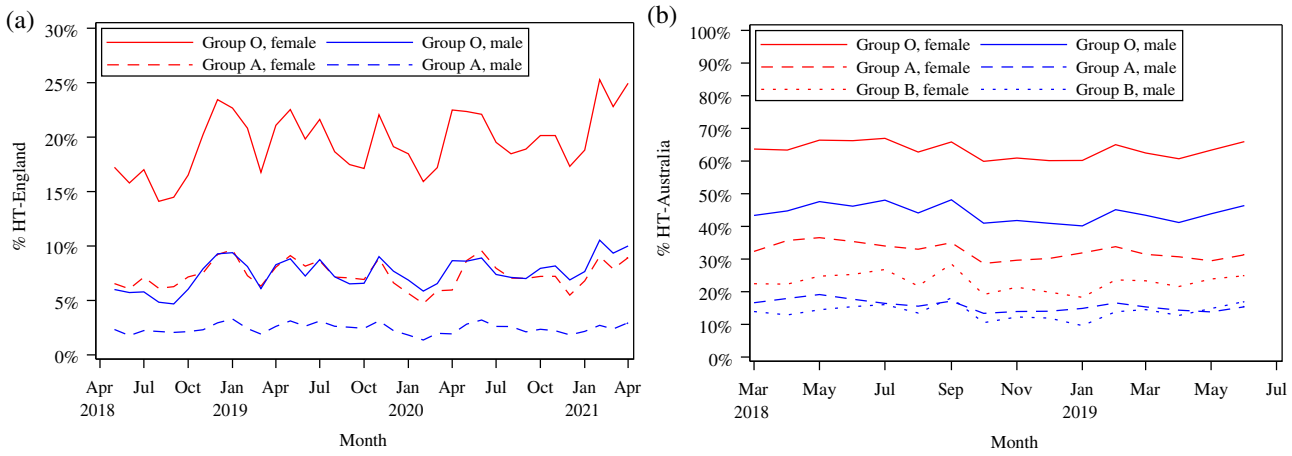

FIGURE 3 Monthly high-titre (HT) positivity rates by ABO group and donor sex in England, May 2018–April 2021 (a) and Australia, March 2018–June 2019 (b).

screening cut-off. Most concerning is the proportion of donors who switched from being negative to then testing positive thereafter—about 4% of group O donors and 1% of group A donors, who may have been missed if a policy of testing donors once only had been followed. Whilst these values appear small, they reinforce our policy of testing every donor every time. Although repeated testing of donors will enhance the likelihood of predicting a donor's HT status at a subsequent donation, this will depend on both the robustness of testing methods as well as environmental factors between donations. There is a paucity of other data on how the levels of anti-A/B vary for a given individual over time. A previous study of 56 healthy volunteers in Denmark showed IgM and IgG anti-A and anti-B titres were stable, over a period of 1 year (measured every 3 months), and suggested donors need not be tested more than once within the same year [9]. Our data suggest that genetic determinants may play a key role in influencing whether an individual has HT anti-A/B. Common and rare variants have been shown to be associated with total immunoglobulin levels in the population [25]. The relative contribution of genetic and environmental factors in determining anti-A/B titres remains to be established. A previous study of anti-A/B titres in families suggested that 20%–30% of variation is genetically determined, lower than that for total IgG and IgM levels for which this value may be as high as 50% [23].

The purpose of screening for anti-A/B in blood donations is to reduce the risk of a HTR that may occur following transfusion of ABO minor incompatible plasma or platelets. There is widespread variation in techniques used to measure anti-A/B for those blood providers who do this routinely, as well as the cut-off used and whether IgM

TABLE 2 Patterns of high-titre-positive/-negative results in group O repeat donors in England, by donor sex and age group.

Sex	Age group (at first donation)	Total repeat donors	Percentage of repeat donors with this pattern of HT results				
			Always negative (%)	Always positive (%)	Flipped − to + (%)	Flipped + to − (%)	Fluctuating (%)
Female	Under 20	2503	55.8	19.9	7.7	4.9	11.7
	20–29	21,518	60.2	18.3	6.3	4.6	10.5
	30–39	23,574	70.3	12.7	5.3	3.3	8.4
	40–49	28,139	78.4	8.1	4.4	2.1	7.0
	50–59	30,136	83.0	4.7	5.4	1.4	5.6
	60–69	19,040	86.1	3.7	3.8	1.1	5.3
	70 and over	4926	87.4	4.1	2.3	1.1	5.1
	All ages	129,836	76.0	9.3	5.0	2.4	7.3
Male	Under 20	1806	73.1	9.4	4.3	3.6	9.7
	20–29	15,170	79.7	6.3	3.0	3.0	8.1
	30–39	20,010	86.3	3.6	2.8	1.5	5.8
	40–49	23,078	90.8	1.8	2.4	0.8	4.2
	50–59	30,763	91.1	1.4	3.3	0.6	3.6
	60–69	21,600	91.7	1.6	2.0	0.7	4.0
	70 and over	6294	92.5	2.1	1.3	0.7	3.5
	All ages	118,721	88.7	2.7	2.7	1.1	4.8
Overall		248,557	82.1	6.1	3.9	1.8	6.1

Abbreviation: HT, high-titre.

TABLE 3 Patterns of high-titre-positive/-negative results in group A repeat donors in England, by donor sex and age group.

Sex	Age group (at first donation)	Total repeat donors	Percentage of repeat donors with this pattern of HT results				
			Always negative (%)	Always positive (%)	Flipped − to + (%)	Flipped + to − (%)	Fluctuating (%)
Female	Under 20	1841	79.3	5.5	4.5	3.0	7.8
	20–29	16,328	83.1	5.3	2.8	2.9	5.9
	30–39	17,535	88.1	4.0	1.9	1.7	4.3
	40–49	21,165	91.9	2.3	1.2	1.2	3.3
	50–59	22,055	94.5	1.3	1.5	0.8	2.0
	60–69	13,909	96.2	0.9	0.8	0.4	1.7
	70 and over	3659	96.9	1.0	0.5	0.5	1.2
	All ages	96,492	90.9	2.7	1.6	1.4	3.4
Male	Under 20	1456	88.6	2.3	1.5	2.1	5.6
	20–29	11,646	92.1	1.5	0.9	1.5	3.9
	30–39	15,510	95.5	0.9	0.6	0.6	2.4
	40–49	17,986	97.3	0.5	0.5	0.3	1.5
	50–59	24,012	97.7	0.3	0.5	0.3	1.2
	60–69	17,010	97.8	0.4	0.4	0.3	1.2
	70 and over	4922	98.3	0.5	0.2	0.2	0.9
	All ages	92,542	96.4	0.7	0.5	0.5	1.8
Overall		189,034	93.6	1.7	1.1	0.9	2.6

Abbreviation: HT, high-titre.

and/or IgG are measured. Defining a critical cut-off is challenging, in part because there is no definitive relationship between titre and risk of HTR [26]. The impact of the testing method on the HT rate obtained is illustrated by our data where striking differences are observed between England and Australia, despite similar testing methods. Overall, 37% of all donations tested as HT-positive in

Australia compared with 9% in England, and this disparity persists after stratification by ABO group, sex and age. It is well known that the variation in testing methods can cause variation in titres of anti-A/B measured, and this is not standardized internationally. Here the only difference in the method was the reagent red cells used: A_2B cells in England and A_1 and B cells in Australia. We postulate that this difference is due to reduced sensitivity of the method used in England as a result of lower antigen expression in A_2B cells compared with A_1 or B cells, rather than differences in our donor populations. We consider that differences in ethnicity are unlikely to explain our findings because >93% of donors in England at the time of study are White and this is not expected to be dissimilar for Australia. We cannot exclude whether differences in donor selection may affect the HT rate between England and Australia—this would require future large prospective studies to assess.

In addition, the volume and antibody levels in incompatible plasma transfusions, recipient factors such ABO zygosity [27] and complement regulatory deficiencies [28] are thought to play a role in determining the likelihood of a HTR occurring. A recent systematic review of reports of HTR to ABO-incompatible plasma or platelets transfusions has shown that whilst anti-A titres as low as 32 have been associated with case reports of HTR, this is rare [29]. Most cases were associated with anti-A group O components transfused to non-O recipients, with IgM levels of 128 or above and/or IgG of 256 or above. However, many reports do not give data on the titre of implicated antibodies, nor the measurement methods used in detail including the choice of reagent red cells. Reports of HTR associated with anti-B from either group O or group A components are far less common, with the associated titres generally exceeding 512, and fatal case reports being very rare [29].

HTRs are infrequent events, despite ABO minor incompatible plasma and platelet transfusion not being an infrequent event worldwide. There is a paucity of data relating to the frequency of HTR to minor ABO-incompatible plasma/platelet transfusion, which has been reported to be 0.01%–0.05% [30], and will depend on clinical policies for transfusion and mitigating actions taken to reduce the risk of HTR, including screening for anti-A/B. It is thought that in part the rarity of HTR may be attributable to anti-A or -B in incompatible plasma or platelet transfusions binding to A/B antigens on the recipients' endothelium, as well as dilution of plasma in the recipient [31]. For platelets, those stored in 60%–65% additive solution are likely to pose a lower risk due to the dilution of plasma. Large-scale data on titre levels in conjunction with haemovigilance data are required to fully estimate the risk reduction afforded.

In summary, our data demonstrate in a large cohort of donors from two national blood providers that there is a clear effect of age, sex and ethnicity on whether donors test as HT-positive for anti-A/B. In addition, small differences in testing methods can have a marked effect on the rate of HT positivity. This is an important consideration in modelling the risk of out-of-group plasma and platelet transfusions. The cut-off we have chosen in the United Kingdom and Australia is a pragmatic choice aimed at balancing the reducing risk of HTR on the one hand, whilst ensuring an adequate supply of donations on the other. This balance is a matter for individual blood providers to decide based on local considerations, and by monitoring the effectiveness of policies using haemovigilance data or other data.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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