

# US-Wide Red Blood Cell Alloantibody Exchange

An initiative to improve transfusion safety

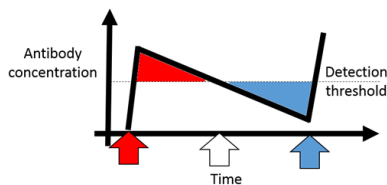
Version Date Feb 14, 2022

## Introduction

Over 12 million red blood cell (RBC) units are transfused annually in the United States. Although lifesaving, transfusions are not risk-free. Transfusions can be thought of as “mini transplants”, transferring the cells of a donor into a recipient. Like any transplant, there exists the possibility of incompatibility between donor and recipient. As such, one major transfusion risk is the development of antibodies (“RBC alloantibodies”) against non-self-antigens (which can be thought of as spikes) present on the donor RBCs. These antibodies develop in more than 40% of some patient populations following transfusion, making alloimmunization the most common serious hazard of transfusion. Individuals with sickle cell disease (SCD) are most likely to be impacted, followed by those with myelodysplastic syndrome, thalassemia, or autoimmunity (Fig 1)<sup>1</sup>.

Red blood cell alloantibodies can cause problems with future transfusions, increasing the risk of incompatibility and hemolytic transfusion reactions. If a hospital blood bank knows a patient has an RBC alloantibody, they will select RBC units lacking that antigen. The problem is that these antibodies can naturally disappear from detection over time, a

*Fig 2: Up to 80% of antibodies evanesce or fall below the level of detection by a hospital blood bank. A negative antibody screen (blue shaded area) is only reassuring if all the patient's past screens have also been negative. If a patient has an evanescent antibody and receives antigen positive RBCs, the alloantibody will typically come back, resulting in a hemolytic transfusion reaction.*

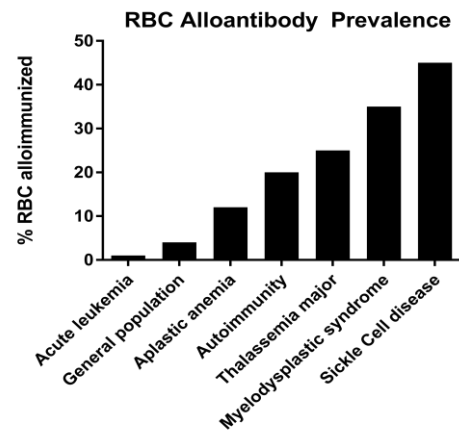


phenomenon called evanescence<sup>2</sup>. Thus, hospital testing may miss antibodies that have fallen below the level of detection (Fig 2). Moreover, patients frequently seek care at multiple facilities<sup>3</sup>, many of which will not have a record of their RBC antibodies on file<sup>4</sup>. An RBC transfusion that appears safe may lead to a delayed hemolytic transfusion reaction (DHTR) if a patient has an evanesced RBC antibody.

Problematically, blood banks in unrelated hospital systems have no digital interface. As such, a patient with an alloantibody that was previously identified at one hospital would be at high risk for transfusion incompatibility if being seen at an unrelated hospital since that hospital would have no knowledge of the antibody and no ability to detect an evanesced antibody. To get around this lack of data sharing, hospital blood banks may call other local hospital blood banks trying to get an accurate transfusion and antibody history. This practice is error-prone, laborious, and inefficient.

Although sharing of data in the electronic medical record between hospitals has begun (“Care Everywhere” for example), the RBC alloantibody data in such records is not easy to find and is not as detailed or as accurate as the data contained in the blood bank information systems (BBIS). Further, systems like Care Everywhere are viewed by direct care providers but not by blood bank staff.

*Fig 1: Prevalence of RBC alloimmunization by disease status.*



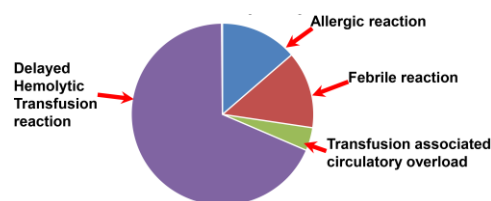
BBIS. A registry like this has been in existence in the Netherlands for more than a decade and has been shown to significantly improve transfusion safety<sup>5,6</sup>.

## Background

- **Hospital blood banks or blood donor center/immunohematology reference laboratories must test patients for antibodies within 3 days of each non-emergent transfusion.** This testing is mandated by regulatory standards, and results must be stored by the local blood bank indefinitely.
- **Patients consent for treatment and transfusion.** By regulatory standards, patients must provide consent prior to non-emergent transfusions. Implicit in that consent is that the hospital will provide blood that is as risk-free as possible.
- **The problem:** The blood a hospital provides is not as risk-free as possible, if the patient has an RBC alloantibody that the hospital blood bank is not aware of and cannot detect through routine patient testing protocols. The lack of a US-wide RBC alloantibody registry puts transfused patients at unnecessary risk, as a unit of blood that is seemingly compatible with the patient may lead to a hemolytic transfusion reaction days to weeks later. These reactions can be associated with significant morbidity and mortality.

**How would a US-wide registry improve transfusion safety?** Quite simply, transfusion safety will be improved by having an accurate antibody history on patients prior to transfusion. Surgeons wouldn't operate without knowing the location of a tumor; how is it safe to transfuse without knowing a patient's transfusion history and RBC antibody profile? Evanescent antibodies and the associated risk of a hemolytic transfusion reaction can be mitigated if a blood bank is aware of the patient's antibody history and can select appropriate RBCs for transfusion.

*Fig 3: This pie chart depicts how frequent delayed hemolytic transfusion reactions are in patients with SCD, compared with other transfusion reactions. Such reactions are underappreciated and potentially fatal.*



### Decrease dangers of hemolytic transfusion reactions for all patients

Anytime a patient with RBC alloantibodies is exposed to a cognate antigen positive RBC unit, that patient is at risk of incompatibility resulting in a delayed hemolytic transfusion reaction. Such reactions can occur in any alloimmunized patient. In individuals with SCD, such reactions occur following ~3-5% of transfusions in patients and are fatal 11% of the time, making this the single most common reaction (Fig 3)<sup>7,8</sup>. The US and other countries have put a large amount of effort into mitigating other transfusion reactions that occur at a significantly lower frequency than delayed hemolytic transfusion reactions, such as transfusion related acute lung injury (TRALI) or septic transfusion reactions.

### Improve health equity for people living with SCD, thalassemia, and other diseases

This proposed RBC alloantibody exchange/registry will improve transfusion safety for all RBC alloimmunized patients seeking care outside of a single hospital/healthcare system.

In addition to having the highest RBC alloimmunization prevalence rate, individuals with SCD have been shown to have a higher RBC antibody evanescence rate than those without SCD<sup>9,10</sup>. Taken in combination, the high RBC alloimmunization rate, the high antibody evanescence rate, and the need to seek medical care at multiple hospitals over a lifetime, put individuals living with SCD at the highest risk for hemolytic transfusion reactions and death from transfusions<sup>11</sup>. Transfusion-

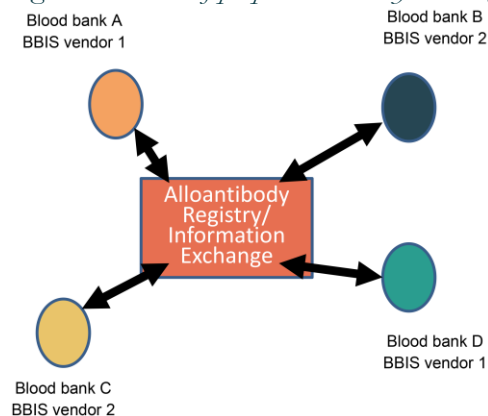
associated morbidity/mortality could be dramatically decreased if blood bank staff could access an exchange/registry to obtain antibody histories of patients prior to transfusion.

Transfused individuals with thalassemia (major or minor) will also benefit from such a registry. Like individuals with SCD, those living with thalassemia are at risk of inadvertently receiving an incompatible RBC transfusion given their relatively high RBC alloantibody prevalence rates<sup>12,13</sup>. Further, in a recent survey, more than half of patients with thalassemia sought care at more than one hospital, with antibody evanescence thus being a risk factor for adverse transfusion events<sup>12</sup>.

## Solution: US-wide, blood bank information system (BBIS) vendor-based RBC alloantibody exchange/registry

The development of a US-wide, RBC alloantibody exchange/registry will improve transfusion safety. We recommend that this exchange/registry be centered on existing blood bank information system (BBIS) vendors (Fig 4), as all RBC alloantibody data is currently stored in such information systems in hospital blood banks and donor center immunohematology reference laboratories across the US.

Fig 4: Schematic of proposed antibody exchange.



The goals of this initiative are to:

- To engage all major US BBIS vendors to participate in this RBC antibody registry.
- This engagement will allow a more complete RBC alloantibody history to be known prior to issuing an RBC unit for transfusion.
- This registry will improve transfusion safety by bringing RBC alloantibody information exchange into the electronic age.
- Knowing a patient's antibody history prior to transfusion will decrease the unnecessary and avoidable risk of hemolytic transfusion reactions and associated morbidity and mortality.

## Conclusion

With an increasing understanding of the importance of data interoperability and with a desire to improve health care equity, we believe the time is right to implement a US-wide RBC alloantibody exchange/registry. Such a registry will improve transfusion safety for alloimmunized patients that seek medical care from more than one hospital system. We are currently convening a group of industry stakeholders to initiate this work. Key stakeholders include hospitals/health systems, blood bank information system vendors, professionals and professional groups, regulatory agencies, and many others. The cover page

## Why make this antibody exchange vendor based?

All blood bank and immunohematology reference laboratory RBC alloantibody data at a hospital is currently stored in a blood bank information system (BBIS).

There are a limited number of large vendors in the US that run these BBIS.

Each hospital/laboratory already has an existing contract with the BBIS vendor.

No additional data entry or labor-intensive steps will be necessary for the blood bank technologists.

signatories have indicated their support and we are continuing outreach to increase awareness and engagement.

## About This Initiative

This is an unfunded, volunteer effort, initiated by individuals concerned about transfusion safety. For more information, please contact Dr. Jeanne Hendrickson ([jeanne.hendrickson@yale.edu](mailto:jeanne.hendrickson@yale.edu)).

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