

Structure and focus of the German Red Cross Blood Transfusion Service Baden-Württemberg - Hestia and its affiliates



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Introduction

The German Red Cross Blood Transfusion Service Baden-Württemberg-Hestia and its affiliates, the German Red Cross Transfusion Service East, the German Red Cross Blood Transfusion Service North, the Center for Clinical Transfusion Medicine at the University of Tübingen, and the Institute for Clinical Transfusion Medicine and Cellular Therapy at the University of Heidelberg, fulfil important functions in the provision of blood components and research in the field of transfusion medicine.

With the above mentioned organisations, our network is comprised of 17 institutions for transfusion medicine and immuno-haematology, with locations in Baden-Baden, Berlin, Chemnitz, Cottbus, Dresden, Frankfurt, Gölrlitz, Heidelberg, Kassel, Lütjensee, Mannheim, Plauen, Potsdam, Schleswig, Tübingen, Ulm and Zwickau.

All together, the institutions comprise a staff of more than 2000 highly qualified experts. Within the medical

Structure of the German Red Cross Blood Transfusion Service Baden-Württemberg - Hestia, East and North

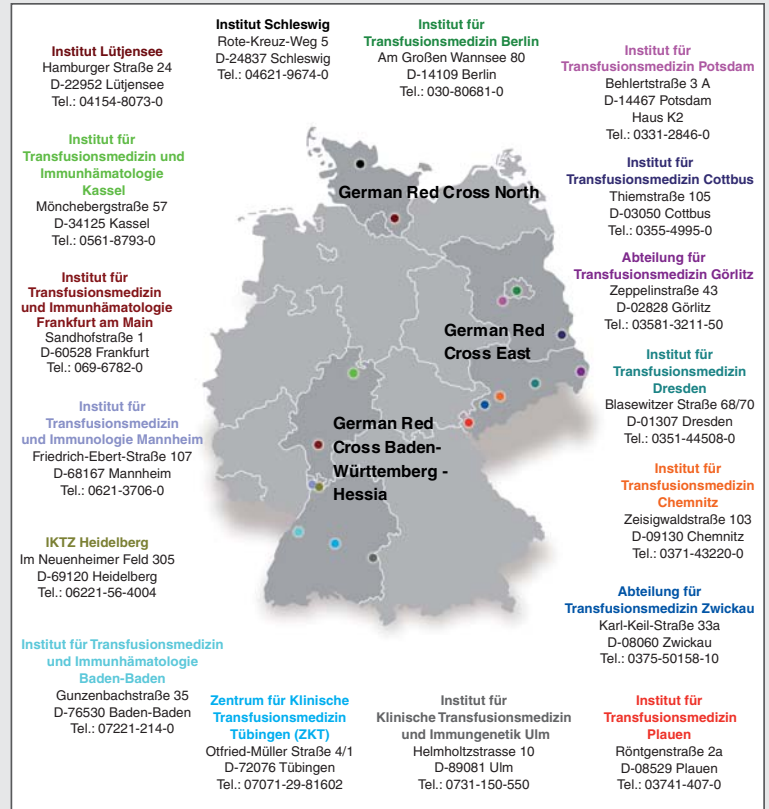


Figure 1

departments, we employ a large number of medical doctors who are board-certified in transfusion medicine, medical doctors in training, PhDs, medical technicians, nurses, and personnel who have been qualified for the respective work in the field by extensive training.

The integration of the institutions in Dresden, Frankfurt/Main, Heidelberg, Mannheim, Tübingen and Ulm into the medical faculties of their respective medical schools, by implementation of chairs for transfusion medicine, has led to extensive scientific co-

operation. This is especially the case in the fields of cellular and gene therapies, which represent important fields of study at our institutions. Cellular and gene therapies will play an increasingly important role within our institutions, which have put a great emphasis on promoting research and development in the fields of transfusion medicine, immuno-haematology and related medical disciplines.

Our work is based on the worldwide accepted ethical code of the International Red Cross, the code of the In-

Areas and populations in Baden-Württemberg - Hestia, East and North

	State	Area km ²	Area-Total km ²	Population n	Population-Total n	Population Density (n habitants / km ²)
East	Brandenburg	29,479	48,786	2,515,896	10,132,466	86
	Berlin	892		3,443,570		3,861
	Sachsen	18,416		4,173,000		227
North	Schleswig-Holstein	15,799	16,555	2,831,860	4,612,608	179
	Hamburg	755		1,780,748		2,351
Baden-Württemberg - Hestia	Baden-Württemberg	35,751	56,866	10,747,905	16,811,588	301
	Hestia	21,115		6,063,683		287

Table 1

ternational Society of Blood Transfusion (ISBT), the German drug act, the transfusion act, the EU directives and further corresponding regulatory guidelines and regulations. The safety and the health of blood donors, the safety and quality of blood products and the safety of the recipients of blood components have the highest priority in the planning and conduct of our medical and pharmaceutical tasks.

A prerequisite for the successful work of our blood transfusion service is the willingness of the population to voluntarily donate blood. The collection of blood donations is one of our most important tasks. Through comprehensive advertising, education and information, the awareness for blood donation is raised among the citizens. To carry out these tasks, our institutions rely on the support of numerous voluntary staff members of the German Red Cross organisation. The diagnostic portfolio of our institutions includes investigations regarding blood group serology, immunohaematology, transplant diagnostics, immunogenetics, and molecular haemostaseology. We provide classical serological as well as modern

molecular biology techniques in all laboratories.

To achieve the high demands within our working field, we have implemented an extensive Quality Management System certified according to DIN EN ISO 9001:2008, which covers all of the institutions. Our laboratories are accredited according to DIN EN ISO 15189:2007 and DIN EN ISO/IEC 17025:2005. In vitro diagnostics produced by our institutions are certified based on the prerequisites of the medical product regulations according to DIN EN ISO 13485:2007.

Mobile Blood Collection

Generation of blood and blood components is one of the major responsibilities of our blood service. With 1.3 million whole blood donations and 300,000 other types of donations such as plasma and platelet apheresis, the service generates the major supply of blood components for clinics and hospitals in the federal states of Baden-Württemberg, Hestia, Saxonia, Schleswig-Holstein, Hamburg, Berlin and Brandenburg. Thus, we bear the responsibility for the continuous and safe supply of blood components for a

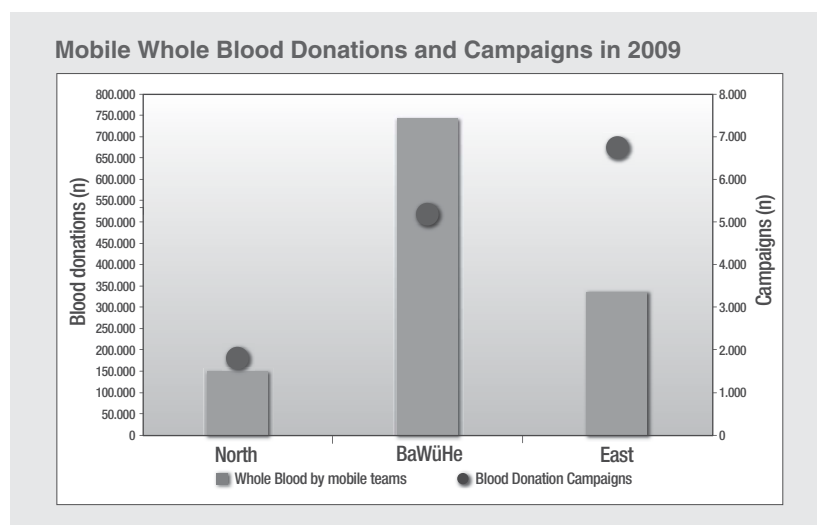


Figure 2

Regions of the German Red Cross blood transfusion service Baden-Württemberg - Hestia

population of over 32 million people in Germany.

The major share of blood donations is collected through mobile donation campaigns. More than 85 mobile collection teams organise about 14,000 donor drives per annum that generate about 93 % of the entire volume. The fraction of first-time donors is approximately 7 %, and the donor deferral rate is approximately 8 %. The mobile collection teams are associated with individual institutes and collect blood donations within their region.

Community blood donor drives are supported by information technology (IT). We use a mobile data management (MOBDM) system. The MOBDM system guarantees that only donors whose medical history and historical laboratory values are within specified ranges will be clear-

ed for donations, therefore indicating them as principle suitable donors.

The MOBDM system permits the registration of donors, donor number assignment, donation data documentation and documentation of certain relevant quality criteria. Upon return of the collection team to the host institute, the data are transferred into the institute's databases using host systems, and, from midnight on, are accessible to laboratories, production personnel, and doctors. These data are integrated into product clearance algorithms.

Fixed-site blood collections

Our institutes maintain blood donation/clinical transfusion medicine

facilities. These supply the following medical interventions:

- Whole blood donations, including autologous blood donations
- Platelet apheresis, plasmapheresis, and erythrocyte apheresis
- Therapeutic apheresis and outpatient transfusions
- Granulocyte and lymphocyte apheresis
- Stem cell apheresis
- Cellular therapeutics and good manufacture practise (GMP) facilities

These blood donor facilities complement the spectrum to provide all-inclusive blood product supplies and transfusion medicine services in all regions served by our institutions.

Allogeneic and autologous whole blood donations:

Even though more than 90 % of allogeneic whole blood donations are collected by mobile blood collection teams, fixed-site whole blood donations within our institutes serve additional important functions. They allow for acute collections, special events during times of blood shortage, or targeted invitations of donors with rare blood types. The number of autologous donations has dwindled by approximately 40 % over the last few years, which represents the general trend of continuously decreasing use of autologous blood products in Germany that is, in part, attributable

Division of Erythrocyte Concentrates derived from Whole Blood Donations in Germany 2009

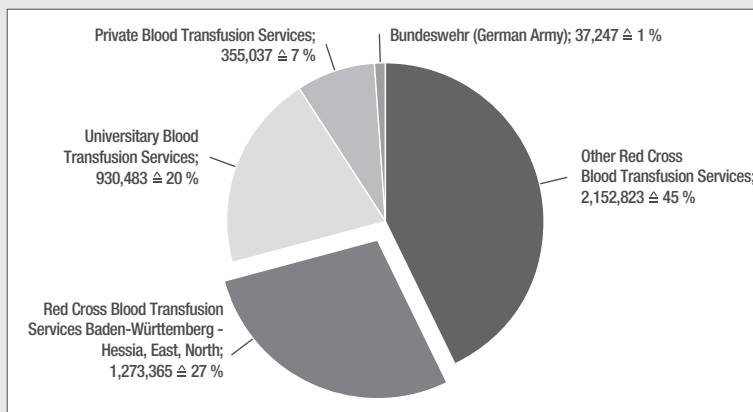


Figure 3

Autologous Blood donations between 2003 and 2009 in Germany

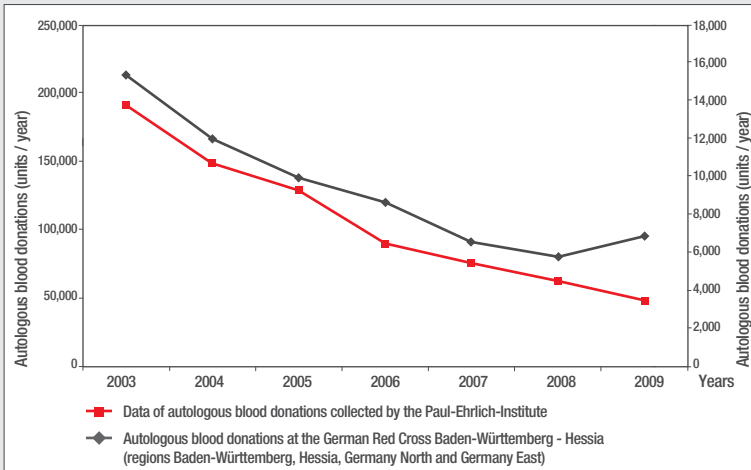


Figure 4
Development of autologous Blood Donations in Germany between 2003 and 2009

to the very high safety of allogeneic blood products.

Platelet apheresis:

The production of platelet concentrates by apheresis is part of the standard operating procedures of our blood service. Platelet apheresis of human leukocyte antigens (HLA)-selected donors accommodates the needs of patients with HLA antibodies. Random apheresis platelet concentrates supplement the supply for pool platelet concentrates during times of shortage, such as during holidays. The capacity to alternatively produce the pool and apheresis platelet concentrates is an important expertise of our blood service and guarantees optimal patient support at all times.

Stem cell apheresis:

Over the last few years, the total number of "stem cell" aphereses (G-CSF stimulated leukocyte apheresis) has increased, to 1,696 in 2009.

Over the last 5 years, the distribution between autologous and allogeneic stem cell aphereses has shifted. In 2005, the majority (54.6 %) of aphereses were autologous. In contrast, the majority of these procedures in 2009 were allogeneic stem cell apheresis (60 %). Among the allogeneic aphereses, the relative share of family donors has decreased, while the number of unrelated donations continues to increase. This pattern holds true for both aphereses of donors of the stem cell registries of the German Red Cross Blood Service and for aphereses done on behalf of other German donor registries. Moreover, in two institutes, stem cells from placenta blood are being processed and stored.

Platelet and plasma apheresis, whole blood donations and out-patient transfusions in 2009

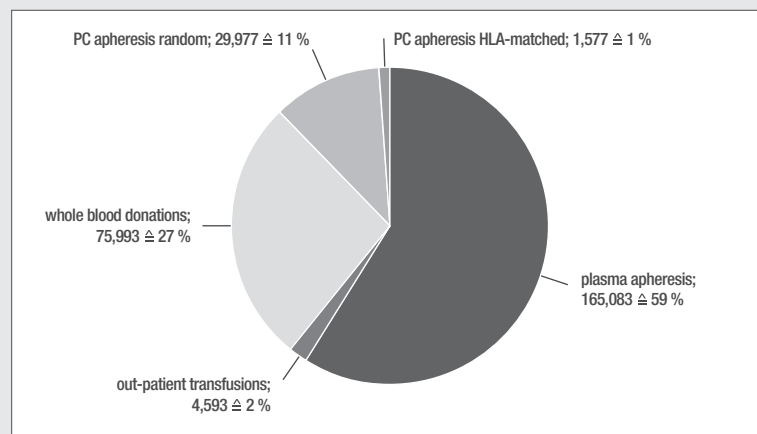


Figure 5
Fixed-site blood donations – platelet concentrates (PCs) and plasma apheresis concentrates, whole blood donations and out-patient transfusions

Cytapheresis and Cord Blood Donations in 2009

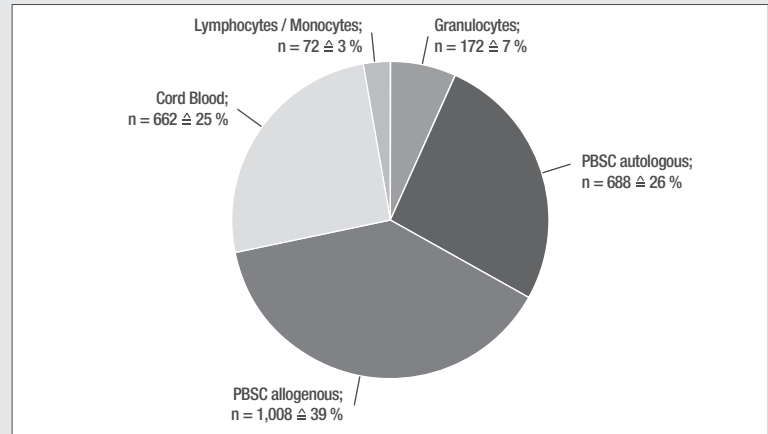


Figure 6

Data of Fixed-site blood donations – peripheral blood stem cells (PBSCs), cord blood donations, granulocyte concentrates, lymphocyte concentrates and monocyte concentrates

Therapeutic aphereses and the transfusion clinic:

Our portfolio also contains therapeutic aphereses. These are performed for patients with critically elevated plasma protein levels or certain cell types to achieve a rapid, targeted reduction of these parameters. In 2009, 324 such aphereses were performed, often as life-saving acute measures.

Chronically transfusion-dependent patients can receive erythrocytes, platelets and plasma transfusions in our transfusion medicine clinics on an outpatient basis. The transfusion clinic rounds out the portfolio of the fixed-site collection departments of our institutes, which support hospi-

tals and private practices with their broad spectrum of services.

Production

All whole blood donations are separated into blood components. This separation yields red cell concentrates, plasma concentrates and buffy coats. Approximately 20 % of the plasma is used as therapeutic fresh frozen plasma (FFP) after 4 months of quarantine storage, where-

as the remaining 80 % is used for further fractionation. Most apheresis procedures are performed as double apheresis.

More than 40 % of the collected buffy coats (BCs) are used to manufacture pooled random platelet concentrates (comprised of 4 BCs). Red cell concentrates and platelet concentrates have been fully produced as leukodepleted blood components since 2001. This blood component separation scheme allows for qualitatively and quantitatively optimal recovery of whole blood donations.

When irradiation is required for individual medical purposes, packed red cells and platelet concentrates are gamma-irradiated at the respective institutions. Some of these products are further processed to yield preparations for specific clinical applications and indications. This may include “baby-erythrocyte concentrates” for premature infants and neonates, volume reduced preparations and blood components for ex-

Blood components produced in 2008 and 2009

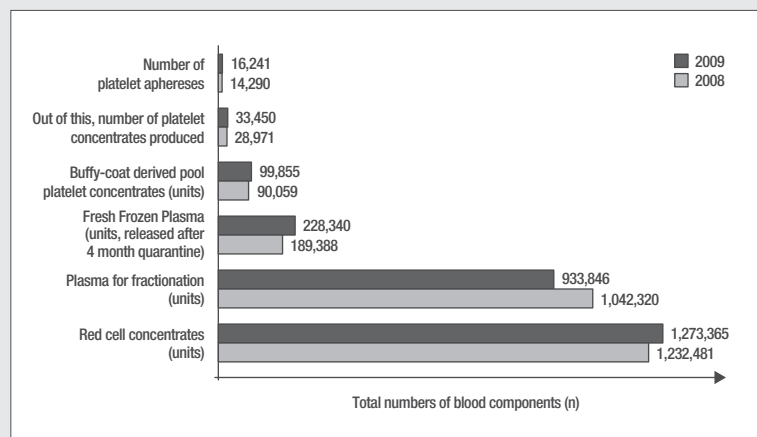


Figure 7

Manufactured pool platelet concentrates

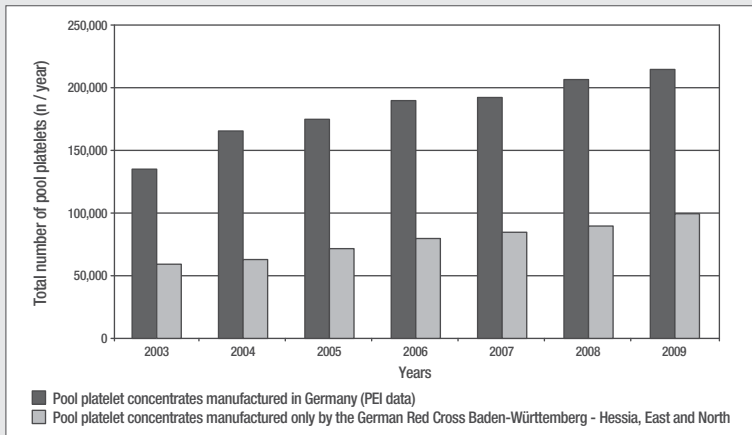


Figure 8

Produced pool-platelets in Germany and by the Blood Transfusion Service Baden-Württemberg - Hestia, East and North

change transfusions, and washed erythrocyte concentrates in rare cases.

The component separation of whole blood donations will be performed in suitable and qualified rooms that comply with the standards for "Good Manufacturing Practice (GMP)". The entire separation process is performed in a closed system. If the blood tubing has to be connected, this will be done using sterile connection devices (TSCD).

Technical equipment such as centrifuges and separation devices, which are used for blood component production, will meet the latest technical standard. Whole blood processing is accomplished with a fully automatic system. Therefore, these separation techniques allow for the optimal recovery of pharmaceutical drugs at a high purity of manufactured blood components.

Plasma components are shock frozen (-60 °C) and stored at or below -30 °C. The cooling systems are

equipped with the latest alarms, enabling immediate action in case of technical disturbances.

In-process controls are performed on a regular basis throughout all critical manufacturing processes. A total of 0.25 % of manufactured blood components are usually considered not to fit specifications and will be excluded from further processing and discarded.

Quality Control

In Germany, blood components are defined as a medical drug and are therefore regulated by the "German Drug Act, (AMG)" and by many other regulations and guidelines. These regulations focus on the highest safety and quality of blood components.

To verify and achieve a high quality of manufactured blood components, quality controls are conducted regularly on 1 % of manufactured products. Sterility controls are conducted on 0.4 x n of the products, in which "n"

represents the number of products manufactured in one month. Products that are submitted to quality controls are randomly assigned from the routine process by quality control department staff. Special blood components, such as haematopoietic stem cells, granulocyte concentrates and bone marrow preparations, will be analysed in 100 % of cases.

The quality control data are collected in different statistical formats and analysed with regard to the statistical values, such as mean values, standard deviations, coefficient of variations and the minimal and maximal counts. In addition, trending analyses are performed to show the distribution of the values within individual groups. The scaling within the trend analysis is chosen to provide a narrower scaling within the specifi-

Special blood products provided

Special blood products
Red cell concentrates (irradiated)
Red cell concentrates (split products)
Concentrates prepared for exchange transfusions
Red cell concentrates (washed)
Red cell concentrates (cryo-preserved)
Red cell concentrates (derived from apheresis)
Apheresis platelet concentrates (irradiated)
Buffy-coat derived pool platelet concentrates (irradiated)
Platelet concentrates (both, apheresis or pooled with reduced volume)
Fresh Frozen Plasma (split products)

Table 2

Platelet numbers in buffy-coat derived pool platelet concentrates in 2009

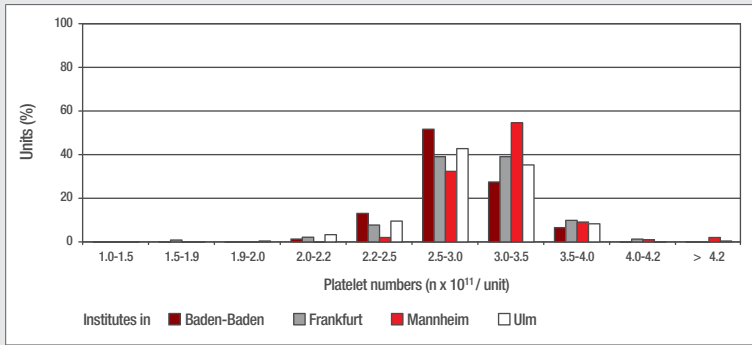
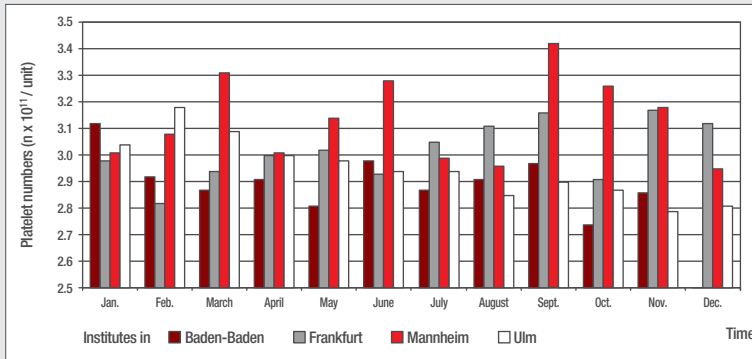


Figure 9 A and 9 B

Quality control data of pool platelet concentrates in 2009 – comparison of products manufactured in four different institutes

Platelet numbers in buffy-coat derived pool platelet concentrates in 2009 – Long term observation over 12 months

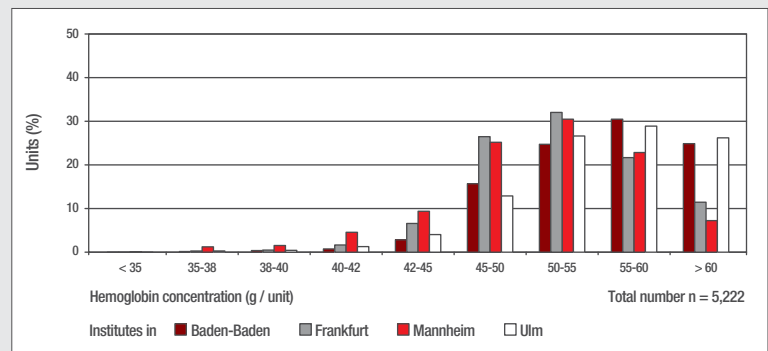


facturing processes and working procedures. The evaluation of the working processes in the blood collection unit and/or the manufacturing department will usually allow for the identification of factors that cause differences in the collected data. By improving and harmonising the work processes, it is feasible to obtain comparable quality standards.

cations and a broader scaling for numbers that are out of the range of acceptable specification values. The narrower scaling for results that meet the specifications allows for a more detailed evaluation of the parameters that are within the critical area, as well of those that do not meet the norm.

The trending analysis will be performed within the individual headquarter institution, between the different institutions, and between the different federal states of the network. A direct comparison of the quality control data (benchmarking) will possibly uncover different manu-

Hemoglobin concentration in red cell concentrates in 2005, comparison of the products produced in four different institutes



Hemoglobin concentration in red cell concentrates in 2007, comparison of the products produced in four different institutes

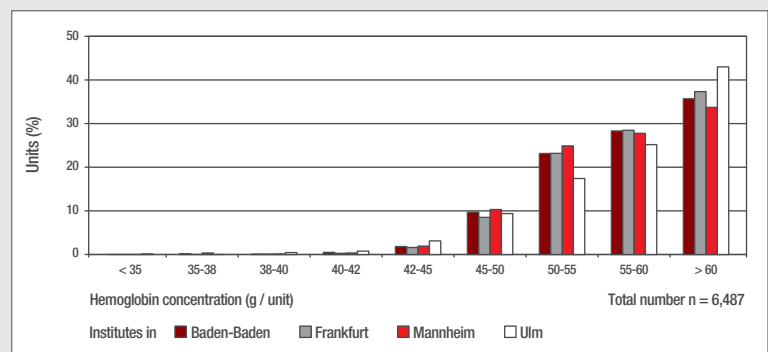


Figure 10 A and 10 B

Development of haemoglobin concentration in red cell concentrates between 2005 and 2007 – comparison of products manufactured in four different institutes

Table 3

Blood donor screening is done by mini-pool NAT (MP-NAT) with a maximum pool size of 96 samples per pool. Confirmatory testing is done by individual donation NAT (ID-NAT). The 95% level of detection of the ID-NAT system fulfil the criteria of the advisory board blood (votum 34) with an analytical sensitivity of at least 12 IU/ml, 50 IU/ml and 100 IU/ml for HBV, HCV and HIV-1, respectively

Blood donor screening and confirmatory tests (mini-pool NAT (MP-NAT) was performed with a maximum pool size of 96 samples per pool).

Parameter	Screening of blood donations		Confirmatory testing	
	Method	System	Method	System
HCV	Antibody	MP-NAT	Immunoblot	ID-NAT
HIV	Antibody	MP-NAT	Immunoblot	ID-NAT
HBV	Antigen / Antibody	MP-NAT	Neutralization-assay	ID-NAT
Lues	TPHA	-	Immunoblot	-
HAV	-	MP-NAT	-	ID-NAT
Parvo B19	-	MP-NAT	-	ID-NAT
CMV (optional)	Antibody	-	-	-

Blood donor screening

Blood safety is one of the highest priorities of our Blood Transfusion Service. The prevention of transfusion-associated adverse reactions is a major challenge in transfusion medicine. In addition to blood typing (including ABO, Kell, Rh antigen testing (complete formula)) and irregular anti-erythrocyte antibody screening, all donations are screened for antibodies and antigens for transfusion-relevant pathogens.

The Institute of Transfusion Medicine and Immunhaematology in Frankfurt am Main, up to our knowledge, was one of the first or may be even the first institute for blood transfusion services in the world that developed its own in-house NAT method using a minipool system and at the same time volunteered to release all blood components including red cell concentrates, Fresh Frozen Plasma (FFP) and platelet concentrates based on negative results in both ELISA and PCR tests for HIV, HBV and HCV.

Figure 11 demonstrates the proportion of initially reactive, repeat reactive and confirmed positive donations out of about 1,500,000 blood donations. The data demonstrate that a high percentage of initially reactive results were non-specific and cannot be confirmed by additional screening tests. The highest specificity is shown for hepatitis B virus screening tests.

Based on all blood donor screening tests for the blood transfusion service of Baden-Württemberg - Hestia, East and North, the prevalence of HIV, HCV and HBV was 5/100,000 donors, 71/100,000 donors and 153/100,000 donors in first time donors, respectively. The incidence (seroconversion rate) for repeat-donors was 0.92/100,000 donors, 0.77/100,000 donors and 0/100,000

Results of blood donor screening in 2007 and 2008

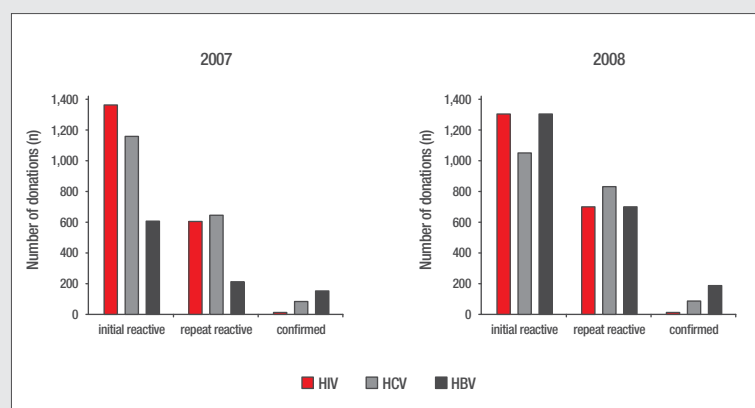


Figure 11

Initial, repeat and confirmed reactive blood donations between 2007 and 2008

donors for HIV, HCV and HBV, respectively.

Experience in NAT for more than 10 years

In 1995, under the guidance of the Medical Director, our Institute in Frankfurt am Main started discussions with relevant industries to develop a nucleic acid technology (NAT) system for blood donor screening in a blood bank setting. In 1996, we established a “PCR-Team”, including our own experienced transfusionists from the Blood Service team and several additional scientists, as well as technicians from different areas of research and an IT specialist from a small company, followed later by an engineer.

In the meantime, the Frankfurt Institute has used this method, which was established in this institute and transferred it to other Blood Transfusion Services to test more than 10 million blood donations for and in several German Red Cross Blood Services including those of Nordrhein-Westfalen, Rheinland-Pfalz and Saarland (DRK-BSD West), for Bavaria (BRK-BSD), Thüringen (now DRK-BSD NSTOB), Baden-Württemberg, Hessa, for Schleswig-Holstein and Hamburg (DRK BSD Nord),

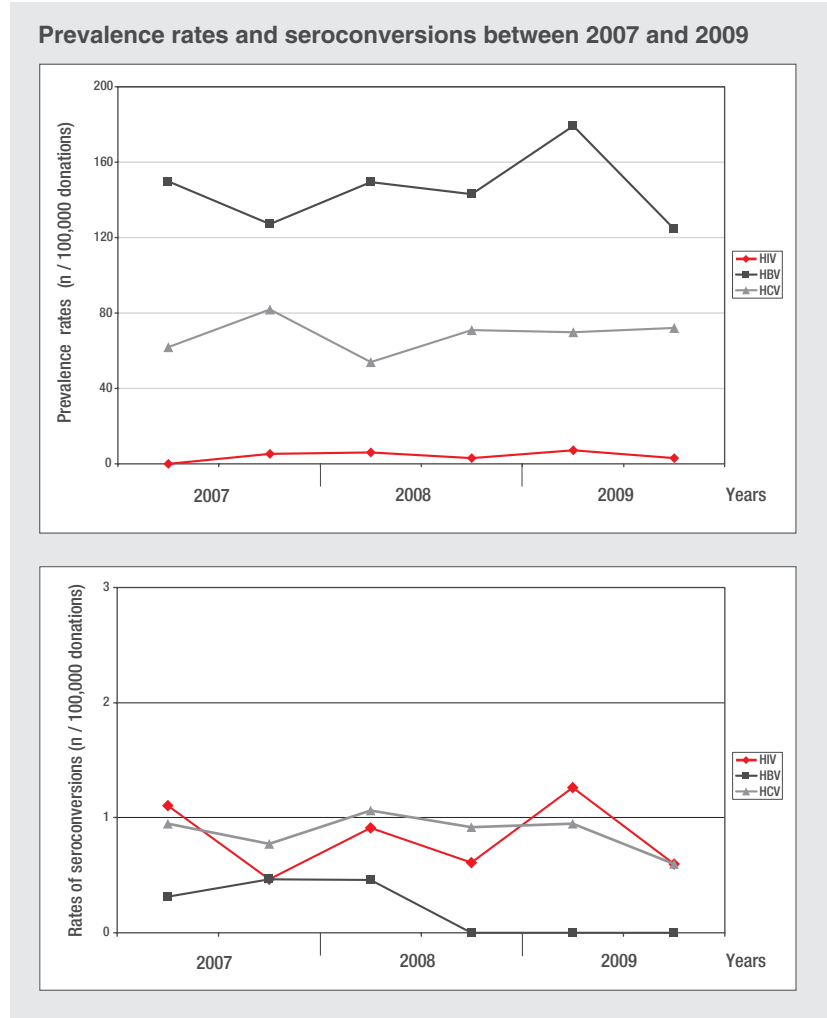


Figure 12 A and 12 B

for Saxonia, Brandenburg and Berlin (DRK-BSD Ost). At the same time, blood donations from Austria, Luxembourg and the German Military Forces Blood Services have been tested.

We developed an “in-house” NAT system that is used to screen donated blood in mini-pools that include up to 96 samples per pool to improve blood safety and to close the diagnostic gap for transfusion-transmitted virus infections, especially in the

early diagnostic window. The mini-pool NAT was introduced at the beginning of 1997 on a voluntary basis and donated blood was tested for HBV, HCV, and HIV-1. The testing was extended to include HAV and parvovirus B19 in 2000. In our Blood Transfusion Service, over a 10 year time period, 9, 10, and 3 NAT-only positive samples were detected during the early infectious window period for HBV, HCV, and HIV-1, respectively (**Table 4**).

Transfusion transmitted infections prevented by NAT

Yield NAT Testing				
	Total number of blood donations between 1999-2007	HBV: NAT only positive blood donations between 1999-2007	HCV: NAT only positive blood donations between 1999-2007	HIV: NAT only positive blood donations between 1999-2007
Hessia	2,381,980	2	2	2
Baden-Württemberg	4,394,857	2	3	0
East	4,145,033	5	4	1
North	1,364,544	0	1	0
TOTAL	12,286,414	9	10	3

Table 4

Four out of nine NAT only positive HBV donations were confirmed later on by anti-HBc

By introducing mini-pool NAT into the blood donor screening process, the diagnostic window periods for HCV, HIV-1, and HBV were reduced from approximately 18 days (HIV 1/2 combo assay) to 10 days, from 55 days (anti-HCV tests) to 8 days, and from 32 days (HBsAg tests) to 20 days, respectively. Hourfar et al. calculated the residual transfusion transmitted infection (TTI) risk ba-

sed on more than 31 million tests at the German Red Cross blood transfusion services. According to a mathematical model, **the residual risk is 1:10.88 million, 1:4.3 million, and 1:360,000 for HCV, HIV-1, and HBV, respectively.**

Although this amounts to essentially a 0 % risk of acquiring HCV or HIV-1 from a blood product transfu-

sion, patients are still afraid of contracting a viral infection from blood transfusions. The “in-house” mini-pool nucleic amplification technology (MP-NAT) was CE-certified in 2006. In 2008, the manual NAT system was transferred to an **automated barcode-controlled robotic system named “Zelos x100”** that allows one technician to analyse up to 12,000 samples in a one-day shift (**Figure 13**). To our knowledge, the Zelos x100 NAT robotic system is currently the only automated CE-certified system in use anywhere in the world that enables blood donor screening for six transfusion-relevant viruses (HAV, HBV, HCV, HIV-1, HIV-2 and B19) to be performed in mini-pools that include up to 96 samples per pool in a single extraction process with appropriate sensitivity and specificity.

The analytical sensitivity of the Zelos x100 NAT system is comparable to that of other commercial NAT systems, such as the Roche MPX test (which is performed on an s201

A) Zelos x100



B) Head for ID-NAT extractions with 96 staves

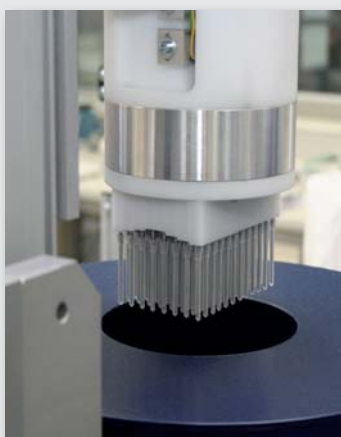


Figure 13

(A)
Automated barcode controlled German Red Cross NAT system on the Zelos x100 platform. Extraction of 22 mini-pools (2,112 donations) including two control pools will be done within 90 min. Initial NAT positive mini-pools can be dissolved by changing the extraction head. Therefore, up to 12,000 blood donations can be analyzed by one technician within one day-shift.

(B)
Extraction head with 12 staves can be replaced by an extraction head with 96 staves. All 96 single extractions for ID-NAT detection will be done within one hour.

platform) or the Novartis Diagnostics Tigris Ultrio Plus.

Nevertheless, viral genomes change over time due to transcriptional failure of the reverse transcriptase. To overcome this challenge, our blood transfusion service is in the process of developing an NAT screening test that involves parallel amplification of two conserved genomic regions.

Fortunately, we have been able to demonstrate that the NAT screening system can be modified to detect these emerging transfusion-relevant pathogens within a short time period (~1 month). The Baden-Württemberg - Hestia blood transfusion service has prepared an additional screening system for new pathogens, including SARS corona virus, West Nile virus, and influenza virus, that can be implemented into blood screening protocols without delay, if necessary. This demonstrates the capacity, flexibility and utility of this type of molecular testing system. Using the Frankfurt Red Cross "in-house method" for one decade, we did not observe a single breakthrough infection by HIV-1, HBV or HCV.

Diagnosics

All of our institutes also deliver the whole range of blood group typing,

immunohaematology, transplantation immunology and molecular medicine laboratory methods for the cooperating university hospitals and many other hospitals in our service area.

As an example, **Table 5** presents the number of immunohaematological analyses performed in patients prior to transfusion. At some of the institutes, expert laboratories have been established that provide the whole range of laboratory tests in platelet immunology (antibodies, human platelet antigen genotyping), molecular haemostaseology and the diagnosis of congenital defects of the immune system and haemopoiesis. More details on the spectrum of diagnostic tests and research and development activities in these fields are presented on page **35** in this issue.

Several institutes perform HLA typing with a broad range of methods ranging from classical serology to sequenced-based typing approaches, HLA antibody testing, and analysis of other polymorphisms that are potentially relevant for transplantation. These institutes have also established stem cell donor centres and cooperate with the German bone marrow donor registry (Zentrales Knochenmarkspender-Register Deutschland (ZKRD), a 100 % affiliate of our Blood Transfusion Ser-

Data of diagnostic laboratory – pre-transfusion testing

Pre-transfusion testing 2009	n
Crossmatching test	534,594
Antibody detection test	255,689
Antibody identification	55,884
Blood grouping (confirmatory test)	194,890
Blood grouping (ABO, RhD)	111,005
Direct antiglobulin test	101,869

Table 5

vice located in Ulm) and the German Foundation for Organ Transplantation (Deutsche Stiftung Organtransplantation (DSO)). All HLA laboratories are accredited by the EFI.

A detailed report on the development of the German Stem Cell Donor Registry (Deutsche Stammzellspenderdatei (DSSD), a joint donor registry of our blood service) and the laboratory methods in transplantation immunology are presented on page **77** in this issue.

All services that are critical in terms of time for optimal patient care are available on a 24 hours a day, 7 days a week basis.