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ORIGINAL ARTICLE

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Haemolytic transfusion reactions caused by non-ABO red cell antibodies reported to the Norwegian Haemovigilance System 2004–2020

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Abstract

Background and Objectives: The aim of this study was to analyse the reports received in the Norwegian Haemovigilance System from 2004 to 2020 on acute and delayed haemolytic transfusion reactions caused by non-ABO red cell antibodies.

Materials and Methods: Antibody specificity, clinical symptoms and outcomes were included when available.

Results: After transfusion of 3.7 million red cell concentrates, reports on 78 cases of haemolytic transfusion reactions caused by non-ABO red cell antibodies were received, corresponding to an incidence of 1 in 47,000 transfused red cell concentrates. There were 30 acute and 48 delayed haemolytic transfusion reactions. A total of 113 red cell antibodies were found: 82 alloantibodies, 6 autoantibodies and 25 cases where the antibody specificity could not be determined. Two fatalities occurred: one caused by anti-Wr^a and one caused by an unidentified red cell antibody. The most frequently reported antibody specificities were those in the Rh and Kidd blood group systems, representing 24% and 14%, respectively, of all the antibodies identified. In six cases, errors occurred, leading to the issuing of blood units without the required phenotype match.

Conclusions: Despite the possible underreporting, the low number of serious haemolytic transfusion reactions reflects an adequate pre-transfusion practice by the Norwegian blood banks.

Keywords

antibody specificity, haemolytic transfusion reaction, haemovigilance, red cell antibody, serological investigations

Highlights

- The overall risk for experiencing a haemolytic transfusion reaction (HTR) caused by non-ABO antibodies is 1 per 47,000 red blood cell (RBC) transfusions.
- The most frequently identified antibody specificities were those in the Rh and Kidd blood group systems. In 32% of all reports, the specificity of the antibody/ies could not be determined.

We present data received in the Norwegian Haemovigilance Working Group in the period 2004–2020, regarding acute and delayed transfusion reactions caused by non-ABO red cell antibodies.

- In 26% of all HTRs, errors regarding the selection of RBCs led to the transfusion of units that did not comply with the antigen requirements according to the patient's records on alloimmunization.

INTRODUCTION

The Norwegian Haemovigilance System was implemented in 2004 as a voluntary reporting and learning system, becoming mandatory in 2007 [1]. Transfusion reactions, blood donor complications and near misses are reported electronically. All reports are validated by the Norwegian Haemovigilance Working Group before inclusion in the database and the annual reports. Serological reactions with no symptoms of haemolytic transfusion reactions (HTRs) are not reported.

The definition of HTR in use in Norway is that proposed by the International Society of Blood Transfusion Working Party on Haemovigilance [2]. Briefly, an acute haemolytic reaction is defined as having one or more symptoms such as fever, chest and/or back pain and hypotension and/or laboratory parameters consistent with haemolysis within 24 h after a transfusion. When similar symptoms occur between 24 h and 28 days after a transfusion, the reaction is regarded as a delayed transfusion reaction.

In Norway, the 'Type & Screen' (T&S) approach for issuing red blood cells (RBCs) has been in use for many years. T&S results are valid for 4 days, regardless of whether the patient is alloimmunized or not, or if the patient has received a transfusion within the 4 days since the last T&S was performed. For patients with no known red cell antibodies, the blood unit may be issued by electronic crossmatch. For patients with past or present red cell antibodies, the antiglobulin crossmatch must always be performed before the transfusion, and the result of a negative crossmatch is valid for 4 days. Transfusion records of previous alloimmunization cannot be automatically accessed across blood banks due to legal restrictions, although in special situations, this information may be requested.

Extended antigen matching for Rh and Kidd blood group systems to reduce the risk of alloimmunization is recommended for certain patient groups, such as patients with haemoglobinopathies, haematological malignancies and/or red cell autoantibodies.

RhD-negative patients with childbearing potential receive RhD-negative RBCs. All patients with childbearing potential should receive K-negative RBCs. There are no other national guidelines for antigen requirements in this patient group, even if some blood banks would avoid giving Rhc-positive blood units to an Rhc-negative patient with childbearing potential, as anti-c alloimmunization may lead to serious complications in pregnancy. We assume that the recommendations for extended antigen matching are followed as far as the blood bank inventory allows it, but we do not have data to confirm this.

In Norway, blood banks are hospital-based, and 47 of them perform routine pre-transfusion tests. Only 24 blood banks do antibody identification. Blood banks that do not perform antibody identification send the blood samples to their local reference laboratory in immunohaematology for further investigations. The Norwegian National Reference Laboratory on Immunohaematology at Oslo University Hospital has been responsible for the National Quality Assessment since 1994, and all Norwegian blood banks participate. The programme includes ABO/RhD typing, phenotyping, crossmatch, direct antiglobulin test (DAT), red cell antibody screening and identification, as well as antibody titration. In addition, once a year, a hypothetical serological case is included for discussion, and the participants may explain which investigations should be performed. Norwegian blood banks appears to perform adequately, as shown in the results of the Norwegian Quality Assessment Program in Immunohaematology (no official report available). Many blood banks also participate in international quality assessment programmes.

An HTR is usually suspected by the nurse in charge of the transfusion when the patient experiences a change in the clinical signs and symptoms compatible with haemolysis under or within days after a red blood cell transfusion. Underreporting cannot be excluded, since many HTRs may be mild or subclinical and therefore not reported to the blood bank by the clinicians. In many cases, symptoms such as fever or changes in the blood pressure may be attributed to the patient's underlying medical condition rather than to an HTR. When an HTR is reported to the blood bank, a serological investigation is performed, both in the pre-transfusion sample and in the sample taken after the transfusion reaction.

There are national recommendations regarding serological investigations after an HTR, which should be performed both in blood samples taken before and after the transfusion reaction. These tests include ABO/RhD typing of the patient and the blood unit, as well as red cell antibody screening and DAT in the patient blood samples, and immediate spin and antiglobulin crossmatch [3]. Additional phenotyping of the blood unit may be necessary. When there are discrepancies in the results before and after the transfusion reaction, or in case new antibodies are identified, an HTR should be suspected and further serological investigations must be performed.

MATERIALS AND METHODS

Haemovigilance reports on acute and delayed HTRs caused by non-ABO red cell antibodies received between 2004 and 2020 were included. The specificity, nature (both alloantibodies and autoantibodies) and number of red cell antibodies identified in patients reported to have an HTR were included. The clinical symptoms, clinical outcome, immunohaematological investigations, additional laboratory test results and information regarding cases of documented alloimmunization prior to the HTR were provided in many reports. We only present the results of the antibody specificities suspected to be related to the HTR. Antibodies identified before transfusion, leading

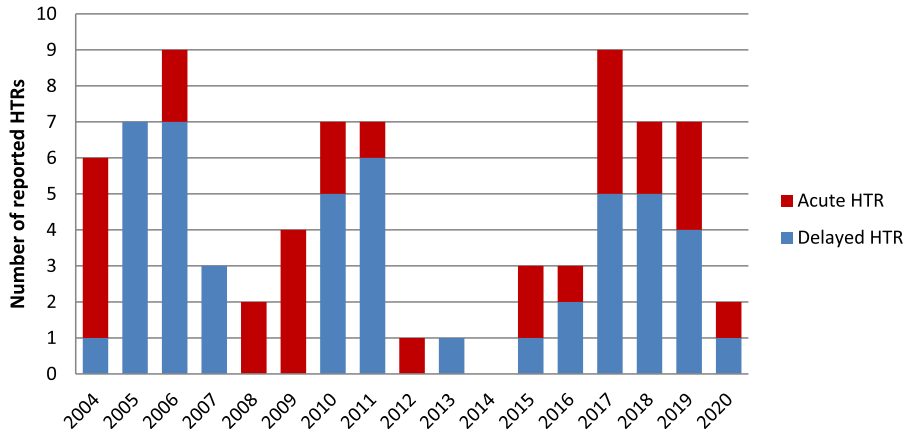

FIGURE 1 Annual distribution of haemovigilance reports for acute and delayed haemolytic transfusion reactions (HTRs) received in the period 2004–2020.

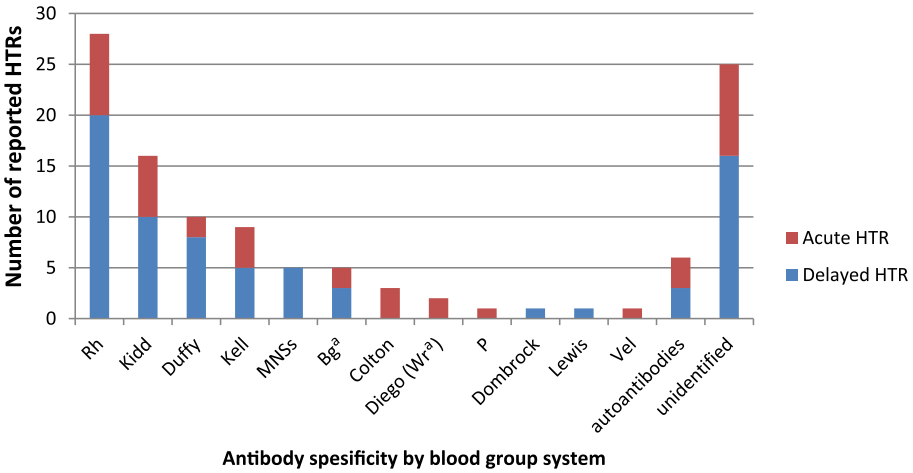

FIGURE 2 Distribution of the reported cases of acute or delayed haemolytic transfusion reactions (HTRs) by blood group system of the red cell antibodies suspected to have been the cause of the reaction.

to the use of blood negative for the corresponding antigen, are not included. HTRs caused by ABO incompatible transfusions are reported as a distinct category to the Norwegian Haemovigilance System and are outside the scope of this study.

RESULTS

We received reports on transfusion reactions from all the blood banks in Norway. The number of reports corresponded with the size of the hospital and the number of transfusions.

From 2004 to 2020, approximately 3.7 million RBCs were transfused in Norway. In this period, 78 cases of HTRs caused by non-ABO red cell antibodies (30 acute and 48 delayed HTRs) were reported (Figure 1). This corresponds to an overall risk of 1 HTR per 47,000 RBCs transfused (1 acute HTR per 123,000 RBCs transfused and 1 delayed HTR per 77,000 RBCs transfused). A total of 113 red cell antibodies were involved in the HTRs, consisting of 82 alloantibodies, 6 autoantibodies and 25 cases where the antibody specificity could not be determined. Two fatalities occurred: one caused by anti-Wr^a [4] and one caused by an unidentified red cell antibody.

Antibody specificities identified in the HTRs

The most frequently reported antibody specificities were those in the Rh and Kidd blood group systems, with 28 and 16 reports, respectively, representing 25% and 14% of all antibodies, respectively (Figure 2). Anti-Jk^a and anti-E were the most frequently identified antibody specificities, with 12 reports each (Figure 3). Anti-E was identified in 12 reports, wherein 10 cases as the only antibody specificity. Anti-Jk^a was found as the only specificity in 11 out of the 12 reports where anti-Jk^a was identified (Figure 4).

Multiple alloantibodies were identified in 19 cases (24% of all the reports) in the serological investigations performed after the HTR, in 7 acute and 12 delayed HTRs. In seven cases with multiple antibodies,

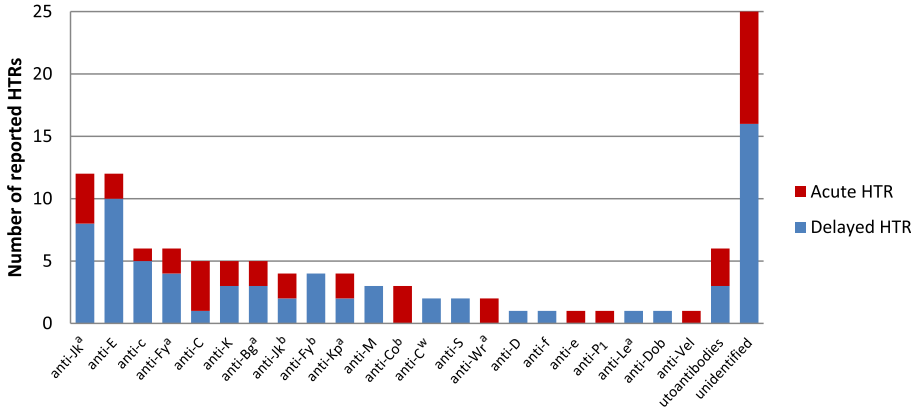

FIGURE 3 Distribution of the reported cases of acute and delayed haemolytic transfusion reactions (HTRs) by the specificities of the red cell antibodies suspected to have been the cause of the reaction.

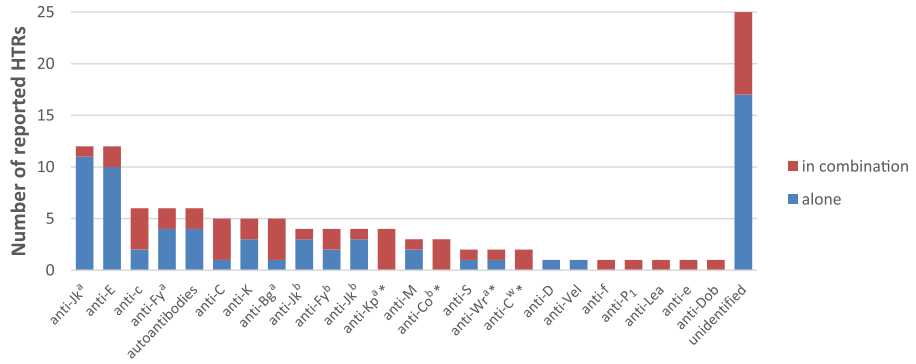

FIGURE 4 Frequencies of the red cell antibodies identified alone or in combination with other identified antibodies. *LIAs, antibodies against low-incidence antigens.

the specificity of one or more of the antibodies present in the patient's plasma could not be determined.

In seven cases (three anti-C, one anti-E, one anti-e and two anti-Jk^a), the alloantibody suspected of having been the cause of the HTR could only be identified by sensitive techniques such as PEG IAT (polyethylene glycol indirect antiglobulin test) and/or enzyme techniques, which are not routinely performed in the pre-transfusion testing.

Eleven red cell antibodies against low-incidence antigens (LIAs) not routinely present on the screening red cells, except for C^w, were identified. These were four cases of anti-Kp^a, two cases of anti-Wr^a, three cases of anti-Co^b and two anti-C^w (Figure 3). Except for one case of anti-Wr^a leading to a fatal acute HTR [4], the antibodies against LIAs were identified together with other antibody specificities. In two cases, two antibodies against LIAs could be found in the same patient, in addition to other red cell antibodies. In five other cases, one antibody specificity against LIAs was present, but other antibody specificities, such as anti-E, anti-P$_1$, anti-Fy^a, anti-Jk^a and others, were suspected to be the main cause of the HTR by the reporting blood bank.

In 12 cases, antibody specificities that usually have little clinical significance were reported as the suspected cause of 3 acute and 10 delayed HTRs. These were three anti-M, two anti-S, one anti-P$_1$, one anti-Le^a and five anti-Bg^a. In the two cases of acute HTR, anti-Bg^a was identified together with other alloantibodies of clinical significance (anti-c, anti-E, anti-Co^b and a possible anti-C). In four cases of delayed HTR (one anti-Bg^a, two anti-M and one anti-S), there were no other additional antibodies identified (Figure 4). One anti-P1 was highly suspected of having been the cause of the acute HTR, as the patient received a P$_1$-positive blood unit. The patient had also anti-Kp^a and anti-K, but the unit was negative for both Kp^a and K antigens.

In 25 cases (32% of all the reports), 9 acute and 16 delayed, the antibody specificity could not be determined.

In six cases when urgent transfusion was required, the blood unit was issued after a negative crossmatch but before the routine antibody screening test was completed. In five of these cases, the blood unit turned out to be positive for the red cell antigen the patient was immunized against, but the antibody was not reactive in the antiglobulin crossmatch, giving a false-negative result. We do not have information regarding the homozygosity or heterozygosity of the red cells used in the crossmatch.

Antibody specificities identified in the acute HTRs

We received 30 acute HTRs: 8 Rh antibodies, 6 Kidd antibodies, 5 antibodies against LIAs, 1 anti-P$_1$, 3 autoantibodies and

9 unidentified antibodies. Figures 3 and 4 show a more detailed overview of the antibody specificities leading to an acute HTR in each blood group system.

There was one fatal case of anti-Wr^a. Anti-Co^b was identified in three cases of acute HTR, leading to a serious reaction.

For antibodies in the Rh system, anti-C was most frequently involved in acute HTRs, with four cases, followed by anti-E (two reports), anti-c (one report) and anti-e (one report). Anti-C was usually identified together with other antibody specificities. Only in one report, anti-C was found as the only antibody in a patient with symptoms of acute HTR (Figure 4). There was one case of acute HTR caused by anti-c. Two cases of anti-C, one anti-E and one anti-e could only be identified by using by sensitive techniques such as PEG-IAT and/or enzyme techniques.

In the Kidd system, anti-Jk^a was identified in four acute HTRs, followed by anti-Jk^b in two reports. Only in two cases of acute HTR, antibodies in the Duffy blood group system were identified (Figures 3 and 4). One anti-P_1 was highly suspected as to have been the cause of an acute HTR, as the patient received a P_1-positive blood unit.

Multiple alloantibodies were identified in seven cases leading to an acute HTR, where specificities against LIAs were present in five cases.

Red cell autoantibodies were identified in three acute HTRs, where no additional antibody specificities could be found (Figures 3 and 4).

Antibodies against LIAs were suspected to have been the cause of five acute HTRs (two anti-Wr^a and three anti-Co^b) (Figures 2 and 3).

Antibody specificities identified in the delayed HTRs

In 48 cases, the patient experienced a delayed HTR. As for acute HTRs, Rh and Kidd antibodies were also the most frequently reported specificities identified in delayed HTRs, with 20 and 10 cases, respectively (Figures 3 and 4). There were five reports on delayed HTR caused by anti-c. One anti-C and two anti-Jk^a, found in three delayed HTRs, could only be identified by using sensitive techniques.

Red cell autoantibodies were identified in one report on delayed HTR with no accompanying alloantibodies. In 16 cases of delayed HTR, the antibody specificity/ies could not be determined. Figures 3 and 4 show a more detailed overview of the antibody specificities leading to a delayed HTR in each blood group system.

Multiple alloantibodies were identified in 12 cases of delayed HTRs, where antibodies against LIAs were identified in two of these cases.

Avoidable HTRs

In 20 cases (26% of all HTRs), the patient was alloimmunized prior to the HTR, and the antibody specificities were known prior to the transfusion, but the blood units did not comply with the antigen requirements according to the patients' alloimmunization. These HTRs could therefore have been avoided. The errors made when issuing the blood units were attributed to stress situations caused by the urgent need for transfusion, that standard procedures were not followed, wrong interpretation of the crossmatch results, practical reasons regarding transfusion to outpatients and/or inadequate data registration in the laboratory information management system (LIMS). Even if all blood banks in Norway have LIMS, the use of warnings is not standardized, and they may be misunderstood or overlooked.

Reported clinical symptoms and laboratory findings related to the HTRs

In 42 cases (23 of the 30 cases of acute HTRs and 19 of the 48 delayed HTRs), information on clinical symptoms or relevant laboratory parameters was provided in the report. Fever and/or chills, alone or with other clinical symptoms, were reported in 18 cases, corresponding to 23% of all the total number of reports, whereas gastrointestinal (GI) symptoms such as nausea and vomiting were described in 11 cases, corresponding to 14% of the reports on HTR. Icterus was reported in six cases, together with other signs of haemolysis.

In 35 cases (16 acute and 19 delayed HTRs), clinical symptoms and/or laboratory findings compatible with haemolysis were provided in the haemovigilance report. Icterus, back pain, Hb fall, haemoglobinuria, haemolysis in the post-transfusion blood sample, reduced haptoglobin, increased bilirubin and/or lack of Hb rise after the transfusion were reported. GI symptoms such as nausea, abdominal pain and diarrhoea were reported together with other symptoms or laboratory findings in 11 cases (14% of all reports). Unfortunately, we have limited information on other clinical symptoms and signs.

Anti-Co^b was identified in three cases of acute HTR, where two patients experienced back pain, and the third patient had oliguria. One of these patients had a transient renal failure requiring haemodialysis, but the patient made a full recovery.

In nine additional cases involving anti-Jk^a, anti-C, anti-c, anti-Fy^a, anti-Fy^b, one unidentified antibody, anti-Jk^b, autoantibodies and anti-E, the patient experienced chest or back pain and/or signs of haemolysis during the HTR. In one fatal case of anti-Wr^a, the patient had severe renal failure [4].

DISCUSSION

In this overview, we present the findings related to haemovigilance reports on acute and delayed HTRs caused by non-ABO antibodies. The number of reports on HTRs has been stable, with one to nine reports per year. Underreporting cannot be excluded, since many HTRs may be mild or subclinical and therefore not reported to the blood bank by the clinicians. In many cases, symptoms such as fever or changes in the blood pressure may be attributed to the patient's underlying medical condition rather than to an HTR.

In our haemovigilance material, Kidd and Rh antibodies were the most frequent specificities identified in the reported HTRs. This is in accordance with data from the SHOT report 2022, which showed that anti-Jk^a remains the most common antibody implicated in delayed HTRs [5]. Antibodies in the Kidd blood group system can be difficult to identify as they tend to become weaker over time, but even weak antibodies in the Kidd system can be capable of causing HTRs [6]. Our data show that even weakly reactive antibodies in the Rh and Kidd blood group systems may lead to an acute or delayed HTR. This is comparable to the results of the SHOT report for 2022, where 9 of the 11 antibodies related to an acute HTR as well as 21 of the 29 cases of delayed HTR were identified only in the post-transfusion sample [5]. The use of more sensitive techniques for the identification of weakly reactive red cell antibodies, such as PEG-IAT and enzyme techniques, has been shown to be useful in reducing the risk of HTRs [7]. These measures may, however, have detrimental effects by delaying a transfusion, as they may lead to false-positive reactions or detect weak antibodies with little clinical significance. The use of more sensitive serological techniques cannot prevent HTRs caused by antibodies against LIAs.

In four cases, antibodies against LIAs were involved in a serious HTR. Even if there have been several reports of severe or fatal HTRs caused by antibodies against LIAs [8], it is not recommended to include red cells positive for LIAs routinely in the screening and/or identification panels [9, 10].

In 12 cases, the HTR was attributed to red cell antibodies that usually have little clinical significance, such as anti-M, anti-S, anti-P_1, anti-Le^a and anti-Bg^a. There are only sporadic reports where strongly reactive Bg^a antibodies were involved in an HTR [11, 12]. It is difficult to assess whether these antibodies were the cause of the reaction or if other, non-identified antibodies might also have been present. In addition, when multiple red cell antibodies are involved in an HTR, such as in the two cases of acute HTR where anti-Bg^a was identified, it is difficult to assess the causative antibody specificity, as we do not usually have detailed information about the phenotype of the transfused blood units involved in the HTR.

In 32% of all reports, the specificity of the antibody/ies could not be determined. Extensive investigations after a serious HTR should be performed in order to try to identify the causative red cell antibody/ies. We strongly recommend the referral of blood samples after serious transfusion reactions highly suspected to be an HTR to a reference laboratory, when the initial antibody identification is inconclusive at the local blood bank. In many cases, the use of special serological techniques, such as differential absorption, antibody elution, red cell antigen genotyping and use of rare red cell panels and antisera may be necessary. We also encourage the reporting blood bank to provide as much information as possible in the haemovigilance report on serological findings, other relevant laboratory results as well as clinical symptoms and patient outcome. In cases were additional information is requested, it is often too late to perform additional tests.

In 14% of the reports, GI symptoms such as nausea and vomiting were described in patients experiencing an HTR. GI symptoms are sometimes reported to the Norwegian Haemovigilance System as the only symptoms of a transfusion complication, and these reactions are considered as a non-specific transfusion reactions. Little is known regarding their pathophysiology, but based on our findings, GI symptoms should perhaps be suspected as a possible sign of the early stage of an HTR, as it has previously been suggested [13].

The overall incidence of alloimmunization in Norway is thought to be 0.57% in the pre-transfusion tests for possible recipients of blood [14]. It is estimated in the literature that only 30% of the present red cell antibodies are actually detected, due to alloantibody evanescence patterns, missed opportunities for alloantibody detection and record fragmentation [15]. Patients with previous history of red cell alloimmunization may be prone to developing additional antibodies [16], putting them at higher risk of experiencing an HTR. The use of extended antigen match in alloimmunized patients is not required in Norway, although it might be beneficial in patients with several antibody specificities and patients expected to have long-term need for transfusion [17]. For patients with warm autoantibodies, however, the use of prophylactic antigen match does not seem to have any protective effects for reducing the risk for new alloimmunization [18].

Urgent transfusions are sometimes required before full pre-transfusion and antibody investigations are completed, and this may lead to HTR if the patient is alloimmunized. This is a risk that clinicians need to be aware of when ordering emergency blood units. Clinicians should be able to promptly recognize the typical clinical symptoms and signs in patients experiencing an HTR.

In summary, in 17 years, we received 78 reports on HTRs corresponding to 1 HTR per 47,000 RBC transfusions. The most frequently identified antibody specificities were those in the Rh and Kidd blood group systems. In 26% of all HTRs, the patient was alloimmunized prior to the HTR, and the antibody specificity was known, but errors led to an HTR in the patient. Even if these HTRs could have been avoided, the low number of reported serious HTRs reflects that the blood banks in Norway have adequate strategies for antibody identification and selection of blood units. We strongly recommend the referral of blood samples to a reference laboratory when the initial antibody identification is inconclusive at the local blood bank.

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A.E. contributed to the original conception of the manuscript, performed the data analysis, elaborated the figures, reviewed the literature and wrote of the first draft of the manuscript; C.T.S. contributed to the review and editing of the manuscript; Ø. F. contributed to the review and editing of the manuscript. All the authors contributed to the revision of the manuscript and approved the submitted version.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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