Pathogen reduction of blood components during outbreaks of infectious diseases in the European Union: an expert opinion from the European Centre for Disease Prevention and Control consultation meeting

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Abstract

Pathogen reduction (PR) of selected blood components is a technology that has been adopted in practice in various ways. Although they offer great advantages in improving the safety of the blood supply, these technologies have limitations which hinder their broader use, e.g. increased costs. In this context, the European Centre for Disease Prevention and Control (ECDC), in co-operation with the Italian National Blood Centre, organised an expert consultation meeting to discuss the potential role of pathogen reduction technologies (PRT) as a blood safety intervention during outbreaks of infectious diseases for which (in most cases) laboratory screening of blood donations is not available. The meeting brought together 26 experts and representatives of national competent authorities for blood from thirteen European Union and European Economic Area (EU/EEA) Member States (MS), Switzerland, the World Health Organization, the European Directorate for the Quality of Medicines and Health Care of the Council of Europe, the US Food and Drug Administration, and the ECDC. During the meeting, the current use of PRTs in the EU/EEA MS and Switzerland was verified, with particular reference to emerging infectious diseases (see Appendix). In this article, we also present expert discussions and a common view on the potential use of PRT as a part of both preparedness and response to threats posed to blood safety by outbreaks of infectious disease.

Keywords: pathogen reduction technologies, blood safety, infectious diseases outbreaks, blood components.

Introduction

In countries where microbial safety strategies are applied to the blood supply, the risk of transfusion-transmitted infections (TTIs) is very low. Such strategies can largely, but not completely, prevent infectious blood from entering the blood supply. Despite the relatively rare occurrence of TTIs, the microbial safety of transfusion continues to arouse substantial medical, public and political interest. Blood safety is continuously challenged by the residual risk from existing blood-borne infections and the threat from newly emergent pathogens.

Emerging infectious threats to blood safety in Europe

In recent decades, all over the world there have been outbreaks and the spread of emerging and re-emerging infectious diseases (EID). Considering existing changes in the epidemiology of communicable diseases[1], the increase in international travel and trade, the projected increase in climate-driven risk of infection transmission from *Aedes aegypti* and *Aedes albopictus* in Europe[2], and the geographical spread of arthropod-vectors[3,4], the European Union and European Economic Area (EU/EEA) countries may be at increased risk of EID outbreaks which can endanger the microbial safety of blood transfusion[5]. Driven by the convergence of EID drivers and ignited by imported cases, arthropod-borne diseases such as dengue, chikungunya, West Nile virus (WNV) infection and malaria have emerged and/or re-emerged in Europe showing an increase in local, sporadic outbreaks (Table I)[6-9]. There is a risk that other arthropod-borne pathogens, such as the Zika virus (ZIKV), could also be introduced into continental Europe. Pathogen strains with increased virulence have also appeared, such as the neuroinvasive WNV lineage 2 which was introduced to Hungary in 2004, although WNV lineage 1 had been detected in Europe as far back as 1958[10-12]. Since 1996, Usutu virus has been widespread among birds throughout Europe[13,14] causing rare sporadic infections in humans[15]. Locally acquired hepatitis E cases, caused by genotype 3 virus, predominantly originating from pigs, have been observed at different rates across Europe[16-18].

Table I - Local transmissions of arthropod-borne diseases in continental EU/EEA Member States in the period 2005-2017 reported to ECDC[6-9].

Year	Disease			
	dengue	*malaria*	*chikungunya*	*West Nile fever*
2005	-	-	-	+
2006	-	-	-	+
2007	-	-	+	+
2008	-	-	-	+
2009	-	+	-	+
2010	+	+	+	+
2011	-	+	-	+
2012	+*	+	-	+
2013	+	+	-	+
2014	+	-	+	+
2015	+	+	-	+
2016	-	+	-	+
2017	-	+	+	+

+: reported cases of local transmission in at least one area of the continental EU Member States; -: no cases reported; *Madeira outbreak.

Microbial safety of the blood supply

In addition to commonly known blood-borne infections, emerging pathogens with a blood phase are potentially transmissible through transfusion and may present challenges to the safety of the blood supply[5]. The prevention of TTIs is primarily based on the exclusion of donors at risk of being infected and, where possible, laboratory screening of donations. Due to the increasing frequency and diversity of EID outbreaks, the traditional response of additional blood donation screening tests and deferring more donors is limited by concerns of cost-effectiveness and feasibility. This reactive approach calls for a re-evaluation of current practices. There are not only quantitative limits to screening and deferring, but also conceptual challenges. These so-called "new pathogens", may disseminate widely through transfusion before being recognised and before a screening test can be developed and implemented. In the US, although the WNV epidemic had started in 1999, that the virus could be transmitted through transfusion was only recognised in 2002[19], and a nucleic acid test (NAT) for blood donation screening was approved under the FDA's Investigational New Drug Application (IND) regulations in 2003[20]. The "diagnostic window" is another critical period when pathogens can go undetected[21]. Furthermore, despite the widespread practice of bacterial contamination prevention and detection techniques applied by blood banks, septicaemia remains the most prevalent complication of blood transfusion. In these situations, PR of blood and blood components is an intervention that may mitigate the risk posed by emerging and other pathogens to the blood supply.

Pathogen reduction technologies

Pathogen reduction technologies (PRT) refer to procedures that irreversibly impede the proliferation of a number of pathogens, either by removal or inactivation with physical and/or chemical methods[22]. Two approaches to PR of blood components are currently available (Table II): 1) the solvent/detergent (S/D) treatment of plasma which inactivates lipid-enveloped viruses by destroying lipids; and 2) methods based on nucleic acid damage, which have been applied in the PR of plasma, platelets (PLTs), whole blood (WB), and red blood cells (RBC). By targeting nucleic acids, PRTs using the second approach also prevent replication of residual leukocytes and block ribonucleic acids in PLTs.

The S/D treatment of plasma involves adding trinitrobutyl phosphate and Triton X-100 to pooled fresh frozen plasma and the removal of residual reagents through both oil extraction and reverse-phase chromatography[23].

The Intercept® system (Cerus Europe B.V.; Amsterdam, The Netherlands) for PR of plasma and

Table II - Methods for pathogen reduction in blood components.

Functional target	Method	Blood component	Usage
Lipids	Solvent and detergent treatment	Plasma	+
Nucleic acids	*Photochemical treatment*		
	Amotosalen + UVA light (Intercept®)	Plasma, platelets	+,+
	Riboflavin + UVA/B light (Mirasol®)	Plasma, platelets, whole blood*	+, +, -
	Methylene-blue + visible light (Theraflex MB®)	Plasma	+
	Photo treatment		
	UVC light (Theraflex®)	Platelets	-
	Chemical treatment		
	Amustaline (S-303) and glutathione (Intercept RBC®)	Red blood cells*	-

*methods under investigation, UV A: ultraviolet light wavelength 315-400 nm; UVB: ultraviolet light wavelength 280-315 nm; UVC: ultraviolet light wavelength 100-280 nm.

PLTs uses a treatment of components with amotosalen (furanocoumarin) that can intercalate in helical regions of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)[24]. Upon photoexcitation with UVA light, amotosalen can form covalent mono-adducts with thymidine bases[25]. The unbound photosensitiser is adsorbed in the final step of the procedure. These chemical modifications efficiently inhibit subsequent DNA or RNA (reverse) transcription, thereby preventing replication of many pathogens and leukocytes[26]. Intercept® PR of RBCs using a reactive small molecule (amustaline, S-303) and glutathione (GSH) is under development[27]. The Mirasol® system (Terumo BCT Europe NV, Zaventem, Belgium) uses riboflavin (vitamin B2) and UVA/B light for PR of plasma, PLTs and, potentially, WB. Guanine bases in nucleic acids may accept electrons directly from photosensitised riboflavin, but in the presence of dissolved molecular oxygen, the reaction shifts towards substantive reactive oxygen species (ROS) formation[28]. ROS seriously damage nucleic acids and efficiently prevent replication and proliferation of many pathogens[29] and leukocytes. Riboflavin is a vitamin and is, therefore, considered safe for injection and an adsorption procedure is not performed. The Theraflex® system (Macopharma, Tourcoing, France) employs a one-step illumination with UVC light in order to reduce pathogens in PLTs. The biochemical mechanism of nucleic acid damage by UVC involves the generation of pyrimidine dimers which prevent replication of the genetic material and effectively inactivate pathogen proliferation[30,31]. The THERAFLEX-MB plasma system uses methylene blue (MB) and visible light to reduce pathogens in single donor units of plasma. It uses a 0.65 µm membrane filter which removes residual leukocytes, RBCs, PLTs and aggregates. After treatment, residual MB combined with its photo products are removed by a special filter[32].

Depending on the PRT method applied, variable levels of *in vitro* reduction have been observed for bacteria, parasites and enveloped viruses[33-65]. Clinical studies and haemovigilance data have shown that such levels of reduction may significantly decrease the transmission of disease through transfusion[66,67]. In many cases, however, the level of reduction does not correlate well with the extent to which infectivity is reduced[68,69]. Sporadic break-through events may be expected when pathogen loads exceed the inactivation capacity of the applied method[35]. Studies to determine which levels of pathogen reduction will significantly reduce the probability of disease transmission are essential to fully determine just how effective PRT methods really are. Moreover, non-enveloped viruses[70], spores[71] and prions are resistant to PR. The main benefit of PRT is the reduction of pathogen load in blood donations:

i) from infected individuals exhibiting no clinical symptoms or having a prolonged diagnostic window period;
ii) which are not mandatory or systematically screened for pathogens, e.g. Dengue virus (DENV), Chikungunya virus (CHIKV), or ZIKV;
iii) where detection is hampered due to the presence of pathogens in low titre, e.g. occult hepatitis B virus (HBV)[72], dilution by sample pooling[73], and other situations including the presence of pathogen variants, the compliance failure of donors on HIV pre-exposure prophylaxis[74] or in donations from donors with low-level parasitaemia in malaria semi-immunity[75]; and/or
iv) contaminated with yet unknown emerging pathogens susceptible to PRT.

Furthermore, blood establishments may prolong the shelf-life of PR PLT components since these technologies prevent bacterial growth[76] and reduce the need to irradiate PR blood components because the proliferation of leukocytes is also impaired by PR treatment[77].

Of note, we cannot fully appreciate the benefits of PRT application until PRTs for RBCs or WB have been licensed. As of April 2019, only PR of plasma and PLTs has been approved for use in the EU/EEA MS. Although CE marked, PR of WB and RBC is awaiting regulatory approval[78-80] (Table II). PRTs also have several limitations in terms of their efficacy[69], possible toxicity[25,28,81], probable overall reduction in component quality[82], and increased costs[83-93]. The pathogen reduction efficacy of these technologies may be limited because of: 1) large pathogen loads; 2) resistant forms of infectious agents; 3) inaccessibility of pathogens

due to bag design; 4) poor light energy delivery due to interfering substances; or 5) potential human error during blood processing[94]. Mechanisms of PR-induced biomolecular changes on PLT function and haemostasis are not well understood but remain under investigation. Photo-excited amotosalen reacts also with nucleic acids and membrane lipids of PLTs that may have an impact on PLT function[31,95,96]. Following PR using riboflavin, ROS may modify proteins including labile proteins like FVIII and PLT metabolism increases leading to increased lactic acid production rates[31,97,98]. UVC treatment impacts integrin PLT structure and metabolism[31,99]. A recent Cochrane review systematically evaluated 12 randomised controlled trials comparing clinical effects of Intercept® and Mirasol® PLTs to standard PLT transfusions in predominantly haematological patients[100]. The review found high-quality evidence that, compared to standard PLT-transfused patients, recipients of PR PLTs require a higher number of PLT transfusions due to lower 24-hour corrected count increments and have an increased risk of PLT refractoriness due to alloimmunisation. The review also found moderate-quality evidence that PR PLT transfusions do not affect all-cause mortality, the risk of clinically significant or severe bleeding, or the risk of a serious adverse event[100]. Two recent trials on haemostatic efficacy found PLTs treated with Intercept® and Mirasol® showed no inferiority to standard PLTs[101,102].

Implementation of pathogen reduction technologies in blood transfusion practice

Including PRT in the existing armamentarium of standard blood safety measures has several benefits. These technologies seem to have a broad range of activity against groups of pathogens (e.g. enveloped viruses) and potentially protect against pathogens that could escape detection by established screening tests. PRTs have been recognised as efficient in reducing bacterial contamination of PLTs and may offer protection against infectious threats from still unknown EID. Additionally, cytomegalovirus (CMV) screening strategies and gamma-irradiation of blood components could cease if all cellular blood components were treated with PRTs. Nevertheless, due to the above-mentioned limitations, PR is currently only accepted as an additional safety intervention and its use as a single line of defence is considered insufficient to fully safeguard the blood supply. Therefore, cessation of donor selection, testing and/or deferral in the current PR setting is not possible. The suitability of PRT to deal with any potential future infectious threat cannot be evaluated purely on the basis of their efficacy against known pathogens. PRT efficacy on high pathogen loads during acute or chronic stages of infections is uncertain. Although published studies support the effectiveness of PR methods in reducing the content of TT pathogens *in vitro*[55], criteria and methodologies to evaluate and compare the efficacy of PRT in reducing the infectivity of treated blood component need to be established[69,103]. Of note, cessation of donor screening may have a negative effect in causing the loss of the "sentinel" role which donor screening has in providing insights about disease incidence, asymptomatic infections and disease seroprevalence. There are also other financial limitations of PRT, and these are considered elsewhere[83-93]. Observed operational consequences of PRT include increased operational complexity, changes in production steps, potential product loss, and generation of additional risks such as leakage of plastic containers.

A continuing additional screening and deferral strategy for the microbial safety of blood components is unlikely to be sustainable in the future. Affordable, efficient PRT of all blood component types may offer opportunities for new safety strategies against known, emerging and re-emerging future threats to blood safety. Potentially, in the future, PRT may allow donor selection criteria, the requirements of a donor selection questionnaire, infectious disease screening and travel deferral to be relaxed.

Expert consultation meeting

In April 2019, the ECDC organised an expert consultation meeting at the National Institute of Health (ISS), Rome, Italy. Organised along with the Italian National Blood Centre, the meeting brought together 26 experts and representatives of national competent authorities for blood from thirteen EU Member States (MS), Switzerland, the World Health Organization, the European Directorate for the Quality of Medicines and Health Care of the Council of Europe, the US Food and Drug Administration (FDA) and the European Centre for Disease Prevention and Control (ECDC). During the meeting, experts discussed and developed a common view on the potential use of PRT as a blood safety intervention during outbreaks of EIDs and the implementation of these technologies to optimise preparedness and response to the outbreak of infectious diseases for which laboratory screening of blood donations is not available. Experts presented details of the current PRT implementation in the selected EU/EEA Member States and Switzerland or its application during infectious disease outbreaks. Data from the Member States not represented at the meeting were obtained through a survey from the national competent authorities for blood and blood components.

Pathogen reduction technologies in the EU/EEA countries and Switzerland

As of April 2019, approximately half of the EU/EEA MS, and Switzerland have introduced PR treatment of PLTs and plasma (Table III). Only two countries (6%), Belgium and Iceland, employ universal PR of both plasma and PLTs. Among other EU/EEA countries, PR of PLTs has been implemented universally in 4 of 31 MS (13%) and partially in 12 of 31 MS (39%). The extent of partial implementation of PR of PLTs varies widely, from a few per cent to 98% (in Slovenia). In 14 of 31 MS (45%), PLTs are not treated with PRT. PR of plasma is applied universally in 5 of 31 MS (16%) and partially in 9 of 31 (29%). Sixteen (52%) of the 31 MS use quarantined or standard plasma. Data on the PR of PLTs and plasma in Lichtenstein are not available. Switzerland implemented universal PR of PLTs and partial PR for plasma.

Pathogen reduction technologies during emerging infectious disease outbreaks

Pathogen reduction technologies have been applied to mitigate the risk of TT CHIKV and/or DENV in Reunion[104], the French West Indies (Martinique and Guadeloupe)[105], French Polynesia, and Italy[106], TT WNV in France, and TT ZIKV infection in the French West Indies[107] and French Polynesia[108]. In areas with outbreaks caused by pathogens for which screening tests were not available, WB collection was interrupted and RBCs were supplied from non-affected areas. Apheresis plasma and PLT collections continued in the affected areas provided that these were treated with PRT. A complete interruption of all donations, especially in big cities or remote islands, could jeopardise the supply of PLTs due to their short storage time. During outbreaks without interruption of blood donation, PRT allowed transfusion of platelets without awaiting NAT results. The transmission of implicated pathogens through PR platelets and/or plasma donated by the residents of an affected area has not been reported. The implementation of PRT requires time and careful operational planning, with seamless integration into the blood processing flow. Data presented at the meeting showed that the time required for planning, implementing changes and receiving approval of the PR process may take over 6 months. This does not take into account the time for scientific evaluation and validation of PRT on a local level. However, once PRT is in place, only a short lead time is required to scale up production to cover the need for PR blood components.

The use of PRT during infectious disease outbreaks has been recommended by the FDA. As an alternative to testing, the FDA recommended the use of approved PRT for PLTs and plasma to reduce the risk of ZIKV transmission by blood and blood components[109]. The EU Directive[110] defines the preventive measures that must be applied to blood donors each time they donate. The

Table III - Implementation of pathogen reduction technologies by EU Member State and Switzerland in 2018.

Country	PR of plasma (% of use)	PR of PLTs (% of use)	Country	PR of plasma (% of use)	PR of PLTs (% of use)
Belgium	u	u	Slovenia	0	p (98%)
Iceland	u	u	Croatia	0	e
France	p (10%-20%)	u	Latvia	0	0
Switzerland	p (30%)	u	Denmark	0	0
Norway	u	p (7%)	Malta	0	0
Luxembourg	0	u	Netherlands	u	0
Germany	p (n.a.)	p (n.a.)	Estonia	0	0
Greece	p (n.a.)	p (n.a.)	Finland	u	0
Austria	p (65%)	p (35%)	Bulgaria	0	0
Italy	p (48%)	p (6%)	United Kingdom	0	0
Poland	p (n.a.)	p (n.a.)	Hungary	0	0
Portugal (Lisbon Centre)	p (~ 5%)	p (~24.%)	Ireland	0	0
Spain	p (31%)	p (37%)	Cyprus	0	0
Sweden	p (17%)	p (52%)	Slovakia	e	e
Czech Republic	0	p (1%)	Romania	0	0
Lithuania	0	p (1%)	Liechtenstein	n.a.	n.a.

PR: pathogen reduction; PLTs : platelets; 0: not implemented; u: universal implementation; p: partial implementation; e: experimental use; n.a.: data not available.

legal basis of this legislation allows the MS to adopt more stringent measures on a national basis. Thus, from the legislative aspect, PRT is not mandatory but may be considered a more stringent intervention that can be applied during an outbreak of infectious disease. The evolving regulatory landscape, driven by the FDA draft guidance, has influenced US health care providers to consider PR to mitigate bacterial contamination of PLTs. The ECDC has recommended the use of PRT in outbreaks of infectious diseases for which screening is not available[111].

Summary of expert opinion

Pathogen reduction technologies represent an opportunity to increase the microbial safety of blood and blood components by applying a proactive strategy. In spite of the enormous advantages in improving the safety of the blood supply, these technologies do have limitations, including increased costs, which hinder their wider use. As of the time of the expert meeting, PRTs alone are, therefore, insufficient to fully safeguard the blood supply and are accepted as an additional line of defence to mitigate the infectious risks of bacterial and protozoal transmission, and risks posed by pathogens (susceptible to PRT) for which screening is not available. Inactivation of leukocytes is a further benefit of PRT which can replace the irradiation of blood components.

The changing epidemiology of existing infections and the increasing frequency of EID outbreaks may continue to challenge the safety of the blood supply. A continuing strategy of additional screening and donor deferral for microbial safety is unlikely to be sustainable in the future. Affordable and efficient PRT of all blood component types may offer a prospect for rationalisation of blood safety strategies.

Pathogen reduction technologies have been combined with conventional blood safety strategies to varying degrees across blood establishments in EU/EEA MS. As of April 2019, sixteen (52%) EU/EEA MS and Switzerland are regularly using PRT in the routine preparation of PLTs and/or plasma. Among them, only two countries implemented universal PRT for both PLTs and plasma. Nevertheless, PRTs are slowly but steadily being incorporated into standard transfusion practices. Since the use of PRTs is not regulated by EU legislation, national competent authorities consider the PR of blood components as a more stringent intervention. Even though published studies support the effectiveness of PR methods against a large spectrum of TT pathogens, specific criteria and methodologies to evaluate and compare the efficacy of PRTs have not been determined. Suitability of PRT for any potential future infectious threat cannot always be assumed if based only on their efficacy against those pathogens that are already known.

Pathogen reduction technologies have been applied during several outbreaks of arthropod-borne viruses, and are now recognised as a major advance and strategy to minimise the risk of TTIs in future EID epidemics. Experience in using PRT during infectious disease outbreaks has shown that, if PRT is already in use, the time to switch on or scale up the use of this technology in an affected area is shorter than it would be if it is not in use, allowing time to produce sufficient PRT-treated blood components to cover the local demand.

Thus, a country at risk of infectious disease outbreaks that threaten the safety of the blood supply may consider implementing PRT (at least partially in strategically selected blood centres) also to improve national capacity and capability to respond to infectious disease outbreaks for which a screening test is not available or practical. Following the principles of public health emergency preparedness, the scale of implementation and components subjected to PR could be determined based on the sustainability of the measure, the anticipated magnitude and geographical spread of an outbreak, and the type of transfusion-transmissible pathogen. The operational decision to implement PRT should, regardless of the benefits and limitations, consider above all the improvement in blood safety achieved by PR during a potential outbreak or epidemic.

Authorship contributions

DD wrote the manuscript, developed the meeting aims and elicited the expert opinion. VC, MF, JG, TJ-M, FK, GML, PM, CN, CP, KS, IS, APS and NV collected and interpreted the national data. PG and SV summarised the use of pathogen reduction technologies during infectious disease outbreaks. VC critically summarised pathogen reduction technologies. MJ addressed cost-effectiveness issues. IUL provided microbiological expertise on the subject and substantially reviewed the manuscript. SB, GM, YM, SP, GR, CV, MV and PR analysed specific questions related to the use of pathogen reduction technologies in blood transfusion. All authors contributed to the expert opinion, critically revised the manuscript, and approved the final version for publication.

Disclosure of conflicts of interest

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Appendix: supplemantal data

Pathogen reduction technologies in selected EU/EEA Member States, Switzerland and USA

Austria

Karmin Saadat reported the status of PRT implementation in Austria. Although there is no legal requirement for the use of PRT during the processing of blood and blood components, more lenient testing requirements are defined for PR products, and shelf life for PRT PLTs is prolonged to 7 days. At the time of the meeting, 6 of 33 blood establishments in Austria use PRT. Two plasma collection (apheresis) centres apply PR of PLTs and four WB collection centres perform PR of PLTs, and two of them also PR of plasma (methylene blue and amotosalen, respectively). Reasons for implementation are a cessation of the sterility testing of PLTs, an increase in blood product safety, implementation of PRT in Switzerland, an increase in shelf life of PLTs, cessation of CMV-testing and replacement of gamma irradiation, and inactivation of pathogens that are not tested for in screening tests. Potential disadvantages are a decrease in PLT activity, higher needs, an additional step in production that may create a new risk spot (i.e. a higher chance of contamination or failure), increased costs, and potential toxicity of substances remaining after the procedure.

Belgium

Veerle Compernolle described three methods for the PR of PLTs and plasma, their adverse effects, and the Belgian experience in the use of PRTs. In Belgium, the PR of plasma using methylene-blue and visible light method has been mandatory since 2004. In 2009, the Belgian national parliament became the first in the world to pass a bill that mandates nationwide PRT for all PLT concentrates (PC) distributed to hospitals for transfusion. The law came into force in 2013 following additional recommendations to the blood establishments. These included a minimal PLT dose criterion of 3.0×10^{11} per PC and a limitation of the shelf life from 7 to 5 days following concerns over PR PLT efficacy after storage. Implementation in the Belgian blood service was further hampered by the risk of aseptic breaches arising from perforation of PRT bag systems. Observed operational consequences of PRT include increased operational complexity, adaptations of previous production steps, potential product loss, and generation of new risks.

Denmark

Jørgen Georgsen emphasised that in 2010 the Danish Health Authorities had published a report regarding PR[1]. Due to several drawbacks, the report indicated that the implementation of PRT should wait for further investigations and that the focus should be on reducing blood usage. After the report, in the region of North Jutland, around 3,300/2,800 units of PR PLTs were produced/transfused annually in the period 2013-2018, but this was stopped due to the increased costs and the absence of clinical requests. In the Capital region, PRT has been experimentally used and investigated[2-6]. National data on viral infections among repeat donors in the period 2009-2018 show a low rate of viral infections: hepatitis B virus (HBV): $0.64/10^5$; hepatitis C virus (HCV): $0.20/10^5$; human immunodeficiency virus (HIV: $0.3/10^5$). On the regional level, in the period 2010-2018, there were 0.01% positive PLT donations in bacterial screening. Currently, in Denmark, there is no routine use of pathogen reduced blood components, no current clinical trials with pathogen reduced blood components, and no plans for routine use or clinical trials in the future. There is also no demand from clinicians, the risk of reduced function of PLTs outweighs the reduction in risk of infection, and the procedure is costly and probably not cost-effective. Danish health authorities may decide to update the 2010 PRT report within the next 12-18 months.

France

Imad Sandid provided statistical and epidemiological data on the blood supply for 2017 in France showing 283.2 adverse reactions (AR) per 10^5 blood components (BC) issued and 302.6 AR per 10^5 BC transfused. According to French legislation, in order to be authorised for therapeutic use, pathogen reduced blood components, such as novel blood components, are evaluated in terms of quality, safety and efficacy. Taking into account the advantages/limitations, and in particular the potential effectiveness in terms of prevention against TT bacterial infections (BI) and arboviruses, and considering the feasibility, it was decided to implement universal PR (amotosalen/UVA) of PLTs in France from November 2017. In the last decade, France has experienced 4-8 TTBIs per year (1 death every 2 years). No TTBI were reported after the implementation of PR-PLTs in 2018. Consideration was given to the need for a continuous supply of non-PR PLTs with an equivalent level of safety for the few individuals who may have allergic reactions to psoralens. PR PLTs have been used in southern France and overseas departments in outbreaks of WNV, dengue, chikungunya and ZIKV. The analysis of PLT allergic reactions reported in France during 2008-2014 showed a lower incidence for PR PLTs than

non-PR PLTs[7]. There were no differences in risk of PLT refractoriness between 2018 (universal PR PLTs) and 2017 (21% PR PLTs and 79% PAS PLTs non-PR). Solvent/detergent (SD) plasma has been in use since 1991 as a therapeutic blood component but in 2015 was reclassified to medicine product derived from plasma. Methylene blue treated plasma was in use from 2008 to 2012 and withdrawn because of more frequent allergic reactions. Amotosalen/UVA treated plasma was implemented in 2006 and represented 10-20% of the plasma transfused in 2017. The remaining 80-90% of plasma transfused in 2017 was quarantine plasma.

Germany

Markus Funk presented data from the German haemovigilance 2016/2017, which show a low incidence of TTIs. There were around 4.8 million blood components distributed annually with 4 confirmed TTIs (three bacterial and one viral) in 2016 and 7 TTIs (six bacterial and one viral) in 2017. The reported rate of bacterial TTIs was $0.28/10^6$ transfused RBC units and $7.1/10^6$ transfused PLT units. Such low rates of TTIs result from the implemented NAT screening of donations for the presence of existing viruses like HIV, pre-donation sampling, and limiting PLT shelf life to 4 days. To mitigate the remaining risk of TTIs in Germany, PRT of PLTs is implemented in 7 blood establishments and of plasma in 4 BEs. Funk also presented Theraflex® UV-PLTs, a novel system for ultraviolet C (UVC)-based PR of PLTs, which is currently undergoing clinical efficacy and safety testing[8]. In contrast to other PRTs, Theraflex® UV-PLTs works without exogenously added photoactive substances. Shortwave UVC light (254 nm) directly interacts with nucleic acids resulting in the formation of cyclobutane pyrimidine and pyrimidine-pyrimidone dimers that prevent nucleic acid transcription[9]. It has been demonstrated that UVC treatment significantly reduces the infectivity of PLT products contaminated by disease-causing bacteria[10], viruses[11-13], and protozoa. UVC-treated PLTs stored for 5 days showed marginal changes in PLT metabolism and activation *in vitro* and were associated with a degree of reduction in recovery and survival similar to other pathogen inactivation systems that are licensed and already in use[14].

Greece

Constantina Politis emphasised that the spread of insect vectors through travel and trade, combined with climate change, pose a significant challenge to public health and transfusion medicine in European and other countries. In the last decade, Greece has experienced several outbreaks of autochthonous malaria and WNV infection. Although there are several interventional procedures in place to prevent TT malaria, the fact that no laboratory test is sufficiently sensitive for the reliable detection of low parasitaemia in asymptomatic blood donors who may have been infected has also raised questions about blood screening strategies. On the other hand, a large spread of WNV may result in the deferral of a large proportion of laboratory-positive donors which may jeopardise the sustainability of blood supply (especially in the big cities). Thus, in situations of malaria and WNV outbreaks, PR for plasma and PLTs may also be considered. In Greece, the Theraflex® Methylene-blue System including the Blueflex filter is used to reduce transfusion-transmissible viruses as well as some of the non-enveloped viruses. Haemovigilance over 11 years has demonstrated the long-term safety of methylene-blue plasma in comparison to untreated quarantine plasma. In addition to lowering the adverse event rate, implementing the system on a national scale in countries at risk would presumably reduce the transmission of severe viral infections, including EIDs by transfusion[15,16]. The Mirasol® system has been used in Greece for the PR of aphaeresis PLTs in 4 blood establishments (2 university hospitals and 2 oncology hospitals). The system uses Riboflavin and UV light. The review of the haemovigilance data in Greece in the period 2010-2017 shows 17 cases of transfusion-associated sepsis due to contamination of RBCs and untreated plasma and PLTs (estimated risk of sepsis 1: 351,869 units). One life-threatening and three fatal transfusion adverse reactions could have been prevented if PR was in place. In 2012, transfusion transmitted West Nile neuroinvasive disease (TT-WNND) with a long severe outcome was associated with apheresis PLTs, and in 2014, a death due to TT-*Serratia marcescens* was associated with apheresis PLTs. Therefore, Politis concluded that the high impact of malaria and WNV infection on blood supply (donor availability) in the affected areas, as well as the continuous threat of bacterial transmission through PLT transfusions, indicate that PRT could be considered as a response intervention solution in such situations.

Italy

Giancarlo Maria Liumbruno reported that PRTs are neither routinely used nor mandatory in Italy. Currently, no nationwide specific guidelines on the use of PRTs are in force. In 2018, based on local/regional decisions, about 13,000 PR PLTs (5.77% of the total PLT concentrates transfused nationwide) have been transfused. Recent clinical effectiveness study in Italy provided a piece of additional information about the safety and efficacy of PR PLTs treated with two commercial PRTs[17]. Another study, developed within a wider health technology assessment (HTA) process, undertaken to estimate the costs of the continuing increase in the use of PLT PRT

in Italy, indicated that further studies based on actual numbers of PLT transfusion complications and their societal cost at a local level are needed to see the full cost to benefit ratio of PLT PRT implementation in Italy, and to promote equal treatment for all citizens[18]. In 2018, around 130,000 PR plasma units (nearly 48% of the total plasma units transfused nationwide) were transfused in Italy. The highest proportion of PR plasma is SD treated (127,954 units) and the remaining quantities are PR by using amotosalen +UVA, riboflavin +UVA/B, methylene-blue + visible light or quarantine plasma. PR PLT concentrates were successfully used during the 2017 CHIKV outbreak in the Latium Region.

Portugal

Ana Paula Sousa reported on the organisation of the Portuguese Blood System and described the multi-layered interventional proactive approaches to blood safety in Portugal. These include voluntary non-remunerated donation, donor education, stringent donor selection, laboratory screening of blood donations, leukoreduction, use of quarantine plasma, industrial viral inactivation, optimal use of blood, haemovigilance programmes, and PRTs. PRTs have been considered to maintain the safety of blood supply because of their potential effectiveness to mitigate infectious and non-infectious risks as well as logistical risks. Donor epidemiological data in Portugal show that, in 2017, the probability of an infected donation for HBV was 1/1.6 million donations, for HCV 1/5 million donations, and for HIV 1/1.1 million donations. Among all severe acute respiratory syndrome (SARE) cases reported in the period between 2008-2017, the proportion of TTBI was 0.09% (2 notifications in 2007 and 2 notifications in 2011) and of TTVI 0.16% (overall, of the 7 notifications, 1 was classified as possible and 3 with demonstrated imputability. The remaining 3 notifications had imputability excluded). In recent years, several pathogens have been added to the list of potentially threatening agents: DENV, WNV, CHIKV, Influenza A (H5N1) virus, HIV and HBV variants. In Portugal, only the Lisbon Blood Centre produces PR PLTs (in house-PR platelet pools) as well as PR plasma (in house-PR fresh frozen plasma). Several studies on the PR of PLTs have been published[19]. Since 2011, the shelf life of PR PLTs has been prolonged to 7 days which provides adequate and timely supply. Rational decisions are made about managing risks in the context of emerging pathogens (outbreaks) and based on an evidence-based risk analysis. However, it is fundamental to identify and prioritise risks to blood safety, taking into consideration social, economic and ethical perspectives that go beyond the economic calculations, and can alter risk tolerability.

Spain

Teresa Jimenez-Marco reported on the structure and data of the blood supply system in Spain. Current implementation of the PR of both plasma and PLTs in Spain remains heterogeneous. Some blood establishments (BEs) have had experience with Mirasol® and Intercept® PR methods for PLTs for more than 10 years. Most BEs have almost 20 years of experience in inactivating plasma with methylene blue. In 2018, Spain produced 250,985 units of PLTs of which 78,372 (31.2%) units had been PR using Intercept® (9,568; 12.2%) units and Mirasol® (68,804; 87.8%) units. Among BEs that employ the Mirasol® system for PLTs, 66% apply the system universally and 34% partially. The PR of PLTs is implemented universally in 34% of BEs and partially in 66% of BEs that are using the Intercept® system. Among 261,224 plasma units issued for transfusion, 165,594 (63.4%) were quarantined and 95,630 (36.6%) treated with PRT: methylene blue 93,086 (97.4%) units, Mirasol® 2,203 (2.3%) units and Intercept® 341 (0.3%) units. In Spain, the rationale for PRT implementation for both plasma and PLTs is not only on achieving transfusion safety, but also logistical advantages (extension of PLT storage time from 5 to 7 days, improving plasma availability in order to preferentially transfuse plasma from male donors). Throughout the years in which PRT have been used in Spain, several studies covering the PR of plasma[20-21] and PLTs[22-24], cost-efficiency of PRT[25], pathogen reduction efficacy[26,27], and haemovigilance[28] have been published.

Slovenia

Polonca Mali provided basic data about non-remunerated blood donation in Slovenia and the structure of the National Blood Service. Epidemiological data of 924,087 screened blood donations in the period 2008-2017 showed the prevalence of positive donations for HBsAg 0.009%, anti-HCV 0.003%, HIV Combo 0.0001%, anti-TP 0.009%, NAT HBV DNA 0.004%, NAT HCV RNA 0.0001%, and NAT HIV RNA 0%. During the mosquito transmission season in 2018, there were 4 cases of WNV infection reported in Slovenia. The decision to implement PR for PLTs in the National Blood Transfusion Centre in Ljubljana had been endorsed in 2007. Switch to the buffy-coat production of PLTs besides apheresis, implementation of the technology and approvals were made in 2008 when production started, and since 2009 PR of PLTs have been regularly produced in the Ljubljana blood centre. Storage period for PRT PLTs is 7 days. However, the remaining two blood establishments in Slovenia, which produce a smaller proportion of PLTs in the country, did not implement this technology. FFP

for clinical use is prepared only from male donations but is not inactivated or quarantined. In 2019, Slovenia is preparing a project aimed at ensuring 100% universal PR of PLTs.

Sweden

Folke Knutson presented a structure of the decentralised Swedish Blood System which is made up of more than 90 blood centres (26 laboratory organisations and 73 hospital-based blood transfusion departments). In 2017, Swedish blood centres collected 407,582 WB units from 213,376 eligible blood donors, 30,070 apheresis plasma units, 53,646 units of PLTs, (approx. 68% from buffy coat and 32% from apheresis). From the total quantity of collected plasma, 43,140 units were transfused to patients and the remaining 113,140 kg of plasma were delivered to fractionation. In 2007, Sweden started implementing the PR of PLTs in Uppsala using the Intercept® system. The aim was to prevent bacterial contamination and prolong storage time of PLTs. To reduce costs, the Uppsala Blood Centre developed an in-house double dose kit. Since then, this type of PR kit has been included in regular commercial production. The Uppsala Blood Centre also stopped performing gamma irradiation and bacterial culture testing of PLTs. Currently, the PR of PLTs in Sweden is increasing, from 39% of all PLTs in 2017 to 52% in 2018. PR of plasma for clinical use remains very limited in Sweden. In 2018, a total of 7,202 units of PR plasma (Octaplas) were used in 2 regions. Knutson also emphasised that the Uppsala Blood Centre is developing a procedure for PR of pooled plasma (4 apheresis plasma donations or 10 plasma units recovered from WB) in order to standardise the component. Simultaneously, the Centre is investigating the impact of PR pooled plasma on reducing the allergic reactions to plasma transfusion. Another research study performed at the Centre showed that the quality of PR RBCs using S-303 amustaline treated RBC is better than irradiated. Knutson concluded that PR is an efficient technology and its use in Sweden has increased over the years.

Switzerland

Christoph Niederhauser presented the organisation of the Swiss Blood Transfusion Service together with data about the production of blood components in Switzerland and epidemiological data related to the blood supply in 2017. He also presented the Haemovigilance data 2005-2011 (i.e. before the implementation of PR). These data show no reports of TTI after RBC transfusion but 16 cases of sepsis; 3 of them were fatal after PLT transfusion. The estimated risks of sepsis due to contaminated PCs in that period was approximately 1: 9,900 (approx. 3-4 per year) with mortality approximately 1: 52,800 (approx. 1 case per 1.6 years)[29]. Two fatal transfusion-transmitted cases in 2009 were a trigger for Swissmedic to take suitable measures to reliably prevent clinically relevant bacterial contamination of PLT products and to implement those measures as soon as possible. In the second half of 2009, PR (Intercept®) for PLTs was approved for use in Switzerland (Approval/Market Authorization of Intercept®). Since summer 2011, all PLTs issued in Switzerland are PR. Haemovigilance data 2011-2017 (i.e. after the implementation of PR) showed no transfusion-transmitted infectious disease case had been detected. Swiss haemovigilance data confirm a favourable safety profile of the Intercept® pathogen inactivation procedure that has been introduced nationwide, and its reliable prevention of septic transfusion reactions and fatalities due to bacterially contaminated PCs.

The USA

Nicole Verdun showed that currently FDA-approved devices are Intercept® Blood System (IBS) for apheresis PLTs and plasma (derived from whole blood or collected by apheresis). Approval for PRT PLTs is specific regarding storage period (5 days), collection platform and additive solution (Amicus collected PLTs in 65% PAS-3 and 35% plasma or Trima collected PLTs in 100% plasma), and type of kits (small volume, dual storage and large volume). PRT for RBCs has not been approved by the FDA. The universal use of PRT has not been adopted, and some hospitals have a dual inventory of PR and conventional blood products. Current laboratory screening of blood components in the US entails testing for HBV, HCV, HIV, HTLV I-II, and Syphilis. Additionally, the FDA recommends testing for WNV, *Trypanosoma cruzi* (Chagas disease), and ZIKV. Besides existing blood-borne infections, EIDs pose a threat to the safety of the blood supply. Experience with the ZIKV outbreak showed that it would be necessary to implement specific testing of donated blood to prevent the transfusion-transmission of a "new" pathogen during a possible outbreak in the future. Each additional test raises the cost of the blood supply. The US experience shows that PRT is an acceptable intervention to ensure that the bacterial contamination risk of PLTs is adequately controlled[30]. Blood establishments may use FDA-approved PRT for indicated blood components (i.e. PLTs and plasma) to reduce the risk of ZIKV transmission by blood and blood components[31]. The FDA had previously granted a variance for PRT of apheresis PLTs in cases in which malaria risk factors are reported. The FDA recently provided draft guidance on the implementation of PRT in the manufacture of blood components in blood establishments[32]. Ongoing studies in the US are investigating the 7-day storage of

apheresis PLTs, especially PLT recovery and survival, compassionate use of passive immune therapy during acute Ebola virus infection using the transfusion of PR (IBS) plasma from donors who recovered from Ebola virus infection, PR of RBC (IBS) in areas affected by ZIKV (RedeS), randomised PR of RBC in complex cardiac surgery (RcCePi), the PR of apheresis PLTs (Mirasol®) in hypoproliferative thrombocytopenia (MiPlate), the PR of WB-Derived RBC (Mirasol®) in Chronic Transfusion (PRAISE). The FDA is expanding its internal scientific research programmes on PR and initiating collaborations with external academic and industry partners to advance the development of novel agents for PR, the optimisation of existing PR technologies, planning future regulatory strategies for a reduction in required testing on PR products. As the safety and sustainability of the blood supply are adversely affected by both existing and emerging pathogens, the goal of the current research is to foster the development of robust PR technologies that can be used on WB prior to separation into components.

The use of pathogen reduction technologies during infectious disease outbreaks

Stefania Vaglio explained that in the summer of 2017, Italy experienced a CHIKV outbreak that spread in the Lazio region and caused a secondary outbreak in the Calabrian village of Guardavalle, with a final number of 436 cases. The epidemiological investigation suggested the occurrence of three main foci of local transmission in the Lazio region. The largest focus, involving 317 persons with a direct link with the town of Anzio and its surrounding area, occurred between week 26 and week 42. The other two foci occurred in people who lived in Rome and Latina and had no link with the area of Anzio. Following the notification of the autochthonous cluster, the surveillance and strengthening vector control activities were carried out. CHIKV diagnosis was based on the detection of the viral genome by real-time-PCR and virus-specific antibodies by serological tests on serum or plasma samples. Testing for CHIKV was not considered for donors' screening since, at that time, CE-marked and validated tests were not available. Given the large and populated area of Rome and the consequences of an interruption in blood donations on the regional blood supply, a risk-benefit evaluation based on daily epidemiological data was performed. Blood safety measures were then developed considering the yearly consolidated need of RBCs in Lazio (about 30,000 units), and that the interruption of donations in the whole municipality of Rome (4 million inhabitants) would have had a massive impact on the regional blood inventory, national self-sufficiency, the local health system, and the ability to limit the spread of infection. Measures taken were[33]: interruption of blood collection in the affected local health district of the Rome municipality (1.3 million inhabitants) and in the municipality of Anzio (around 54,000 inhabitants), application of a 5-day quarantine in the remaining areas of Rome for RBCs collected from donors with a history of travel in the municipality of Anzio or in the affected district of Rome. The 5-day quarantine was based on an active recall of all donors and release of quarantined blood components in case of declared absence of any symptom or illness by the donor. None of the donors referred to symptoms or illness at recall and, as a consequence, none of the blood products were discarded after quarantine. The clinical assessment of donors was reinforced. Blood authorities introduced mandatory post-donation information for donors who travelled in the affected areas and for all donors resident in the Lazio region. Donors diagnosed with CHIKV infection were deferred for 4 weeks after the resolution of symptoms. The National Blood Centre activated a national emergency blood supply plan, which in the first 10 days allowed more than 2,500 red blood cell units to be sent to the Lazio region from other Italian regions. Collection of plasma for fractionation was allowed, as well as that of PLTs and plasma for clinical use, provided pathogen inactivation had been used. The outbreak of CHIKV infection highlights the importance of an integrated surveillance system to promptly identify autochthonous transmission, and the importance of an effective and efficient national emergency blood supply plan. According to available data, it seems that the applied measures successfully prevented TT CHIKV infections during the outbreak.

Pierre Gallian reviewed the implementation history of PRT in France and presented their experiences in applying this technology in different contexts. Early in the 2000s, PRT for PLTs using the IBS was introduced for evaluation by the French National Blood Service (Etablissement Français du Sang - EFS) in the French region of Alsace. During the 2005-2006 CHIKV epidemic in La Réunion Island (Indian Ocean), more than 30% of the 750,000 inhabitants were infected[34]. Local blood donation was suspended to prevent TT-CHIKV infection. To sustain the availability of PLT components, the EFS, using the experience in Alsace, rapidly implemented PR (IBS) of PLTs collected locally by apheresis (CPAs). Over one year, 1,950 PR CPAs were transfused to 335 adults, 51 paediatric and 41 infant patients. No cases of TT-sepsis, or TT-CHIKV were detected[35]. Of note, no cases of TT-CHIKV have been reported worldwide. This was the first French experience of implementation and operational logistics of PRT during a large outbreak of infectious disease that led to the implementation of PR (IBS) of PLTs in all other overseas territories in 2006.

A decade later, French West Indies (Martinique and Guadeloupe) faced 2 major outbreaks: CHIKV in 2014 and ZIKV in 2016. In both epidemics, blood collection was not interrupted and a systematic individual NAT testing for viral RNA was implemented. During these outbreaks, IBS treated PLTs could be transfused without awaiting NAT results. Studies indicated that PRT using amotosalen and UVA light has the capacity to prevent (by a significant log reduction of viral load) CHIKV or ZIKV transmission in human blood components collected from infected donors in or travelling from areas of ongoing transmission[36-38]. Viral loads of positive CHIKV or ZIKV donations were below the maximum efficacy tested in the laboratory for IBS validation studies reported in the literature. ZIKV NAT testing performed on blood donations showed higher viral loads in symptomatic blood donors compared to asymptomatic ones[39]. IBS treated PLT concentrates issued from CHIKV or ZIKV NAT positive donations who had been issued for transfusion before final NAT release were investigated. Haemovigilance survey of IBS treated PLT concentrates did not report clinical signs evocative of CHIKV or ZIKV infection in those recipients. In continental France, the main challenge with arboviral diseases is the periodic re-emergence of WNV in the southern part of the country. In the summer of 2018, during the most important WNV circulation in France, the production of IBS-treated PLTs has been useful also for blood safety and blood supply management. The prevention of transfusion-transmitted bacterial infections (TTBI) by PLTs was the main argument taken into account in the decision for the national implementation of the IBS for PLTs in November 2017. Since then, no TTBI caused by PLT concentrates has been reported. Gallian emphasised that, besides the prevention of TTBI through PLT, an additional benefit of PR methods is the mitigation of residual risk of TTI caused by a low infectious dose of pathogens currently tested in routine practice. This could be illustrated by the recent description of transfusion of the human immunodeficiency virus (HIV)-infected blood donated during the HIV pre-ramp-up phase that was tested individual NAT negative due to a low viral load (< 95% limit of detection)[40]. Similarly, PR methods may be useful in preventing TT malaria when (even if the case is very rare) serological testing fails to detect immune-silent donors, with very low levels of both antibodies and parasites[41]. Moreover, PRT (IBS-treated plasma) has also been applied to optimise blood safety in the context of the 2014 Ebola virus outbreak in West Africa. In one clinical trial for the treatment of Ebola virus in Guinea (The Ebola Tx project funded by the UE), the EFS experience was used for rapid implementation of a local production (including IBS treatment) of immune plasma collected from convalescent donors[42]. Besides the known advantages and limitations (cases of TTI by non-enveloped virus such as hepatitis E virus[43]), Gallian pointed to difficulties in the evaluation and the comparison of PRT performance because a variety of units of measurement are used to quantitate pathogen levels in blood components (IU/mL, copies/mL, Geq/mL, TCID50/mL)[44].

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