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Use and Waste of Reconstituted Whole Blood Exchange Transfusions: An 11-year National Observational Study

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Objectives To identify indications for exchange transfusions, assess the use and waste of exchange transfusion products (ie, reconstituted whole blood exchange transfusions), and determine nationwide distribution and prevalence of these transfusions in the Netherlands.

Study design All 9 neonatal intensive care units and 15 non-neonatal intensive care unit hospitals participated in this retrospective, observational, cohort study. We retrieved data on the indications for and use of all exchange transfusion products ordered by participating centers over an 11-year period.

Results A total of 574 patients for whom 1265 products were ordered were included for analyses. Severe ABO (32.6%) and non-ABO (25.2%) immune hemolysis and subsequent hyperbilirubinemia were the most frequent indications. Rare indications were severe leukocytosis in *Bordetella pertussis* (2.1%) and severe anemia (1.5%). Approximately one-half of all ordered products remained unused. In 278 of 574 neonates (48.4%), ≥1 products were not used, of which 229 (82.7%) were due to the resolving of severe hyperbilirubinemia with further intensification of phototherapy. The overall prevalence of neonates who received an exchange transfusion was 14.6:100 000 liveborn neonates.

Conclusions A considerable proportion of products remained unused, and annually a limited number of patients are treated with an exchange transfusion in the Netherlands, highlighting the rarity of the procedure in the Netherlands. *(J Pediatr 2024;275:114225)*.

The introduction of phototherapy in the 1960s for the treatment of neonatal hyperbilirubinemia resulted in a gradual reduction of exchange transfusions in neonates with severe hyperbilirubinemia. Anti-D immunoprophylaxis for RhD-negative mothers carrying RhD-positive fetuses, further innovations in phototherapy and development of hyperbilirubinemia guidelines in the decades thereafter have made exchange transfusions increasingly rare.[1-8] Additionally, the administration of intravenous immunoglobulins to prevent or delay an impending exchange transfusion in neonatal hyperbilirubinemia may affect the exchange transfusion frequency, although it is rarely used in the Netherlands as evidence of its effectiveness in such situations is limited.[9] Neonatal exchange transfusions are performed commonly for neonatal hyperbilirubinemia owing to ABO and non-ABO blood group antigen incompatibilities. Other indications to order reconstituted whole blood exchange transfusions (hereinafter referred to as exchange transfusion products), such as for sickle

NICU Neonatal intensive care unit

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cell disease, malignancy, or infection-related leukocytosis, may occur occasionally, as generally reported upon in case reports or case series only.[10-14]

Exchange transfusions are most commonly performed in neonates with acute bilirubin encephalopathy or when intensive phototherapy proves insufficient and hyperbilirubinemia persists above exchange transfusion thresholds. To avert potentially severe or lethal consequences in infants with severe neonatal hyperbilirubinemia, clinicians usually preorder and prepare the blood products required for the exchange transfusion before being able to assess the effect of phototherapy, taking into account the time required to prepare and issue the blood products. Consequently, there is the possibility that the prepared blood products might go unused. However, studies on the indications for exchange transfusions and the use and waste of exchange transfusion products do not exist because such endeavors are hampered by the rarity of the procedure and a lack of centralization of blood organizations in many countries. The Netherlands has centralized its blood supply into a single collection and distribution agency since 1998.

To sustain a qualitatively high level of care, it is in the direct interest of physicians to procure knowledge on the indications for exchange transfusions, and knowledge on the actual use of blood products to prevent unnecessary waste of the voluntary donations of blood donors.[15] We, therefore, aimed to assess the use and waste of exchange transfusion products, to study the disease-specific prevalence of exchange transfusions and to evaluate the distribution of exchange transfusions in the Netherlands.

Methods

National Supply of Exchange Transfusion Products

The Dutch blood supply organization is centralized at Sanquin, a single collection agency with multiple fixed and mobile sites. Erythrocyte blood products are prepared from whole blood donations after removal of plasma and the buffy coat. For storage, saline adenine glucose mannitol is added. The erythrocyte suspension, at a hematocrit of 0.50-0.65 L/L, is leucocyte reduced subsequently. Exchange transfusion products are prepared freshly upon ordering in an open system and consist of an erythrocyte suspension from a single donor, <5 days of age, after removal of the storage solution. Fresh frozen apheresed plasma from a male, never-transfused, group AB donor is added. The volume and hematocrit of the end product can be specified by the clinicians' order. The end product has no free calcium ions, a citrate level of 12-19 mmol/L, physiological levels of potassium and glucose, a sodium level of 168 mmol/L at a pH of 6.9. The product contains no isohemagglutinins (eg, anti-A or anti-B), no platelets and $<1 \times 10^6$/L leucocytes. The product is stored at 2-6°C until use with a shelf-life of 24 hours.

In case of an imminent exchange transfusion, clinicians place an order at the institutional transfusion laboratory through local procedures. The institutional laboratory transfers this order to the closest production site of Sanquin Blood Supply. Upon arrival of the product, the institutional laboratory links it to the corresponding patient if the request for a product is still open. The production process from receipt of the order until dispatch averages at 90 minutes, but may last up to a maximum of 3 hours.

During the study period, Sanquin Blood Supply had 9 sites with a 24/7 service for the preparation of exchange transfusion products. Since November 4, 2019, and January 1, 2020, 2 of the 9 sites are closed between 23:00 and 07:00 and on the weekends. As a result, nearly all Dutch hospitals can be supplied within 1 hour.

Study Design

We performed a national, multicenter, retrospective, observational cohort study to assess the use and waste of exchange transfusion products in an 11-year time period, between January 1, 2011, and December 31, 2021. We evaluated the frequency of underlying disorders requiring exchange transfusions or the use of an exchange transfusion product and we assessed the distribution of exchange transfusions in hospitals with a neonatal intensive care unit (NICU) and in hospitals without a NICU. We acquired a list of all exchange transfusion products ordered in the study time period from the Transfusion Medicine Unit of Sanquin Blood Supply. All hospitals that ordered at least one exchange transfusion product were invited to participate.

Data Collection

A list of exchange transfusion products ordered by the participating center was provided to the local transfusion laboratory that linked the products to the patient for whom the product was ordered. Data from medical records were collected by local investigators and entered in an online CastorEDC electronic case report form. Data consisted of baseline characteristics, indication for ordering exchange transfusion products, use of exchange transfusion products, and reasons for not using the ordered exchange transfusion product if applicable. The electronic case report form contained built-in validations, was validated by 2 independent researchers, and remaining data inconsistencies or missing data were queried to local investigators.

Statistical Analysis

Continuous data were presented as median (IQR) and categorical data as proportions. To calculate the prevalence of exchange transfusions we used the number of all liveborn neonates born in the study period as reported by the Dutch Central Statistical Office as the denominator. To assess the prevalence of *Bordetella pertussis* we retrieved data on the number of reported infections from the National Institute for Public Health and the Environment. *B pertussis* is a notifiable disease that must be reported when patients have had coughing symptoms for 14 days or have typical coughing symptoms, combined with a positive laboratory test or recent contact with a confirmed *B pertussis* case.

Ethical Considerations

The non-WMO (Medical Research Involving Human Subjects Act, Dutch: Wet medisch-wetenschappelijk onderzoek met mensen) medical review committee of the LUMC reviewed the study and confirmed that the Medical Research Involving Human Subjects Act did not apply. The study adhered to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013; version 2013), complied with the General Data Protection Regulation (GDPR, Dutch: Algemene verordening gegevensbescherming, AVG) and the Code of Conduct for Health Research. We received approval from local institutional review boards or ethical committees of participating centers. Informed consent was obtained by local investigators when required.

Results

Patient Inclusion and Characteristics

A total of 1923 exchange transfusion products were ordered by 55 centers (**Figure 1**). One academic center with 60 ordered products had to be excluded owing to a merge of pediatric departments and no legal permission to access records for this study and 1 nonacademic center with 4 ordered products owing to closure. The remaining 53 centers with 1859 ordered products were invited and 24 centers with a total of 1564 (84.1%) agreed to participate. This cohort included all 9 NICUs, 14 non-NICU hospitals, and 1 pediatric oncology hospital. The remaining 295 products (15.9%) were ordered by 29 non-NICU hospitals that did not participate. Among the 1564 products from participating centers, 198 (12.7%) were not linked to a patient because the order was cancelled before the arrival of the product to the hospital. Thus, a total of 1331 products (87.1%) were linked to 627 patients. Of these, 61 products were ordered for 53 patients, which included 51 patients with neuroblastoma stage IV to prime cell separator devices for peripheral blood stem cell apheresis, and 2 patients with severe leukocytosis owing to *B pertussis* treated with leukapheresis. Finally, 574 patients with a total of 1265 products were included for further analyses. These patients were born at a median gestational age of 37.3 weeks (IQR, 35.7-39.0 weeks) with a median birthweight of 3061 g (IQR, 2420-3500 g). A total of 265 (44.7%) were female.

Indications for Ordering Exchange Transfusion Products

Among the 574 patients for whom a product was ordered, the majority was due to neonatal hyperbilirubinemia (534 [92.7%]) (**Table**). These encompassed 188 neonates (35.2%) with ABO-incompatibility, 145 (27.2%) with non-ABO immune hemolysis, and 84 (15.7%) with hyperbilirubinemia

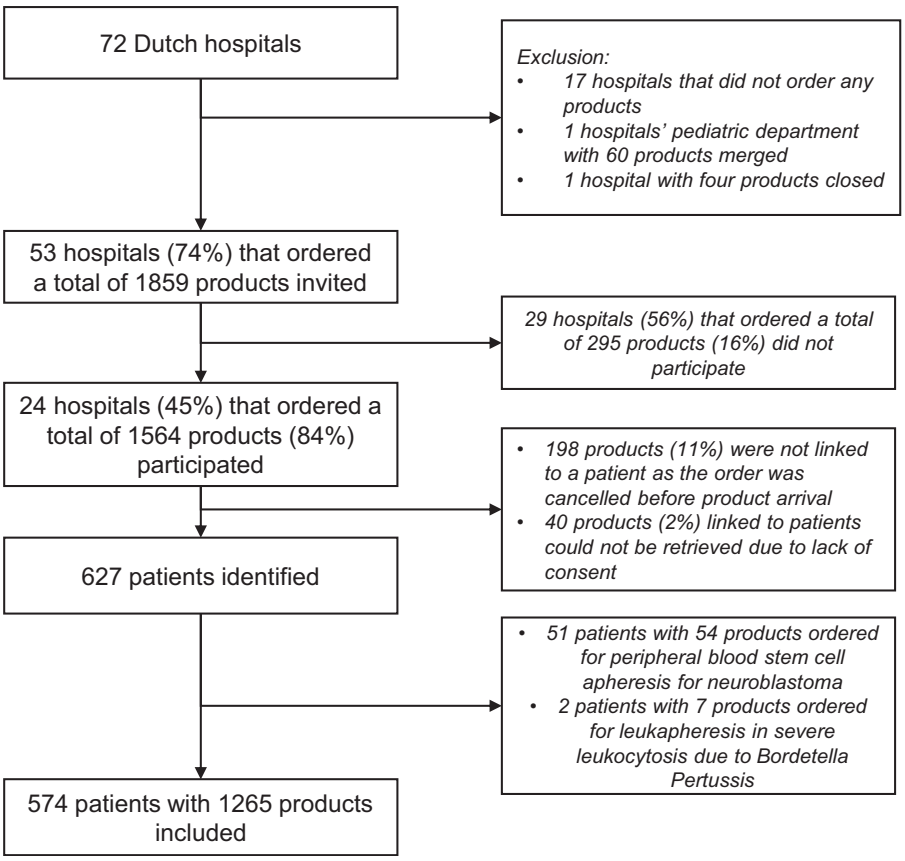

Figure 1. Flowchart detailing the process of identifying and including the study sample.

Table. Distribution of the indications for which ET products were ordered, and the distribution of the actual performance of exchange transfusions

Primary indications	Total (n = 574)	With ET (n = 349)	Without ET (n = 225)
Hyperbilirubinemia			
ABO incompatibility	188 (31.7)	114 (60.6)	74 (39.4)
Non-ABO incompatibility	145 (24.5)	111 (76.6)	34 (23.4)
Prematurity/dysmaturity	88 (14.8)	36 (40.9)	52 (59.1)
Unknown despite full diagnostic workup	52 (8.8)	16 (30.8)	36 (69.2)
Dehydration	16 (2.7)	4 (25.0)	12 (75.0)
G6PD deficiency	13 (2.2)	12 (91.7)	1 (8.3)
Hematoma or bleeding	9 (1.5)	4 (44.4)	5 (55.6)
Hereditary spherocytosis	5 (0.8)	4 (80.0)	1 (20.0)
Others	8 (1.2)	4 (50.0)	4 (50.0)
Gestational alloimmune liver disease	16 (2.7)	16 (100)	0 (0)
Severe leukocytosis			
B pertussis	13 (2.1)	11 (84.6)	2 (15.4)
Acute lymphatic leukemia	2 (0.3)	1 (50.0)	1 (50.0)
Myeloproliferative disease in trisomy 21	1 (0.2)	1 (100)	0 (0)
Acute myeloid leukemia	1 (0.2)	1 (100)	0 (0)
Severe anemia	6 (1.0)	6 (100)	0 (0)
Others	11 (2.0)	8 (72.7)	3 (27.3)

ET, exchange transfusion; *G6PD*, glucose-6-phosphate dehydrogenase.
Values are number (%).

attributable to prematurity or dysmaturity. Noteworthy, the exact cause of hyperbilirubinemia, despite full diagnostic workup of alloimmunization or other causes for jaundice was unknown in 52 neonates (9.7%). Other less common indications included severe leukocytosis in *B pertussis* (13 [2.3%]) and severe anemia (9 [1.5%]). Detailed specifications and distribution of indications are outlined in **Supplementary Table 2** (online; available at www.jpeds.com). Exchange transfusions were performed in 350 patients (61.0%) for the indications displayed in **Table** and **Figure 2**.

Use and Waste of Exchange Transfusion Products

The use of products for exchange transfusions and clinical information was collected in 1243 of 1265 products (98.3%), with an additional 198 unused products that were produced upon ordering, but were cancelled before delivery at the hospital (**Figure 1**). Among the total of 1441 products, 718 (49.8%) were used and 723 (50.2%) were not used. Of the unused products, 278 (38.5%) were not returned to the blood supply organization. We found a relative increase in the proportion of unused products throughout the study period, increasing from 42% in 2011 to 55% in 2021 (**Figure 3**, A). In 601 of 718 used products (82.7%), the time between dispatch from a location of the blood supply and actual use of the product was known and was a median of 179 minutes (IQR, 120-263 minutes). Including the average time required to produce exchange transfusion products (90 minutes), the time between placement of the order by the institutional laboratory and actual use of the product totaled at 269 minutes (IQR, 210-353 minutes).

In 278 of 574 patients (48.4%), ≥1 products were not used. In 229 patients (82.7%), this was due to the resolving of severe hyperbilirubinemia owing to a successful lowering of total serum bilirubin with an intensification of phototherapy. Eight patients (2.9%) did not require a subsequent product based on bodyweight and 5 (1.8%) did not require a subsequent product owing to a sufficient decrease in the total serum bilirubin using the first product. Among 4 patients (1.5%) with severe leukocytosis owing to *B pertussis*, 2 remained under the exchange transfusion threshold and did not receive any exchange transfusion, 1 remained under the exchange transfusion threshold after the initial exchange transfusion, and, last, 1 patient was clinically too unstable to perform a subsequent exchange transfusion. One (0.4%) patient died before the procedure, 1 patient (0.4%) was misdiagnosed for severe hyperbilirubinemia and 1 patient (0.4%) did not receive a subsequent product owing to a miscommunication between laboratory and clinic. Last, in 1 patient (0.4%) a product was not used owing to procedure-related complications. In 28 patients (10.1%), the reason for not using all products was unknown.

Notably, although it concerns relatively few patients, the proportion of patients for whom a product was ordered but who did not receive an exchange transfusion was highest in hyperbilirubinemia owing to dehydration (75.0%), hyperbilirubinemia owing to an unknown cause despite full diagnostic workup (69.2%), and in hyperbilirubinemia owing

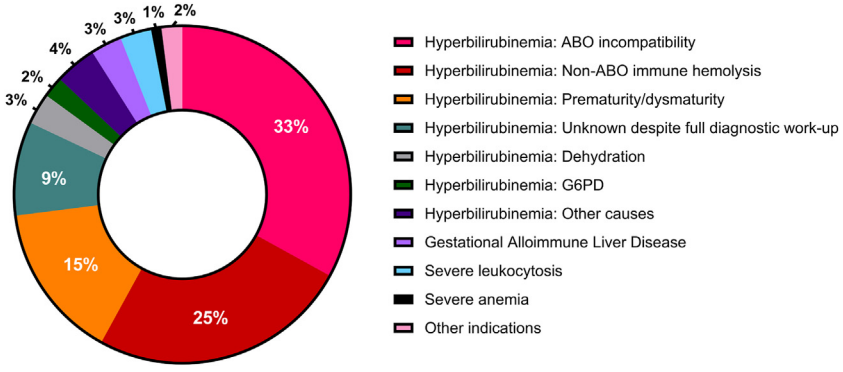

Figure 2. Distribution of indications for which exchange transfusions were performed.

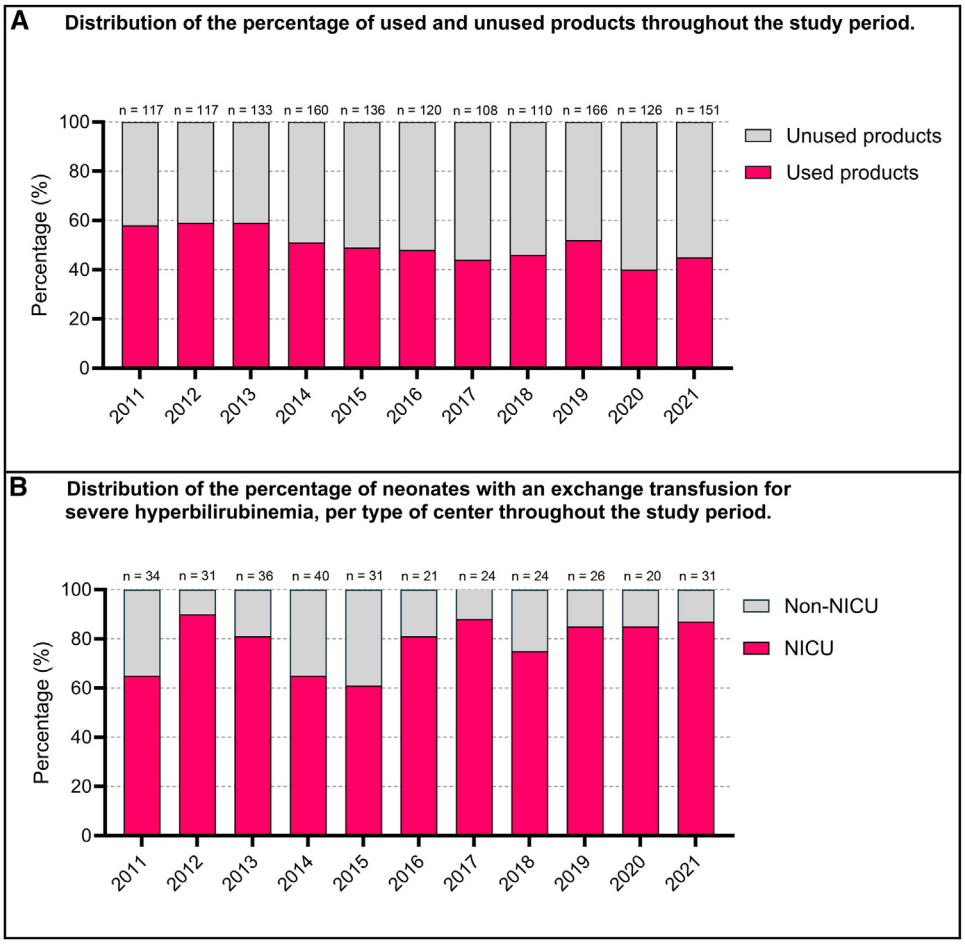

Figure 3. Distribution of used and unused products and distribution of neonates with an exchange transfusion for hyperbilirubinemia throughout the study period.

to prematurity or dysmaturity (59.1%) (**Table** and **Supplementary Table 2**, online; available at www.jpeds.com).

National Distribution of Performed Exchange Transfusions

Among 576 patients, 352 (61.1%) received a total of 414 exchange transfusions during the study period. Among these, 304 (86.4%) received 1 exchange transfusion, 39 (11.1%) received 2 exchange transfusions, and 9 (2.5%) received ≥3 exchange transfusions.

The majority of exchange transfusions were performed in NICUs, totaling at 279 neonates (79.3%) with 319 (77.1%) exchange transfusions. Thus, the remaining 73 neonates (20.7%) with 95 (22.9%) exchange transfusions were managed in the 14 participating non-NICU hospitals. This translates to annually 31 patients with 35 exchange transfusions in NICUs, and 5 patients with seven exchange transfusions in the participating non-NICU hospitals.

We separately evaluated the distribution of exchange transfusions in neonatal hyperbilirubinemia specifically. We found that a total of 369 of 414 exchange transfusions (89.1%) were performed in 318 of 352 neonates (90.3%) with severe hyperbilirubinemia. Of these, 276 exchange transfusions (74.8%) in 246 neonates (77.3%) were performed in NICUs. Thus, a total of 93 exchange transfusions (25.2%) in 72 neonates (22.6%) with hyperbilirubinemia were performed in non-NICU settings. We additionally found an increasing proportion of neonates with an exchange transfusion for severe hyperbilirubinemia treated in NICUs in recent years in comparison to the proportion treated in non-NICUs (**Figure 3**, B). In 2021, 85% of neonates with an exchange transfusion for severe hyperbilirubinemia were managed in NICUs.

Prevalence of Exchange Transfusions

A total of 1 901 734 children were liveborn in the study period in the Netherlands. The overall prevalence of neonates who received an exchange transfusion was 14.6:100 000.0 liveborn neonates. The prevalence of neonates with an exchange transfusion for severe hyperbilirubinemia owing to ABO incompatibility was therefore 5.9:100 000.0 pregnancies, and 5.6:100 000.0 pregnancies in non-ABO immune hemolysis. According to the National Institute for Public Health and the Environment, a total of 1505 children under the age of

6 months were reported to have *B pertussis*. This translates to a prevalence of 7.3:1000.0 infants with severe leukocytosis owing to *B pertussis* requiring leukapheresis or an exchange transfusion, and 6.0:1000.0 infants with *B pertussis* requiring an exchange transfusion for severe leukocytosis.

Discussion

The findings from this national, multicenter, observational study show that one-half of the exchange transfusions products ordered were not used. We found that the majority of products were ordered for severe ABO or non-ABO blood group antigen-related immune hemolysis and subsequent hyperbilirubinemia, which frequently resolved owing to phototherapy treatment. The majority of exchange transfusions were performed in NICU settings.

The acute and urgent clinical situations in which exchange transfusions are performed urges the caregiver to request the preparation of blood products in advance to ensure timely treatment to prevent severe or lethal complications, while also considering the time required to prepare the exchange transfusion product. Intensive phototherapy in severe neonatal hyperbilirubinemia has proven to decrease total serum bilirubin rapidly and may effectively resolve early stages of bilirubin encephalopathy while awaiting the ordered exchange transfusion product. As such, exchange transfusion may eventually be deemed unnecessary and the prepared products might go unused. This possibility is confirmed by our findings that the majority of products ordered for severe hyperbilirubinemia remained unused owing to the successful decreasing of total serum bilirubin with an intensification of phototherapy thereby preventing the need for invasive exchange transfusions. Nevertheless, approximately 800 exchange transfusion products remained unused that directly translates to approximately 800 whole blood donations and 800 plasma donations used in the preparation of unused exchange transfusion products within the study time period. It is imperative to find a balance in the timing of ordering exchange transfusion products to limit waste and ultimately ensure a timely treatment of the patient, while taking into account the time needed to prepare, dispatch and transport the product, which in general is within 4 hours. However, this may be challenging because the exact causes of neonatal hyperbilirubinemia, such as dehydration, that showed a relatively high rate of unused products, may be unknown in many cases at the time in which these urgent clinical situations present themselves. in contrast, blood banks need a certain number of orders to remain compliant with quality standards.

This study has enabled us to pinpoint several rare indications for exchange transfusions, such as hereditary spherocytosis, severe leukocytosis, severe anemia and multiple very rare diseases. Evidence on the effectiveness and outcomes of these invasive procedures in these rare conditions is extremely limited. Considering the rarity, international collaborations are essential to gather such knowledge. This may be especially important for severe leukocytosis in *B pertussis* as the past decades have shown a resurgence of outbreaks in countries with regularly high vaccination coverages.[16-20] Pertussis may cause a reduction of leukocyte retention in lymphoid tissues causing extravasation and a consequent surge in circulating leukocytes.[21] A global increase in the hesitancy toward vaccination leads to more frequent and extensive pertussis outbreaks nowadays and in the near future.[22] This factor highlights the urgent need to assess the effectiveness of exchange transfusions, and other treatment options, for severe leukocytosis owing to *B pertussis*, and to describe the outcome of those who have undergone such a procedure to ensure that future patients receive evidence-based treatment.[12]

We retrieved data on approximately 84% of all exchange transfusion products ordered across a continuous period of 11 years, among 24 participating centers including all NICUs. In doing so, we found that the vast majority of exchange transfusions are performed in intensive care settings. Although 29 non-NICU hospitals did not participate, these represented only 16% of the total number of ordered exchange transfusions and therefore our findings may only slightly underestimate the number of procedures performed in non-NICU centers. Last, despite the retrospective study design and its reliance on available data, the indications for ordering products was known in 99.7% of the identified patients, further underlining the reliability of this study.

Although we did not retrieve data on procedure-related complications, it is likely that a considerable proportion of patients may have experienced thrombocytopenia, potentially requiring a platelet transfusion, considering the fact that reconstituted whole blood exchange transfusions do not contain platelets.

This study was enabled by the infrastructure of a centralized blood supply distributing exchange transfusion products to all Dutch hospitals, thereby providing a unique insight on the exchange transfusion landscape on a national scale. Ideally, blood transfusion organizations should register the underlying disease for which blood products are requested to monitor trends in the use and waste of products, as well as the actual performance of exchange transfusions and to identify opportunities for improvement in the logistical challenges in these invasive procedures.

In conclusion, the majority of reconstituted whole blood exchange transfusions to perform a whole blood exchange transfusion for severe hyperbilirubinemia were not used, whereas products ordered for rare indications, such as severe leukocytosis, were nearly all used. We have identified several rare indications for exchange transfusions and thereby provide a framework for future studies. Annually, only 15 patients per 100 000 liveborn neonates receive an exchange transfusion in the Netherlands, highlighting the rarity of the procedure. Maintaining a high quality in this procedure poses a challenge for both blood banks and hospitals. ■

CRediT Authorship Contribution Statement

Derek P. de Winter: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project

administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Enrico Lopriore:** Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Christian V. Hulzebos:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Visualization, Writing – review & editing. **Michaël V. Lukens:** Data curation, Investigation, Writing – review & editing. **J.H. (Harriët) Klinkspoor:** Data curation, Investigation, Project administration, Writing – review & editing. **Michaela van Bohemen:** Data curation, Investigation, Project administration, Writing – review & editing. **Gijs den Besten:** Data curation, Investigation, Project administration, Writing – review & editing. **Karen M.K. de Vooght:** Data curation, Investigation, Project administration, Writing – review & editing. **Sabine L.A.G. Vrancken:** Data curation, Investigation, Project administration, Writing – review & editing. **Amanda M.P. Trompenaars:** Data curation, Investigation, Project administration, Writing – review & editing. **Angelique Hoffmann-Haringsma:** Data curation, Investigation, Project administration, Writing – review & editing. **N.C.V. (Nathalie) Péquériaux:** Data curation, Investigation, Project administration, Writing – review & editing. **Peter Andriessen:** Data curation, Investigation, Project administration, Writing – review & editing. **Karlijn Gijzen:** Data curation, Investigation, Project administration, Writing – review & editing. **J.L.A.M. (Jacqueline) van Hillegersberg:** Data curation, Investigation, Project administration, Writing – review & editing. **Janneke C. Zant:** Data curation, Investigation, Project administration, Writing – review & editing. **Maaike C. van Rossem:** Data curation, Investigation, Project administration, Writing – review & editing. **A.J. Adriaan van Gammeren:** Data curation, Investigation, Project administration, Writing – review & editing. **Floor Weerkamp:** Data curation, Investigation, Project administration, Writing – review & editing. **Clare E. Counsilman:** Data curation, Investigation, Project administration, Writing – review & editing. **F.R. (Rachel) Knol:** Data curation, Investigation, Project administration, Writing – review & editing. **I.A.M. (Irene) Schiering:** Data curation, Investigation, Project administration, Writing – review & editing. **Gerdina H. Dubbink-Verheij:** Data curation, Investigation, Project administration, Writing – review & editing. **E.J.T. (Joanne) Joanne Verweij:** Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – review & editing. **Masja de Haas:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

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