

The Frequency of Transfusion Related Sepsis Imputed to Platelet Components: Impact of Pathogen Inactivation

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Background

Transfusion related sepsis (TRS) is a serious and highly relevant adverse outcome that may result from transfusion of platelet components (PC). The frequency of TRS is poorly characterized due to under recognition by primary care physicians (Jacobs, Good et al. 2008). In contrast, recent studies have documented that the initial prevalence and the residual risk of bacterial contamination of PC, despite preparation with optimal methods to limit or detect bacterial contamination, ranges from 1/213 to 1/1567 PC respectively (Pearce, Rowe et al. 2010). Preparation of PC with pathogen inactivation (PI) (INTERCEPT™, Cerus, Amersfoort, Netherlands, **Figures 1 A & B**) provides robust inactivation of contaminating bacteria, and offers the potential to prevent TRS (**Table 1**).

Figure 1A: INTERCEPT Mechanism of Action

The INTERCEPT Blood System uses a combination of amotosalen HCl and long wavelength ultraviolet A (UVA) light. The amotosalen compound penetrates cellular and nuclear membranes and intercalates into the helical regions of DNA and RNA. Covalent crosslinks to the nucleic acid base pairs form upon exposure to UVA light, blocking DNA and RNA replication. This process inactivates leukocytes and pathogens, rendering them unable to cause disease, while retaining the function of plasma/platelets, which do not require nucleic acid replication for therapeutic efficacy.

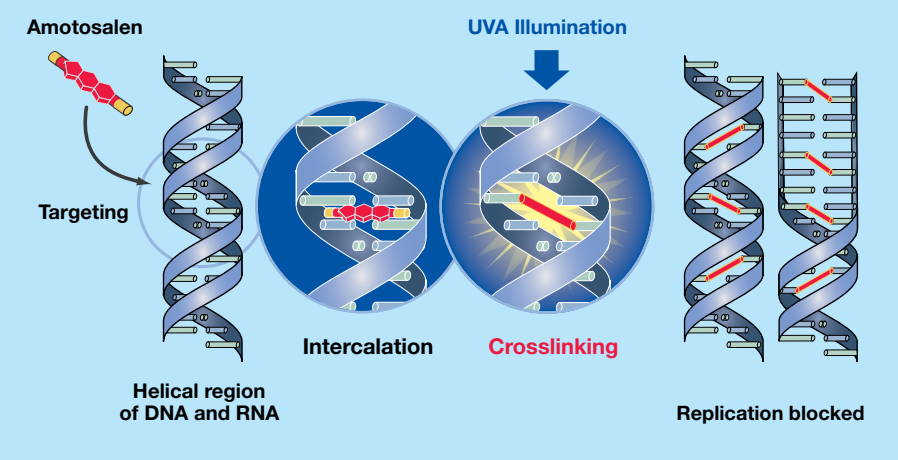


Figure 1B: The INTERCEPT Blood System for Platelets

Using a sterile connecting device (SCD), the platelet container is sterilyly connected to the INTERCEPT kit. Amotosalen (1) is added by gravity flow and the platelet mixture is illuminated with UVA light (2). Residual amotosalen and its photoproducts in the platelet mixture are reduced to low levels using a compound adsorption device (CAD) (3) before the platelets are transferred to the storage container.

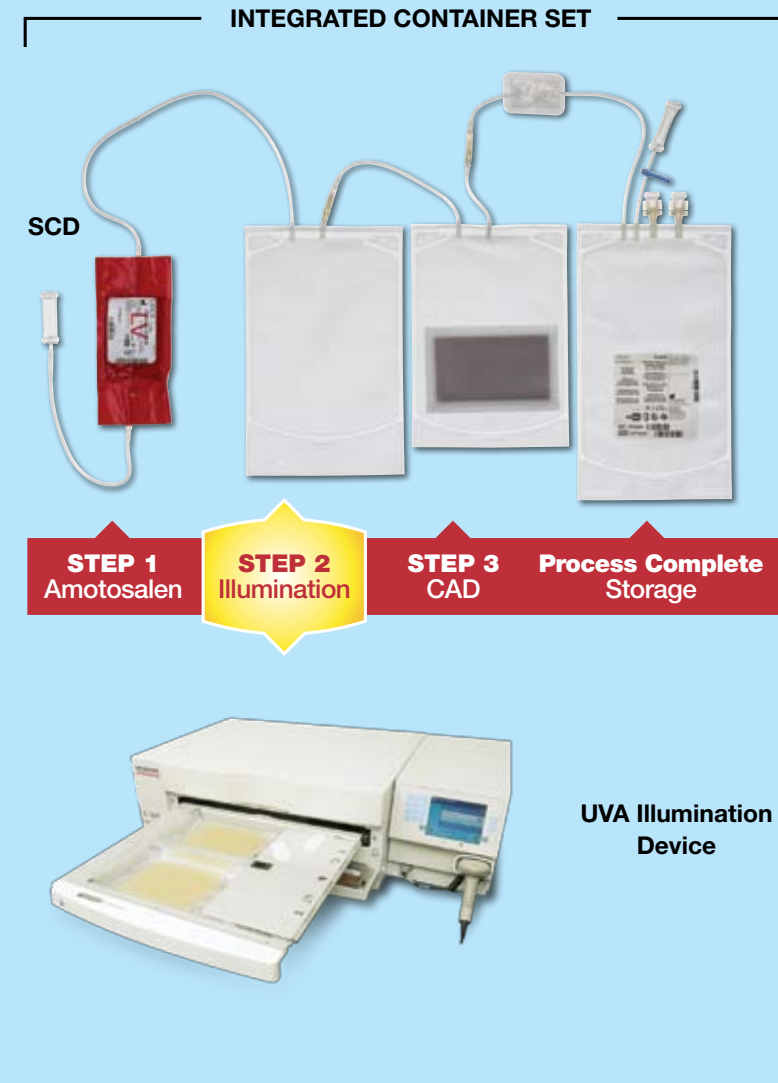


Table 1: Pathogens Inactivated by the INTERCEPT Process

Pathogens routinely tested for are indicated in **rose color**. Emerging pathogens not tested for are indicated in **red color**. **Green** indicates prevalent pathogens for which testing or other measures are used variably.

Enveloped Virus	Bactéria: Gram-négative	Spirochètes
HIV-1 (free,cell)	<i>Klebsiella pneumoniae</i>	<i>Treponema pallidum</i>
HIV-2	<i>Yersinia enterocolitica</i>	<i>Borrelia burgdorferi</i>
HBV	<i>Escherichia coli</i>	
DHBV	<i>Pseudomonas aeruginosa</i>	Protozoa
HCV	<i>Salmonella choleraesuis</i>	<i>Trypanosoma cruzi</i>
BVDV	<i>Enterobacter cloacae</i>	<i>Plasmodium falciparum</i>
HTLV-I (cell)	<i>Serratia marcescens</i>	<i>Leishmania mexicana</i>
HTLV-II (cell)		<i>Leishmania major</i>
HCMV (cell)/EBV/HHV-8	Bactéria: Gram-positive	<i>Babesia microti</i>
WNV	<i>Staphylococcus epidermidis</i>	
SARS	<i>Staphylococcus aureus</i>	Leucocytes
Vaccinia	<i>Streptococcus pyogenes</i>	<i>T lymphocytes, cytokines</i>
Chikungunya	<i>Listeria monocytogenes</i>	
Dengue	<i>Corynebacterium minutissimum</i>	Bacterial spores resistant
Influenza virus (H1N1)	<i>Bacillus cereus (vegetative)</i>	
Avian flu virus (H5N1)	<i>Lactobacillus sp.</i>	
XMRV	<i>Bifidobacterium adolescentis</i>	Prions resistant
	<i>Propionibacterium acnes</i>	
	<i>Clostridium perfringens</i>	
Non-enveloped Virus	Rickettsiae	
Bluetongue virus, type 11	<i>Orientalis tsutsugamushi</i>	
Simian Adenovirus-15		
Feline calicivirus		
Parvovirus B19		
Human adenovirus 5		
Calicivirus (HEV)		

Aims

Following implementation of universal PI of PC in Alsace, EFS Alsace compared the reported frequency of TRS for Alsace with that of EFS centers not using PI of PC. TRS frequency was determined from data collected by the active hemovigilance Afssaps program – eFIT.

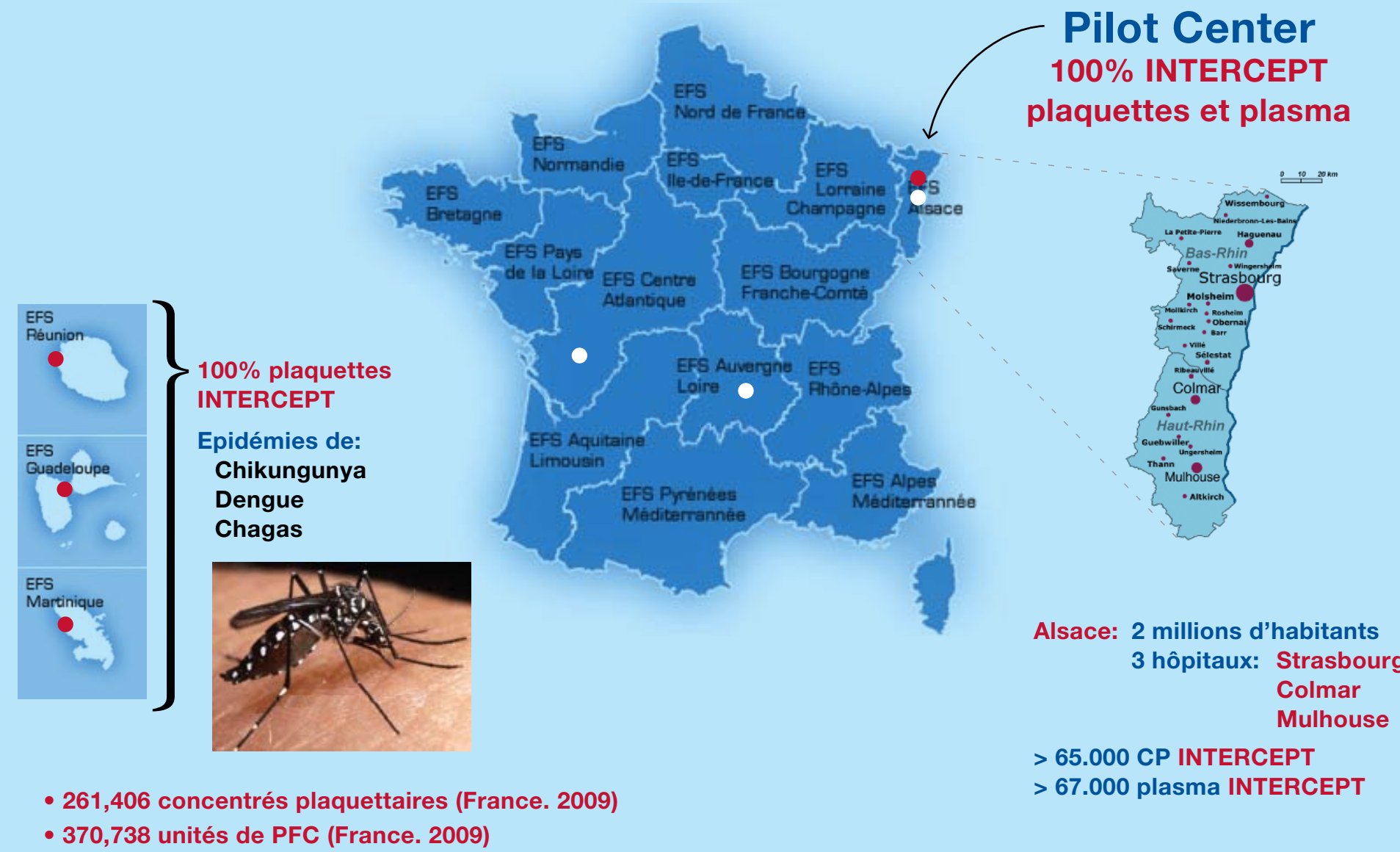
Methods

Starting in September 2006, EFS Alsace implemented universal PI of PC to support the transfusion requirements of 2 million inhabitants of the Alsace Department (**Figure 2**). In addition, the overseas blood centers including: EFS La Reunion, EFS Guadeloupe, and EFS Martinique initiated PI of PC to deal with epidemics of Dengue and Chikungunya virus and limit the risk of *Trypanosoma cruzi* infection (**Figure 2**). Platelet and plasma components are prepared from whole blood and apheresis collections using conventional platforms. The INTERCEPT process for platelet and plasma components is conducted on a common platform in a dedicated space for component preparation (**Figure 3**) according to the same production schedule as previously used for conventional components (**Figure 4**).

The frequency of TRS per 10,000 PC for PC prepared with conventional methods was determined from the Afssaps Rapport Hemovigilance Annuel for the years 2006, 2007, 2008, and 2009. The frequency of TRS for EFS Alsace was determined after implementation of PI (9.2006 through 9.2010) from hemovigilance records of EFS Alsace as part of the Afssaps eFit database. TRS cases with imputability of Grade 2 or higher were included in the analysis.

Figure 2: Regions in France Using INTERCEPT Platelet and Plasma Components

INTERCEPT platelets are produced in the following regions: Alsace and the overseas departments of La Reunion, Guadeloupe, and Martinique. INTERCEPT plasma components (white dots) are produced by EFS Alsace, EFS Auvergne Loire, and EFS Centre Atlantique. In 2009, EFS produced 261,406 platelet components and 370,738 plasma components. From implementation of INTERCEPT, EFS Alsace has produced more than 65,000 INTERCEPT platelet components and 67,000 INTERCEPT plasma components.



Results

During the years 2006 through 2009 the annual issuance of PC by EFS has increased. The number of TRS cases reported each year has increased from 2006 through 2009, but the frequency has been relatively stable for 3 years (**Table 2**). During the period from 9.2006 through 9.2010, 67,571 PC were issued by EFS Alsace. No cases of TRS were reported. In addition to surveillance of the response to transfusion of PC to detect TRS, EFS Alsace cultures all expired PC. From 2006 to 2010, 260 PC prepared with PI were tested with aerobic and anaerobic bacteria cultures for 48 hours, and 250 were cultured for 10 days. No positive cultures were detected.

Table 2: The Frequency of TRS Associated With Transfusion of Conventional and PI Platelet Components

The number of components transfused in regions not using INTERCEPT and the number of reported cases of TRS were summarized from Afssaps annual reports. The number of PC treated with INTERCEPT in Alsace were derived from the records of EFS Alsace.

Year	Conventional PC			Pathogen Inactivated PC		
	PC Issued	TRS	TRS per 10 ⁴ PC	PC Issued	TRS	TRS per 10 ⁴ PC
2006	231,853	4	0.17	6,420	0	0
2007	245,326	8	0.32	15,393	0	0
2008	252,887	9	0.35	15,544	0	0
2009	261,406	10	0.38	17,550	0	0
2010 ¹	NA	NA	NA	12,664	0	0
Total	991,472	31	0.31	67,571	0	0

1. Nine months data were used for 2010.

Figure 3: Organization of Production of INTERCEPT Components

Dedicated space is used for the production of INTERCEPT platelet and plasma components. Approximately 17,000 INTERCEPT Components are prepared in this facility each year.

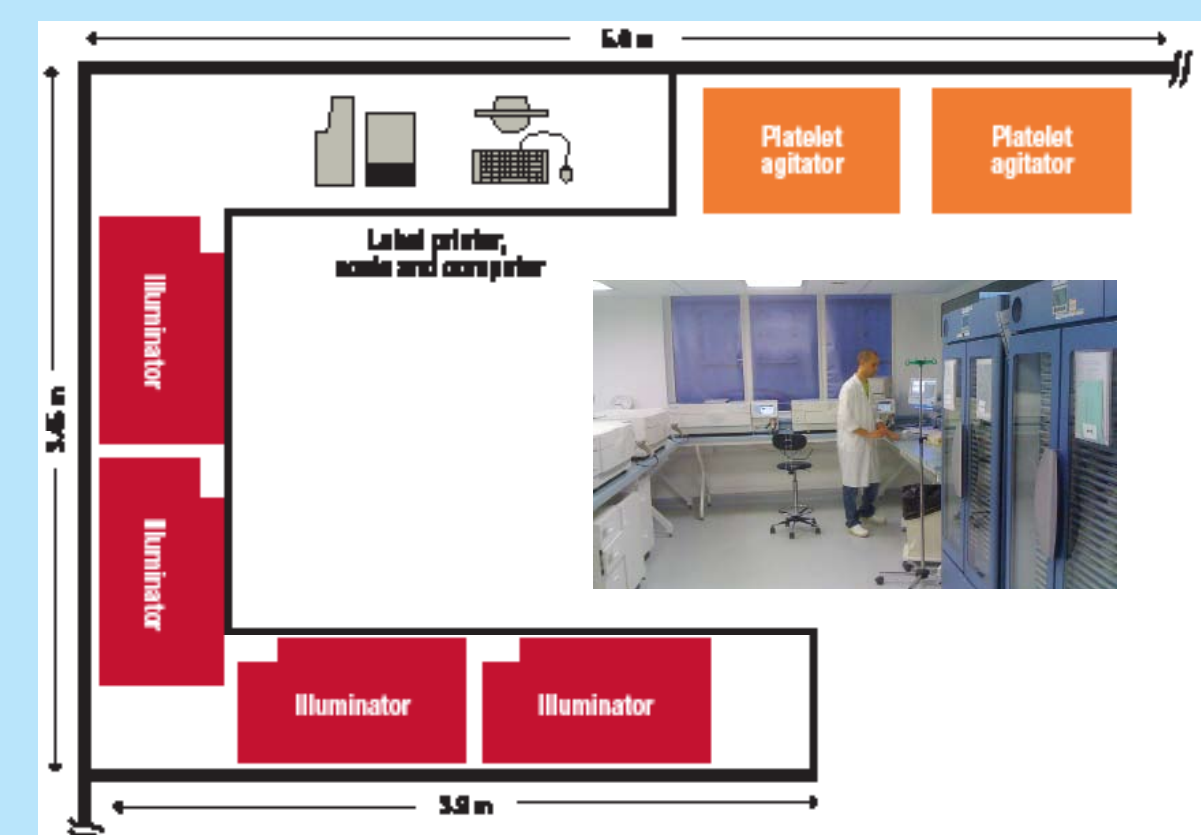
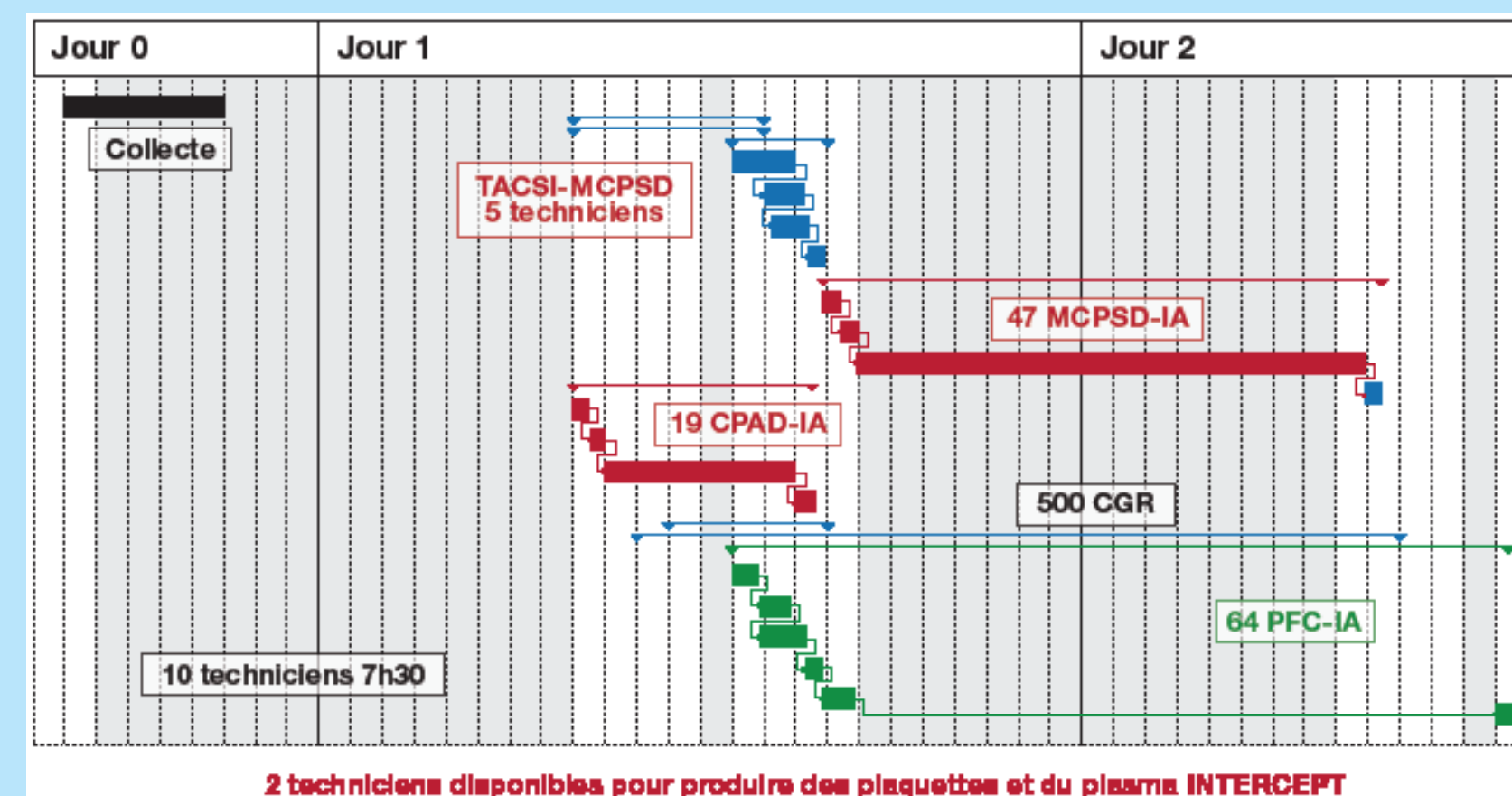


Figure 4: Schedule for the Preparation and Release of Platelet Components

Typical daily production schedule for blood components by EFS Alsace. The day following collection of 500 whole blood units (Jour 1), 47 whole blood derived buffy coat pools (MCPSPD-IA) are prepared and treated with INTERCEPT (IA). The MCPSPD-IA are released on Day 2. 19 platelet apheresis collections are collected and are ready for release at the end of Day 1. 64 plasma components (650 mL) each, collected by apheresis, are treated with INTERCEPT and divided into 200 mL units frozen within eight hours of collection. Two technicians are required for the INTERCEPT treatment of platelet and plasma components. PFC = Fresh Frozen Plasma. CGR = Red Blood Cells.



Conclusions

Implementation of PI treatment of PC appears to have reduced the frequency of TRS in the Alsace Department compared to other regions not using PI technology.

References

- Jacobs, M. R., C. E. Good, et al. (2008). "Relationship between bacterial load, species, virulence, and transfusion reaction with transfusion of bacterially contaminated platelets." *Clinical Infectious Diseases* 46: 1214-20.
- Pearce, S., G. P. Rowe, et al. (2010). "Screening of platelets for bacterial contamination at the Welsh Blood Service." *Transfusion Medicine*.